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SCIENTIFIC OPINION

Update of the risk assessment of polybrominated diphenyl ethers (PBDEs) in food

EFSA Panel on Contaminants in the Food Chain (CONTAM) | **Dieter Schrenk** | **Margherita Bignami** | **Laurent Bodin** | **James Kevin Chipman** | **Jesús del Mazo** | **Bettina Grasl-Kraupp** | **Christer Hogstrand** | **Laurentius (Ron) Hoogenboom** | **Jean-Charles Leblanc** | **Carlo Stefano Nebbia** | **Elsa Nielsen** | **Evangelia Ntzani** | **Annette Petersen** | **Salomon Sand** | **Tanja Schwerdtle** | **Heather Wallace** | **Diane Benford** | **Peter Fürst** | **Andy Hart** | **Martin Rose** | **Henri Schroeder** | **Martine Vrijheid** | **Sofia Ioannidou** | **Marina Nikolič** | **Luisa Ramos Bordajandi** | **Christiane Vleminckx**

Correspondence: contam@efsa.europa.eu

Abstract

The European Commission asked EFSA to update its 2011 risk assessment on polybrominated diphenyl ethers (PBDEs) in food, focusing on 10 congeners: **BDE-28**, **-47**, **-49**, **-99**, **-100**, **-138**, **-153**, **-154**, **-183** and **-209**. The CONTAM Panel concluded that the neurodevelopmental effects on behaviour and reproductive/developmental effects are the critical effects in rodent studies. For four congeners (**BDE-47**, **-99**, **-153**, **-209**) the Panel derived Reference Points, i.e. benchmark doses and corresponding lower 95% confidence limits (BMDLs), for endpoint-specific benchmark responses. Since repeated exposure to PBDEs results in accumulation of these chemicals in the body, the Panel estimated the body burden at the BMDL in rodents, and the chronic intake that would lead to the same body burden in humans. For the remaining six congeners no studies were available to identify Reference Points. The Panel concluded that there is scientific basis for inclusion of all 10 congeners in a common assessment group and performed a combined risk assessment. The Panel concluded that the combined margin of exposure (MOET) approach was the most appropriate risk metric and applied a tiered approach to the risk characterisation. Over 84,000 analytical results for the 10 congeners in food were used to estimate the exposure across dietary surveys and age groups of the European population. The most important contributors to the chronic dietary Lower Bound exposure to PBDEs were meat and meat products and fish and seafood. Taking into account the uncertainties affecting the assessment, the Panel concluded that it is likely that current dietary exposure to PBDEs in the European population raises a health concern.

KEYWORDS

food, human exposure, occurrence, PBDEs, Polybrominated diphenyl ethers, risk assessment, toxicology

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SUMMARY

Brominated flame retardants (BFRs) are anthropogenic chemicals, which are used in a wide variety of consumer/commercial products to improve their resistance to fire. Concern has been raised because of the occurrence and persistence of several BFRs in the environment, food and in humans. This has led to bans on the production and use of certain formulations.

The European Commission (EC) asked the European Food Safety Authority (EFSA) to update its 2010–2012 risk assessments on the different classes of BFRs, i.e. hexabromocyclododecanes (HBCDDs), polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A (TBBPA) and its derivatives, brominated phenols and their derivatives, and novel and emerging BFRs. The CONTAM Panel is updating the risk assessments of different classes of BFRs in a series of separate Opinions.

The similarities in chemical properties and effects identified in the previous EFSA assessments for the different BFR classes warrant the consideration of a mixture approach. The Panel on Contaminants in the Food Chain (CONTAM Panel) will evaluate the appropriateness of applying a mixture approach for the different classes of BFRs in an additional Opinion once the risk assessment for each BFR class has been updated. It will be based on the EFSA Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals.

The first Opinion in the current series updated the risk assessment of HBCDDs in food (EFSA CONTAM Panel, 2021). This second Opinion updates the risk assessment of PBDEs in food previously performed by EFSA and published in 2011. The current assessment focusses on 10 PBDE congeners -**28**, -**47**, -**49**, -**99**, -**100**, -**138**, -**153**, -**154**, -**183** and -**209** as requested in the Terms of Reference by the EC. Except for **BDE-49** and -**138**, the previous Opinion considered the same congeners as the present assessment.

PBDEs had widespread use as additive flame retardants in the past. They were applied as technical mixtures, termed PentaBDE, OctaBDE and DecaBDE in construction materials, furniture and electric and electronic equipment, generally at concentrations between 5 and 30% by weight. As they were not chemically bound to the plastic or textiles, PBDEs could leach into the environment and consequently had global distribution. The congeners are persistent in the environment and they bioaccumulate at high levels in the food chain. PBDEs are listed in Annex A of the Stockholm Convention, with specific exemptions for use or production.

The present assessment takes into account the occurrence data in food and biological samples submitted to EFSA after the publication of the previous Opinion, as well as the newly available scientific information of relevance to hazard identification and characterisation.

The draft scientific Opinion underwent a public consultation from 8 June 2023 to 20 July 2023. The comments received were taken into account when finalising the scientific Opinion and are presented and addressed in Annex I.

The analytical determination of PBDEs is performed by gas chromatography (GC)/mass spectrometry (MS)-based methods, that generally allow the quantification of all 209 possible PBDE congeners. In routine analysis, the analysis of PBDEs is often focused on eight congeners (**BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183** and -**209**) which were considered by the CONTAM Panel in 2011 to be of primary interest. Nevertheless, there are many surveys that are limited to fewer (predominant) PBDEs or include a number of additional congeners, which makes a comparison of results based on summed concentrations difficult.

Hazard identification and characterisation

Oral absorption rates and/or bioavailabilities of PBDEs have been studied in rats and mice. Absorption of **BDE-47** (mice and rat), -**100** (rat), -**154** (rat) from the gastrointestinal tract is almost complete (> 75%) and is lower for **BDE-99** (50% in rat). It seems that **BDE-209** is less efficiently absorbed compared to the other congeners (10%–26% in rat). Nevertheless, no clear trend in the oral bioavailability according to the bromination degree could be concluded.

In rodents, differences in distribution were observed between congeners: **BDE-47**, -85, -**99**, -**100** and -**153** are predominantly distributed to adipose tissue, whereas **BDE-209** is predominantly distributed to highly perfused tissues (e.g. liver). The reported (terminal) half-lives after repeated oral administration of PBDEs in rats and mice ranged from 2.5 to 75.9 days. PBDEs are maternally transferred to rodent offspring in utero and via lactation. In rats and mice PBDEs are mainly metabolised by a CYP-mediated oxidative pathway and by debromination, leading to the formation of OH-metabolites. Glucuronide- and sulfate-conjugate metabolites have also been detected. The excretion of PBDEs in rats is mainly via the faeces, whereas urinary excretion is the principal route for mice.

In humans, transfer of PBDEs and OH-PBDE metabolites from maternal blood to the placenta and human milk has been reported. Based on studies with human liver microsomes and primary hepatocytes, the main metabolic pathway of PBDEs in humans is CYP-mediated hydroxylation, followed by phase II metabolism with the formation of glucuronide and sulfate conjugates. There are limited data regarding the excretion of PBDEs in humans. Half-lives were estimated using different methodologies. The half-lives of **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154** and -**183** were estimated to be in the range of 280 (for **BDE-99**) to 2700 days (for **BDE-153**). For **BDE-209**, it was estimated to be 7–18 days.

Transfer of PBDEs from feed to food of animal origin has been studied in different animal species, i.e. ruminants, pigs, laying hens, broilers, ducks and fish. PBDEs are distributed to a number of tissues and accumulate in those with high-fat content. Transfer to eggs (laying hens) and milk (cows, goats and reindeer) has also been reported. Debromination of

PBDEs is an important factor in the retention of PBDEs. The predominant congeners found in fish seem to be the result of direct absorption of the parent PBDEs to which they were exposed, as well as debromination from congeners such as **BDE-209**, -**99** or -**183** into lower brominated congeners such as **BDE-47**.

In the previous Opinion it was concluded that the main targets for PBDE toxicity were the liver, and the thyroid hormone, reproductive and nervous systems. Toxicological studies in rodents published since then provide additional data in relation to effects on the liver, on thyroid hormone, reproductive, nervous and immune systems, and on lipid and sugar metabolism. The congeners studied were predominantly **BDE-47**, -**99** and -**209**, with limited data on BDE-3, -15, -**183**, -203 and -206. New data were also available for the technical products DE-71, PentaBDE, OctaBDE and DecaBDE. No new studies were available for **BDE-153**. No studies were identified for **BDE-28**, -**49**, -**100**, -**138** and -**154**.

The presence of trace amounts of brominated dioxins and furans (PBDD/Fs) has been reported in PBDE technical products used as test substances in the toxicity studies. No information on the presence of such impurities in individual congeners has been identified. Therefore, the Panel noted that the possible impact of dioxin-like constituents in the effects observed cannot be evaluated.

Repeated exposure of rats or mice to **BDE-47** and **-209** induced effects in the liver, e.g. increased liver weight, centrilobular hepatocyte hypertrophy, lipid accumulation/steatosis, changes in serum hepatic chemistry, microsomal enzyme induction. Similar effects, including inflammation and necrosis, were seen in offspring exposed in utero and/or postnatally until weaning. Increases in oxidative stress markers were noted in the liver of rat offspring exposed in utero and during lactation to **BDE-99**.

Increased thyroid weight, changes in the thyroid hormone system and thyroid follicle structure occurred in adult rats after repeated exposure to **BDE-47** and -**209**. There were also reductions of total triiodothyronine (TT3) and/or total thyroxine (TT4) levels with increased serum thyroid stimulating hormone (TSH) levels in offspring exposed in utero and during lactation.

BDE-47, -**99** and -**209** affected the reproductive systems of both male and female adult rats and mice. Exposure of offspring to these compounds during gestation and/or lactation caused reproductive toxicity. Changes in serum testosterone and oestradiol levels were observed in adult male rats and mice exposed perinatally or in adulthood.

BDE-47 administered to male adult rats or mice resulted in effects on the testes with changes in the organisation of the seminiferous tubules, germ cell loss, decreases in sperm production and motility. Exposure in utero or during lactation until weaning caused the same adverse effects in male offspring of exposed rat dams. Decreased ovarian weight and alteration of folliculogenesis occurred in female rat offspring exposed during gestation.

Degeneration of gonadal system histology was shown in adult male rats after exposure to **BDE-99**. Administration to pregnant animals resulted in reproductive tract changes in female rats of the F1 generation that were apparent at adulthood, and in changes in reproductive organs in male mice. Incomplete or delayed ossification and internal variations were also observed in rat fetuses exposed during gestation as well as impaired spermatogenesis in male offspring.

Repeated exposure of adult male rats or mice to **BDE-209** affected testicular histopathology, steroidogenesis and germ cell dynamics resulting in decreased spermatogenesis. Exposure of offspring in utero and/or during lactation resulted in decreased mating and fertility index, and litter size. Embryotoxicity occurred in mice exposed during gestation. In addition, a significant reduction in anogenital distance was reported in mice exposed in utero.

BDE-47 and -**209** exerted toxic effects to the immune system, e.g. changes in spleen and thymus, reduction of leucocytes, cytokine production and CD4+ and CD8+ T cells proliferation, inflammation of the gastrointestinal tract.

BDE-47, -**99** and -**209** induced effects on energy metabolism, such as changes in liver and serum lipids, serum glucose and serum insulin levels. However, contradictory results were reported when comparing studies, even those using the same test substance, making conclusions difficult.

BDE-47 induced long-term behavioural impairments in young adult rats or mice exposed in utero and/or during lactation, or at the adult stage, which are related to locomotor activity and spatial learning and memory. **BDE-99**, -**153** and -**209** were also demonstrated to induce the same types of behavioural disorders in rodents exposed during the early phase of brain development or at the adult stage. In addition, the exposure to **BDE-47** or -**99** was identified as being able to induce a reduction in the level of anxiety, and **BDE-99** and -**209** to impair the locomotor coordination and self-reactivity of the animals.

PBDEs have not been shown to induce gene mutations *in vitro* or *in vivo*. *In vitro* tests indicate that some PBDEs (**BDE-47**, -**99**, -**100**, -**153**, -**154** and **-209**) can cause DNA damage (single and double strand breaks). Induction of micronuclei was shown *in vitro* in cells expressing xenobiotic-metabolising CYP enzymes (human neuroblastoma cells or V79) exposed to **BDE-47** but not in HepG2 cells. Two metabolites, 6-OH-BDE-47 and 6-MeOH-BDE-47, were also positive for induction of micronuclei *in vitro*. *In vivo*, negative results were obtained in micronucleus tests in peripheral blood and bone marrow cells with **BDE-47** and -**209** and the technical product DE-71. The CONTAM Panel noted that while the micronucleus tests do not show evidence of toxicity to the bone marrow, systemic exposure was evident from toxicokinetics and from systemic toxicity and thus these are lines of evidence of bone marrow exposure to the test substance. There is evidence that PBDEs can induce DNA damage via an indirect mechanism of action, i.e. involving reactive oxygen species (ROS) production. Although there is evidence of genotoxicity *in vitro* for some congeners, there was no evidence for *in vivo* genotoxicity. The CONTAM Panel concluded that the 10 congeners considered in the Opinion are not genotoxic *in vivo*.

Individual PBDE congeners have not been tested for carcinogenicity. In studies with technical products, there was an increase in liver adenoma in Fischer 344/N rats and in liver adenoma and carcinoma in male B6C3F1 mice exposed to

DecaBDE (containing 94%–97% **BDE-209**) at very high doses (> 1000 mg/kg body weight (bw) per day). These tumours were not considered relevant as they were observed at very high dose levels, and because of the mode of action underlying their generation. There is evidence of carcinogenic activity of the PentaBDE technical product DE-71 in Wistar Han rats (liver, thyroid and uterine tumours) and in B6C3F1/N mice (liver tumours). Liver tumours are likely due to constitutive androstane receptor (CAR) activation, which is a well-documented key event for rodent liver tumour development. This mode of action is not plausible for humans. The thyroid tumours observed in rodents may result from adaptive thyroid proliferation. Furthermore, the Panel noted that it is unclear if one or more congeners present in the technical product are responsible for the effects observed. Moreover, the presence of impurities in the technical product DE-71 (e.g. PBDD/Fs) may have a possible impact on the effects including tumours observed in the thyroid as well as elsewhere. Based on the above and the lack of evidence for a direct mechanism of genotoxicity *in vivo*, carcinogenicity was not considered a critical effect.

The number of epidemiological studies has increased considerably since the previous Opinion, covering a large number of endpoints, including thyroid function and disease, neurodevelopment, lipid and sugar metabolism (diabetes and obesity), cardiovascular effects, effects on male and female reproduction, birth outcomes, effects on the immune system and inflammation and cancer. For most of the endpoints assessed, the currently available body of evidence is weak and characterised by a small number of prospective studies, generally short follow-up periods, relatively small sample sizes, considerable heterogeneity in the assessed populations, congeners, exposures and outcomes, and varying methodological quality.

For cognitive function, there is a growing evidence base stemming from longitudinal studies on the associations between PBDE levels and cognitive function indices that is characterised by a harmonised endpoint assessment through the Wechsler scales. However, statistically significant associations that were replicated in other studies are scarce.

For attention deficit hyperactivity disorder (ADHD)-related outcomes, although the evidence was enriched with new studies, results are heterogeneous with both positive and null associations reported in relation to prenatal and childhood PBDE levels. Some statistically significant associations were replicated across studies, in particular associations between levels of **BDE-47** and attention deficit subscales, and similarly for Sum PBDE (sum of **BDE-47**, -**99**, -**100** and -**153**).

For thyroid function, the reported associations are occasionally characterised by an opposite effect direction between and within studies. The prospective data showed mostly non-replicated statistically significant associations for **BDE-47**, -**99**, -**100**, -**153**; only **BDE-47** and -**99** were inversely statistically significantly associated with TSH and TT3 levels in two studies. Statistically significant associations across the whole panel of thyroid function biomarkers were seen for **BDE-47**, and partially for **BDE-99**, but with discordant effect direction in both cases.

For male fertility, the evidence on the association between PBDE exposure and relevant clinical endpoints is not sufficient, and the same applies for semen quality and sex hormones which are assessed in a larger number of studies but with a high risk of bias and no replication efforts.

For female reproductive effects, pubertal development in girls was assessed in three studies (one cohort, two cross-sectional studies) with all of them reporting some statistically significant results but with no consistency of effect direction; the proposed delayed pubertal development described in the longitudinal study is not supported by the statistically significant associations with premature pubertal development reported in the two cross-sectional studies.

For birth outcomes, birth weight was the most studied outcome. Reductions in birth weight and null associations in relation to maternal PBDE levels were reported, and evidence is therefore classified as inconclusive. For other birth outcomes (e.g. birth length, head circumference, gestational age) and outcomes measured in the early years of life (e.g. anogenital distance), there were not enough studies to draw conclusions.

For obesity, the few statistically significant findings related to prenatal PBDE levels and obesity attributes (e.g. body mass index, waist circumference, % body fat), pointed to an inverse association that is difficult to put into context and integrate with the respective data on Type 2 diabetes or on cardiometabolic risk factors.

Regarding the mode of action, there is a growing body of evidence that the tested PBDEs and OH-metabolites interfere with mitochondrial calcium homeostasis, leading to oxidative stress and apoptosis in neuronal cells. Changes in neurotransmitters (or in expression of related genes) and migration and differentiation of neuronal cells in culture are also observed. The data do not provide a clear picture of how PBDEs affect neurotransmission and synapses. The relative potency of the neurotoxicity of different PBDE congeners is unclear. There is a separate and additional line of evidence relating to involvement of the thyroid hormones in neurotoxicity of **BDE-209** although no data are available on similar involvement for other PBDE congeners.

There is some evidence that PBDEs and their metabolites can act as weak agonists or antagonists of the aryl hydrocarbon receptor (AHR). It is difficult to assess however whether these results were influenced by any contamination with dioxin-like compounds.

There is mechanistic evidence that PBDEs, and in particular their OH-metabolites, interfere with the thyroid hormone system by: (i) competing with T4 for thyroid binding proteins and (ii) altering expression and activities of enzymes that metabolise thyroid hormones. This could explain the observed effects of PBDEs on neurodevelopment and reproduction. It remains to be determined how relevant these two mechanisms are for humans. There is evidence of the involvement of sex and thyroid hormones, oxidative stress, mitochondrial dysfunction, apoptosis, oxidative damage to DNA, changes in gene expression and epigenetic mechanisms in the generation of adverse effects on reproduction.

Available evidence suggests that several PBDEs are capable of activating CAR/pregnane X receptor (PXR)-dependent gene expression, at least at relatively high exposure levels, and that PXR has higher sensitivity than CAR to PBDEs in mouse. CAR/PXR-dependent expression of biotransformation enzymes would be expected to accelerate metabolism of steroid

and thyroid hormones and provides one possible explanation of decreased concentrations of circulating oestradiol, testosterone and T4.

The evidence from the available human data did not provide a sufficient basis for the risk assessment. Thus, the CONTAM Panel considered the data from studies in experimental animals to identify Reference Points for the human hazard characterisation. The CONTAM Panel concluded that the neurodevelopmental effects on behaviour and reproductive/developmental effects are the critical effects for the hazard characterisation.

The CONTAM Panel performed benchmark dose (BMD) modelling according to the 2022 EFSA Guidance on the use of the BMD approach in risk assessment (EFSA Scientific Committee, 2022), applying endpoint-specific benchmark responses. For **BDE-47**, the lowest $BMDL_{10}$ was 0.023 mg/kg bw per day for reproductive effects (impaired spermatogenesis after repeated exposure), while a $BMDL_{10}$ of 0.15 mg/kg bw per day was obtained for neurodevelopmental effects (impaired spatial learning and memory after repeated exposure). For **BDE-99**, the lowest $BMDL_{10}$ was 0.05 mg/kg bw for developmental effects (increased resorption rates in dams following single dose administration on gestation day (GD) 6), while a $BMDL_{10}$ of 0.43 mg/kg bw per day was obtained for neurodevelopmental effects (reduction in the level of anxiety), after repeated exposure). For **BDE-153**, the Panel identified a $BMDL_{10}$ of 0.11 mg/kg bw for neurodevelopmental effects (impaired learning and memory after single exposure on postnatal day (PND) 10 from the only toxicological study identified for this congener. For **BDE-209**, the lowest $BMDL_5$ was 0.91 mg/kg bw per day for reproductive effects (decreased sperm motility after repeated exposure), while a $BMDL_{10}$ of 1.59 mg/kg bw per day was obtained for neurodevelopmental effects (impaired learning and memory after repeated exposure).

Repeated exposure to PBDEs results in increasing concentrations of these chemicals in the body. For this reason, the accumulated concentrations in the body or body burden, rather than the daily exposure, is considered as the appropriate dose metric for the risk assessment. Thus, the CONTAM Panel first calculated the body burden at the BMDL, based on the tissue concentrations in rodents reported in the literature. Next, the chronic dietary intake that would lead to the same body burden in humans was calculated assuming an absorption of **BDE-47**, -**99** and -**153** in humans of 100%, of 30% for **BDE-209** and the median half-lives in humans as reported in the literature.

For neurodevelopmental effects, this resulted in the following estimated chronic human dietary intakes corresponding to the body burden at the BMDL, expressed as ng/kg bw per day: 1096 for **BDE-47**, 3575 for **BDE-99**, 3.2 for **BDE-153** and about 5000 for **BDE-209**. For reproductive effects, this resulted in the following estimated chronic human dietary intakes, expressed as ng/kg bw per day: 168 for **BDE-47**, 38.4 for **BDE-99** and about 3000 for **BDE-209**.

Assignment of chemicals to an assessment group for combined risk assessment as a mixture is based on whether the chemicals have a common mode of action or a common target/system. The four PBDE congeners for which there are experimental data to derive a Reference Point (**BDE-47**, -**99**, -**153**, -**209**) all affect neurodevelopment, and for three of these data are also available showing effects on reproduction (**BDE-47**, -**99**, -**209**). This forms a scientific basis for inclusion of these four congeners in a common assessment group. The evidence that changes in the thyroid hormone system could be a mode of action in the effects of PBDEs on both neurodevelopment and reproduction further supports a combined risk assessment. No studies were available to identify Reference Points for **BDE-28**, -**49**, -**100**, -**138**, -**154** and -**183**. However, mechanistic studies conducted *in vitro* with neural cells with these six congeners indicate that they could share common modes of action with **BDE-47**, -**99**, -**153** and -**209**, and therefore a conservative approach would also include all the congeners of interest in the assessment group.

The Panel concluded that the combined margin of exposure (MOET) approach was the most appropriate risk metric for the combined risk characterisation.

The CONTAM Panel considered that a MOET smaller than 25 would raise a health concern. This would allow for interspecies differences in toxicodynamics and intraspecies differences in toxicokinetics and toxicodynamics.

Occurrence and dietary exposure assessment for the European population

A total of 84,249 analytical results (10,879 samples) generated by either GC–MS or GC-electron capture detection (ECD) for PBDEs in food fulfilled the quality criteria applied and were used in the assessment. The left-censored data accounted for 51% of the occurrence values. Both limit of quantification (LOQ) and limit of detection (LOD) were provided for 21% of all left-censored data, while only LOD or only LOQ were provided for 4% and 75% of the reported left-censored occurrence values, respectively. Out of the food categories in which high concentrations of PBDEs were expected, the highest percentage of quantified data was found in 'Fish, seafood, amphibians, reptiles and invertebrates'. The highest mean concentration was reported for 'Fish liver' ranging from 0.002 μg/kg wet weight (ww) for **BDE-138** at the lower bound (LB) to 11.15 μg/kg ww reported for **BDE-47** at the upper bound (UB). The second highest mean concentration was reported for **BDE-100**, again in 'Fish liver', where both LB and UB were 2.47 μg/kg ww.

For infant formula only few data on PBDE concentrations were submitted to EFSA, and the percentage of left-censored data ranged between 31% and 100%. For **BDE-49** and -**138**, fewer than six sample results were reported, which were all left-censored. The LB concentrations ranged between 0 and 0.006 (**BDE-209**) μg/kg ww, and the UB concentrations between < 0.001 and 0.028 (**BDE-209**) μg/kg ww.

Occurrence data on PBDEs in European human milk were taken from pooled samples that were collected and analysed as part of the World Health Organisation/United Nations Environment Programme (WHO/UNEP) field studies between 2014 and 2019. The average levels ranged between 0.007 μg/kg lipid (**BDE-49**) and 0.326 μg/kg lipid (**BDE-47**).

The highest mean exposure to PBDEs at the LB across all congeners was estimated for the age groups of 'Toddlers' and 'Other children', with the tendency to decrease moving to the older age groups. The daily mean exposure to PBDEs at the UB generally decreases moving from the younger to the older age groups with 'Toddlers' having the highest exposure to all PBDE congeners.

The highest mean exposure across the European dietary surveys was estimated for **BDE-209** followed by **BDE-47**. For **BDE-209** the mean exposure ranged from 0.17 ('Elderly') to 5.98 ng/kg bw per day ('Toddlers') for the minimum LB and the maximum UB, respectively and the highest P95 exposure was estimated for **BDE-209** ranging from 0.34 ('Elderly') to 13.46 ng/kg bw per day ('Toddlers') for the minimum LB and the maximum UB, respectively. For **BDE-47**, the mean exposure ranged from 0.08 ('Adults' and 'Very elderly') to 1.80 ng/kg bw per day ('Toddlers') for the minimum LB and the maximum UB, respectively. The highest P95 exposure ranged from 0.01 ('Infants') to 3.92 ng/kg bw per day ('Toddlers') for the minimum LB and the maximum UB, respectively. The lowest exposure for **BDE-49** and **-138** was estimated for 'Infants', whilst for **BDE-47**, and -**209** the lowest exposure was for 'Adults', and for **BDE-28**, -**99**, -**100**, -**153**, -**154** and -**183** it was for 'Elderly'.

Consumption of 'Meat and meat products' and 'Fish, seafood, amphibians, reptiles and invertebrates' contributed the most to the dietary exposure to **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**183** and -**209**. For **BDE-49**, -**138** and -**154** the main food category contributing to the exposure was 'Animal and vegetable fats and oils and primary derivatives thereof'.

An exposure scenario for formula fed infants resulted in daily exposure estimates for mean consumption between 0.0001 (**BDE-28**) and 0.35 (**BDE-209**) ng/kg bw at the LB, and between 0.71 (**BDE-183**) and 1.13 (**BDE-209**) ng/kg bw at the UB. For P95 infant formula consumption, the daily exposure estimates were between 0.0002 (**BDE-28**) and 0.43 (**BDE-209**) ng/kg bw at the LB, and between 0.88 (**BDE-183**) and 1.39 (**BDE-209**) ng/kg bw at the UB.

An exposure scenario for breastfed infants, resulted in median daily exposure estimates for average human milk consumption between 0.03 (**BDE-49**) and 1.50 (**BDE-47**) ng/kg bw, and highest exposures estimates for **BDE-209**, -**153**, -**47** and -**99** (4.06, 3.77, 3.44 and 2.52 ng/kg bw per day, respectively). For high human milk consumption, the median exposures were around 50% higher, with estimates between 0.05 (**BDE-49**) and 2.25 (**BDE-47**) ng/kg bw per day, and highest exposure estimates of 6.09, 5.66, 5.16 and 3.79 ng/kg bw per day for **BDE-209**, -**153**, -**47** and -**99**, respectively.

Exposure to PBDEs, especially to **BDE-209**, via dust and dermal contact is an additional source of exposure especially for children.

Changes in concentrations of PBDEs during cooking and processing are mainly associated with changes in lipid content and moisture loss. **BDE-209** can undergo debromination to produce congeners with fewer bromine atoms, in line with degradation pathways observed in the environment. The few studies on PBDE metabolites indicate that in general methoxylated PBDEs (MeO-PBDEs) behave in the same way as parent PBDE compounds.

Risk characterisation

The Panel applied four tiers in the combined risk assessment of PBDEs as a sensitivity analysis for the effects of PBDEs:

- As a conservative first tier (Tier 1), the Panel used the lowest Reference Points for each of the four congeners with data (**BDE-47**, -**99**, -**153**, -**209**). For the congeners for which no Reference Points were identified (**BDE-28**, -**49**, -**100**, -**138**, -**154**, -**183**), the Panel applied the Reference Point of **BDE-47**, the congener with the most complete and robust toxicological data.
- As a second tier (Tier 2), the Panel included only the four congeners with data, and used their lowest Reference Points.
- In a third tier (Tier 3) the Panel included only the four congeners for which Reference Points for neurodevelopment were identified (**BDE**-**47**, -**99**, -**153**, -**209**).
- In a fourth tier (Tier 4), in order to investigate the impact of the lack of data for **BDE-153** and the uncertainties linked to its Reference Point, the Panel including only the three congeners for which Reference Points for neurodevelopment were identified and for which there are sufficient/robust data, i.e. **BDE-47**, -**99**, -**209**.

The individual margins of exposure (MOEs) for each congener were first calculated by dividing their estimated chronic human dietary intakes at the BMDL body burden by the estimated mean and P95 dietary exposure. The MOET was then calculated for each survey participant as the reciprocal sum (also known as the harmonic sum) of the reciprocals of the MOEs for the individual congeners. However, combining P95 MOE estimates at the level of consumption survey or age class was not considered appropriate because survey participants highly exposed to one congener, will not necessarily be highly exposed to all other congeners. To avoid an excessive overestimation of the risk, i.e. an underestimation of the MOET at the P95 of the combined potency-adjusted exposure estimates, the individual MOEs were calculated for each congener and survey participant. In a final step, the MOETs at the mean and P95 exposure estimates were derived for each dietary survey and age group. This process was repeated for all tiers and the results across consumption surveys were summarised per age class.

For Tier 1, the MOETs for the mean exposure estimates were all above 25 for the LB estimates, while they were all below 25 for the UB exposures for all age groups. The MOETs for the P95 exposure estimates were above 25 for the LB estimates except for Toddlers and Other Children at the Median and Max exposure estimates, and for Adolescents at the Max exposure. For the UB estimates, they were all below 25 for all age groups.

For Tier 2, the MOETs for the mean exposure estimates were all above 25 for the LB estimates, while they were all below 25 for the UB exposures for all age groups. The MOETs for the P95 exposure estimates were similar to those in Tier 1; they were above 25 for the LB estimates except for Toddlers and Other Children at the Median and Max exposure estimates, and for Adolescents at the Max exposure. For the UB estimates, they were all below 25 for all age groups.

Comparing the results of Tier 1 with Tier 2, it was concluded that exposure to the congeners for which there are no toxicological data (**BDE-28**, -**49**, -**100**, -**138**, -**154**, -**183**) does not have a great impact provided that they are not more toxic than **BDE-47**.

For Tier 3, and similar to Tier 2, the MOETs for the mean exposure estimates were all above 25 for the LB estimates, while they were all below 25 for the UB exposures for all age groups. The MOETs for the P95 exposure estimates were above 25 for the LB estimates except for Toddlers at the Max exposure, and they were all below 25 for the UB estimates for all age groups.

For Tier 4, the MOETs at the mean and P95 exposure were all well above 25 (typically several orders of magnitude higher) for all age groups.

The CONTAM Panel concluded that estimates of exposure according to Tier 1, 2 and 3 raise a health concern at the LB P95 estimates in some surveys of Toddlers, Other children and Adolescents. There are large uncertainties in the estimates of hazard/risk due to the lack of toxicological data on most of the congeners. The estimates indicate no health concern for Tier 4. However, the Panel emphasises that Tier 4 is not representative of dietary exposure to all of the PBDEs considered.

Comparing the results from Tiers 1 to 3 with those of Tier 4, demonstrates the importance of the Reference Point for **BDE-153** in its contribution to the MOET. This was the lowest Reference Point and the one with the highest uncertainty.

For formula fed infants, for Tier 1, 2 and 3 the estimates of exposure were above 25 when considering the LB estimates and below 25 when considering the UB estimates. For Tier 4, the MOETs were in all cases above 25. The Panel noted the uncertainty in the exposure estimates due to the large difference between the LB and UB estimates.

For breastfed infants, the MOETs were calculated, and for Tier 1, 2 and 3 the MOETs obtained were all below 25, while for Tier 4 they were above 25. However, based on the body burden approach, the CONTAM Panel concluded that, the MOETs based on median human milk levels do not raise a health concern for the median exposure.

An uncertainty analysis was performed. It was concluded with more than 90% certainty[1] that the 10 congeners considered in the Opinion are either not genotoxic *in vivo* or, if they were genotoxic *in vivo*, this would be by a thresholded indirect mechanism.

The risk assessment was affected by considerable uncertainties, including left-censored occurrence data (as indicated by the contrasting MOETs for LB and UB exposures), lack of occurrence data for some relevant food categories, the uncertainty of the Reference Point for **BDE-153**, the lack of neurotoxicity data for 6 out of the 10 congeners considered and lack of reproductive/developmental toxicity data for seven congeners.

All of the identified uncertainties were taken into account in a quantitative uncertainty analysis using expert knowledge elicitation. For half of the dietary surveys considered, the Panel concluded with more than 70% certainty that the mean of the combined potency-adjusted exposure estimates for all 10 congeners for Toddlers raises a health concern for reproductive/developmental toxicity effects.

The certainty of a health concern is higher at the P95 of the combined potency-adjusted exposure estimates and in the surveys with higher exposures, e.g. there is a maximum of more than 90% certainty of a health concern for reproductive/developmental effects at the P95 for Toddlers.

The probability of a health concern is lower for neurobehavioural effects than for reproductive/developmental effects, e.g. for half of the surveys considered, there is more than 50% certainty at the mean of the combined potency-adjusted exposure estimates for Toddlers. The probability of a health concern is lower for both categories of effects in Adults than in Toddlers, reflecting the differences in exposure between age groups, but for reproductive/developmental effects, is still greater than 60% for the maximum survey at the P95 exposure.

Overall, the CONTAM Panel concluded that the resulting MOETs support the conclusion that it is likely that the current dietary exposure to PBDEs in the European population raises a health concern.

Recommendations

In order to refine the risk assessment and reduce the uncertainties, the CONTAM Panel made the following recommendations:

- As numerous products containing PBDEs are still in use, and end-of-life disposal may result in environmental contamination and consequently their presence in food, surveillance of PBDEs should continue with more sensitive analytical methods, including determination of congeners other than the 10 PBDEs included in the TORs.
- More data on occurrence of PBDEs in infant formula, with more sensitive analytical methods, are needed to enable a more robust exposure assessment for formula fed infants.
- Additional information on human toxicokinetics, e.g. absorption, half-life values and biotransformation of PBDE congeners is needed. More information is needed on the body burden in mothers and in relation to transfer of PBDE to the fetus and during lactation. This information should be used to develop a toxicokinetic model for PBDEs, including excretion into breast milk and placental transfer.
- Information is needed that would allow hazard identification and characterisation for the individual PBDE congeners included in the Terms of Reference for which such data are lacking, in particular for **BDE-153**, and especially related to reproduction/development and neurobehaviour with perinatal exposure. Studies should be conducted with characterised individual congeners of high purity.

[1]Probabilities assessed by the uncertainty analysis are reported in conclusions as % certainty for the more probable outcome, following EFSA's guidance on communication of uncertainty (EFSA, 2019).

- Information to develop Adverse Outcome Pathways is needed, especially related to neurobehaviour, reproduction/development and effects on thyroid function. This would enable prediction of hazard of congeners which have not been studied, and help to refine the integrated assessment.
- Additional effort is needed to align adverse effects observed in humans with endpoints observed in animal studies. Further research should focus on assessment of combined exposure to multiple PBDE congeners and other chemicals.

1 | INTRODUCTION

1.1 | Background and Terms of Reference as provided by the requestor

Background

Brominated flame retardants (BFRs) are anthropogenic chemicals, which are added to a wide variety of consumer/commercial products in order to improve their fire resistance. The major classes of BFRs are brominated bisphenols, diphenyl ethers, cyclododecanes, phenols, biphenyl derivatives and the emerging and novel BFRs.

Concern has been raised because of the occurrence of several chemical compounds from the group of BFRs in the environment, including feed and food, and in humans. This has led to bans on the production and use of certain formulations of polybrominated diphenyl ethers (PBDEs).

Between September 2010 and September 2012, the Scientific Panel on Contaminants in the Food of EFSA adopted six scientific Opinions on different classes of brominated flame retardants.[2] Because in the Opinion EFSA highlighted several data gaps, hampering the consumer risk assessment for these substances, by means of Commission Recommendation 2014/118/EU[3] on the monitoring of traces of brominated flame retardants in food, Member States were recommended to collect in 2014 and 2015 occurrence data for specific substances in specific foodstuffs.

The newly available occurrence data would enable an updated consumer exposure assessment. Furthermore, since the publication of the EFSA scientific Opinions between 2010 and 2012, new scientific information has become available, therefore it would be necessary to verify whether an update of these scientific Opinions would be appropriate, including an update of the consumer risk assessment.

Terms of reference

In accordance with Art. 29 (1) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority for an updated exposure assessment for the brominated flame retardants, covered by Recommendation 2014/118/EU, taking into account the occurrence data in food, submitted after the publication of the 2010–2012 EFSA scientific Opinions, and an updated consumer risk assessment, taking into account newly available scientific information.

1.2 | Interpretation of the Terms of Reference

Following the request from the EC, the CONTAM Panel will update its 2010–2012 risk assessments on the different classes of BFRs: hexabromocyclododecanes (HBCDDs), polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A (TBBPA) and its derivatives, brominated phenols and their derivatives and novel and emerging BFRs (EFSA CONTAM Panel, 2011a, 2011b, 2011c, 2012a, 2012b).

The first Opinion in the series updated the risk assessment of HBCDDs in food (EFSA CONTAM Panel, 2021). This second Opinion updates the risk assessment of PBDEs in food previously performed by EFSA (EFSA CONTAM Panel, 2011b). The assessment also covers the transfer from feed to food of animal origin as a relevant source of PBDEs in food.

In the previous Opinion, the CONTAM Panel considered the following eight PBDE congeners to be of primary interest for dietary PBDE exposure: **BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**, **-183** and **-209**. This was based on the composition of the technical PBDE products, occurrence in the environment and in food. In this update, the Panel evaluated the occurrence data in food submitted to EFSA since then, as well as the new published data, to determine whether any changes should be made to this selection. In addition to these eight PBDEs, the CONTAM Panel noted that Commission Recommendation 2014/118/EU also recommended the inclusion of **BDE-49** and **-138** for the monitoring of BFRs in food. In the current Opinion these 10 PBDE congeners are highlighted in bold throughout the document.

The similarities in chemical properties and effects identified in the previous EFSA assessments for the different BFR classes warrant the consideration of a mixture approach. The CONTAM Panel will evaluate the appropriateness of applying a mixture approach for the different classes of BFRs in an additional Opinion once the risk assessment for each BFR class has been updated. It will be based on the EFSA Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA Scientific Committee, 2019).

[2]EFSA Panel on Contaminants in the Food Chain (CONTAM); Scientific Opinion on Polybrominated Biphenyls (PBBs) in Food. EFSA Journal, 8(10), 1789.

Scientific Opinion on Polybrominated Diphenyl Ethers (PBDEs) in Food. EFSA Journal, 9(5), 2156.

Scientific Opinion on Hexabromocyclododecanes (HBCDDs) in Food. EFSA Journal, 9(7), 2296.

Scientific Opinion on Tetrabromobisphenol A (TBBPA) and its derivatives in food. EFSA Journal, 9(12), 2477.

Scientific Opinion on Brominated Flame Retardants (BFRs) in Food: Brominated Phenols and their Derivatives. EFSA Journal, 10(4), 2634.

Scientific Opinion on Emerging and Novel Brominated Flame Retardants (BFRs) in Food. EFSA Journal, 10(10), 2908.

[3]Commission Recommendation of 3 March 2014 on the monitoring of traces of brominated flame retardants in food (Text with EEA relevance) (2014/118/EU). L 65/39–40.

1.3 | Supporting information for the assessment

1.3.1 | Physico-chemical properties

The physicochemical properties of PBDEs were described in section 1.3 (Chemical characteristics) of the previous EFSA Opinion on PBDEs (EFSA CONTAM Panel, 2011b) and are summarised in Table 1 below. PBDEs are a class of brominated aromatic compounds with a basic structure consisting of two phenyl rings linked by an ether bond as shown in Figure 1. There are 209 possible compounds, referred to as PBDE congeners, which differ in the number and position of the bromine atoms in the two phenyl rings (Figure 1). PBDEs show the same number of congeners and substitution patterns as polychlorinated biphenyls (PCBs), and share the same numbering system (Ballschmiter et al., 1993).

To avoid confusion, names starting with a capital letter will be used throughout the Opinion when referring to the commercial technical products (e.g. PentaBDE), whereas names starting with a lowercase letter will refer to the homologues themselves (e.g. pentaBDEs).

The three main commercial classes of technical products of PBDEs are: PentaBDE, OctaBDE and DecaBDE. They are composed of a mixture of congeners and are named according to their predominant bromine substitution pattern, but they also contain other PBDE congeners. An overview of the content of six common commercial products and their respective brand names, i.e. two PentaBDE products (DE-71 and Bromkal 70-5DE), two OctaBDE products (DE-79 and Bromkal 79-8DE) and two DecaBDE products (Saytex 102E and Bromkal 82-ODE), can be found in Appendix A and in the previous EFSA Opinion on PBDEs (EFSA CONTAM Panel, 2011b).

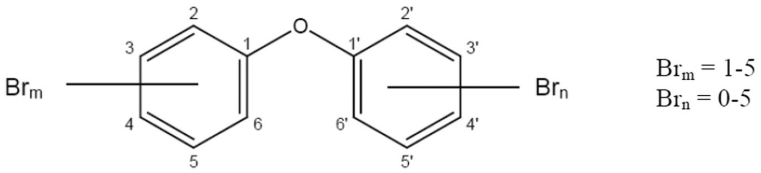

FIGURE 1 General structure of PBDEs.

TABLE 1 Physico-chemical properties of PBDEs. For more details, see EFSA CONTAM Panel (2011b).

Property	Value
Molecular mass	249–959 g/mol (monoBDEs–decaBDE)
Octanol–water partitioning coefficients (log Kow)	5.94–12.11 (triBDEs–decaBDE; includes measured and modelled values) (from EFSA CONTAM Panel, 2011b)
Volatility (vapour pressure)	2.32×10^{-5}–1.64×10^{-12} Pa (triBDEs–decaBDE)
Water solubility at 25°C (μg/L)[a]	13.3 (PentaBDE); < 1 (OctaBDE and DecaBDE)

[a]Determined for the congeners present as a mixture not for the pure congeners.

In the previous Opinion, the CONTAM Panel considered the following eight PBDE congeners to be of primary interest for dietary PBDE exposure: **BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**, **-183** and **-209**. This was based on the composition of the technical PBDE products, occurrence in the environment and in food. Congener, bromine substitution and Chemical Abstracts Service (CAS) numbers are given in Table 2, for these congeners and for **BDE-49** and **-138** included in Commission Recommendation 2014/118/EU.

TABLE 2 Congener, bromine substitution and CAS number of the 10 PBDE congeners included in Commission Recommendation 2014/118/EU.

Congener	Bromine substitution	CAS number
BDE-28	2,2′,4-triBDE	41318-75-6
BDE-47	2,2′,4,4′-tetraBDE	5436-43-1
BDE-49	2,2′,4,5′-tetraBDE	243982-82-3
BDE-99	2,2′,4,4′,5-pentaBDE	60348-60-9
BDE-100	2,2′,4,4′,6-pentaBDE	189054-64-8
BDE-138	2,2′,3,4,4′,5′-hexaBDE	182677-30-1
BDE-153	2,2′,4,4′,5,5′-hexaBDE	68631-49-2
BDE-154	2,2′,4,4′,5,6′-hexaBDE	207122-15-4
BDE-183	2,2′,3,4,4′,5′,6-heptaBDE	207122-16-5
BDE-209	2,2′,3,3′,4,4′,5,5′,6,6′-decaBDE	1163-19-5

1.3.2 | Production and industrial use

The processes used to produce PBDEs were described in Section 4.1 of the previous EFSA Opinion (EFSA CONTAM Panel, 2011b). In brief, technical PBDE products were manufactured by bromination of diphenyl ether in the presence of a catalyst in a solvent.

Total annual market demand by region around the time of peak usage (year 2001) was 7500 tonnes PentaBDE, 3790 tonnes OctaBDE and 56,150 tonnes DecaBDE making a total of 67,440 tonnes combined production (Palm et al., 2004).

They were used as additive flame retardants, i.e. mixed into polymers, generally at concentrations between 5 and 30% by weight. They were not chemically bound to the plastic or textiles (EFSA CONTAM Panel, 2011b).

PentaBDE was mainly used as an additive in flexible polyurethane foam in upholstery and furniture, OctaBDE was primarily used in Europe in acrylonitrile-butadiene-styrene polymers, and DecaBDE was used in textiles (drapery and furnishing fabric), in different plastics, and in electronics and electrical supplies such as printed circuit boards and other electronics (EFSA CONTAM Panel, 2011b).

Following the adoption of a risk reduction strategy for PentaBDE and OctaBDE, the production and use of these mixtures was phased out in Europe in 2004. Restrictions for DecaBDE followed in subsequent years (see **Section 1.3.6**). Most other regions of the world adopted similar restrictions in the following years, and production and use of PBDEs has been phased out worldwide. There are however many products still in use that contain PBDEs, and they can leach out of these products into the environment either during use or when they are disposed of at end-of-life.

In 2018, the global amount of combined in-use and waste stocks of certain PBDEs such as **BDE-28**, **-47**, **-99**, **-153**, **-183** were estimated to be 25 and 13 kilotons (kt), respectively, and equivalent values for **BDE-209** were 400 and 100 kt, respectively (Abbasi et al., 2019; Maddela et al., 2020).

1.3.3 | Environmental levels and fate

PBDEs are widespread in the global environment. Due to the properties associated with bioaccumulation and persistence, high levels can be found in wildlife, especially in top predators. When comparing data published in the scientific literature, it is important to be aware of different methodologies used in gathering and reporting data; different congeners may have been measured, different approaches to reporting left-censored data (< limit of detection [LOD]) may have been used (upper, lower or median bound approach), etc. The time at which samples were taken is also an important factor due to different patterns of use at different periods and due to restrictions being implemented at different times in different locations.

Whilst parent PBDE compounds are always associated with anthropogenic activity and use of synthetic products, hydroxy and methoxy metabolites (OH-PBDEs and MeO-PBDEs) can also be synthesised naturally by marine organisms, especially through the symbiosis of sponges with bacteria (Schmitt et al., 2021; Belova et al., 2021). 6-OH-BDE-47 was the most frequently detected compound and was found in 31% of samples of biota tested by Belova et al. (2021). Several newly identified naturally occurring halogenated compounds including heptabrominated di-OH-BDE, monochlorinated pentabrominated di-OH-BDE, hexabrominated OH–MeO-BDE and other compounds identified based on the analysis of fragmentation spectra resulting from non-target analysis were also identified (Belova et al., 2021). Due to the non-target analytical approach that was used, the results should only be considered as a qualitative screen rather than a quantitative analysis.

Since production of PBDE technical products was restricted in Europe (see **Section 1.3.6**), release from production sites is less likely, although there still may be legacy contamination around former production sites in some locations. There are still however problems associated with potential release of PBDEs associated with transport, handling and usage of existing consumer products containing PBDEs, and with end-of-life processes such as degradation, recycling and disposal. Release via air (particles and gaseous phase) is increased if particles are heated and burned in accidental or other types of uncontrolled fires. Emissions into air of the more volatile PBDEs (typically PBDE congeners with 6 or fewer bromine atoms) are likely to exist in both vapour and particulate phases and to be subject to long-range atmospheric transport (Qiao et al., 2020). PBDEs may also enter the environment as a result of the use of municipal sewage sludge as fertiliser (EFSA CONTAM Panel, 2011b; Rigby et al., 2015, 2021).

Environmental levels differ in different parts of the world, reflecting different patterns of use, with highest levels being found in North America. Highest background levels in Europe have been found in the United Kingdom and Ireland, but these levels are orders of magnitude lower than those that have been found in North America.

As part of a recent review on levels and distribution of PBDEs in humans and environmental compartments, Klinčić et al. (2020) made a comprehensive review of the levels and distribution of PBDEs in the aquatic environment, air and soil, in indoor dust, and in humans as reported in the previous five-year period. Significant amounts of PBDEs were still being found in various sample types across the world, giving evidence that PBDE contamination is an ongoing problem. Secondary sources of PBDEs like contaminated soils and landfills, especially those with electronic and electrical waste (e-waste), were identified as a particular future risk. PBDE contamination has also been associated with plastic debris in the marine environment (Aretoulaki et al., 2021).

The sections below, which do not claim to be a comprehensive review of the literature, give an overview of some aspects related to the environmental fate and levels of PBDEs.

1.3.3.1 | *Biodegradation/transformation*

The main degradation pathways for PBDEs consist of debromination and hydroxylation, which have been shown to occur in air, plants, animals, soil and sediments (EFSA CONTAM Panel, 2011b). The octa- and nonaBDE congeners can be found in the environment either as a result of direct input from use of materials containing these compounds, or from the decomposition of decaBDE. Congeners deriving from PentaBDE and OctaBDE technical products peaked in the environment in the early 2000s, and from DecaBDE some years later (Sahu et al., 2021).

Polybrominated dioxins and furans (PBDD/Fs) as well as mixed chloro-bromodioxins and furans (PXDD/Fs) may be generated when materials containing PBDEs are combusted (Altarawneh, 2001; Cormier et al., 2006; Gullett et al., 2007; Lönnermark & Blomqvist, 2005; Sakai et al., 2021), or can be formed in accidental fires where BFRs are present (Lundstedt, 2009; Söderström & Marklund, 1999). Liang et al. (2020) suggested that PBDEs can transform into PBDFs and PBDDs with the same or fewer bromine substituents if certain structural requirements are met. Yang et al. (2020) investigated the formation of PBDD/Fs from DecaBDE in cement kilns, which had been identified as a promising technology for destruction of waste materials containing various persistent organic pollutants (POPs), and gave an indication of the amounts of PBDD/Fs that may be formed. The major products of thermal decomposition of DecaBDE in flue gas were HBr/Br2 (average 26.6%/70.6%) > 2.7% PBDEs > 0.2% PBDD/Fs. The main pathways for formation of PBDD/Fs was from precursors, particularly those that were dominated by hepta- to decaBDEs. Debromination of decaBDE was also an important pathway for the formation of PBDD/Fs throughout the thermal process (Yang et al., 2020). Optimisation of furnace conditions to minimise formation of PBDD/Fs and PXDD/Fs from PBDEs has been described by Sakai (2016). Even a small amount of these compounds could be significant due to their high toxicity (Van den Berg et al., 2013).

PBDEs can undergo photocatalytic degradation using a composite photocatalyst, but photocatalytic degradation of PBDEs is a complex process and challenges remain before this can be widely used as a method to treat waste. Debromination of PBDEs is the key part of this process (Wang, Ma, et al., 2020).

In addition to PBDD/Fs, a wide variety of other organic pollutants, including brominated benzenes and phenols, are formed and emitted from combustion processes in which PBDEs, or some other source of bromine, are present (Altarawneh, 2021; Cormier et al., 2006; Gullett et al., 2007; Lönnermark & Blomqvist, 2005).

1.3.3.2 | *Differences in PBDEs profiles and bioaccumulation*

A number of factors can influence the PBDE profiles that are observed in environmental and food samples. These include the profile of the source, which can be very different in different global regions, and also can vary according to local pollution sources. Time can be a factor, with debromination resulting in a gradual shift to congeners containing fewer bromine atoms over time. The matrix can also be a factor with differences in profiles observed in not only environmental samples such as soil, sediment, air and dust, but also animal species can have a major influence on the profile observed in food products due to differences in bioaccumulation and metabolism.

Zhu et al. (2020) showed that in experimental conditions, deposition of PBDEs is driven by the gas/particle partitioning of the compound. Uptake in plants of lower-brominated PBDEs (tri- to hexaBDEs) was influenced primarily by gaseous deposition, whereas uptake of higher-brominated PBDEs (hepta- to decaBDEs) was governed primarily by particle-bound deposition.

PBDEs can accumulate at different rates in different foods, or even in different varieties or cultivars of the same food types as reviewed by Dobslaw et al. (2021). For example, Zhao, Ye, et al. (2020) used ^{14}C tracing to investigate the uptake and transformation of **BDE-209** from soil into three rice cultivars, and found a significant difference. Soil spiked with **BDE-209** to give an initial concentration of 2.50 ug/g and a radioactivity of 49.96 Bq/g (dw) (close to the average environmental rates reported in soil), produced resulting concentrations of **BDE-209** and 25 debrominated congeners in the three different rice varieties of 421.8, 454.2 and 967.0 ng/g, respectively.

1.3.3.3 | *Occurrence in the environment*

Soil, vegetation and the terrestrial environment

Plants have been shown to take up and transform PBDEs and other contaminants from soil and the environment (Zhang, Yao, et al., 2021). Analysis of UK archived pasture (collection period 1930–2004) showed that PBDEs could not be detected in the pre-1970 samples, with levels rising through the 1970s peaking in the mid-1980s (strongly influenced by one particularly high sample for 1984) (Covaci & Malarvannan, 2016; Hassanin et al., 2005). Values remained high through the late 1980s/1990s followed by a decline for all PBDEs until 2004. This pattern is consistent with usage and restrictions of the Penta- and OctaBDE technical products in Europe. PBDEs in earthworms collected in 2000 in Sweden showed that biota–sediment accumulation factors decreased as the molecular size increased from tetraBDE to decaBDE congeners, showing that the more bromine atoms on a PBDE molecule, including **BDE-209**, the greater the bioavailability from soils and potential to accumulate in earthworms, presenting an exposure pathway into the terrestrial food web (Covaci & Malarvannan, 2016; Law et al., 2006; Sellström et al., 2005). **BDE-209** concentrations in bird eggs, sewage sludge and surficial sediments were not found to change significantly in an 8-year period ending in 2012, although there was evidence of debromination (Leslie et al., 2021).

A critical review of the scientific literature regarding PBDE (and novel BFR) contamination of surface soils with an aim to identify pollution sources, showed that principal production and use in secondary polymer manufacture appears to have a strong potential to contaminate surrounding soils (McGrath et al., 2017). PBDEs were also found to be released from products during disposal via landfill, dumping, incineration and recycling. Land application of sewage sludge is another major pathway of soil contamination. PBDEs are commonly detected at background locations including Antarctica and northern polar regions. Congener profiles in soil were broadly representative of the major constituents in PentaBDE, OctaBDE and DecaBDE technical products and related to predicted market demand. **BDE-209** dominated soil profiles, followed by **BDE-99** and **-47**. The review gives a comprehensive summary of PBDE concentrations in surface soil from around the world, including rural background locations and potential hot-spots such as close to e-waste recycling locations. Because many of the studies included different PBDEs reported, and were conducted at different times, great care needs to be taken when making comparisons. The ranges found in different continents were as follows: Africa 0.14–34,700 ng/g, the Americas 0.02–765 ng/g, Asia 0.00245–227,000 ng/g, Australia 0.05–13,200 ng/g, Europe 0.02–49 ng/g, Middle East 0.29–203 ng/g, Polar regions 0.00276–1810 ng/g. The maximum levels reported for Europe were lower than the maximum levels for other regions. It is not clear whether this reflects lower use or is a consequence of global movement of, e.g. e-waste to other regions for recycling and disposal.

Higher amounts of PBDEs were found in soil taken from flood-prone land compared to control land (median 770 vs. 280 ng/kg dry weight) (Lake et al., 2011). The higher values were not reflected in the grass that was collected, indicating that PBDE contamination on soils is not transferred efficiently into the grass. The facts that cows on flood-prone farms also spend time on non-flood-prone land, and that their feed is supplemented with commercial feed were suggested as reasons why no higher PBDE concentrations were found in milk produced from flood-prone farms (median 300 vs. 250 ng/kg fat weight). The ratios **BDE-47**:**BDE-99** were similar in soil and grass samples as compared to the commercial PBDE technical product used in the region where the study was conducted, indicating few differences in source-pathway transfer efficiencies between these congeners.

Yao et al. (2021) reviewed degradation and remediation methods for PBDEs from water and soil and found that a combination of different techniques (adsorption, thermal treatment, photolysis, photocatalytic degradation, reductive debromination, oxidation processes and biological degradation) offered the best solution. The authors also noted that more toxic intermediates could be generated as a result of incomplete degradation.

Sediment

Concentrations of PBDEs in sediment are also related to both geographical location and the time at which they were taken for analysis. They are known to be found in particularly high concentrations in the sediments of river-basins (Köck-Schulmeyer et al., 2021). PBDEs in sediment cores from the Pearl River estuary, South China (not including **BDE-209**), increased gradually from the bottom of the core (corresponding to mid-1970s) to the middle layer (corresponding to 1980s and early 1990s) followed by more variation in the surface sediments (Covaci & Malarvannan, 2016). **BDE-209** levels however remained fairly constant until 1990 after which an exponential increase was observed, doubling approximately every 4.5 years, reflecting the increasing market demands for the DecaBDE in China after 1990. In sewage sludge samples from South Korea and Italy, **BDE-209** was the most dominant congener found. In Chicago (USA) from 1975 to 2008, concentrations of pentaBDEs increased initially to a plateau at around year 2000, a little before the production of PentaBDE technical products ceased in the USA in 2004. Concentrations of **BDE-209** in biosolids rose from 1995 to 2008, with concentrations doubling approximately every 5 years, which provided an indication of the size of the environmental reservoir of **BDE-209** (Covaci & Malarvannan, 2016). Concentrations of legacy BFRs including PBDEs along the river Rhone achieved peak concentrations from the mid-1970s to the mid-2000s, but have stabilised since the mid-2010s (Vauclin et al., 2021).

Karakas et al. (2020) reported that the greatest impact on the reduction of total PBDE concentrations in sediment taken from close to San Francisco, was achieved by a reduction in water column concentrations, i.e. source control and dredging. The most effective method to reduce bioaccumulative PBDE congener concentrations was to use microorganisms combined with source control, which was almost as effective as dredging for the rest of the congeners (Karakas et al., 2020).

Peters et al. (2021) noted a positive correlation between the occurrence of PBDEs and PBDFs and suggested that an increased use of PBDEs contributed to environmental contamination with PBDFs which can be formed from PBDEs (see **Section 1.3.3.1**). An examination of PBDF homologue patterns indicated that emissions from combustion activities are likely also important sources of contamination. Mixed halogenated PXDD/Fs were not correlated and had reduced in concentration over time.

In a study by Leslie et al. (2021), **BDE-209** concentrations in sediments from seven countries were measured and concentrations ranged from very low ng/g (88 ng/g on an organic carbon basis) concentrations, in the rivers Elbe, Ems, Seine and the Outer Humber, to high µg/g (120 µg/g on an organic carbon basis), in the Western Scheldt, Liverpool Bay and River Mersey. Apart from decreasing values in the Western Scheldt sediment no further decreases in **BDE-209** concentrations were observed over time, neither in sediment nor in sewage sludge.

It should be noted that temporal trends in PBDE levels in sediment cores vary considerably, depending on the region or country studied, with possible correlations with the historic and current use of PBDEs. Low brominated PBDE congeners have the potential for bioaccumulation in marine organisms, whereas **BDE-209** has a very low potential for bioaccumulating within the marine food web (Lee & Kim, 2015).

Aquatic environment

PBDEs are ubiquitous in worldwide marine environments, but only few recent data have been reported for PBDEs in seawater, probably because partitioning and accumulation characteristics results in low concentrations of PBDEs in seawater, making other matrices a better alternative to study in most cases. The available data were reviewed by Lee and Kim (2015). In different marine environmental compartments, concentrations can vary from a few ng/g to several μg/g, with the differences relating to the exposed species and the geographical location. PBDE congener profiles in biota are usually dominated by congeners with fewer bromine atoms, such as **BDE-47** and -**99**, and this is different to sediments, where **BDE-209** is dominant.

It has been estimated that more than three quarters of the PBDEs in water samples are associated with the particulate phase (Oros et al., 2005).

Pollutants generally tend to be present at higher concentrations in freshwater systems due to the fact that many pollution sources are inland and because of the dilution effect that occurs when rivers empty into seas. Because most of the PBDEs in water are associated with the particulate phase, water concentrations can vary according to specific conditions that may disturb sediment and increase particulates in the water. Because of this, and the relatively low levels of PBDEs in water, most studies focus on fish and biota which can be used as an integrative matrix to give an indication of overall water contamination levels.

PBDEs were more widely used in North America than in other parts of the world, and this included wide use in polymer matrices in the Laurentian Great Lakes region starting in the 1970s. As a consequence, water and fish from that region contain relatively high levels of PBDEs (Zhou et al., 2019). In the USA, production and usage of PentaBDE and OctaBDE was phased out in 2004, and the production of DecaBDE products ceased in 2013. In Canada, restrictions on PBDEs began in 2008. PBDEs are still widely found in the Great Lakes region in air, water, sediment, wildlife and human milk, and due to the higher concentrations found and size of the area, this region acts as a useful model for observation. Concentrations of PBDEs in the Great Lakes generally decreased between 2004 and 2007 reflecting the phasing out of PentaBDE and OctaBDE products starting in 2004. Once PBDEs were no longer manufactured in the region, sources such as sediment release, long distance transport, release from consumer goods (e.g. e-waste), and transformation resulting from debromination became more important. Total PBDE concentrations have stabilised between 2011 and 2015 because of the increases in **BDE-99**, **-100**, **-153** and **-154** balancing decreases observed for other congeners (Zhou et al., 2019).

The UK Environment Agency took samples at water monitoring sites between 2016 and 2018 where a total of 272 freshwater and 51 saline sites were assessed for PBDE contamination. The mean concentrations of PBDEs in freshwaters ranged from 0.0006 to 1.6 ng/L. For saline waters, the concentrations of PBDEs ranged from 0.0006 to 0.77 ng/L (UK Environment Agency, 2019).

Air

The previous EFSA Opinion on PBDEs (EFSA CONTAM Panel, 2011b) reported that concentrations in air had been decreasing over the previous decade as a result of restrictions that had been placed on the production and use of PBDEs.

PBDEs have relatively low vapour pressures which means that, in indoor environments, they partition preferentially to dust. Consequently, most studies on indoor contamination address human exposure via ingestion of settled dust, rather than via inhalation of indoor air. Björklund et al. (2012) reported concentrations of PBDEs (including **BDE-209**) in air inside 33 buildings to be similar to those measured in air ventilating the same buildings. The authors concluded that contaminated indoor air is a more important source of PBDEs than outdoor air for most people. Zhang, Diamond, et al. (2011) measured concentrations of tri- to hexaBDE congeners in indoor air from 20 indoor locations (homes, offices and laboratories) in Toronto, Canada, in 2006. The concentrations of the sum of seven PBDEs in office air (average = 0.79 ng/m^3) exceeded those in homes (average = 0.49 ng/m^3), and both exceeded those reported for Toronto outdoor air, supporting the conclusion that ventilation of indoor air is a source of PBDEs to the external environment. For congeners with five or fewer bromine atoms, a correlation between air and dust concentrations was observed, confirming the hypothesis that PBDEs in dust arise from gaseous deposition from air. The lack of such a correlation for congeners with six or more bromine atoms suggests this process to be less important, with other processes such as abrasion of PBDE-containing materials playing a greater role.

Jiang et al. (2019) conducted a review of PBDEs in the environment in China, including occurrence in the atmosphere and indoor air and dust. Highest levels of PBDEs in the atmosphere were generally observed around PBDE production facilities and e-waste recycling sites where concentrations as high as 1.17×10^4 pg/m^3 were found. Total PBDE atmospheric concentrations in most cities in China were generally < 200 pg/m^3, which are comparable to or slightly higher than those from other countries and regions worldwide. PBDEs in indoor air were found to have mainly focused on large cities and e-waste dismantling areas. Highest levels were found close to the e-waste sites.

A recent investigation into the presence of emerging and legacy POPs in European domestic (indoor) air (de la Torre et al., 2020) reported mean concentrations of PBDEs (sum of BDE-17, **-28**, -**47**, -66, -**99**, -**100**, -**153**, -**154**, -**183**, -206, -207, -**209**) to be just over 6 pg/m^3.

Hites et al. (2020) examined PBDEs in about 700 atmospheric samples collected every 12 days from 2005–2018 (inclusive) from two urban sites: Chicago (Illinois) and Cleveland (Ohio). In Chicago, the concentrations of **BDE-47** and -**99** decreased by a factor of two every 5.9 ± 0.9 and 8.0 ± 1.4 years, respectively, but the concentrations of **BDE-209** doubled every 7.6 ± 1.8 years. In Cleveland, the concentrations of **BDE-47** and **-99** decreased by a factor of two every 5.1 ± 0.4 and

5.7 ± 0.5 years, respectively, and the concentrations of **BDE-209** decreased by a factor of two every 9.2 ± 1.6 years. The time lag observed in environmental responses was found to be related to when these compounds were removed from the market.

Dust. PBDEs can be found in dust as a result of their use in household appliances and furniture. Concentrations found in some studies reported from Europe since the previous Opinion (EFSA CONTAM Panel, 2011b) are collated in **Appendix B**. Most data are on dust from homes, but offices, schools, cars, aircraft and other locations are also used in some studies. In the same way as for other sample types, care needs to be taken when comparing data due to the specific PBDE congeners measured. Where a high concentration of PBDEs is reported, this is often due to the contribution of **BDE-209** which can be present at much higher concentrations than other PBDEs, with reports of over 300,000 ng/kg in UK and Swedish homes and 680,000 ng/kg in UK car dust. PBDEs have been found in indoor dust from all regions of the globe, including Antarctica (Corsolini et al., 2021).

Table 3 below summarises the spread of data found in Appendix B and is based on the sum of PBDEs measured excluding **BDE-209**, and for **BDE-209** separately. Where the reported data did not separate **BDE-209**, this was not included in the summary. Whilst some of the data are not directly comparable primarily because of different PBDEs measured and included in the sum, but also because of differences in LOD and treatment of < LOD data, it nevertheless illustrates the vast differences in concentrations found. In general, the high levels are much higher than the median or mean, but values that are high are regularly found and so are likely to be true reflections of the distribution. It is likely that they reflect dust samples taken where furniture or equipment is located that contains high levels of PBDEs that are associated with dust within the vicinity. The levels summarised in Table 3 are for Europe, but data from global sources are broadly similar (e.g. Akinrinade et al., 2020; Hoang et al., 2021). In a review by Jiang et al. (2019) concentrations reported in dust in China were typically $1–10 \times 10^3$ ng/g with **BDE-209** being the dominant congener. The highest values were those taken from close to industrial and e-waste recycling sites.

TABLE 3 Summary of PBDEs in dust reported within Europe (see Appendix B).

	Sum of PBDEs[a] (excluding BDE-209)		BDE-209	
	ng/g			
	Min	Max	Min	Max
Homes (apartments or houses)	< 0.3	310,000	< 0.5	460,000
Offices	< 0.3	10,880	< 1.3	1000,000
Cars	< 0.1	54,666	< 5	680,000
Aggregated sample, e.g. vacuum cleaner bag	4.5	15,000	10	9300

[a]Different studies measure different combinations of PBDE congeners included in the sum. Details can be found in Appendix B and the references as indicated.

Coelho et al. (2014) reviewed the levels of flame retardants in indoor dust from different global regions and compared the levels of PBDEs found by continent (see Figure 2) showing that concentrations in dust from North America are generally higher than from Europe and other continents. The same authors also compared dust taken from different indoor environments, and overall, levels were broadly similar (see Figure 3). A comparison of levels in dust collected by different methods showed that this is an important factor influencing the concentrations measured, with brushes giving notably lower results than other methods (see Figure 4).

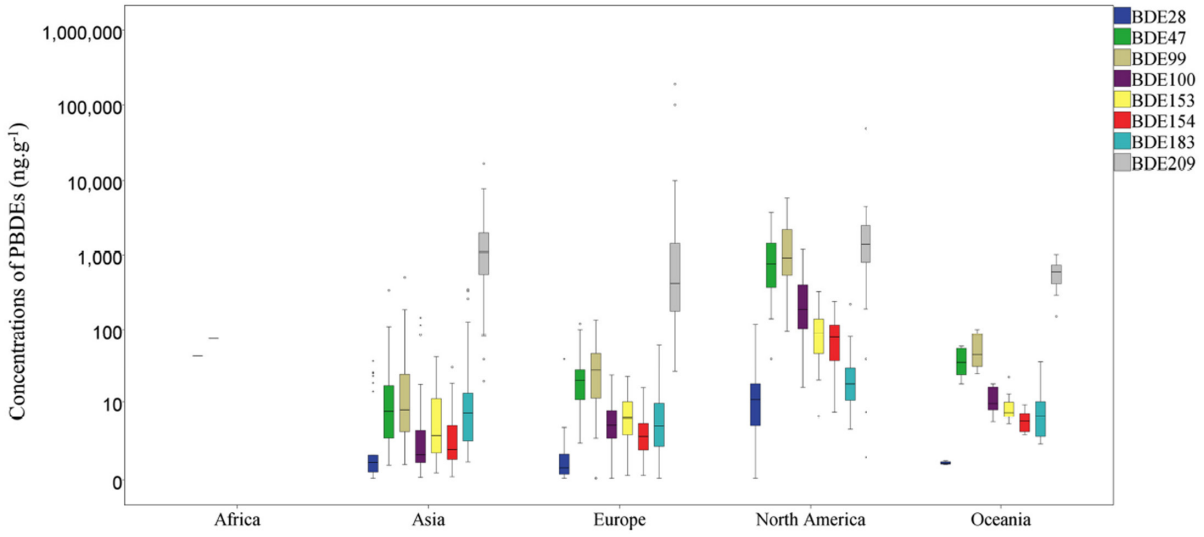

FIGURE 2 Levels of PBDEs in indoor dust samples from different continents (from Coelho et al., 2014).

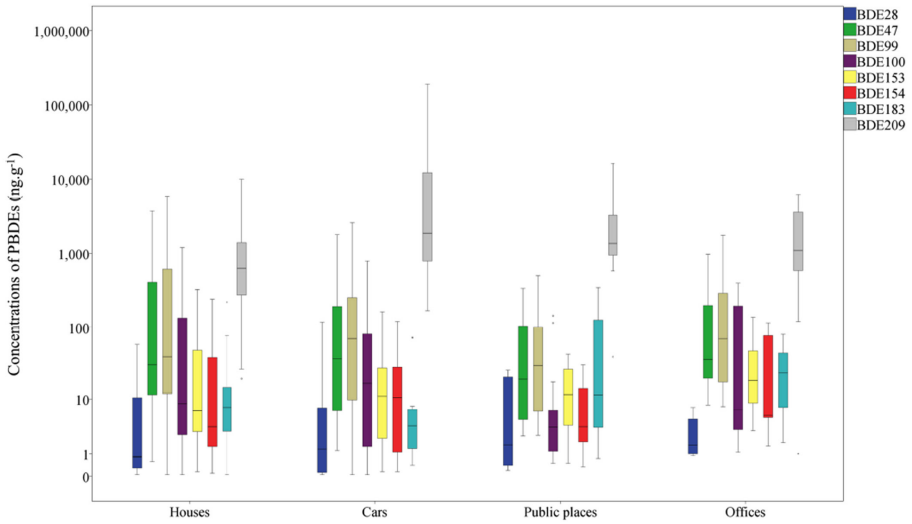

FIGURE 3 Levels of PBDEs in indoor dust samples from different environments (houses, cars, public places and offices (from Coelho et al., 2014).

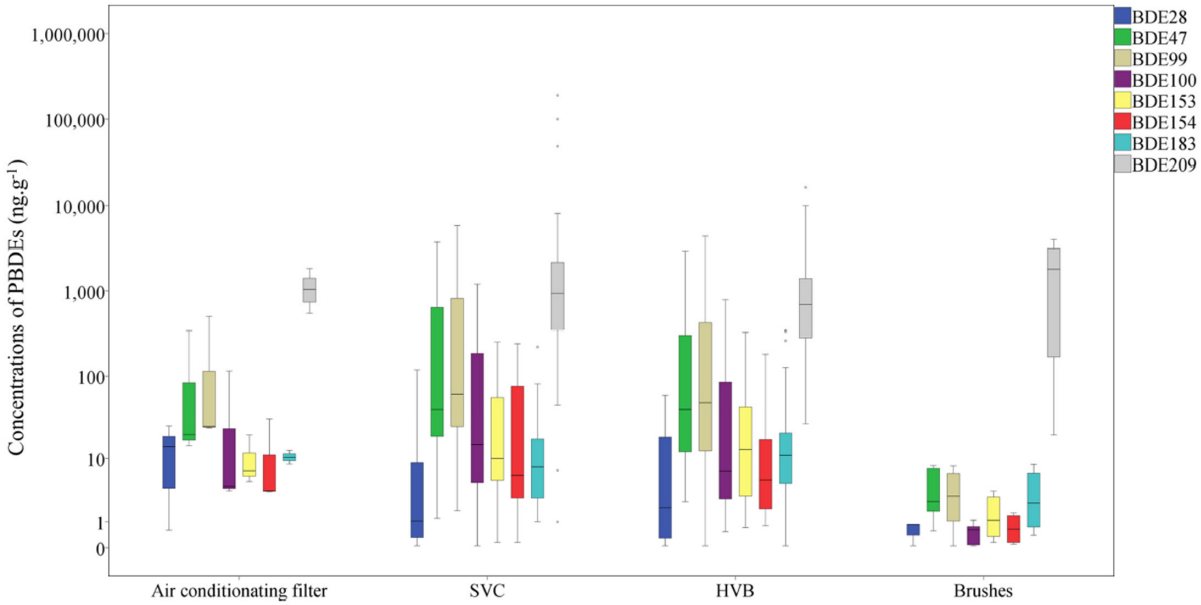

FIGURE 4 Levels of PBDEs in indoor dust samples collected by different methods. SVC: specific vacuum cleaner or domestic cleaner with a nylon sock; HVB: Household vacuum cleaner (from Coelho et al., 2014).

Wildlife

EFSA CONTAM Panel (2011b) reported that PBDE congeners from technical products degrade slowly in the environment, and that they bioaccumulate and biomagnify in wildlife. An increase in concentrations can be found in biota with increasing trophic level in pelagic and Arctic food webs. A large number of studies show concentrations of concern in top predators, indicating the potential of PBDEs to bioaccumulate/biomagnify in the food chain. Recent attention has been given to the potential that exposure to microplastics can have with respect to PBDEs and other contaminants in wildlife, especially aquatic species (Angnunavuri et al., 2020; EFSA CONTAM Panel, 2016; Newmann et al., 2021; Sun et al., 2021), although the overall contribution from this source is not large compared to overall burden.

There are many studies and reviews of PBDEs in wildlife that indicate levels have been decreasing over the past two decades following restrictions on their production and use. Some recent studies are summarised below to give an indication of current levels in wildlife, and do not claim to be a comprehensive review of the literature.

Aquatic wildlife including marine mammals

(i) Invertebrates

An understanding of the accumulation of lipophilic pollutants such as PBDEs is important for assessing the occurrence, transport and distribution of these contaminants in the aquatic environment. Phytoplankton uptake plays a key role in the

transfer of pollutants from water to fish and hence influences the fate and transport of pollutants (Del Vento & Dachs, 2002; Wallberg & Andersson, 2000). Phytoplankton uptake and subsequent transfer to zooplankton results in depositional fluxes of organic pollutants in aquatic environments (Baker et al., 1991). Much of the reported data on invertebrates pre-dates the last EFSA Opinion on PBDEs (EFSA CONTAM Panel, 2011b), but Peltonen et al. (2014) measured PBDEs and other pollutants in zooplankton in the Baltic Sea and investigated spatial and temporal shifts in congener-specific concentrations. **BDE-47** and **-99** were the most abundant (concentrations from 1.2 to 4.6 and from 0.4 to 3.3 ng/g fat, respectively). The concentrations of most PBDE congeners were lower in 2010 than in 2001/2002 except in the eastern Gulf of Finland.

(ii) Fish and shellfish

There are many reports of PBDEs in fish in the scientific literature. Some of these have a focus on fish as food for human consumption, whereas others have a focus on wildlife and are used as an assessment of the health of an ecosystem. The aim of the study can have an influence on the study design, for example only commonly consumed parts of a fish may be analysed if the focus of the study is food and human dietary exposure, whereas the whole fish is likely to be analysed in studies with a focus on wildlife or the environment. Since the skin and some internal organs can contain high concentrations of PBDEs and other pollutants, this can have a bearing on overall results.

When comparing data, it is important to consider the species. Concentrations of PBDEs in food webs from the Baltic Sea and the northern Atlantic Sea showed that PBDE levels (sum of **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183**, -**209**) varied greatly between perch (17.13 ng/g fat) and pike (111.94 ng/g fat) (Zhang, Wang, et al., 2016). Such variation can be due to the fat content of the fish (oily fish have higher concentrations of lipophilic pollutants), whether the fish is benthic (bottom feeders) or pelagic (top feeders), and the position of the species within the food web, i.e. whether or not it is a predatory species. A summary of a large number of studies reported for PBDEs in shrimp was included in a study by Maia et al. (2020) who concluded that highest concentrations were found in Asia.

The most commonly used bioindicator species for pollutants, including PBDEs, is bivalves. Concentrations of the sum of PBDEs in bivalves is typically a few hundred ng/g fat, but can be as high as several thousand ng/g fat. Often the profile is dominated by **BDE-209**, but the data reported in the literature vary substantially with some studies designed to establish background levels whereas other studies are focussed around hot spots or pollution sources (Dondero & Calisi, 2015; Zhang, Wang, et al., 2016).

(iii) Turtles

Snapping turtles (*Chelydra serpentina*) have been commonly used to evaluate the extent of organic chemical contamination and trends in the Great Lakes and the Hudson River of New York since the 1970s (She et al., 2016). Snapping turtle eggs are also excellent bioindicators of the health conditions in wetlands and the bioavailability of organic contaminants (Basile et al., 2011). Snapping turtle eggs provide comprehensive information concerning the temporal and spatial trends of contaminants including PBDEs. Concentrations of PBDEs up to around 40 ng/g fat were found from off the coast of North Carolina (Alava et al., 2011). Keller et al. (2004) found that pollutants might affect the health of loggerhead sea turtles even though sea turtles, with an herbivorous diet, tend to accumulate lower concentrations of POPs compared with other wildlife. PBDEs and several other POPs were measured in the blood of three different species of sea turtles in Brazil, and concentrations were found to vary significantly between species (Filippos et al., 2021).

(iv) Marine birds

Guigueno and Fernie (2017) noted in a review on the toxic effects on birds associated with a variety of historical and novel flame retardants, that birds integrate chemical information (exposure, effects) across space and time which makes them ideal sentinels of environmental contamination.

Barentsportal is a joint Norwegian/Russian organisation for monitoring the environmental status of the Barents Sea.[4] The portal reports that PBDEs (sum of 11 congeners) increased in the period from 1983 to 1993 and then remained steady from 1993 to 2003, followed by a decrease in levels. PBDEs in seabirds are reported to constitute about 2%–5% of the total organic pollution in the seabirds. The temporal plateau and decline seen in PBDEs was associated with reduced production and usage due to the ban and regulation of the three primary PBDE technical products (PentaBDE, OctaBDE and DecaBDE).

Miller et al. (2015) reviewed recent temporal trends in marine and estuarine birds from European countries. Trends were shown to have not been consistent, with a mixture of stable, increasing and even decreasing trends, with five trends showing subsequent decreases since the late-1980s (Sweden), mid-1990s (UK) and late 1990s/early-2000s (Norway). Two trends for white tailed sea eagles (*Haliaeetus albicilla*) from the Baltic Sea, Sweden, show increases in PBDEs since the late-1990s. These inconsistencies were considered to be due to, e.g. species differences in life history, diet and local marine food chains. The maximum PBDE concentration for congeners measured within the European region was in great skuas (*Stercorarius skua*) in samples from the Shetland Islands to the North of Scotland (22,128.6 ng/g fat) (Leat et al., 2011). Overall, the picture from Europe and North America generally shows decreasing trends when time series for PBDEs have been evaluated after 2000 (Miller et al., 2015).

[4]https://www.barentsportal.com/barentsportal/index.php/en/maps/101-pollution/pollution-contaminants-in-seabirds/671-persistent-organic-pollutants-in-seabird-eggs-pbde-sum-of-11-individual-polybrominated-diphenyl-ethers

PBDE contamination is typically higher in coastal-based biota from urbanised areas compared with that taken from more rural locations due to the proximity of sources (Gauthier et al., 2007, 2008; Yogui & Sericano, 2009). Historically, the USA has produced and used more of these chemicals than in other regions (Yogui & Sericano, 2009), and it is therefore not surprising that an extremely high PBDE concentration was observed for a North American seabird (Forster's tern, 63,000 ng/g fat), coming from San Francisco Bay which is a densely populated urban area. Local sources rather than long-range transport of PBDEs are likely to be responsible for high PBDE concentrations found close to most urban/industrial locations (Miller et al., 2015).

(v) Marine mammals

PBDE levels in marine mammals may be generally one or more orders of magnitude higher than those in the invertebrates and fish collected from the same sampling sites, as shown in **Figure 5** (from Zhang , Wang, et al., 2016). Generational transfer has also been shown to occur for PBDEs and other contaminants in porpoises (van den Heuvel-Greve et al., 2021).

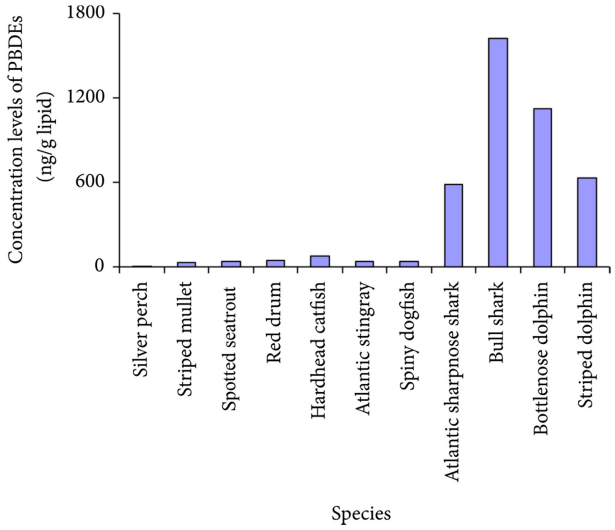

FIGURE 5 Concentrations of the sum of 8 PBDEs (**BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183**, -**209**) in different species from Florida coastal waters (lipid-normalised concentrations) (from Zhang, Wang, et al., 2016). © 2016 Zhang et al Creative Commons Attribution License.

Terrestrial wildlife including birds

Studies reporting levels of PBDEs in wildlife tend not to be systematic and are difficult to use to make an assessment of typical levels. Most have been conducted to demonstrate local sources of contamination, e.g. near e-waste sites or long-range transport, e.g. studies on polar bears or polar marine food webs (Tongue et al., 2019; Sun, Li, Hao, et al., 2020).

It has been suggested that biomagnification of lipophilic POPs is generally higher in terrestrial than in aquatic food chains (e.g. Gobas et al., 2003). Biomagnification factors for terrestrial wildlife, such as wolves and birds, can be around an order of magnitude higher than for aquatic organisms, such as fish and aquatic invertebrates (Gobas et al., 2003). Aquatic feeding birds were shown to accumulate **BDE-47** at a faster rate than bird6s that fed primarily on land, which instead had a greater accumulation of **BDE-153** and increasing roughly in accordance with the degree of bromination (de Solla, 2016). Furthermore, the fugacity of many POPs is very high from water to aquatic organisms, leading to bioconcentration or direct accumulation of POPs through passive partitioning, which can easily be mistaken for biomagnification (de Solla, 2016).

Bioaccumulation of PBDEs was studied in a terrestrial ecosystem near Antwerp (Belgium), with both avian predatory species (buzzard [*Buteo buteo*], sparrowhawk [*Accipiter nisus*]) and fox [*Vulpes vulpes*] (de Solla, 2016; Voorspoels et al., 2007). A significant degree of biomagnification was observed for predatory birds, with biomagnification factors (BMFs) ranging between 2 and 34, but foxes had body burdens that were lower than their rodent prey. It was suggested that this may be due to the high metabolic capacity of the fox (de Solla, 2016; Voorspoels et al., 2007). Although all are predatory species, the diet of the fox is more omnivorous in content when compared to the two predatory birds, which may result in lower dietary exposure of the fox compared to the avian species.

The BMFs of a number of POPs, including DDTs, PCBs, PBDEs, HBCDDs and dechlorane plus (DP), were determined in two food chains from an urban area near Beijing, China (Yu et al., 2013). The first food chain consisted of the common kestrel (*Falco tinnunculus*) and their frequent prey, the Eurasian tree sparrow (*Passer montanus*). According to the authors, the second consisted of the eagle owl (*Bubo bubo*) and little owl (*Athene noctua*) and their frequent prey, the brown rat (*Rattus norvegicus*). Overall, the order of BMFs was DDE > PCBs > PBDEs in both food chains.

The review by Maddela et al. (2020) summarised several factors that make it complex to form conclusions about PBDEs in the environment. Data can be generated using a different selection of congeners; there are difficulties in assessing the environmental levels and behaviour due to differences in climate, soil type, etc, and temporal trends; BFR-containing wastes disposed in landfills get re-released (data are limited and uncertain); some techniques designed to reduce emission are counterproductive (e.g. co-combustion of BFRs increases the total formation of brominated and mixed halogenated dioxins/

furans, PXDD/Fs); it is uncertain whether all the PBDE congeners and their derivatives are subject to the same degree of migration from the source material to the environment; and details relating to the lipophilicity of PBDE congeners are inconsistent.

Due to the fact that PBDEs are persistent, lipophilic and bioaccumulate, they can be found in all animal species including humans, in particular in lipid rich compartments, such as adipose tissue and breast milk (see **Section 3.1.1.4**).

1.3.4 | Sampling and methods of analysis

1.3.4.1 | *Sampling*

The primary objective of sampling is to obtain a representative and homogeneous laboratory sample with no secondary contamination. Therefore, basic rules for sampling of organic contaminants or pesticides should be followed. Respective requirements are legislated, e.g. in Commission Regulation (EU) No 2017/644[5] laying down methods of sampling and analysis for the control of levels of dioxins, dioxin-like PCBs and non-dioxin-like PCBs in certain foodstuffs. This Regulation contains, inter alia, a number of provisions concerning methods of sampling depending on the size of the lot, packaging, transport, storage, sealing, labelling, interpretation of analytical results and requirements for assessing the compliance of a lot or sublot with the legislation. With Commission Recommendation 2014/118/EU on the monitoring of traces of BFRs in food, the EU Commission recommended that Member States should perform monitoring on the presence of PBDEs in food including the congeners **-28**, **-47**, **-49**, **-99**, **-100**, **-138**, **-153**, **-154**, **-183** and **-209**. For this, the Member States should follow the sampling procedures laid down in Annex II of the predecessor version of the Regulation (EU) No 2017/644 to ensure that the samples are representative of the sampled lot.

1.3.4.2 | *Methods of analysis*

Current analytical methods generally allow the quantification of all 209 possible PBDE congeners. However, in routine analysis, the analysis of PBDEs is often focused on eight congeners (**BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**, **-183** and **-209**), which were considered by the CONTAM Panel in 2011 to be of primary interest. Nevertheless, there are many surveys that are limited to fewer (predominant) PBDEs or include a number of additional congeners, which makes a comparison of results based on summed concentrations difficult.

Detailed information on methods of analysis for PBDEs in food and biological samples, as well as parameters that influence the validity of results were described in the previous EFSA Opinion on PBDEs (EFSA CONTAM Panel, 2011b). In summary, the analytical approaches for the PBDE extraction and clean-up generally follow the methodologies for the analysis of persistent lipophilic compounds, such as Soxhlet extraction, supercritical fluid extraction (SFE), microwave-assisted extraction (MAE), pressurised liquid extraction (PLE) and solid-phase extraction (SPE). The development of greener, faster and simpler sample preparation approaches has increased in recent years. Berton et al. (2016) reviewed the state-of-the-art sample preparation approaches based on green analytical principles proposed for the determination of PBDEs and their metabolites (hydroxylated- (OH-PBDEs) and methoxylated-PBDEs (MeO-PBDEs)) in environmental and biological samples (see **Sections 3.1.1.3 and 3.1.1.2.3**). In this respect, special attention is paid to miniaturised sample preparation methodologies and strategies proposed to reduce organic solvent consumption. Cruz et al. (2017) reviewed the most common methodologies covering sample preparation and instrumental analysis for the determination of PBDEs, OH-PBDEs and MeO-PBDEs in sea food. Ayala-Cabrera, Santos, and Moyano (2021) focused in their review on the latest advances in the analytical methodologies regarding sample treatment, chromatographic separation and mass spectrometry analysis for the determination of PBDEs and other halogenated organic contaminants. Śmiełowska and Zabiegała (2020a) reviewed current solutions used for sample preparation and respective future trends for PBDE analysis. Hajeb et al. (2021) performed a critical review of analytical methods for the determination of PBDEs and a number of other BFRs in human matrices. Co-extracted lipids and other interfering compounds can be removed in several ways, such as gel permeation chromatography (GPC), aluminium-oxide chromatography and multilayer silica chromatography. These steps are greatly performed automatically by commercial clean-up instruments. The quick, easy, cheap, effective, rugged and safe (QuEChERS) method which comprises an integrated extraction and clean-up approach has gained increased importance and application in food laboratories. Cruz et al. (2019) developed and validated a method for seven PBDEs and eight MeO-PBDEs in three distinct seafood matrices (muscle, liver and plasma) and in feed, using a QuEChERS extraction approach for solid samples and a dispersive liquid–liquid microextraction method (DLLME) for plasma.

Various studies have shown that PBDEs, in particular high brominated congeners, in particular **BDE-209**, may undergo photolytic debromination under laboratory conditions in the presence of UV light with a wavelength above 290 nm. Due to this fact, it is recommended that all analytical work is carried out in such a manner that UV light is kept out, e.g. treatments can be undertaken in brown glass or in glassware covered with aluminium foil.

As the degradation of **BDE-209** in particular to octa- and nona-brominated PBDEs was demonstrated on unsuitable GC conditions, such as high temperatures, time spent at elevated temperatures and presence of catalytic sites, the choice of the injection system and capillary columns for the chromatographic separation is of great importance. Common injection systems for GC analysis of PBDEs are splitless injection, programmable temperature vaporisation injector (PTV) as well as on-column injectors. The GC analysis is often performed on two capillary columns, a short one (10–15 m) with a thin

[5]Commission Regulation (EU) 2017/644 of 5 April 2017 laying down methods of sampling and analysis for the control of levels of dioxins, dioxin-like PCBs and non-dioxin-like PCBs in certain foodstuffs and repealing Regulation (EU) No 589/2014. OJ L 92, 6.4.2017, p. 9–34.

stationary film thickness for the determination of **BDE-209** and a longer column (25–60 m) with a greater film thickness for the other PBDE congeners.

Due to the relatively low levels of PBDEs and their metabolites in food and biological samples, their determination requires high sensitivity combined with high selectivity. Approaches that fulfil these requirements are GC-electron capture negative ionisation–mass spectrometry (GC-ECNI–MS) and GC-high resolution mass spectrometry (GC–HRMS) for the parent compounds, and LC-tandem mass spectrometry (LC–MS/MS) for the metabolites. Modern GC-ECNI–MS systems allow under optimal conditions limits of detection (LODs) similar to GC–HRMS, but are less costly. The predominant ions formed, especially for the low brominated PBDE congeners under ECNI-conditions are the bromine isotopes *m/z* 79 and 81. Thus, isotope labelled standards cannot be used with GC-ECNI–MS, except for some high brominated congeners, such as **BDE-209**, where a good sensitivity and selectivity is achieved using fragment ions for the native and isotope labelled **BDE-209**. HRMS has a higher selectivity than ECNI-MS, since the accurate mass of the molecular ion or fragment ion is recorded. Moreover, isotope labelled PBDEs can be used as ideal internal standards which increase the accuracy of the analytical results. In the last decade also GC-tandem mass spectrometry (GC–MS/MS), GC–time-of-flight mass spectrometry (GC–TOF/MS) and GC–Ion Trap (GC–IT) mass spectrometry were applied for the determination of PBDEs. In their review, Pietroń and Małagocki (2017) compared the detection techniques and MS ionisation modes applied for PBDE determination in food of animal origin. Current trends in analytical strategies for the determination of PBDEs in different matrices are reviewed by Śmiełowska and Zabiegała (2020b). An alternative approach that increasingly is applied in the past years in the analysis of PBDEs is the quantification of bromine using inductively coupled plasma (ICP) mass spectrometry, either as GC-ICP–MS or LC-ICP–MS. The latter technique has the advantage that also polar metabolites can be detected without derivatisation (Song et al., 2020). The recent progress in analytical GC and LC mass spectrometric based methods for emerging halogenated contaminants, including PBDEs and their transformation products, is reviewed by Badea et al. (2020).

Polar metabolites, such as OH-PBDEs cannot be analysed directly by GC techniques without derivatisation. The preferred technique for their determination is LC–MS/MS, either as conventional high performance liquid chromatography (HPLC) or ultra-performance liquid chromatography (UPLC) combined with tandem mass spectrometry (MS/MS). Lai, Chen, Hon-Wah Lamb, and Caia (2011) demonstrated the potential of the UPLC–MS/MS technique by direct determination of nine OH-PBDEs in rat plasma (see also the reviews by Berton et al. (2016) and Cruz et al. (2017)). In their review, Wei et al. (2021) summarised analytical methodologies for determination of OH-PBDEs from sample treatment to various MS-based detection techniques. Other polar metabolites that can be formed from PBDEs are bromophenols. Ho et al. (2012, 2015) synthesised and characterised the glucuronide and sulfate conjugates of 2,4-dibromophenol (2,4-DBP) and 2,4,6-tribromophenol (2,4,6-TBP), and determined them by direct LC–MS/MS analysis in in human urine. Feng, Xu, et al. (2016) analysed the bromophenols in deconjugated form in urine following derivatisation by GC–MS/MS (**see Section 3.1.1.4.5**).

The application of non-target analysis in analytical chemistry is becoming increasingly popular. Pourchet et al. (2021) developed a non-targeted workflow from sample preparation to data processing for human milk. The approach is based on a simple and fast sample preparation followed by a comprehensive analysis by both liquid and gas phase chromatography coupled to high resolution mass spectrometry, using LC-ESI (+/–)-Q-Orbitrap and GC-EI-Q-Orbitrap. The method performance was assessed using a mixture of 30 halogenated compounds with different physico-chemical properties including **BDE-153** and OH-BDE-137. Although the recovery of **BDE-153** was relatively low compared to those of other halogenated compounds, the approach indicates that non-target screening may be a powerful tool for screening of unknowns in complex biological matrices.

The regular control for laboratory blanks is an important requisite for a reliable PBDE determination in food and biological samples as considerable blank contributions are easily encountered for the major congeners **BDE-47**, **-99**, **-100** and **-209**. Moreover, **BDE-209** is often present in high levels in dust and special care must be taken to avoid contamination of samples and extracts. In this respect, quality control (QC) and quality assurance (QA) represent important tools of the total analytical procedure.

1.3.4.3 | *Analytical quality assurance*

The analysis of PBDEs in food is complex and involves several critical steps. As mentioned earlier, exposure to high temperature and to UV irradiation should be avoided as this may lead to degradation of high brominated congeners, such as **BDE-209**.

A prerequisite for laboratories to demonstrate that their applied methods of analysis are fit for purpose is the successful participation in proficiency tests or interlaboratory studies. Information on interlaboratory studies performed in biota and food samples before 2010 are summarised in the previous EFSA Opinion on PBDEs (EFSA CONTAM Panel, 2011b). The European Reference Laboratory (EURL) for Halogenated Persistent Organic Pollutants (POPs) in Feed and Food as well as the Norwegian Institute of Public Health (NIPH) regularly offer proficiency tests for analysing various persistent organic pollutants, including PBDEs in food and feed. The proficiency tests of both the EURL and the NIPH are open to all laboratories, whether official or private. The NIPH interlaboratory studies cover besides dioxins, PCBs and HBCDDs also the eight PBDE congeners (**BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**, **-183** and **-209**) in a number of non-spiked food matrices with a broad concentration range depending on matrix and congener. Besides a standard solution submitted by the organisers in each round, the matrices involved between 2015 and 2019 were, beef, salmon and cheese in 2015, sheep liver, salmon and fish oil in 2016, sheep meat, cod liver and herring in 2017, reindeer meat, salmon and fish oil in 2018, and veal, herring and brown meat in 2019. A total of 20–40 laboratories reported results in each round for the eight PBDE congeners. Concerning

the standard solution, the relative standard deviations (RSDs) for all congeners were in most cases between 5 and 10%. Higher RSDs were calculated for the reported PBDE congeners in the various food matrices. Depending on the extent of the PBDE contamination in the different food samples and the congener, the range of RSDs on a fresh weight basis was between 10% and 110% with averages generally between 30% and 40% including **BDE-209**. The results indicate that the lowest RSDs were obtained for the highest concentrations. All results of the various interlaboratory comparison studies by NIPH are published on their website.[6]

Fernandes et al. (2021) provided guidance on analytical criteria, such as precision and trueness, limits of quantitation, recovery and positive identification to allow validated and reliable determination of PBDEs and HBCDDs in food and animal feed. The criteria approach is based on several years of collective experience. The effectiveness of this approach has been demonstrated by a successful proficiency testing scheme conducted by the EURL for Halogenated Persistent Organic Pollutants in Feed and Food that has been used for a number of years and has attracted an increasing number of participants.

Dvorakova et al. (2021) investigated the analytical comparability and accuracy of laboratories analysing PBDEs and further flame retardants in serum and urine by a quality assurance and control (QA/QC) scheme comprising interlaboratory comparison investigations (ICIs) and external quality assurance schemes (EQUASs). Four rounds between 2018 and 2020 were performed in the frame of the European Human Biomonitoring Initiative (HBM4EU). The PBDEs included were **BDE-47**, -**153** and -**209** in human serum at two concentration levels. In general, the number of satisfactory results reported by laboratories increased during the four rounds. The majority of participants achieved more than 70% satisfactory results over all rounds for **BDE-47** and -**153**, for which also the highest participation rate was reached.

The EURL for Halogenated POPs in Feed and Food published a guidance on the essential analytical parameters to be used for organobromine contaminant analysis in food and feed, including PBDEs, intended for laboratories involved in the official control of these contaminants in food and feed.[7]

1.3.5 | Previous assessments

In 2011, the EFSA CONTAM Panel published its first risk assessment on PBDEs in food (EFSA CONTAM Panel, 2011b). Eight PBDE congeners were considered by the Panel to be of primary interest based on the composition of the technical PBDE products, occurrence in the environment and in food: **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183** and -**209**. The Panel considered at that time the potential for additivity of the different congeners, acknowledging there were similarities in the effects of the various PBDE congeners, e.g. interactions with nuclear receptors. However, the Panel indicated that the divergent responses of the different toxicological endpoints and the limited information available, precluded establishment of a common mode of action. Therefore, the Panel decided to perform the risk assessment on the basis of the individual congeners. Relevant toxicity data were only available for **BDE-47**, **-99**, -**153** and -**209**, and therefore, the Panel could perform a risk assessment only for these four individual congeners.

The Panel identified at that time neurodevelopmental effects on behaviour as the critical endpoint for these congeners based on single oral dose studies in mice. The Panel derived benchmark doses (BMDs) and their corresponding lower 95% confidence limit for a benchmark response of 10% ($BMDL_{10}$) of:

- 309 μg/kg bw for **BDE-47**, based on the effects in locomotion in mice reported by Eriksson et al. (2001), using single oral administration on postnatal day (PND) 10,
- 12 μg/kg bw for **BDE-99**, based on the effects in total activity in mice reported by Eriksson et al. (2001),[8] using single oral administration on PND10,
- 83 μg/kg bw for **BDE-153**, based on the effects in total activity in mice reported by Viberg, Fredriksson, and Eriksson (2003), using single oral administration on PND10,
- 1700 μg/kg bw for **BDE-209**, based on the effects in total activity in mice reported by Viberg et al. (2007), using single oral administration on PND3.

For **BDE-47**, -**99** and -**153**, since the elimination kinetics in rodents and humans differ considerably, the CONTAM Panel converted the $BMDL_{10}$ into an estimated chronic human dietary intake associated with the body burden at the $BMDL_{10}$ as the basis for the risk assessment. For this, the Panel first estimated the body burden at the $BMDL_{10}$, that resulted in values of 232, 9 and 62 μg/kg bw for, respectively, **BDE-47**, -**99** and -**153**, considering an oral absorption for these congeners in rodents of about 75%. Second, the chronic human dietary intake associated with the body burden at the $BMDL_{10}$ was estimated. This was done assuming the human absorption of these congeners to be 100%, in the absence of robust information on the actual absorption, and using the 'worst-case' longest human half-life identified for these congeners of 926, 1442 and 4530 days, respectively (Geyer et al., 2004, extended abstract). This resulted in estimated chronic human dietary intakes associated with the body burden at the $BMDL_{10}$ of 172, 4.2 and 9.6 ng/kg bw per day for, respectively, **BDE-47**, -**99** and -**153**.

Due to limitations and uncertainties in the database, the Panel did not find it appropriate at that time to establish health-based guidance values (HBGVs), and instead used a margin of exposure (MOE) approach for the risk characterisation

[6] https://www.fhi.no/en/sys/search-result/?term=interlaboratory%20comparison

[7] https://eurl-pops.eu/news/guidance-document-bcon-parameters-2

[8] This was wrongly cited as Viberg et al. (2004b) in Table 40 of the EFSA CONTAM Panel (2011b).

by comparing the estimated the estimated human intake associated with the body burden at the $BMDL_{10}$ with the dietary exposure for different age groups based on PBDE levels in food collected in 11 European countries covering the period 2000–2010.

For **BDE-209**, the elimination half-life between animals and humans did not differ by orders of magnitude, and therefore the $BMDL_{10}$ was directly used and compared with the estimation of the dietary exposure.

The Panel considered that an MOE larger than 2.5 might indicate that there is no health concern. In reaching this conclusion, the Panel at that time considered that since the MOE approach was based on a body burden comparison and associated daily intake between animals and humans, the potential kinetic differences had been accounted for. However, interspecies differences in toxicodynamics for the effects observed had to be covered (uncertainty factor of 2.5). Regarding intraspecies differences, the Panel considered that by assuming 100% absorption of PBDEs in humans, and the use of the worst-case maximum half-lives estimated in humans, the kinetic differences had been accounted. Also, by focusing on the body burden associated with a $BMDL_{10}$ for neurobehavioural effects in mice induced during a relevant period for brain development, and applying this body burden to the entire life span in humans, individual differences in susceptibility (toxicodynamics) had been covered.

The chronic human dietary intakes estimated for the **BDE-47**, -**99** and -**153** were compared with the estimate of the dietary exposure for different age groups based on the PBDE levels in food collected in 11 European countries covering the period from 2001 to 2009. The CONTAM Panel concluded that for **BDE-47**, **-153** and -**209** the dietary exposure across age groups and consumption surveys estimated at the time of the assessment did not raise a health concern. For **BDE-99**, the Panel concluded that there was a potential health concern with respect to the estimated dietary exposure.

Since then, several bodies have performed risk/hazard assessments for PBDEs. The details of these assessment are reported in Table 4 and summarised below.

In European countries, the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), published in 2015 a statement on the potential risks from PBDEs in the infant diet (COT, 2015) that was updated in 2017 (COT, 2017). It reviewed the new available toxicological and epidemiological data since the EFSA 2011 assessment. The COT overall concluded that the new data did not call into question the Reference Points identified by EFSA for **BDE-47**, **-99** and -**153**. However, for **BDE-209**, COT considered it appropriate to also calculate the chronic human daily intake in a similar way as done for **BDE-47**, -**99** and -**153**, resulting in a value of 19,640 ng/kg bw per day (COT, 2015). It also concluded that the new studies did not provide a basis on which to establish Reference Points for other congeners. On the MOE that would indicate no health concern, the COT agreed with the EFSA 2011 Opinion that '*interspecies differences in toxicokinetics were accounted for by the body burden approach, and that the use of a relatively high elimination half-life for humans, and of data relating to a critical period of development, reduced uncertainties in the risk assessment*'. However, COT considered that MOEs '*should be rather higher than 2.5 to provide assurance of safety*' and concluded that MOEs of somewhat above 2.5 would be considered of low concern (COT, 2015, 2017). COT provided estimates of exposure to dust, air, breast milk and food, and concluded on a possible health concern regarding **BDE-99** and -**153** exposure from breast milk at age 12–18 months, and to a lesser extent for **BDE-47**. Exposure via infant formula and commercial infant foods did not indicate a concern. A potential concern for young children due to exposure to **BDE-99** and **-209** in dust and soil in children aged 1–5 years was raised (COT, 2015, 2017).

The Dutch National Institute for Public Health and the Environment (RIVM) published in 2016 its update of the dietary exposure of the Dutch population to five PBDE congeners (**BDE-47**, -**99**, -**100**, -**153**, -**183**), and translated the EFSA $BMDL_{10}$ values into 'guidance values' to estimate the risk (RIVM, 2016). This was done by dividing the chronic human intake estimated by EFSA for **BDE-47**, -**99** and -**153** by the value of 2.5 corresponding to the MOE that would indicate no health concern. An additional guidance value was established for **BDE-99** based on reproductive toxicity (0.23 ng/kg bw per day, Bakker et al., 2008) (RIVM, 2016). The authors concluded that the intake of **BDE-47**, -**99** and -**153** was so low that the risk to health was negligible. No conclusions were drawn for **BDE-100** and -**183** due to the absence of 'guidance values'.

In 2017, the French Agency for Food, Environmental and Occupational Health Safety (ANSES) published three reports on the knowledge related to polybrominated compounds, related to the 'identification, chemical properties, production and uses in particular of BDE-47 and -209' (ANSES, 2017a), the 'occurrence and exposure' (ANSES, 2017b), and the 'toxicity of polybrominated compounds' (ANSES, 2017c). ANSES estimated the dietary exposure to the sum of 7 PBDEs (**BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183**), to the sum of 8 PBDEs (the 7 PBDEs plus **BDE-209**), and to **BDE-209** alone in the general and young populations. It also reviewed the new toxicological studies since the previous EFSA Opinion. For the risk assessment of **BDE-209**, ANSES used the $BMDL_{10}$ values calculated by the CONTAM Panel in its 2011 assessment (1700 µg/kg bw per day) to calculate the MOE. It was concluded that the margins of safety for **BDE-209** are largely above the MOE of 2.5 proposed by EFSA. For its risk assessment to the sum of 7 PBDEs, ANSES used the tolerable daily intake of 10 ng/kg bw per day for NDL-PCBs, in the absence of a 'toxicological reference value' for PBDEs, based on the similar chemical structures of NDL-PCBs and PBDEs and assumed similar mode of action (AFSSA, 2007; ANSES, 2017a).[9] It was concluded that there was no exceedance of the tolerable daily intake.

In non-European countries, Health Canada published in 2012 its final report on the human health state of the science on **BDE-209** (Health Canada, 2012). A LOAEL of 2.22 mg/kg bw was identified, based on neurodevelopmental effects in

[9]The Anses (2017a, 2017b, 2017c) reports indicate that the tolerable daily intake (TDI) of 10 ng/kg bw per day for the sum of seven PBDEs was established by EFSA in its previous risk assessment. This statement is not correct as EFSA did not establish a TDI for the sum of seven PBDEs. Such tolerable daily intake was established by Afssa (2007). This misreporting has been acknowledged by Anses.

mice dosed at PND3 and assessed at 2 and 4 months resulting in a decreased capacity to habituate to new environments (Johansson et al., 2008). This LOAEL had also been identified as the critical effect level for the risk characterisation in Health Canada's previous assessment in 2006 based on other studies, and reported to be supported by other publications. Health Canada concluded that comparison of the critical effect level of 2.22 mg/kg bw per day with the BDE-209 UB exposure estimates resulted in an MOE that was considered *'adequate to address uncertainties in the health effects and exposure databases'*. This report did not provide an estimate of the exposure and thus no risk characterisation was performed.

In 2017, the ATSDR published its toxicological profile of PBDEs (ATSDR, 2017) including minimal risk levels (MRLs)[10] for acute-, intermediate- and chronic-duration oral exposure. For **BDE-209**, an MRL of 0.01 mg/kg per day was derived for acute duration oral exposure (14 days or less), based on a NOAEL of 1.34 mg/kg for neurobehavioural effects in 2–4-month-old mice following a single exposure to **BDE-209** on PND3 (Johansson et al., 2008; Buratovic et al., 2014) and an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability). For intermediate-duration oral exposure, an MRL of 0.0002 mg/kg per day was derived, based on a LOAEL of 0.05 mg/kg per day for a 12% increase in serum glucose in adult rats exposed to **BDE-209** (Zhang, Sun, et al., 2013) and applying an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for animal to human extrapolation and 10 for human variability). For '***lower-brominated PBDEs***'[11] an MRL of 0.00006 mg/kg per day was derived for acute duration oral exposure. This was based on a LOAEL of 0.06 mg/kg per day for endocrine effects in rat dams and reproductive and neurobehavioural effects in F1 offspring exposed to **BDE-99** (Kuriyama et al., 2005, 2007; Talsness et al., 2005) and applying an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for animal to human extrapolation and 10 for human variability). For intermediate-duration oral exposure (15–364 days) an MRL of 0.000003 mg/kg per day was derived, based on a minimal LOAEL of 0.001 mg/kg per day for a 34% reduction in serum testosterone in male rats exposed to **BDE-47**[12] (Zhang, Zhang, et al., 2013), and applying an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for animal to human extrapolation and 10 for human variability). A chronic-duration oral MRL was not derived for '*lower-brominated PBDEs*' due to insufficient data, and the authors indicated that the intermediate-duration oral MRL could be used as a value for chronic exposure (ATSDR, 2017). This document did not provide an estimate of the exposure and thus no risk characterisation was performed.

In 2017, US-EPA established chronic oral reference doses (RfDs) for **BDE-47**, -**99**, -**153** and -**209**, as well as for PentaBDE and OctaBDE (US-EPA, 2017) of 1×10^{-4}, 1×10^{-4}, 2×10^{-4}, 7×10^{-3}, 2×10^{-3} and 3×10^{-3} mg/kg per day, respectively. In addition, for **BDE-209**, EPA assigned an oral slope factor for carcinogenic risk of 7×10^{-4} mg/kg per day. This document did not provide an estimate of the exposure and thus no risk characterisation was performed.

[10]An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure (ATSDR, 2017).

[11]Referring to PBDE congeners other than **BDE-209**.

[12]The ATSDR (2017) assessment considered that *'The change in testosterone is considered a minimal LOAEL because it is unclear if the magnitude of change represents a biologically adverse effect; however, this statistically significant reduction in serum testosterone is considered an early indication of damage to the male reproductive system, considering the additional effects observed at ≥ 0.03 mg/kg per day (histological lesions in testes, sperm effects)'*.

TABLE 4 Assessments on PBDEs since the publication of the previous EFSA CONTAM Panel Opinion (2011b), including details about the latter for comparison.

Reference	Country	Congener	NOAEL/LOAEL/BMD	HBGV/MOE	Dietary exposure (ng/kg bw per day)	Conclusion
EFSA CONTAM Panel (2011b)	Europe	**BDE-47**	**$BMDL_{10}$ = 309 μg/kg bw** (based on alterations in spontaneous behaviour and decreased habituation in mice exposed to a single dose at PND10, Eriksson et al., 2001) Associated chronic intake related to the BB at the $BMDL_{10}$ = 172 ng/kg bw per day	MOE	Mean exposure[a]: Young children[b]: 1.04–6.40 Adults: 0.29–1.91 P95 exposure[a]: Young children[b]: 4.44–15.6 Adults: 1.10–4.51 High and frequent fish consumers: 5.39–7.27	*'The CONTAM Panel concluded that for BDE-47 the MOEs do not indicate a health concern with respect to current dietary exposure in the EU'*
		BDE-99	**$BMDL_{10}$ = 12 μg/kg bw** (based on decreased habituation in mice exposed to a single dose at PND10, Eriksson et al. (2001)[e] Associated chronic intake related to the BB at the $BMDL_{10}$ = 4.2 ng/kg bw per day	MOE	Mean exposure[a]: Young children[b]: 0.58–2.99 Adults: 0.11–0.65 P95 exposure[a]: Young children[b]: 1.36–6.16 Adults: 0.30–1.07 High and frequent fish consumers: 0.6–1.40	*'The CONTAM Panel concluded that BDE-99 there is a potential health concern with respect to current dietary exposure'*
		BDE-153	**$BMDL_{10}$ = 83 μg/kg bw** (based on altered spontaneous behaviour indication decreased habituation, and decreased performance in Morris swim maze indicating impaired learning and memory capability in mice exposed to a single dose at PND10, Viberg, Fredriksson, & Eriksson, 2003) Associated chronic intake related to the BB at the $BMDL_{10}$ = 9.6 ng/kg bw per day	MOE	Mean exposure[a]: Young children[b]: 0.09–1.62 Adults: 0.03–0.42 P95 exposure[a]: Young children[b]: 0.2–3.18 Adults: 0.07–0.67 High and frequent fish consumers: 0.24–0.89	*'The CONTAM Panel concluded that for BDE-153 the MOEs do not indicate a health concern with respect to current dietary exposure in the EU'*
		BDE-209	**$BMDL_{10}$ = 1700 μg/kg bw** (based on alterations in spontaneous behaviour indicating decreased habituation and alterations in nicotine response in mice exposed to a single dose at PND3, Viberg et al., 2007) Since for BDE-209 the elimination half-life between animals and humans did not differ by orders of magnitude, the $BMDL_{10}$ was directly used and compared with the estimation of the dietary exposure	MOE	Mean exposure[a]: Young children[b]: 1.55–9.69 Adults: 0.35–2.82 P95 exposure[a]: Young children[b]: 2.90–17.6 Adults: 0.70–4.58 High and frequent fish consumers: 0.46–4.59	*'The CONTAM Panel concluded that for BDE-209 the MOEs do not indicate a health concern with respect to current dietary exposure in the EU'*

TABLE 4 (Continued)

Reference	Country	Congener	NOAEL/LOAEL/BMD	HBGV/MOE	Dietary exposure (ng/kg bw per day)	Conclusion
COT (2015, 2017)	UK	**BDE-47**	Used the $BMDL_{10}$ calculated by EFSA CONTAM Panel (2011b) and its corresponding chronic human intake related to the BB at the $BMDL_{10}$ = 172 ng/kg bw per day	MOE	Mean (high level) – breast milk: 0–4 months: 70 (100) 4–12 months: 20–53 (59–79) 12–18 months: 13–15 (27–39) Mean (high) – exclusive infant formula: 0–6 months: 0.092–0.12 (0.14–0.18)	'… the *analysis indicated possible concerns regarding exposure of infants to BDE-47, -99 and -153* via *breast milk, although there is perhaps less concern for BDE 47'*. *'The new data on concentrations of PBDEs in infant formula and in commercial infant foods do not indicate a concern for dietary exposure'*. The current analysis does not indicate any possible concern regarding BDE-99 and -153 in young children aged 1–5 years from foods other than commercial infant food.
		BDE-99	Used the $BMDL_{10}$ calculated by EFSA CONTAM Panel (2011b) and its corresponding chronic human intake related to the BB at the $BMDL_{10}$ = 4.2 ng/kg bw per day	MOE	Mean (high level) – breast milk: 0–4 months: 18 (27) 4–12 months: 5–13 (15–21) 12–18 months: 3.3–3.9 (6.8–9.8) Mean (high) – exclusive infant formula: 0–6 months: 0.092–0.12 (0.14–0.18)	
		BDE-153	Used the $BMDL_{10}$ calculated by EFSA CONTAM Panel (2011b) and its corresponding chronic human intake related to the BB at the $BMDL_{10}$ = 9.6 ng/kg bw per day	MOE	Mean (high level) – breast milk: 0–4 months: 21 (32) 4–12 months: 5.9–16 (18–25) 12–18 months: 4.0–4.6 (8.1–12) Mean (high) – exclusive infant formula: 0–6 months: 0–0.041 (0–0.061)	
		BDE-209	Used the $BMDL_{10}$ calculated by EFSA CONTAM Panel (2011b) and calculated its corresponding chronic human intake related to the BB at the $BMDL_{10}$ = 19,640 ng/kg bw per day	MOE	Mean (high level) – breast milk: 0–4 months: 5 (7.4) 4–12 months: 1.4–3.7 (4.2–5.8) 12–18 months: 0.92–1.1 (1.9–2.7) Mean (high) – exclusive infant formula: 0–6 months: 2.4–3.2 (3.6–4.7)	
RIVM (2016)	The Netherlands	**BDE-47**	Used the $BMDL_{10}$ calculated by EFSA CONTAM Panel (2011b) to translate into a Guidance Value of 69 ng/kg bw per day	MOE	Median exposure: 2–6 years old = 0.10 7–69 years old = 0.05 P99 exposure: 2–6 years old = 0.43 7–69 years old = 0.28	*'Overall, we conclude that health risk related to the intake of PBDE-47, -99 and -100 in the Dutch population is negligible'*
		BDE-99	Used the $BMDL_{10}$ calculated by EFSA CONTAM Panel (2011b) to translate into a Guidance Value of 1.7 ng/kg bw per day Used an additional 'Guidance Value' of 0.23 ng/kg bw per day, based on reproductive toxicity (Bakker et al., 2008)	MOE	Median exposure: 2–6 years old = 0.10 7–69 years old = 0.05 P99 exposure: 2–6 years old = 0.18 7–69 years old = 0.12	
		BDE-100	Used the $BMDL_{10}$ calculated by EFSA CONTAM Panel (2011b) to translate into a Guidance Value of 3.8 ng/kg bw per day	MOE	Median exposure: 2–6 years old = 0.02 7–69 years old = 0.01 P99 exposure: 2–6 years old = 0.11 7–69 years old = 0.08	

(Continues)

TABLE 4 (Continued)

Reference	Country	Congener	NOAEL/LOAEL/BMD	HBGV/MOE	Dietary exposure (ng/kg bw per day)	Conclusion
ANSES (2017a, 2017b, 2017c)	France	Sum of 7 PBDEs (**BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183**) Sum of 8 PBDEs (7 PBDEs + **BDE-209**) **BDE-209**	Reviewed new toxicity data since EFSA CONTAM Panel (2011b). For the sum of seven PBDEs, ANSES used the tolerable daily intake of 10 ng/kg bw per day for NDL-PCBs, in the absence of a 'toxicological reference value' for PBDEs, based on the similar chemical structures of NDL-PCBs and PBDEs and consequently similar mode of action (AFSSA, 2007; ANSES, 2017a). For **BDE-209**, used the $BMDL_{10}$ calculated by EFSA CONTAM Panel (2011b)	MOS	Sum 7 PBDEs, mean UB: Adults: 0.212 Children (3–17 years): 0.331 Sum 7 PBDEs, P95 UB: Adults: 0.643 Children (3–17 years): 0.894 Sum 8 PBDEs (7 PBDEs + **BDE-209**): 2- to 3-fold increase compared to the sum of 7 PBDEs only, mean UB: Adults: 0.550 Children (3–17 years): 1026 **BDE-209**, mean UB: Infants (13–36 months old): 1.12 Infants (1–4 months old): 2.62	*'The MOS related to the dietary exposure to BDE-209 are largely above the value of 2.5 proposed by EFSA.* *No exceedence of the tolerable daily intake is observed for the sum of the 7 PBDE, whatever the hypothesis adopted. Following the UB, the exposure at the 90th percentile represent at most 15% of the TDI whatever the age group considered.* *Food exposure of the children population to BDE-209 and to the sum of the 7 PBDEs is considered tolerable'*[c]
Health Canada (2012)	Canada	BDE-209	**LOAEL** = 2.22 mg/kg bw (based on neurodevelopmental effects in mice dosed at PND3 and assessed at 2 and 4 months resulting in a decreased capacity to habituate to new environment) (Johansson et al., 2008 and other studies)	MOE	0–6 months breast milk: 0.016–0.187 0–6 months formula: 0.00 (2.1×10^{-4}) 0–6 months not formula fed: 0.038 6 months–4 years: 0.024 5–11 years: 0.014 12–19 years: 0.0074 20–59 years: 0.0047 > 60 years: 0.00 (3.4×10^{-3})	*'The margins of exposure are considered adequate to address uncertainties in the health effects and exposure databases'*
ATSDR (2017)	USA	*'Lower-brominated PBDEs'*[d]	Acute duration oral exposure: **LOAEL** = 0.06 mg/kg bw per day (based on endocrine effects in rat dams and reproductive and neurobehavioural effects in F1 offspring exposed to **BDE-99**) (Kuriyama et al., 2005, 2007; Talsness et al., 2005)	MRL acute duration oral exposure: 0.00006 mg/kg bw per day	Not estimated	–
			Intermediate-duration oral exposure: Minimal LOAEL = 0.001 mg/kg per day (based on a 34% reduction in serum testosterone in male rats exposed to BDE-47 for 8 weeks via gavage) (Zhang, Zhang, et al., 2013)	MRL intermediate-duration oral exposure: 0.000003 mg/kg bw per day	Not estimated	–
		BDE-209	Acute duration oral exposure: **NOAEL** = 1.34 mg/kg (based on neurobehavioural effects in 2–4-month-old mice following a single exposure on PND3) (Buratovic et al., 2014; Johansson et al., 2008)	MRL acute duration oral exposure: 0.01 mg/kg bw per day	Not estimated	–
			Intermediate-duration oral exposure: Minimal **LOAEL** = 0.05 mg/kg per day (based on a 12% increase in serum glucose in adult rats exposed for 8 weeks via gavage) (Zhang, Sun, et al., 2013)	MRL intermediate-duration oral exposure: 0.0002 mg/kg bw per day	Not estimated	–

TABLE 4 (Continued)

Reference	Country	Congener	NOAEL/LOAEL/BMD	HBGV/MOE	Dietary exposure (ng/kg bw per day)	Conclusion
US-EPA (2017)	USA	**BDE-47**	–	Chronic oral RfD: 1×10^{-4} mg/kg bw per day	Not estimated	–
		BDE-99	–	Chronic oral RfD: 1×10^{-4} mg/kg bw per day	Not estimated	–
		BDE-153	–	Chronic oral RfD: 2×10^{-4} mg/kg bw per day	Not estimated	–
		BDE-209	–	Chronic oral RfD: 7×10^{-3} mg/kg bw per day	Not estimated	–
		PentaBDE	–	Chronic oral RfD: 2×10^{-3} mg/kg bw per day	Not estimated	–
		OctaBDE	–	Chronic oral RfD: 3×10^{-3} mg/kg bw per day	Not estimated	–

Abbreviations: $BMDL_{10}$, benchmark dose lower confidence limit for a benchmark response of 10%; bw, body weight; HBGV, health-based guidance value; LOAEL, lowest-observed adverse effect level; MOE, margin of exposure; MOS, margin of safety; MRL, minimal risk level; NOAEL, no-observed adverse effect level; RfD, reference dose.

[a]Mean exposure across dietary surveys in European countries. Range of minimum LB to maximum UB.

[b]Young children 1–3 years old.

[c]Original text: '*Les marges de sécurité (MOS) liés à l'exposition alimentaire au BDE-209 sont largement supérieures à la valeur de 2,5 proposée par l'EFSA. Aucun dépassement de la dose journalière tolérable n'est observé pour la somme des sept PBDE, quelle que soit l'hypothèse retenue. Sous l'hypothèse haute (UB), le ème 90 centile d'exposition représente à peine 15% de la DJT, quelle que soit la classe d'âge considérée. L'exposition alimentaire de la population infantile au BDE-209 ainsi àla somme des sept PBDE est jugée tolerable*'.

[d]Referring to PBDE congeners other than **BDE-209**.

[e]This was wrongly cited as Viberg et al. (2004b) in Table 40 of the EFSA CONTAM Panel (2011b).

1.3.6 | Legislation

In this Opinion, where reference is made to European legislation (Regulations, Directives, Recommendations, Decisions), the reference should be understood as relating to the most recent amendment at the time of publication of this Opinion, unless otherwise stated.

In order to protect public health, Article 2 of Council Regulation (EEC) No 315/93[13] of 8 February 1993 laying down Community procedures for contaminants in food stipulates that, where necessary, maximum tolerances for specific contaminants shall be established. A number of maximum levels (MLs), are currently laid down in Commission Regulation (EU) 2023/915 of 25 April 2023 that repeals Commission Regulation (EC) No 1881/2006.[14] PBDEs are not regulated so far under this Regulation or under any other specific European Union (EU) regulation for food.

Council Directive 2002/32/EC[15] regulates undesirable substances in animal feed. PBDEs are so far not regulated under this Directive or any other specific EU regulation for feed.

The placing on the market of the technical products PentaBDE and OctaBDE as well as their use as substances or as a constituent of substances or of preparations in concentrations higher than 0.1% by mass was already prohibited by Directive 2003/11/EC of the European Parliament and the Council.

Directive 2002/95/EC of the European Parliament and of the Council on the restriction of the use of certain hazardous substances (RoHS) in electrical and electronic equipment, recast by Directive 2011/65/EU, stipulated that Member States should ensure that, from 1 July 2006, new electrical and electronic equipment put on the market does not contain higher than 0.1% of PBDEs by weight in homogenous materials. By Commission Decision 2005/717/EC the use of DecaBDE in polymeric applications was exempted from these requirements. However, in January 2006, the European Parliament and Denmark launched legal proceedings against the European Commission for the exemption of DecaBDE from the RoHS Directive. On 1 April 2008, the European Court of Justice annulled the Commission Decision on the basis that procedural errors were made when establishing the exemption. As of July 2008, therefore, DecaBDE could no longer be used in electronics and electrical applications as decided by the Europe an Court of Justice.

Restriction on the manufacture, placing on the market and use of OctaBDE and DecaBDE are currently laid down in Annex XVII of Regulation (EC) No 1907/2006 (REACH). In March 2023, ECHA released its regulatory strategy for flame retardants,[16] in which it is highlighted the need to minimise aromatic brominated flame retardants and suggesting a wide and generic restriction. The restriction scope intends to cover all aromatic brominated flame retardants that are confirmed or will be confirmed to be PBT/vPvB hazards through harmonised classification or identification as SVHCs.

Tetra-, penta, hexa-, hepta- and DecaBDE are listed in Annex A of the Stockholm Convention,[17] with specific exemptions for use or production.[18] The compounds are further defined in Part III of Annex A as PBDE congeners **-47**, -**99**, and other tetra- and pentaBDEs present in commercial PentaBDE, and as **BDE-153**, -**154**, -175, -**183**, and other hexa- and heptaBDEs present in commercial OctaBDE. For chemicals in Annex A, parties must take measures to eliminate the production and use of it. The EU has registered exemptions for production and use of DecaBDE in specific vehicles, aircrafts and additives in plastics for heating application. The specific exemptions expire at the end of the service life of the products or in 2036, whichever comes earlier. The same PBDE congeners mentioned in the Stockholm Convention are also listed in Annex I of the UNECE Protocol to the 1979 Convention on Long-Range-Transboundary Air Pollution on Persistent Organic Pollutants (LRTAP POPs), as amended in 2009. The intention of the Protocol is to ban the production and use of specific products, and it includes provisions for dealing with the waste of these products.

Tetra-, penta-, hexa-, hepta- and decaBDEs are listed in Annex I, Part A of Regulation (EU) 2019/1021 of the European Parliament and of the Council on persistent organic pollutants (POPs). The objective of this Regulation is to protect human health and the environment by prohibiting, phasing out as soon as possible, or restricting the manufacturing, placing on the market and use of POPs.

Directive 2000/60/EC of the European Parliament and of the Council establishing a framework for Community action in the field of water policy classifies tetra-, penta-, hexa- and heptaBDEs as priority hazardous substances, for which discharges, emissions and losses must be ceased or phased out. In the Annex of Directive 2013/39/EU, environmental quality standards (EQS) are laid down for surface water and biota for the sum of **BDE-28**, -**47**, -**100**, -**153** and -**154**. The maximum allowable concentration (MAC-EQS) for inland surface waters (rivers, lakes and related artificial or heavily modified water bodies), and other surface waters are 0.14 µg/L and 0.014 µg/L, respectively. For fish, an EQS of 0.0085 ng/g is established.

With Commission Recommendation 2014/118/EU, the EU Commission recommended that Member States should perform monitoring on the presence of BFRs in food. Besides various other BFRs, the Recommendation also includes the PBDE congeners -**28**, -**47**, -**49**, -**99**, -**100**, -**138**, -**153**, -**154**, -**183** and -**209**. The aim of the monitoring is to include a wide variety of individual foodstuffs reflecting consumption habits to give an accurate estimation of exposure. Regarding PBDEs, it is recommended to analyse eggs and egg products, milk and dairy products, meat and meat products, animal and vegetable

[13]Council Regulation (EEC) No 315/93 of 8 February 1993 laying down Community procedures for contaminants in food. OJ L 37, 13.2.1993, p. 1.

[14]Commission Regulation (EU) No 2023/915 of 25 April 2023 on maximum levels for certain contaminants in food. OJ L 119/103, 5.5.2023, p. 103–157.

[15]Directive 2002/32/EC of the European Parliament and of the Council of 7 May 2002 on undesirable substances in food. OJ L 140, 30.2.2002, p. 10.

[16]https://echa.europa.eu/documents/10162/2082415/flame_retardants_strategy_en.pdf/

[17]https://chm.pops.int/TheConvention/Overview/TextoftheConvention/tabid/2232/Default.aspx

[18]Annex A of the Stockholm Convention includes chemicals for which parties must take measures to eliminate the production and use. Specific exemptions for use or production are listed and apply only to Parties that register for them.

fats and oils, fish and other seafood, products for specific nutritional uses and food for infants and small children, using analytical methods with a limit of quantification of 0.01 ng/g wet weight (ww) or lower.

2 | DATA AND METHODOLOGIES

The current updates of the EFSA risk assessments on BFRs, including this one on PBDEs, were developed applying a structured methodological approach, which implied developing a priori the protocol or strategy of the full risk assessments and performing each step of the risk assessment in line with the strategy and documenting the process. The protocol in Annex A of this Opinion contains the method that was proposed for all the steps of the risk assessment process, including any subsequent refinements/changes made.

The CONTAM Panel used its previous risk assessment on PBDEs in food (EFSA CONTAM Panel, 2011b) as a starting point for drafting the current Opinion.

The draft scientific Opinion underwent a public consultation from 8 June 2023 to 20 July 2023. The comments received were taken into account when finalising the scientific Opinion and are presented and addressed in Annex I.

2.1 | Supporting information for the assessment

Information on physicochemical properties, production and industrial use, environmental fate and levels, analytical methods, previous assessments and legislation was gathered from the previous EFSA Opinion on PBDEs (EFSA CONTAM Panel, 2011b), assessment by international bodies (by checking the original websites of the relevant organisations), and from current EU legislation. Literature searches were conducted to identify new information in reviews and other peer-reviewed publications. Details about the literature searches are given in Appendix C. The information was summarised in a narrative way based on expert knowledge and judgement.

2.2 | Hazard identification and characterisation

Information relevant for the sections under hazard identification and characterisation was identified by an outsourced literature search. EFSA outsourced a call for 'Identifying and collecting relevant literature related to the toxicity of polybrominated diphenyl ethers (PBDEs), Tetrabromobisphenol A (TBBPA) and brominated phenols'. The call was launched as a reopening competition for a specific contract under multiple framework contract CT/EFSA/AMU/2014/01 Lot 2. The technical University of Denmark (DTU) was awarded with the contract and a final project report was delivered in October 2019. The aim of the assignment was to identify and collect all relevant literature related to the toxicity of PBDEs (as well as TBBPA and BPs) to support the preparatory work for the hazard identification and characterisation steps in the human health risk assessment of these substances. Literature searches were designed and performed to retrieve all potentially relevant studies within the following four areas: Area 1: Data on toxicokinetics in experimental animals and humans and from *in vitro* studies, Area 2: Data on toxicity in experimental animals, Area 3: Data on *in vitro* and *in vivo* genotoxicity and mode of action, and Area 4: Data on observations in humans (including epidemiological studies, case reports, biomarkers of exposure). Details of the methodology and the results are reported in Bredsdorff et al. (2023).

The selection of the scientific papers for inclusion or exclusion was based on consideration of the extent to which the study was relevant to the assessment or on general study quality considerations (e.g. sufficient details on the methodology, performance and outcome of the study, on dosing, substance studied and route of administration and on statistical description of the results), irrespective of the results. Limitations in the information used are documented in this Scientific Opinion.

Benchmark dose (BMD) analysis was carried out according to the latest EFSA guidance (EFSA Scientific Committee, 2022). To perform the BMD modelling, EFSA used the Bayesian BMD Modelling web-app (https://zenodo.org/record/7334435#.Y5osYXbMLD4) available at the EFSA R4EU platform (https://efsa.openanalytics.eu/). All analyses were performed using Bridge sampling because of the higher level of accuracy with respect to Laplace approximation set as default (EFSA Scientific Committee, 2022; Hoeting et al., 1999; Morales et al., 2006). Extended dose range assumption was not applied in order to avoid confidence intervals falling outside of the dose range tested.

2.3 | Occurrence data submitted to EFSA

The general steps followed for the acquisition of the food occurrence and consumption data for the exposure assessment of BFRs are documented in Annex A. Specific details on the occurrence data on PBDEs in food submitted to EFSA are described below.

2.3.1 | Data collection and validation

Following an EC mandate to EFSA, a call for annual collection of chemical contaminant occurrence data in food and feed, including PBDEs, was issued by the former EFSA Dietary and Chemical Monitoring Unit (now Evidence Management Unit[19]) in December 2010[20] with a closing date of 1 October of each year. European national authorities and similar bodies, research institutions, academia, food business operators and other stakeholders were invited to submit analytical data on PBDEs in food.

The data submission to EFSA followed the requirements of the EFSA Guidance on Standard Sample Description (SSD) for Food and Feed (EFSA, 2010a). Occurrence data were managed following the EFSA standard operational procedures (SOPs) on 'Data collection and validation' and on 'Data analysis of food consumption and occurrence data'.

Data on PBDEs in food available in the EFSA database from 2010 until the end of December 2019 were used for the present assessment.

2.3.2 | Data analysis

Following EFSA's SOP on 'Data analysis of food consumption and occurrence data' to guarantee an appropriate quality of the data used in the exposure assessment, the initial dataset was carefully evaluated by applying several data cleaning and validation steps. Special attention was paid to the identification of duplicates and to the accuracy of different parameters, such as 'Sampling strategy', 'Analytical methods', 'Result express' (expression of results, e.g. fat weight), 'Reporting unit', 'Limit of detection/quantification' and the codification of analytical results under FoodEx classification (EFSA, 2011a, 2011b). The outcome of the data analysis is presented in **Section 3.2.1**.

The left-censored data (analytical data below the LOD or LOQ) were treated by the substitution method as recommended in the 'Principles and Methods for the Risk Assessment of Chemicals in Food' (WHO/IPCS, 2009). The same method is described in the EFSA scientific report 'Management of left-censored data in dietary exposure assessment of chemical substances' (EFSA, 2010b) as an option for the treatment of left-censored data. The guidance suggests that the LB and UB approach should be used for chemicals likely to be present in the food. At the LB, results below the LOQ or LOD were replaced by zero; at the UB, the results below the LOD were replaced by the numerical values of the LOD and those below the LOQ were replaced by the value reported as LOQ.

2.4 | Food consumption data

The EFSA Comprehensive European Food Consumption Database (Comprehensive Database) provides a compilation of existing national information on food consumption at individual level and was first built in 2010 (EFSA, 2011c; Huybrechts et al., 2011; Merten et al., 2011). Details on how the Comprehensive Database is used are published in the Guidance of EFSA (EFSA, 2011c). The latest version of the Comprehensive Database, updated in July 2021, contains results from a total of 75 different dietary surveys carried out in 25 different Member States covering 144,645 individuals.

Within the dietary studies, subjects are classified in different age classes as follows:

Infants[21]:	< 12 months old
Toddlers:	≥ 12 months to < 36 months old
Other children:	≥ 36 months to < 10 years old
Adolescents:	≥ 10 years to < 18 years old
Adults:	≥ 18 years to < 65 years old
Elderly:	≥ 65 years to < 75 years old
Very elderly:	≥ 75 years old

Nine surveys provided information on specific population groups: 'Pregnant women' (Austria: ≥ 19 years to ≤ 48 years old, Cyprus: ≥ 17 years to ≤ 43 years old; Latvia: ≥ 15 years to ≤ 45 years old, Romania: ≥ 19 years to ≤ 49 years old, Spain: ≥ 21 years to ≤ 46 years old, Portugal: 17 years old to 46 years old), 'Lactating women' (Greece: ≥ 28 years to ≤ 39 years old, Estonia: 18 years old to 45 years old) and 'Vegetarians' (Romania: ≥ 12 years to ≤ 74 years old).

For chronic exposure assessment, food consumption data were available from different dietary surveys carried out in 22 different EU Member States. When for one particular country and age class two different dietary surveys were available, only the most recent one was used. This resulted in a total of 47 dietary surveys selected to estimate chronic dietary exposure.

For the purpose of this Opinion and given that food consumption data on very young infants (0 to up to 3 months old) were scarce, a separate exposure scenario was done for them (see **Section 3.3.1**). Therefore, the food consumption data

[19]From 1 January 2014 onwards, Evidence Management Unit (DATA).

[20]http://www.efsa.europa.eu/en/consultations/call/190410

[21]For the purpose of this Opinion the age group of 'Infants' covers subjects from 3 to < 12 months of age.

available in the Comprehensive Database for this subgroup were not considered in the exposure estimates for the general population.

In Annex B (Table B.2), these dietary surveys and the number of subjects available for the chronic exposure assessment are described.

The food consumption data gathered by EFSA in the Comprehensive Database are the most complete and detailed data currently available in the EU. Consumption data were collected using single or repeated 24- or 48-h dietary recalls or dietary records covering from 3 to 7 days per subject. Because of the differences in the methods used for data collection, direct country-to-country comparisons can be misleading.

2.5 | Food classification

Consumption and occurrence data were classified according to the FoodEx2 classification system (EFSA, 2011a, 2011b). This system was developed with the aim of simplifying the linkage between occurrence and food consumption data when assessing the exposure to hazardous substances. Following its first publication, a testing phase was carried out in order to highlight strengths and weaknesses of the classification and to identify possible issues and needs for refinement. Based on the outcome of the testing phase, EFSA revised the system and in 2015 the second revision of the food classification and description system (FoodEx2 revision 2) was published (EFSA, 2015).[22]

The FoodEx2 catalogue hosts several hierarchies used for different data collections, e.g. 'Reporting hierarchy' for the collection of occurrence data and 'Exposure hierarchy' for the collection of food consumption data. It consists of a large number of individual food items aggregated into food groups and broader food categories in a hierarchical parent–child relationship. It contains 21 main food categories at the first level of the 'Exposure hierarchy', which are further divided into subcategories resulting in seven levels with more than 4000 items in total. In addition, FoodEx2 allows the further description of food items with facets. Facets are descriptors that provide additional information for a particular aspect of a food and are divided into two categories: implicit facets which are integrated in the catalogue, and explicit facets which are added by users while coding a food item.

The previous classification system (FoodEx) had only four levels and included about 1800 items, whereas FoodEx2 includes more than 4000 items in total allowing more precise linkage between occurrence and food consumption data.

2.6 | Exposure assessment

The CONTAM Panel considered that only chronic dietary exposure to PBDEs had to be assessed. As suggested by the EFSA Working Group on Food Consumption and Exposure (EFSA, 2011d), dietary surveys with only 1 day per subject were not considered for chronic exposure as they are not adequate to assess repeated exposure. Similarly, subjects who participated only 1 day in the dietary studies, when the protocol prescribed more reporting days per individual, were also excluded for the chronic exposure assessment. Not all countries provided consumption information for all age groups, and in some cases the same country provided more than one consumption survey.

For calculating the chronic dietary exposure to PBDEs, food consumption and body weight data at the individual level were accessed in the Comprehensive Database. Occurrence data and consumption data were linked at the relevant FoodEx level.

The mean and the high (95th percentile) chronic dietary exposures were calculated by combining mean occurrence values for each food collected in different countries (pooled European occurrence data) with the average daily consumption of each food at individual level in each dietary survey and age class. Consequently, individual average exposures per day and body weight were obtained for all individuals. Based on the distributions of individual exposures, the mean and 95th percentile exposures were calculated per survey and per age class. Dietary exposure was assessed using overall European LB and UB mean occurrence of PBDEs. All analyses were run using the SAS Statistical Software (SAS enterprise guide 8.2).

2.7 | Risk characterisation

The general principles of the risk characterisation for chemicals in food as described by WHO/IPCS (2009) will be applied as well as the different EFSA guidance documents relevant to this step of the risk assessment (see Annex A) and the EFSA guidance on uncertainty analysis in scientific assessments (EFSA Scientific Committee, 2018a, 2018b).

[22]Until 2018 occurrence data were submitted to EFSA using the first version of the FoodEx classification system (FoodEx1). A rigorous translation of those data to the most detailed food description available under the currently used classification FoodEx2 has been performed, based on both English and national language description'.

3 | ASSESSMENT

3.1 | Hazard identification and characterisation

3.1.1 | Toxicokinetics

This section provides an overview of the data on absorption, distribution, metabolism and excretion of PBDEs in animals and humans. It provides a summary of the studies considered in the previous EFSA Opinion (EFSA CONTAM Panel, 2011b), together with the new studies identified since then.

3.1.1.1 | *Toxicokinetic studies in experimental animals*

3.1.1.1.1 | *Absorption*

EFSA CONTAM Panel (2011b) described several toxicokinetic studies in rats and mice that addressed the absorption rate/bioavailability of **BDE-47**, -**99**, -**100**, -**154** and -**209**. These studies are summarised in Table 5.

Since the previous Opinion, one study on **BDE-209** has been identified. Mi, Bao, et al. (2017) performed a toxicokinetic study on female Sprague–Dawley rats dosed orally by gavage at 1 mg/kg bw of non-labelled **BDE-209** for 7 days. However, this study did not allow estimation of the oral bioavailability.

Following administration of ^{14}C-labelled PBDE congeners in lipophilic vehicles, the available studies (Table 5) indicate that the oral bioavailability is in the range 75%–90% for **BDE-47**, about 50% for **BDE-99**, about 73% for **BDE-100**, about 77% for **BDE-154** and 10%–26% for **BDE-209**. It seems that **BDE-209** is less absorbed compared to the other congeners. The CONTAM Panel noted, however, that in the study by Mörck et al. (2003), regarding **BDE-209** absorption, the value could be higher than 10%, since 65% of the dose excreted in faeces were **BDE-209** metabolites. Nevertheless, no clear trend in the oral bioavailability according to the bromination degree could be concluded.

TABLE 5 Summary of toxicokinetic studies on PBDEs addressing absorption rate/bioavailability (EFSA CONTAM Panel, 2011b).

PBDE congener	Dose(s) tested	Route of exposure	Bioavailability	Species	Reference
BDE-47	^{14}C-BDE-47 15 mg/kg bw	Oral	90%[a]	Mice, C51B1 (M)	Örn and Klasson-Wehler (1998)
	^{14}C-BDE-47 15 mg/kg bw	Oral	86%[a]	Rats, Sprague–Dawley (M)	Örn and Klasson-Wehler (1998)
	^{14}C-BDE-47 0.0, 0.1, 1.0, 10, 100 mg/kg bw	Oral / i.v.	80%[b]	Mice, C57BL/6J (F)	Staskal et al. (2005)
	^{14}C-BDE-47 1 µmol/kg bw (~0.5 mg/kg bw)	Oral/i.v.	75%[b]	Rats, F344 (M, F)	Sanders et al. (2006)
	^{14}C-BDE-47 1 µmol/kg bw	Oral/i.v.	85%[b]	Mice, B6C3F1 (M, F)	Sanders et al. (2006)
BDE-99	^{14}C-BDE-99 2.2 mg/kg bw	Oral	50%[a]	Rats, Sprague–Dawley (M)	Hakk et al. (2002)
BDE-100	^{14}C-BDE-100 7.7 mg/kg bw	Oral	73%[a]	Rats, Sprague–Dawley (M)	Hakk et al. (2006)
BDE-154	^{14}C-BDE-154 7.7 mg/kg bw	Oral	77%[a]	Rats, Sprague–Dawley (M)	Hakk et al. (2009)
BDE-209	^{14}C-BDE-209 2.8 mg/kg bw	Oral	10%[a]	Rats, Sprague–Dawley (M)	Mörck et al. (2003)[c]
	^{14}C-BDE-209 1.9 mg/kg bw	Oral/i.v.	26%[b]	Rats, Sprague–Dawley (M)	Sandholm et al. (2003)

Abbreviations: bw, body weight; F, female; M, male.

[a]These values estimated the % of absorption, based on the recovery rate after single oral exposure only.

[b]These values correspond to the bioavailability (comparison oral vs. i.v. route).

[c]According to the authors it cannot be excluded that more than 10% of the oral dose had been absorbed since 65% of the radioactivity excreted in faeces was metabolites.

3.1.1.1.2 | *Distribution*

EFSA CONTAM Panel (2011b) described several toxicokinetic studies in rats and mice that addressed the distribution of **BDE-47**, -85, -**99**, -**100**, -**153**, -**154** and -**209**. Since the previous EFSA assessment, new studies have been identified addressing the distribution of **BDE-47** (Costa et al., 2015) and -**209** (Feng et al., 2015; Mi, Bao, et al., 2017; Seyer et al., 2010; Wang et al., 2010; Wang, Wang, et al., 2011). These studies are summarised in Table 6. The CONTAM Panel noted that according to the distribution of radioactivity between organs, there were indications for selective distribution in the liver for **BDE-47** and -**209**.

TABLE 6 Summary of toxicokinetic studies on PBDEs addressing distribution.

PBDE congener	Dose(s) tested	Route of exposure	Tissues distribution	Species	Reference
BDE-47	^{14}C-BDE-47 15 mg/kg bw	Gavage	Adipose tissue = liver > kidney > lung. Trace in brain after 5 days[a]	Mice, C51B1	Örn and Klasson-Wehler (1998)
	^{14}C-BDE-47 15 mg/kg bw	Gavage	Adipose tissue > lung > kidney = liver > brain. After 5 days[a]	Rats, Sprague–Dawley	Örn and Klasson-Wehler (1998)
	^{14}C-BDE-47 0.0, 0.1, 1.0, 10, 100 mg/kg bw	Oral	Adipose tissue > skin > liver > muscle > lung > kidney > blood > brain. After 5 days[b]	Mice, C57BL/6J (F)	Staskal et al. (2005)
	^{14}C-BDE-47 2.1 µmol/kg	i.v.	Adipose tissue > muscle > skin > liver > blood > kidney > brain. After 5 days[b]	Mice, C57BL/6J (F)	Staskal et al. (2006)
	^{14}C-BDE-47 1 µmol/kg bw (~0.5 mg/kg bw)	Oral	Adipose tissue > liver > brain > adrenal > skin > thymus and kidney. After 5 days[b]	Rats, F344 (M, F)	Sanders et al. (2006)
	^{14}C-BDE-47 1 µmol/kg bw	Oral	Adipose tissue > muscle > liver > skin > blood > kidney = lung > brain. After 5 days[b]	Mice, B6C3F1 (M, F)	Sanders et al. (2006)
	BDE-47 0, 0.03, 0.1, 1 mg/kg bw	Oral exposure during gestation and until PND21	Adipose tissue > liver > brain > blood (in dams) at PND21[c]	Mice, C57BL/6J (F)	Ta et al. (2011)
	BDE-47 10 mg/kg bw	Oral	Liver > cerebellum > blood, 24 h after administration[a]	Mice, wt	Costa et al. (2015)
BDE-85	^{14}C-BDE-85 2.0 nmol/g bw	i.v.	Adipose tissue, liver (whole body autoradiography), at PND15[d]	Mice, C57BL	Darnerud and Risberg (2006)
BDE-99	^{14}C-BDE-99 2.2 mg/kg bw	Oral	Adipose tissue > kidney > lung > liver. At 72 h[b]	Rats, Sprague–Dawley (M)	Hakk et al. (2002)
	^{14}C-BDE-99 2.0 nmol/g bw	i.v.	Adipose tissue, liver (whole body autoradiography), at PND15[d]	Mice, C57BL	Darnerud and Risberg (2006)
	^{14}C-BDE-99 1.9 µmol/kg	i.v.	Adipose tissue > muscle > skin > liver > blood > kidney > brain. After 5 days[b]	Mice, C57BL/6J (F)	Staskal et al. (2006)
	^{14}C-BDE-99 1 µmol/kg bw	Oral	Adipose tissue > skin > muscle > liver > kidney. 24 h after a single oral dose[b]	Rats, Sprague–Dawley (M)	Chen et al. (2006)
BDE-100	^{14}C-BDE-100 7.7 mg/kg bw	Oral	Gastrointestinal tract > adipose tissue > kidney > lung > liver > heart. At 72 h[a]	Rats, Sprague–Dawley (M)	Hakk et al. (2006)
	^{14}C-BDE-100 1.9 µmol/kg bw	i.v.	Adipose tissue > muscle > skin > liver > blood > kidney > brain. After 5 days[b]	Mice, C57BL/6J (F)	Staskal et al. (2006)
BDE-153	^{14}C-BDE-153 1.8 µmol/kg bw	i.v.	Adipose tissue > muscle > skin> liver > blood > kidney > brain. After 5 days[b]	Mice, C57BL/6J (F)	Staskal et al. (2006)
BDE-154	^{14}C-BDE-154 7.7 mg/kg bw	Oral	Gastrointestinal tract > adipose tissue > kidneys > lung > liver > heart. At 72 h[a]	Rats, Sprague–Dawley (M)	Hakk et al. (2009)
BDE-209	^{14}C-BDE-209 2.8 mg/kg bw	Oral	Adipose tissue > adrenal > kidney > liver = lung > heart > thymus > small intestine. After 3 and 7 days[e]	Rats, Sprague–Dawley (M)	Mörck et al. (2003)
	^{14}C-BDE-209 20.1 mg/kg bw	Oral	Liver > brain > heart. At 7 days[b]	Mice	Viberg, Fredriksson, Jakobsson, et al. (2003)
	^{14}C-BDE-209 2 mg/kg bw	Oral, exposure during gestation (GD16 to GD19)	Adrenals > ovaries > liver > kidney > heart, small fraction in adipose tissue on GD20 0.5% of the dose retrieved in the fetus[a]	Rats, Wistar (pregnant F)	Riu et al. (2008)
	BDE-209 0.3 µg/g diet during 21 days	Oral	Liver > gastrointestinal tract > carcass > plasma at 21 days[a]	Rat, Sprague–Dawley (M)	Huwe and Smith (2007)
	2 mg/kg bw per day	Oral	Adrenal glands and ovary, at 4 days (by TOF-SIMS imaging)[d]	Wistar rats (F)	Seyer et al. (2010)
	100 mg/kg bw per day	Oral (gavage)	Liver > kidney > adipose tissue, at 90 days[e]	Sprague–Dawley (M)	Wang et al., (2010)
	0, 10, 50 mg/kg bw	Oral (gavage)	Liver > kidney > adipose tissue, at 90 days[e]	Sprague–Dawley (M)	Wang, Wang, et al. (2011)
	800 mg/kg bw	Oral (gavage)	Ovary/uterus > liver > lung > kidney > spleen > heart > brain, after 2 years[e]	C57BL/6 mice	Feng et al. (2015)
	1 mg/kg bw	Oral (gavage)	Liver and highly perfused tissues, at 7 days[a]	Sprague–Dawley (F)	Mi, Bao, et al. (2017)

Abbreviations: bw, body weight; F, female; M, male.

[a]Mean concentrations based on wet tissue weight.

[b]Percentage of the dose based on absolute amount of wet tissue weight.

[c]Mean concentration based on dry tissue weight.

[d]Detected but not quantified (qualitative technique).

[e]Mean concentration based on lipid weight.

Koenig et al. (2012) exposed female C57Bl/6J mice to 0.03, 0.1 and 1 mg/kg per day **BDE-47** from 4 weeks prior to breeding, throughout gestation and until postnatal day PND21. The authors reported tissue level at GD15, PND1, 10 and 21 in both dam (blood, fat, brain and milk) and pups (total body, brain and blood). The authors showed a substantial dose-related accumulation of **BDE-47** in dams and pup for all tissues measured, with a higher rate of accumulation in fat stores compared to brain and milk.

In addition to the studies with individual congeners, two studies on the technical product DE-71 have been identified.

Bondy et al. (2011) exposed male and female Sprague–Dawley rats by gavage to DE-71 (congener profile: 43% **BDE-47**, 43% **BDE-99**, 8% **BDE-100**, around 2% each **BDE-153**, **-154**, -85 and < 1% each **BDE-28** and **-183**) at 0, 0.5, 5 and 25 mg/kg bw per day for 21 weeks. Then, F0 rats were mated and exposure continued throughout breeding, pregnancy, lactation and postweaning until pups were PND42 (F1 generation). Adipose and liver tissues from the F0 and F1 were analysed, and milk was collected to assess the transfer during lactation. The authors showed that PBDEs distributed into adipose tissues, liver (for F0 and F1 generations) and were excreted via milk.

Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Rescio, et al. (2018) exposed female Wistar Han rats by gavage 5 days per week from GD6–PND21 to 0, 3, 15 and 50 mg DE-71/kg bw per day and their offspring were also dosed by direct gavage at the same dose levels from PND12–PND21 and for an additional period of 13 weeks. In the same study, the authors exposed B6C3F1/N mice by gavage for 2 years (5 days per week) to DE-71 at 0, 3, 30 and 100 mg/kg bw per day. The authors found **BDE-47**, **-99** and **-153** in different tissues, including liver, fat and plasma of male and female rats, and in liver and fat of male and female mice.

Maternal transfer

Several studies have been identified on the maternal transfer of individual congeners and technical products, and these are described below.

BDE-47

Koenig et al. (2012) showed that during lactation, a marked decrease in the levels of **BDE-47** in dam tissues occurs with a continuous transfer of the compounds from fat stores into milk. Results obtained in pups at the same ages showed a dose-related transfer level of **BDE-47** during gestation with levels still increasing during lactation, especially in the brain of pups.

Shin et al. (2017) investigated the placental and lactational transfer of **BDE-47** in rat dam-offspring pairs following repeated administration to pregnant Sprague–Dawley rats. The animals were sacrificed at GD14, PND0 or PND4. The authors measured the distribution of **BDE-47** during the gestation and lactation periods in maternal serum and whole body of the offspring. The concentrations of **BDE-47** in dam serum did not change significantly at GD14, PND0 and PND4, while the level of **BDE-47** increased in offspring.

BDE-209

Five studies have been identified on the maternal transfer of **BDE-209**.

Riu et al. (2008) administered ^{14}C-**BDE-209** to pregnant Wistar rats at 2 mg/kg bw per day during gestation (GD16 to GD19). The authors found that a small fraction of the dose (0.5%) was able to cross the placental barrier.

Biesemeier et al. (2010) administered non-labelled **BDE-209** (1, 10, 100, 300 or 1000 mg/kg bw per day) to female Sprague–Dawley rats from GD7 to PND4. The **BDE-209** concentrations in maternal or offspring blood collected on PND4 did not increase with increasing dose levels. This study did not show evidence of maternal transfer.

Cai et al. (2011) and Zhang, Cai, et al. (2011) administered **BDE-209** at 5 µmol/kg bw per day (4.8 mg/kg bw per day) to female Sprague–Dawley rats from GD7 to PND4. Rats were sacrificed at GD15 and GD21 and pups at PND4. The concentrations of **BDE-209** increased in the whole fetus during the gestational period, and during the lactation period **BDE-209** concentrations continued to increase in the pup whole bodies. The authors also detected **BDE-209** and its metabolites (debrominated congeners including BDE-196, -197, -198, -203, -204, -206, -207 and -208) in tissues of dams, fetal rats and pups (whole fetal/pup body) and suggested that **BDE-209** exposure and distribution could occur during the gestational and lactation periods (via placenta and breast milk).

Shin et al. (2017) also measured the distribution of **BDE-209** and its debrominated metabolites (**BDE-99**, **-153**, **-183**, -184, -196, -197, -206 and -207) during the gestation and lactation periods in maternal serum and whole body of the offspring. The authors found that **BDE-209** was increased in both maternal serum and whole body of the offspring. At GD14, PND0 and PND4, the level of **BDE-209** increased in both dam and offspring.

PBDE technical products

In the Bondy et al. (2011) study on DE-71, the authors found PBDEs in milk from F0 rats in the following order: **BDE-47** > **-99** > **-100** > **-153**. The authors showed that PBDEs were transferred from maternal tissues to milk during lactation.

Kozlova et al. (2021) investigated the effects of DE-71 on behaviour and neurochemical/endocrine profiles in C57Bl6/N mouse (See **Section 3.1.2.5** and Appendix E, Table E.6). Animals were treated by oral administration of 0, 0.1 and 0.4 mg/kg bw per day of DE-71 from 3 weeks prior to gestation through end of lactation. The authors measured individual PBDE

congeners in F1 female brain on a wet-weight basis at PND15, suggesting maternal transfer of PBDEs to offspring brain via gestation and lactation. The mean concentrations of total PBDEs (sum of BDE-7, -17, -30, -**47**, -85, -**99**, -**100**, -**138**, -139, -140, -**153**, -**154**, -**183** and -184) in brain at PND15 (F1 female) after exposure to DE-71 through the dam was 78 ng/g (ww basis) at 0.1 mg/kg bw per day DE-71, and 296 ng/g (ww basis) at 0.4 mg/kg bw per day DE-71. The authors reported that seven congeners (**BDE-47**, -85, -**99**, -**100**, -139, -**153**, -**154**) accounted for 98.5 and 98.7%, respectively in the low dose and high dose, of all PBDEs penetrating the brain during lactation. These seven congeners were reported to comprise 97.1% of the DE-71 administered.

Studies with several congeners

Ruis et al. (2019) exposed Wistar rats to **BDE-28**, **-47**, **-99**, **-100**, **-153** and **-209** from GD6 to GD15. The concentration ratios for **BDE-28**, -**47**, -**99** and -**153** (measured concentrations in the fetal side/ measured concentrations in the maternal side) ranged from 1.9 to 3.2. The authors found that PBDE concentrations in the fetus were lower (around 10- and 3-fold lower) compared to fetal and maternal side of the placenta.

Yu, Li, et al. (2021) studied the placental transfer of 10 PBDE congeners (**BDE-28**, **-47**, -66, -85**, -99, -100**, -**138**, **-153**, **-154**, **-183**) in Sprague–Dawley rats. The authors exposed female rats to a single dose of PBDEs[23] at GD14 or GD18 to investigate immature (GD14) and mature placenta (GD18) influence, and found that:

- at GD14, the concentration ratios between the fetus (umbilical cord serum) and maternal serum ranged between 0.14 to 0.54 for the different congeners.
- at GD18, the concentration ratios between the fetus (umbilical cord serum) and maternal serum ranged between 0.11 and 0.42.
- at GD14, the concentration ratios between placenta and maternal serum ranged between 0.46 to 0.73.
- at GD18, the concentration ratios between placenta and maternal serum ranged between 0.28 to 0.48.

The authors showed a transfer of BDE-66, **-138**, **-153**, **-154** and **-183** from mother to fetus, and concluded that this transfer was higher in immature placenta (GD14) than in mature placenta (GD18). For **BDE-28**, -85, **-99** and **-100** the transfer was similar in mature or immature placenta.

In summary, the available studies on the distribution of PBDEs in rodents indicate that **BDE-28**, **-47**, -66, -85, **-99**, **-100**, -**138**, **-153**, **-154**, **-183**, -196, -197, -206, -207 and **-209** are distributed in the lipid content of tissues and are predominantly accumulated in adipose tissues and in the liver. For **BDE-47** and **-209** there were indications for selective distribution in the liver.

BDE-47, -85, -**99**, -**100** and -**153** predominantly distributed in adipose tissues, while **BDE-209** predominantly distributed to highly perfused tissues (liver). However, no clear trend in the distibution according to the bromination degree could be concluded.

Studies showed that **BDE-28**, -47, -66, -85, -**99**, -**138**, -**153**, -**154**, -**100**, -**183** and -**209** and/or its metabolites (octa- and nonaBDEs) are maternally transferred to the offspring in utero. Maternal transfer to the offspring could also occur during lactation for **BDE-209** (Bondy et al., 2011; Kozlova et al., 2021; Shin et al., 2017; Zhang, Cai, et al., 2011).

3.1.1.1.3 | *Metabolism*

EFSA CONTAM Panel (2011b) described several toxicokinetic studies in rats and mice addressing the metabolism of **BDE-47**, -**99**, -**100**, -**153**, -**154** and -**209**. Since then, additional studies have been identified on **BDE-47** (Erratico et al., 2011; Zhai et al., 2014) and -**99** (Dong et al., 2010; Erratico et al., 2011). These studies are summarised in Table 7, indicating the metabolites and metabolic pathways identified for each congener as reported by the authors.

General mammalian metabolic pathways of **BDE-47**, -**154** and -**209** were presented in the previous EFSA Opinion and are shown in **Figures 6**, **7** and **8**, respectively, indicating the major metabolites formed:

- The metabolism of **BDE-47** has been described with first epoxidation, then formation of OH-metabolites, which can be followed by debromination.
- For **BDE-154**, a similar metabolic pathway has been suggested as for **BDE-47**.
- For **BDE-209**, the first step of metabolism is debromination, followed by hydroxylation to form phenols or catechols, potentially via an epoxide involving CYP enzymes. The catechols are then methylated, potentially by catechol-O-methyltransferases, to form the observed MeO-PBDEs.

It is anticipated that congeners with a similar degree of bromination to those used in these studies may behave in a similar way.

Most of the studies listed in Table 7 did not provide the percentage of OH-metabolite in relation to the parent compounds. Only Qiu et al. (2007) and Staskal et al. (2006) provided this information. Staskal et al. (2006) investigated the metabolism of **BDE-47, -99, -100, -153** in mice after single i.v. administration. The authors performed a metabolite analysis

[23]The dose administered to the animals is not clearly reported by the authors.

expressed as a percent daily-excreted dose. After 5 days, the percentage of OH-metabolites found in faeces was 50% for **BDE-47**, 25% for **BDE-99**, 22% for **BDE-100** and 39% for **BDE-153**. In another study, Qiu et al. (2007) exposed mice to DE-71 at 45 mg/kg (oral and s.c. route). The authors found that 4-OH-BDE-42 was the main metabolite of **BDE-47** and accounted for 56% of the total OH-tetraBDEs in mouse plasma, while 3-OH-BDE-47 and 4-OH-BDE-49 accounted for 16% and 13%, respectively.

Phase II metabolism was reported in two studies with **BDE-47** and **-99**. In rats treated by **BDE-47**, Sanders et al. (2006) identified two glutathione conjugates in the bile, and a glucuronide and a sulfate conjugate of 2,4-dibromophenol (2,4-DBP) were detected in urine. In rats treated with **BDE-99**, Chen et al. (2006) identified unconjugated 2,4,5-TBP in faeces and urine and glucuronide-, sulfate- and glutathionyl-conjugates of 2,4,5-TBP in bile and urine in conventional and bile duct cannulated male rats. These two studies provide evidence for cleavage of the ether bond, by the identification of conjugates of 2,4-DBP and 2,4,5-TBP.

di-OH PBDEs and PBDE quinones

Hydroxylation of PBDEs is a main metabolic pathway that has been described in rodents. Di-OH-PBDE metabolites have also been detected and could result from oxidation of OH-metabolites by cytochrome P450s.

Several authors reported the presence of di-OH metabolites in rodents (Chen et al., 2006; Hakk et al., 2002, 2006, 2009; Staskal et al., 2006) where the proposed pathway would be the formation of an arene oxide intermediate catalysed by cytochromes P450.

Chen et al. (2006) identified a di-OH-S-glutathionyl and tribromophenol (TBP) metabolite of **BDE-99**. The authors suggested that a first arene oxide intermediate metabolite could be metabolised by different pathways, such as:

- Formation of a mono-OH **BDE-99** followed by glucuronidation,
- The arene oxide could be metabolised by epoxide hydrolase and dihydrodiol dehydrogenase to form di-OH **BDE-99** metabolite,
- Reaction of the arene oxide with glutathione to form a di-OH-S-glutathionyl metabolite,
- Metabolic cleavage of the ether bond in **BDE-99** to form 2,4,5-TBP followed by glucuronide and sulfate conjugation.

Sanders et al. (2006) detected a glucuronide and a sulfate conjugate of 2,4-DBP in rat urine (but not in mice). The mechanism proposed by the authors was the cleavage of **BDE-47**, and from an arene oxide intermediate, the formation of a diol following addition of H_2O. The final metabolite resulting from this pathway would be 2,4-DBP.

Lai, Lu, Gao, et al. (2011) suggested that OH-PBDE metabolites can be further metabolised to form di-OH-PBDEs and be further oxidised to PBDE-quinones.[24] The authors incubated three OH-PBDEs (6′-OH-BDE-17, 3′-OH-BDE-7 and 6-OH-BDE-47) with rat liver microsomes. Four di-hydroxy metabolites of 6′-OH-BDE-17 were detected but the structures of these metabolites were not reported, and no information was provided for di-hydroxy metabolites of 3′-OH-BDE-7 and 6-OH-BDE-47. When the di-hydroxy metabolites of 6′-OH-BDE-17 were further incubated with deoxyguanosine, horseradish peroxidase and H_2O_2, analysis by UPLC-ESI-MS/MS revealed the presence of deoxyguanosine adducts (see **Section 3.1.2.6**). Since the authors also found that incubation of synthetic PBDE-quinones[25] with calf thymus DNA under the same conditions resulted in formation of DNA adducts, they attributed the deoxyguanosine adducts observed with the PBDE metabolites to the formation of PBDE-quinones. However, formation of PBDE-quinones has not been demonstrated either *in vitro* or *in vivo*.

In summary, the available studies in rodents indicate that metabolism of PBDEs involves debromination and an oxidative pathway that results in the formation of OH-metabolites. Differences in metabolism were observed between congeners. While **BDE-47** and **-154** were reported to be metabolised by an oxidative pathway followed by debromination, **BDE-209** was first metabolised by debromination followed by an oxidative pathway. The relative abundance of OH-metabolite compared to the parent compound is not well established.

Phase II metabolism was also detected in rats with two glutathione conjugates and a glucuronide and sulfate conjugate of 2,4-DBP and 2,4,5-TBP in the bile and urine, respectively, also providing evidence for cleavage of the ether bond.

[24]In general, catechols contain two OH- groups *ortho* to each other, whereas in hydroquinones the two OH- groups are para to each other. Upon oxidation they can form *ortho*- or *para*-quinones.

[25]2-(2′,4′-Bromophenoxyl)-benzoquinone, 2-Phenoxyl-6-bromo-benzoquinone, 2-(2′-Bromophenoxyl)-6-bromo-benzoquinone, 2-(2′,4′-Bromophenoxyl)-6-bromo-benzoquinone, 2-(2′,4′,6′-Bromophenoxyl)-6-bromo-benzoquinone.

TABLE 7 Summary of toxicokinetic studies on PBDEs addressing metabolism.

PBDE congeners	Doses tested	Route of exposure	Metabolites	Metabolic pathways	Species	Reference
BDE-47	^{14}C-BDE-47 30 µmol/kg bw	Gavage	Six OH-tetraBDEs and three OH-triBDEs identified in faeces	CYP450 mediated (suspected)	Rats	Marsh et al. (2006)
	^{14}C-BDE-47 15 mg/kg bw	Gavage	OH-metabolites. No structural identification	–	Mice, C51B1	Örn and Klasson-Wehler (1998)
	^{14}C-BDE-47 15 mg/kg bw	Gavage	OH-metabolites. No structural identification	–	Rats, Sprague–Dawley	Örn and Klasson-Wehler (1998)
	^{14}C-BDE-47 2.1 µmol/kg bw	i.v.	3 mono-OH-metabolites (only faecal metabolites reported by the authors)	Debromination and oxidative pathways	Mice, C57BL/6J (F)	Staskal et al. (2006)
	^{14}C-BDE-47 1 µmol/kg bw (approx 0.5 mg/kg bw)	Oral	Glucuronide and sulfate conjugate of 2,4-DBP	–	Rats, F344 rats (M, F)	Sanders et al. (2006)
	BDE-47 2 mM	*In vitro*	6-OH-BDE-47, 5-OH-BDE-47, 3-OH-BDE-47 and debrominated metabolites (BDE-17, -**28**)	Debromination and CYP2B1, 2A2 and 1A1 mediated oxidation	Rat liver microsomes and rat CYP isoforms incubation	Zhai et al. (2014)
	BDE-47 50 µM	*In vitro*	4-OH-BDE-42, 3-OH-BDE-47, 5-OH-BDE-47, 6-OH-BDE-47	CYP3A1 and CYP1A1	Rat liver microsomes (from phenobarbital-, dexamethasone- and 3-methylcholanthrene-treated rats)	Erratico et al. (2011)
BDE-99	^{14}C-BDE-99 2.2 mg/kg bw	Oral	OH-tetraBDEs, presence of thiol metabolites in bile	Debromination and oxidative pathways	Rats, Sprague–Dawley (M)	Hakk et al. (2002)
	^{14}C-BDE-99 1 µmol/kg bw	Oral	In bile: Two di-OH-S-glutathionyl and two S-glutathionyl conjugates of **BDE-99**, 2,4,5-TBP glucuronide, two mono-OH-BDE-99 glucuronides and three mono-OH-tetraBDE glucuronides. In urine: 2,4,5-TBP and its glucuronide and sulfate conjugates. In faeces: 2,4,5-TBP, one mono-OH-tetraBDE and two mono-OH-BDE-99.	Debromination and oxidative pathways	Rats, F344 (M)	Chen et al. (2006)
	^{14}C-BDE-99 1.9 µmol/kg	i.v.	Four mono-OH, two mono-OH/debrominated and a single di-OH metabolite (only faecal metabolites reported by the authors)	Debromination and oxidative pathways	Mice, C57BL/6J (F)	Staskal et al. (2006)
	BDE-99 10 µM	*In vitro*	Debrominated metabolite (**BDE-47**) and 2,4,5-TBP, 5-OH-BDE-47, 5′-OH-BDE-99	Debromination and CYP3A4 and CYP1A2 mediated	Rat primary hepatocytes	Dong et al. (2010)
	BDE-99 100 µM	*In vitro*	4′-OH-BDE-49, 4-OH-BDE-90, 6′-OH-BDE-99	Debromination and CYP3A1 and CYP1A1 mediated oxidation	Rat liver microsomes (from phenobarbital-, dexamethasone- and 3-methylcholanthrene-treated rats)	Erratico et al. (2011)

(Continues)

TABLE 7 (Continued)

PBDE congeners	Doses tested	Route of exposure	Metabolites	Metabolic pathways	Species	Reference
BDE-100	^{14}C-BDE-100 7.7 mg/kg bw	oral	Mono-OH and di-OH metabolites	Debromination and oxidative pathways	Rats, Sprague–Dawley (M)	Hakk et al. (2006)
	^{14}C-BDE-100 1.9 μmol/kg	i.v.	Three mono-OH, mono-OH/debrominated and a single di-OH/dibrominated metabolite (only faecal metabolites reported by the authors)	Debromination and oxidative pathways	Mice, C57BL/6J (F)	Staskal et al. (2006)
BDE-153	^{14}C-BDE-153 1.8 μmol/kg	i.v.	Three mono-OH, two mono-OH/debrominated and one mono-OH/di-debrominated metabolite (only faecal metabolites reported by the authors)	Debromination and oxidative pathways	Mice, C57BL/6J (F)	Staskal et al. (2006)
BDE-154	^{14}C-BDE-154 7.7 mg/kg bw	Oral	Mono-OH and di-OH metabolites	Debromination and oxidative pathways	Rats, Sprague–Dawley (M)	Hakk et al. (2009)
BDE-209	^{14}C-BDE-209 2.8 mg/kg bw	Oral	Debrominated and OH-metabolite	Debromination and oxidative pathways	Rats, Sprague–Dawley (M)	Mörck et al. (2003)
	^{14}C-BDE-209 1.9 mg/kg bw	Oral and i.v.	Debrominated and OH-metabolite	Oxidative debromination	Rats, Sprague–Dawley (M)	Sandholm et al. (2003)
	0.3 μg/g of diet for 21 days	Oral	Debrominated metabolites formation of BDE-197 and -207	Debromination	Rats, Sprague–Dawley	Huwe and Smith (2007)
	^{14}C-BDE-209 2 mg/kg bw	Oral, exposure during gestation (GD16 to GD19)	Octa- and nonaBDEs, OH-octaBDE	–	Rats, Wistar	Riu et al. (2008)

Abbreviations: bw, body weight; F, female; M, male; 2,4-DBP, 2,4-dibromophenol; 2,4,5-TBP, 2,4,5-tribromophenol.

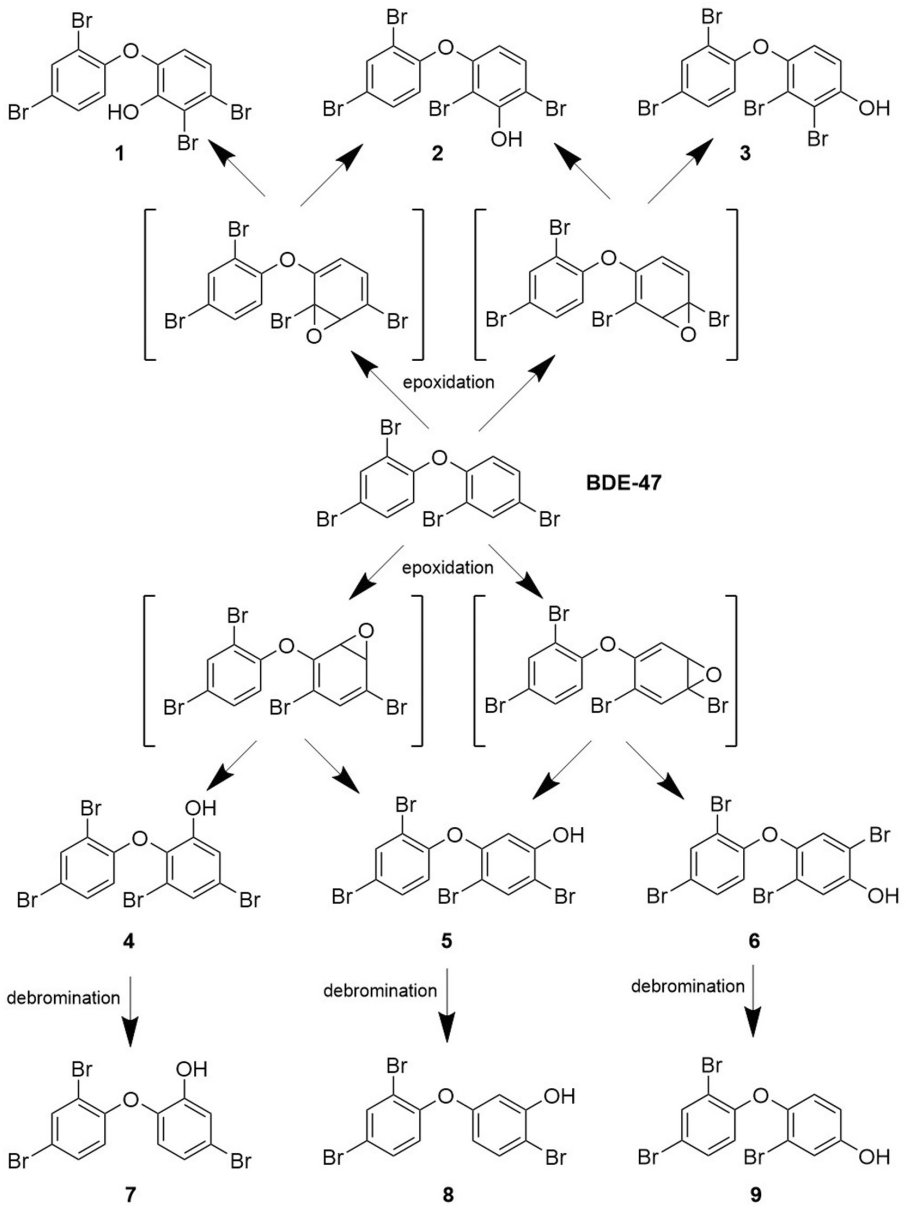

FIGURE 6 Suggested general mammalian metabolic pathway of **BDE-47** based on Marsh et al. (2006). Four postulated **BDE-47** epoxide intermediates lead to formation of six OH-tetraBDE metabolites ((1) to (6)). Each OH-tetraBDE may undergo debromination to form the three OH-triBDE metabolites ((7) to (9)). *Note:* **(1)** 6-OH-2,2′,4,4′-tetraBDE, **(2)** 5-OH-2,2′,4,4′-tetraBDE, **(3)** 4-OH-2,2′,3,4′-tetraBDE, **(4)** 2′-OH-2,3′,4,4′-tetraBDE, **(5)** 3′-OH-2,2′,4,4′-tetraBDE, **(6)** 4′-OH-2,2′,4,5′-tetraBDE, **(7)** 2′-OH-2,4,4′-triBDE, **(8)** 3′-OH-2,4,4′-triBDE, **(9)** 4′-OH-2,2′,4-triBDE.

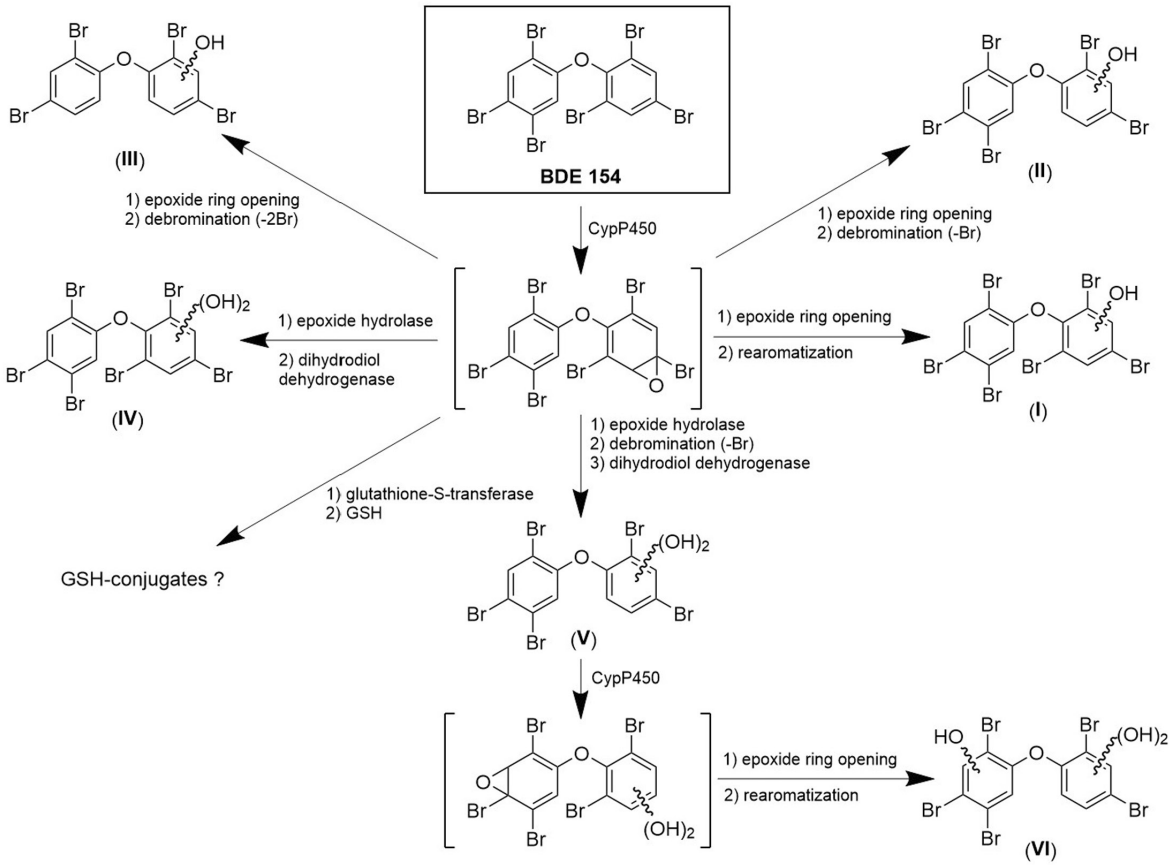

FIGURE 7 Suggested metabolic pathway of **BDE-154** in male rats based on characterisation of metabolites in faecal extracts (reproduced from Hakk et al., 2009) © Taylor and Francis Online. **(I)** mono-OH-hexaBDE (five isomers), **(II)** mono-OH-pentaBDE (four isomers), **(III)** mono-OH-tetraBDE (two isomers), **(IV)** di-OH-hexaBDE (one isomer), **(V)** di-OH-pentaBDE (two isomers), **(VI)** tri-OH-pentaBDE (one isomer).

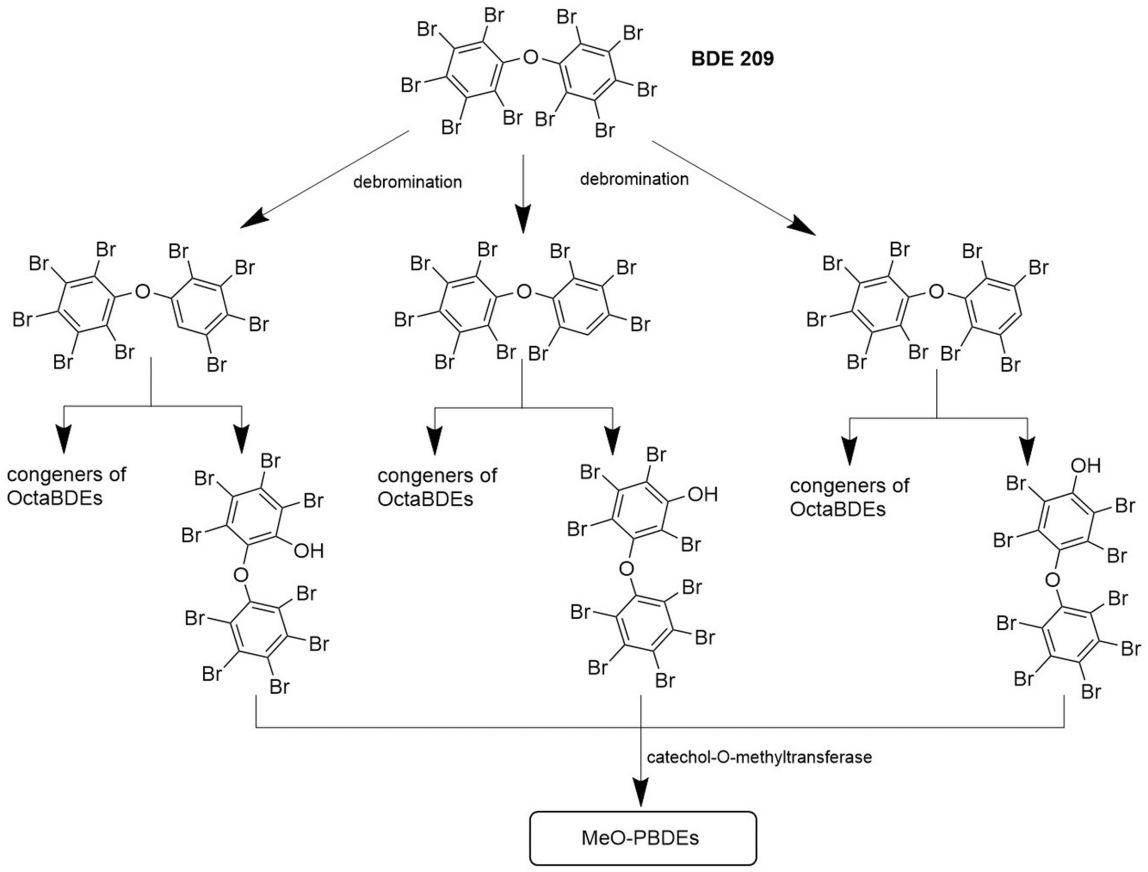

FIGURE 8 Suggested general mammalian metabolic pathway of **BDE-209**. Debromination of BDE-209 is a prerequisite for the formation of OH-nonaBDE metabolites (from EFSA CONTAM Panel, 2011b).

3.1.1.1.4 | *Excretion*

EFSA CONTAM Panel (2011b) described several toxicokinetic studies in rats and mice that addressed the excretion of **BDE-47**, **-99**, **-100**, **-153**, **-154** and **-209**. Since the previous EFSA assessment, one new study has been identified regarding the excretion of **BDE-47** (Xu et al., 2019). These studies are summarised in Table 8.

TABLE 8 Summary of toxicokinetic studies on PBDEs addressing excretion.

PBDE congeners	Doses tested	Route of exposure	Excretion route	% of retention/ half life	Species	Reference
BDE-47	^{14}C-BDE-47 15 mg/kg bw	Gavage	20% of the dose excreted in faeces and 33% via urine	80% of the dose was retained after 5 days	Mice, C51B1	Örn and Klasson-Wehler (1998)
	^{14}C-BDE-47 15 mg/kg bw	Gavage	14% of the dose excreted in faeces	86% of the dose was retained after 5 days	Rats, Sprague–Dawley	Örn and Klasson-Wehler (1998)
	^{14}C-BDE-47 0.0, 0.1, 1.0, 10, 100 mg/kg	Oral	37% of the dose excreted in faeces and 42% in urine at 5 days	Terminal half-life = 23 days[b]	Mice, C57BL/6J (F)	Staskal et al. (2005)[a]
	^{14}C-BDE-47 2.1 µmol/kg	i.v.	40% of the dose excreted in the urine at 5 days, 32% excreted in faeces	No information	Mice, C57BL/6J (F)	Staskal et al. (2006)
	^{14}C-BDE-47 1 µmol/kg bw (approx 0.5 mg/kg bw)	Oral	20% (for F) and 30% (for M) of the dose excreted in faeces and 1% in urine over 24 h	No information	Rats, F344 (M, F)	Sanders et al. (2006)
	^{14}C-BDE-47 1 µmol/kg bw	Oral	20% (for F) and 30% (for M) of the dose excreted in urine and 25% (for F) and 20% (for male in faeces over 24 h	No information	Mice, B6C3F1 (M, F)	Sanders et al. (2006)
	1.5, 10, 30 mg/kg bw	Oral	Urine (59%–70%) and faeces (24%–32%), after 6 weeks	No information	C57BL/6J	Xu et al. (2019)
BDE-99	^{14}C-BDE-99 2.2 mg/kg bw	Oral	< 1% of the dose excreted in urine, 43% excreted in faeces at 3 days	Terminal half-life = 6 days[b]	Rats, Sprague–Dawley (M)	Hakk et al. (2002)
	^{14}C-BDE-99 1 µmol/kg bw	Oral and i.v.	43%–46% of the dose excreted in faeces, 2% excreted in urine, at 24 h following oral route	No information	Rats, F344 (M, F)	Chen et al. (2006)
	^{14}C-BDE-99 1 µmol/kg bw	Oral and i.v.	27%–32% of the dose excreted in faeces, 4.1–7.8% excreted in urine, at 24 h following oral route	No information	Mice, B6C3F1 (M, F)	Chen et al. (2006)
	^{14}C-BDE-99 1.9 µmol/kg	i.v.	16% of the dose excreted in urine, 21% of the dose excreted in faeces at 5 days	No information	Mice, C57BL/6J (F)	Staskal et al. (2006)
BDE-100	^{14}C-BDE-100 7.7 mg/kg bw	Oral	< 1% of the dose excreted in urine, 20% excreted in faeces at 72 h	No information	Rats, Sprague–Dawley (M)	Hakk et al. (2006)
	^{14}C-BDE-100 1.9 µmol/kg	i.v.	6% of the dose excreted in urine, 13% excreted in faeces at 5 days	No information	Mice, C57BL/6J F)	Staskal et al. (2006)
BDE-153	^{14}C-BDE-153 1.8 µmol/kg	i.v.	1% of the dose excreted in urine, 18% excreted in faeces at 5 days	No information	Mice, C57BL/6J F)	Staskal et al. (2006)
BDE-154	^{14}C-BDE-154 7.7 mg/kg bw	Oral	< 1% of the dose excreted in urine, 62% excreted in faeces at 72 h	No information	Rats, Sprague–Dawley (M)	Hakk et al. (2009)
BDE-209	^{14}C-BDE-209 2.8 mg/kg bw	Oral	90% of the dose excreted in faeces after 3 days (with 10% into the bile)	No information	Rats, Sprague–Dawley (M)	Mörck et al. (2003)[a]
	^{14}C-BDE-209 1.9 mg/kg bw	Oral and i.v.	Not reported	Terminal half-life = 2.5 days[b]	Rats, Sprague–Dawley (M)	Sandholm et al. (2003)
	BDE-209 0.3 µg/g diet	Oral	Not studied	Initial half-life = 3.9 days Terminal half-life = 75.9 days[b]	Rats	Huwe and Smith (2007)
	^{14}C-BDE-209 2 mg/kg bw	Oral, exposure during gestation (GD16 to GD19)	30% of the dose excreted in urine at 4 days, 70% excreted in the faeces	–	Rats, Wistar (F pregnant)	Riu et al. (2008)

Abbreviations: bw, body weight; F, female; M, male.

[a]Dose dependency in excretion via this route of elimination.

[b]Some toxicokinetic studies present different half-lives. In the case of monophasic curve decay, only one half-life is reported. In the case of biphasic decay curve, this leads to calculation of initial half-life or alpha phase and terminal half-life or beta phase This latter is referred to elimination half-life. In this Opinion, the CONTAM Panel decided to present, when reported, the more relevant half-life for the risk assessment, e.g. the terminal half-life.

The available rodent studies indicate that in rats, **BDE-99**, **-100**, **-153**, **-154** and **-209** are mainly excreted in the faeces. A different excretion pattern has been observed in mice, where urinary excretion is the principal route of excretion for **BDE-47** and **-99**.

3.1.1.1.5 | *Summary on toxicokinetic studies in rodents*

Oral absorption rates and/or bioavailabilities of PBDEs have been studied in rats and mice. For **BDE-47**, **-99**, **-100**, **-154** and **-209**, bioavailability of 75%–90%, 50%, 73%, 77% and 10%–26% have been reported, respectively. It seems that **BDE-209** is less efficiently absorbed compared to the other congeners (10%–26% in rat), nevertheless no clear trend in the oral bioavailability according to the bromination degree could be concluded.

Differences in distribution were observed between congeners: **BDE-47**, -85, **-99**, **-100** and **-153** are predominantly distributed to adipose tissues, whereas **BDE-209** is predominantly distributed to highly perfused tissues (e.g. liver).

After repeated oral administration of PBDEs in rats and mice, accumulation in the body was reported mainly in adipose tissue and liver. The reported (terminal) half-lives ranged from 2.5 to 75.9 days.

Maternal transfer of PBDEs has been demonstrated in female rats. **BDE-209** concentrations in blood in fetuses and neonates increased with duration of exposure (GD7 to PND4). Other PBDE congeners were also detected in whole-bodies of fetuses and neonates at lower concentrations than **BDE-209**. Studies showed that **BDE-47** and **-209** and/or its debrominated metabolites (octa- and nonaBDEs) are maternally transferred to the offspring in utero and via lactation. Similar results were found for **BDE-28**, -66, -85, **-99**, **-100**, **-138**, **-153**, **-154** and **-183**.

The principal metabolic pathways of PBDEs are oxidative pathway and debromination leading to the formation of OH-metabolites from the parent compound but also to debrominated congeners. Studies have shown the involvement of phase II enzyme in the metabolism of PBDEs: glucuronide- and sulfate conjugates of 2,4-DBP have been detected in rats exposed to **BDE-47**, as well unconjugated 2,4,5-TBP, glucuronide-, sulfate- and glutathionyl-conjugates of 2,4,5-TBP in rat exposed to **BDE-99**. These findings provide evidence for cleavage of the ether bond.

In rats, PBDEs are mainly excreted in the faeces, whereas urinary excretion is the principal route for mice.

3.1.1.2 | *Toxicokinetic studies in humans*

3.1.1.2.1 | *Absorption*

Quantitative data on the absorption of PBDEs in humans were only identified for **BDE-209**. Zhang, Hu, et al. (2022) reported an oral absorption in humans of 0.286 predicted by a PBK model (see **Section 3.1.1.5**).

3.1.1.2.2 | *Distribution*

Limited data are available on the distribution of PBDEs in humans.

Some studies have demonstrated the transfer of PBDEs from the mother to the infant during pregnancy and breastfeeding (see **Section 3.1.1.4**).

Darnerud et al. (2015) analysed the concentrations of **BDE-28**, **-47**, -66, **-99**, **-100**, **-138**, **-153**, **-154**, **-183** and **-209** in 30 paired samples of blood serum and mother's milk samples, and found a ratio maternal serum/milk for lipid-based levels that ranged from 0.83 to 17, with the highest ratio for **BDE-209**.

Ruis et al. (2019) analysed PBDE concentrations in human placenta ($n = 10$). The placental tissue was sampled in two parts; fetal and maternal side. The concentration ratios for **BDE-28**, **-47**, **-99** and **-153** (measured concentrations in the fetal side/measured concentrations in the maternal side based on wet tissue weight) ranged from 1.2 to 5.5, indicating that PBDEs accumulate on the fetal side of the placenta.

Yu, Li, et al. (2021) collected 32 paired human samples of maternal serum, umbilical cord serum and placentas. The authors measured the concentrations based on lipid weight of 12 PBDE congeners (BDE-17, **-28, -47**, -66, **-**85, **-99**, **-100, -138, -153, -154, -183**, -190) in placenta, maternal serum and umbilical cord serum samples. The authors found a significant linear relationship ($p = 0.01$) between umbilical cord serum and maternal serum for the total concentrations of PBDEs, with a linear slope of 0.46 ($R^2 = 0.33$). The authors calculated the umbilical cord-maternal serum median concentrations ratios for only three congeners with values of 0.54, 1.0 and 0.62 for **BDE-28**, **-47** and **-153**, respectively (see **Section 3.1.1.4.5** on correlation between different human tissues).

The same authors, in a recent review examined the ratios for fetal cord serum to maternal serum concentration for **BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**, **-183** and **-209** (Zhang, Cheng, et al., 2021). Based on different studies, the authors reported an average ratio (lipid-based) ranging between 0.76 and 1.67. The authors also reported that 6-OH-BDE-47 and 5-OH-BDE-47 were found at higher concentrations in the fetus than in maternal serum, and that they cross the placenta more efficiently than the parent compounds (see **Section 3.1.1.4**).

Kim et al. (2021) reported a method based on multiple linear regression analysis to predict the feto-maternal ratio from 20 pairs of maternal and cord blood. For **BDE-28**, **-47**, **-99**, **-100** and **-153**, the results suggested that the feto-maternal ratio (lipid-adjusted) ranged between 0.34 and 2.3.

Chen, Liu, et al. (2014) analysed the concentrations of 17 PBDE congeners (BDE-17, -**28**, -**47**, -85, -**99**, -**100**, -**138**, -**153**, -**154**, -**183**, -184, -191, -196, -197, -206, -207, -**209**), in placenta, human milk, fetal cord blood and neonatal urine in 30 paired samples collected in China. The mean concentrations for the sum of the 17 congeners were 13.3 ng/g lipid in placenta, 11.4 ng/g lipid in breast milk, 9.92 ng/g lipid in cord blood and 1.30 ng/mL in neonatal urine. The median ratio between fetal cord blood and maternal placenta for the sum of the 17 PBDEs was 0.73 in 30 mother–fetal pairs. When individual congeners were analysed, the authors observed differences in placenta transfer, with an increasing transfer associated with an increasing degree of bromination. The ratios for BDE-196 and -197 were 5.49 and 4.49, respectively whereas it was 1.13 for **BDE-47**.

3.1.1.2.3 | *Metabolism*

The previous EFSA Opinion described two studies which identified metabolites of **BDE-47**, -**99** and -**209**. Briefly, Lupton et al. (2009) incubated **BDE-47** and **-99** with human liver microsomes and reported the formation of di-OH-BDE-47, 2,4-DBP, di-OH-BDE-99 and 2,4,5-TBP. The authors suggested as a first step the formation of di-OH metabolites from **BDE-47 and -99** of an arene oxide by CYPs. The authors did not characterise the specific location (*ortho-/para-*) of the two hydroxyl groups, and consequently the formation of intermediate reactive metabolites (e.g. quinones) was not described.

Stapleton et al. (2009) identified several metabolites of **BDE-99** after incubation for 72 h with human liver microsomes: 2,4,5-TBP, two mono-OH-pentaBDE and a tetrabrominated metabolite (unidentified). The same authors also incubated **BDE-209**, however, specific metabolites were not identified.

Since then, several *in vitro* studies have been identified on the metabolism of **BDE-47**, -**99** and -**100**. In addition, studies on the analysis of OH-, MeO-PBDEs and bromophenols in human tissues have been performed, and these are discussed in **Section 3.1.1.4.5**.

BDE-47

Erratico et al. (2013) incubated **BDE-47** with human liver microsomes and described the formation of nine metabolites (including seven identified metabolites, namely 2,4-DBP, 4′-OH-BDE-17, 2′-OH-BDE-28, 4-OH-BDE-42, 5-OH-BDE-47, 6-OH-BDE-47 and 4′-OH-BDE-49, and two unknown ones). The authors reported that CYP2B6 was the most active human P450 enzyme in the formation of OH-metabolites. In addition, the same authors investigated the Phase-II metabolism of OH-metabolites of **BDE-47** and found that all OH-metabolites were glucuronidated and sulfated, the major ones being 2,4-DBP-Gluc and 5-Gluc-BDE-47, and 2′-Sulf-BDE-28, 4-Sulf-BDE-42 and 3-Sulf-BDE-47, respectively (Erratico et al., 2015).

The study from Feo et al. (2013) supported the role of CYP2B6 in the metabolism of **BDE-47**. The authors incubated **BDE-47** with recombinant human CYPs (CYP1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4) and found that CYP2B6 was capable of forming six OH-metabolites (3-OH-BDE-47, 5-OH-BDE-47, 6-OH-BDE-47, 4-OH-BDE-42, 4′-OH-BDE-49 and a metabolite tentatively identified as 2′-OH-BDE-66). In addition, on the basis of the GC–MS analysis, the authors hypothesised the formation of two other metabolites (a di-OH-tetraBDE and a di-OH-tetrabrominated dioxin).

BDE-99

Erratico et al. (2012, 2015) observed a similar metabolism for **BDE-99** as described for **BDE-47** above. The authors described that CYP2B6 was responsible for the formation of 10 OH-metabolites (including six identified metabolites, namely 2,4,5-TBP, 4-OH-BDE-90, 5′-OH-BDE-99, 6′-OH-BDE-99, 4-OH-BDE-101, and 2-OH-BDE-123, and 3 unknown metabolites). The authors also found that all OH-metabolites were glucuronidated or sulfated, the major ones in this case being 2,4,5-TBP-Gluc, 60-Gluc-BDE-99, and 3′-Sulf-BDE-99 and 5′-Sulf-BDE-99, respectively.

BDE-100

Gross et al. (2015) investigated the *in vitro* metabolism of **BDE-100** in human liver microsomes and/or recombinant human P450 (CYPs 1A1, 1A2, 2A6, 3A4, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E). Of these 10 CYPs, only CYP1A1, 3A4, 2B6 and 2C19 displayed a catalytic activity in the formation of OH-BDE-100 metabolites. The authors stated that mainly CYP2B6 was found to biotransform **BDE-100**, resulting in eight metabolites: six mono-OH pentaBDEs (four identified via reference standards: 3-OH-BDE-100, 5′-OH-BDE-100, 6′-OH-BDE-100, 4′-OH-BDE-103 and two hypothesised based on the mass spectral fragmentation patters: 2′-OH-BDE-119, 4-OH-BDE-91), two di-OH pentaBDE metabolites (not identified) and one mono-OH tetraBDE (6-OH-BDE-47).

Studies with several congeners

Butryn et al. (2020) assessed the partitioning profiles of PBDEs and OH-PBDEs in 48 paired human milk and serum samples (see **Section 3.1.1.4.4**) and evaluated the relationship between variants in CYP2B6 genotype and PBDE accumulation in humans. The authors showed that the retention of **BDE-47** and -85 in serum was higher in individuals carriers of the

variant genotype CYP2B6*6 (leading to a reduced CYP2B6 activity) compared to individual carriers of the wild type genotype. Similar observations were made in human milk for **BDE-28**, -**47**, -**85** and -**100**.

OH-BDEs

Ho et al. (2015) detected 17 PBDEs, 22 OH-PBDEs, 13 MeO-PBDEs and 3 bromophenols in human urine ($n = 100$) collected from 100 volunteers from Hong Kong (see **Section 3.1.1.4.5** and Appendix D). The authors also detected the presence of glucuronide and sulfate conjugates of 2,4-DBP and 2,4,6-TBP in the range of 0.08–106.5 µg/g creatinine.

Cisneros et al. (2019) studied the *in vitro* human hepatic phase II metabolism (glucuronidation and sulfation) of four metabolites of OH-BDEs (6-OH-BDE-47, 2-OH- and 4-OH-BDE-68, and 2-OH-6'-MeO-BDE-68) using liver microsomes and cytosols, respectively; sulfation was also investigated with recombinant human SULT1A1, 1B1, 1E1 and 2A1 enzymes. The authors found that all the OH-BDE metabolites studied were more efficiently conjugated to glucuronides than to sulfates.

3.1.1.2.4 | *Excretion*

Limited data are available on the excretion of PBDEs in humans.

Based on serum concentrations of PBDEs in Swedish workers, Jakobsson et al. (2003) calculated half-lives for octaBDEs (ranging from 37 to 84 days), for **BDE-183** (about 111 days), for **BDE-153** (about 671 days) and for **BDE-154** (about 271 days).

Thuresson et al. (2006) estimated apparent half-lives of eight PBDE congeners (**BDE-183**, -196, -197, -201, -203, -206, -207, -208, -**209**) from blood of exposed rubber workers and electronics dismantlers (based on studies by Jakobsson et al. (2003) and Sjödin et al. (1999)). The blood samples were taken before and after the vacation period (30 days). The data are summarised in Table 9.

Geyer et al. (2004, extended abstract) estimated the terminal elimination half-life for humans of **BDE-47**, **-99**, **-100**, **-153** and **-154**. The authors used a linear one-compartment open toxicokinetic model based on body burden and daily intakes in non-occupationally exposure adults. The half-lives reported in this study were those used in the previous EFSA assessment on PBDEs (EFSA CONTAM Panel, 2011b) (see **Section 1.3.5**). The results are presented in Table 9. The CONTAM Panel noted that the method to estimate the half-life is not fully described in the extended abstract and this leads to uncertainties regarding the half-life calculation (see **Section 3.5.4**).

Trudel et al. (2011) also used a pharmacokinetic model to derive elimination half-lives with an estimation of intake levels and using biomonitoring data from the literature. For their calculations, the authors estimated the concentrations of PBDEs in different exposure media (including soil, dust, air, food) and in combination with biomonitoring data (concentration of PBDEs in human lipid tissue) from the literature, different half-live values were determined. According to the authors, the median half-lives were 1100, 510, 280, 670, 2700, 480 and 1000 days for **BDE-28, -47, -99, -100, -153, -154** and **-183**, respectively. The authors used another equation to calculate the **BDE-209** half-life. Considering that **BDE-209** was not equally distributed in body fat, they estimated the half-life from rat data applying an allometric scaling factor. They obtained a median value of 7 days for **BDE-209** (Table 9).

Zhang, Hu, et al. (2022) developed two oral PBK human models (without and with enterohepatic circulation) for **BDE-209**. The models were evaluated according to the WHO recommendations, and internal and external exposure data of **BDE-209** were used for model calibration and validation (see details in **Section 3.1.1.5**). After model calibration, the authors reported a half-life of **BDE-209** in humans of about 15 and 18 days for the model without and with enterohepatic circulation, respectively.

TABLE 9 Half-lives (days) of PBDE congeners reported in the literature.

	Trudel et al. (2011)[a]	Geyer et al. (2004, extended abstract)[b]	Thuresson et al. (2006)[c]	Zhang, Hu, et al. (2022)[d]
BDE-28	1100	–	–	–
BDE-47	510	664 (556–926)	–	–
BDE-99	280	1040 (663–1142)	–	–
BDE-100	670	573 (469–660)	–	–
BDE-153	2700	2380 (1300–4530)	–	–
BDE-154	480	1214 (837–1560)	–	–
BDE-183	1000	–	94 (68–120)	–
BDE-196	–	–	91 (0–280)	–
BDE-197	–	–	85 (29–140)	–
BDE-201	–	–	72 (0–150)	–
BDE-203	–	–	37 (16–59)	–
BDE-206	–	–	18 (15–20)	–
BDE-207	–	–	39 (4–73)	–
BDE-208	–	–	28 (17–39)	–
BDE-209	7	–	15 (11–18)	15.1, 18.1

[a]Estimates based on a pharmacokinetic model to derive elimination half-lives with an estimation of uptake values and biomonitoring data from the literature.

[b]Estimates based on the use of a linear one-compartment open toxicokinetic model based on body burden and daily intakes in non-occupationally exposure adults. In brackets the range is presented.

[c]Estimates based on a pharmacokinetic model where serum level of rubber workers and electronics dismantlers were recorded. In brackets the 95% confidence interval is presented.

[d]Predicted from two human PBK models without and with enterohepatic circulation after calibration using measured **BDE-209** serum concentrations from 26 Chinese participants and their estimated **BDE-209** oral intakes from diet and dust.

3.1.1.2.5 | *Summary on toxicokinetic studies in humans*

Quantitative data on the absorption of PBDEs in humans were only identified for **BDE-209**. Zhang, Hu, et al. (2022) reported an oral absorption in humans of 0.286 predicted by a PBK model.

There is conclusive evidence for the transfer of PBDEs from maternal blood to the placenta and human milk, based on levels in cord blood and in human milk. Transfer of OH-PBDEs (such as 5-OH-BDE-47 and 6-OH-BDE-47) across the placental membrane has also been reported.

Based on studies with human liver microsomes and primary hepatocytes, the main metabolic pathway of PBDEs in humans is CYP-mediated hydroxylation. Comparison of the results from Erratico et al. (2011, rat liver microsomes, see **Section 3.1.1.1.3**) and Erratico et al. (2012, 2013, human liver microsomes) revealed that the metabolism of **BDE-47** and **-99** is catalysed by different CYP enzymes in rats and humans, and produces different OH-metabolites. In humans, the primary CYP responsible for the formation of hydroxylated metabolites of **BDE-47**, **-99** and **-100** is the CYP2B6 (Erratico et al., 2011, 2015). The study using rat liver microsomes revealed that metabolism of **BDE-47** is mediated by CYP1A1, CYP2A2 and CYP3A1, and by CYP3A1 for **BDE 99** (Erratico et al., 2011).

Studies have shown phase II metabolism of the OH-derivatives with the formation of glucuronide and sulfate conjugates.

Limited data are available regarding the excretion of PBDEs in humans. Half-lives were estimated using different methodologies for **BDE-28** (1100 days), **BDE-47** (510–664 days), **BDE-99** (280–1040 days), **BDE-100** (573–670 days), **BDE-153** (2380–2700 days), **BDE-154** (480–1214 days) and **BDE-183** (94–1000 days). The half-lives of several highly brominated PBDEs were estimated from biomonitoring studies: **BDE-209** (7–15 days), nonaBDEs (18–39 days) and octaBDEs (37–91 days), or based on oral PBK human models: **BDE-209** (15 and 18 days for the model without and with enterohepatic circulation, respectively).

3.1.1.3 | *Transfer of PBDEs in food-producing animals*

Several studies have been identified on the transfer of PBDEs from feed into a number of food-producing animals, i.e. ruminants, chickens, ducks, pigs and fish.

3.1.1.3.1 | *Ruminants*

Kierkegaard et al. (2007, 2009) performed a mass balance study in lactating cows ($n = 2$) exposed to PBDEs via silage (main contributor), concentrate and minerals, over a 3-month period. Feed consumption and milk production were measured on a daily basis, whereas faeces were collected 1 day per week. The PBDE congeners BDE-173, -182, **-183**, -184, -191, -196, -197, -203, -206, -207, -208 and **-209** were detected and quantified in feed (silage, concentrate and mineral) but only **BDE-183**, -196, -197, -203, -206, -207, -208 and **-209** were detected and quantified in silage (Kierkegaard

et al., 2007). The congeners **BDE-28**, **-47**, **-49**, -66, -85, **-99**, **-100**, **-153** and **-154** were all detected and quantified in feed (Kierkegaard et al., 2009). One cow was slaughtered after the experiment and fat tissues (omental fat, ventral abdominal fat, lumbar fat, dorsal thoracic fat, kidney and heart fat) and organs (kidneys, liver, heart and leg muscles) were sampled. The second cow was not slaughtered and only faeces and milk were collected. The authors reported that 90% of the PBDE body burden was measured in the adipose tissue. **BDE-209** was the predominant congener found in adipose tissues, faeces and milk. Each congener had similar concentrations in all fat tissues based on a lipid weight basis, and the PBDE concentrations were in the following order: **BDE-209** > -207 > -196 > -197 > -206 > -182 > -208 > -183 > -191 > -173 > -183. Whereas the order in feed was **BDE-209** > -206 > -207 > -208 > -196 > -203 > -197. According to the authors, this difference in concentration order between the feed and fat tissue could be explained by debromination of certain congeners and/or a different absorption. Compared to the faeces, the milk concentrations were low: for BDE-206, -208 and **-209**, the excretion in milk accounted for less than 1%, whereas it was up to 41% for BDE-207, -196 and - 197. The milk/adipose tissue concentration ratios (on a lipid weight basis) ranged from 0.012 (**BDE-209**) to 1.7 (BDE-66). The authors observed a correlation between the milk fat/adipose tissue concentration ratio and the Log K_{OW}: PBDEs with Log K_{OW} > 7 have a smaller fraction transferred to the milk. The estimated transfer rate of **BDE-209** from feed to milk in the two cows was 0.0016 and 0.0024. The transfer rate from feed to milk for **BDE-28**, **-47**, **-49**, -66, -85, **-99**, **-100**, **-153** and **-154** ranged from 0.015 to 0.34, being lowest for **BDE-28** and **-49**.

Ounnas et al. (2010) exposed goats ($n = 3$) to feed containing 5% of soil contaminated with **BDE-47** (0.02 ng/g dry weight) and **-99** (0.01 ng/g dry weight) for 80 days. The measured concentrations in milk were 0.05 and 0.04 ng/g lipid for **BDE-47** and **-99**, respectively. The estimated soil to milk transfer rate for these two congeners was 30%. The bioconcentration factor (BCF) of **BDE-47** and **-99** was in the range from 2 to 3 in adipose tissue, and >2 for both congeners in the liver (no numerical data, i.e. concentrations in other tissues were provided by the authors).

Rhind et al. (2011) studied the accumulation of PBDEs (**BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**, **-183**) among other POPs, in ewe's and lamb's liver after different time exposures (6, 18 or 30 months) to sewage sludge-treated pastures ($n = 12$/treatment/year). The PBDE concentrations in the sludges applied were estimated from a previous study (Rhind et al., 2009), and ranged from 3 to 300 µg/kg. In ewes, concentrations of **BDE-28**, **-153**, **-154** and **-183** were at or near the LOD, while **BDE-47**, **-99** and **-100** were detected in most liver samples with a range of concentrations of, respectively, 3, 2–3 and 1–2 ng/kg liver. In lambs, the levels of **BDE-47, -99** and **-100** detected in livers were 3.5, 1.5–3 and 1–1.5–3 ng/kg liver, respectively. The levels of **BDE-47** detected in liver were higher than those of **BDE-99** and **-100** in both ewes and lambs. Except for **BDE-99** and **-100**, the authors did not find statistical differences with treatment duration.

Holma-Suutari et al. (2014) studied the presence of PBDEs (**BDE-28**, **-47**, -66, -71, -75, -77, -85, **-99**, **-100**, -119, **-138**, **-153**, **-154**, **-183**, **-209**) in different tissues of pregnant reindeer slaughtered for human consumption ($n = 2$) that were fed reindeer food concentrates and lichen. The measured PBDE concentrations in reindeer food concentrates and in lichen were low. The authors found that in reindeer tissues (muscle samples, liver and placenta) **BDE-209**, **-153**, **-99** and **-47** were the most abundant congeners, especially **BDE-209** that accounted for 90%, 58% and 77%, in muscle, liver and placenta, respectively. **BDE-47**, **-99** and **-153** were found to be the most abundant congeners in reindeer milk. PBDE concentrations were higher in fetuses than in placentas.

3.1.1.3.2 | *Chicken, broilers, laying hens and ducks*

Chicken

Hakk et al. (2010) studied the metabolism and tissue distribution of **BDE-47** in chicken. Four chickens were fed with a gelatin capsule containing [^{14}C]-**BDE-47** (2.7 mg/kg bw) for 72 h. **BDE-47** was highly absorbed from the gastrointestinal tract of chickens with an estimation of the bioavailability > 60%–70%. The greatest amounts of radioactivity were found in adipose tissue, skin, gastrointestinal tract and lung, and 77% of the radioactivity was estimated to be retained in body fat. In the liver 35% was present as **BDE-47** metabolites. 22% of the administered dose was eliminated in excreta (at 72 h). The authors found **BDE-47** metabolites (two OH-metabolites and one debrominated metabolite) in faeces similar to those described in rat and mouse studies (see **Section 3.1.1.1.3**).

Zheng et al. (2015) studied chicken tissues (liver, muscle, heart, lung, fat, brain, stomach, intestine, ovary/testis, kidney and serum, from 12 *Gallus gallus* domesticus; 1 cock, 11 hens) and chicken dietary sources (soil and feed) from an e-waste recycling site. The congeners **BDE-47**, **-99**, **-100**, **-153**, **-154**, **-183**, -196, -197, -203, -206, -207 and - **209** were detected in soil, with concentrations ranging between 20,600 and 44,200 ng/g dry weight. Only **BDE-47**, -206, -207 and - **209** were also detected in chicken feed, with concentrations between 0.03 and 4.4 ng/g dry weight. The authors measured PBDEs in chyme, intestinal contents and excreta, with concentrations varying from 16 to 16,300, from 52 to 4290 and from 47 to 5600 ng/g dry weight, respectively. In chicken tissues, PBDEs were detected at median concentrations ranging from 157 to 1660 ng/g lipid.

Wang et al. (2017) studied the distribution of PBDEs in chicken ($n = 30$) dosed with **BDE-209** at 85 mg/kg bw for 56 days. The average PBDE concentrations (sum of **BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**, **-183** and **-209**) in chicken tissues followed the order: liver > blood > skin > intestine > stomach > leg meat > breast meat (ranged from 456 ng/g ww in breast meat to 4050 g/g ww in liver). The authors calculated the absorption/distribution efficiency of **BDE-209** in various tissues and faeces. They found the following sequence and values (corresponding to the percentage of the

dose): liver (0.15 ± 0.032%) > skin (0.14 ± 0.038%) > intestine (0.071 ± 0.021%) > breast meat (0.062 ± 0.020%) > leg meat (0.059 ± 0.016%) > stomach (0.021 ± 0.0095%). The authors estimated that 9.3% of **BDE-209** was excreted via faeces. The remainder (90% of the dose) was not retrieved by the authors.

Fernandes et al. (2023) exposed chickens to different recycled bedding materials (shredded cardboard, dried paper sludge, shawings recycling woods at concentrations 223, 420 and 0.36 µg/kg, respectively) and measured the concentration of total PBDEs (sum of **BDE-28**, -**47**, **99**, -**100**, -**153**, -**154**, -**183** and -**209**) in liver, muscles, skin and eggs. The authors found that the greatest amounts of total PBDEs were in the liver, except for dried paper sludge where the greatest amounts were found in muscles. The authors estimated biotransfer factors for the individual congeners, whose values were between 16 and 188 for muscles, between 21 and 125 for skin, between 7 and 146 for eggs and between 11 and 251 for liver. The authors also found a correlation between the number of bromine atoms and the biotransfer factors for muscle, eggs and liver, but not for skin.

Broilers and laying hens

Pirard and De Pauw (2007) performed a toxicokinetic study on laying hens. The animals ($n = 7$) were fed with 3.4 mg DE-71/kg feed) for 14 weeks. Absorption was calculated by comparing the amounts found in excreta and the ingested levels. PBDEs were found in the liver, abdominal fat and eggs. The BCF (ratio between abdominal fat concentration expressed in ng/g fat and feed concentration in ng/g ww) was calculated for **BDE-47** (0.7), **BDE-100** (1.8), **BDE-99** (0.6), **BDE-154** (2.2), **BDE-153** (2.0) and **BDE-183** (1.0). The authors measured excretion of the individual congeners during the second week and these were 62% for **BDE-47**, 24% for **BDE-100**, 37% for **BDE-99**, 13% for **BDE-153** and -**154**, and 7% for **BDE-183**.

Berge et al. (2011) fed six groups of 10–13 broiler chickens with **BDE-47** and -**99** (1.63 ng/g feed). The authors found an increase in **BDE-47** and -**99** levels in liver and adipose tissue samples (no numerical data were provided).

Yang, Li, et al. (2011) examined the liver, brain, pectoral muscle, intestine and mesenteric fat of hens ($n = 4$). Animals were sampled from a village which had been exposed to e-waste recycling for years. Contamination of feed was reported as 4-fold below that in the recycled materials. The sum of **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183** and -**209** was measured in brain (14.76 ng/g lipid), but at lowest concentrations among other hen tissues (48.31, 82.47, 142.75, 106.82 and 149.51 ng/g lipid in blood, liver, muscle, intestine and mesenteric fat tissues, respectively).

Zheng et al. (2014) studied the maternal transfer, tissue distribution and chicken embryo development of several PBDEs in chicken living in a region contaminated due to e-waste recycling (1 male and 11 females). **BDE-47**, -**99**, -**100**, -**153**, -**154**, -171, -180, -**183**, -196, -197, -206, -207 and -**209** were detected in hen muscle (range: 20–7470 ng/g lipid) and eggs (range: 106–15,700 ng/g lipid). In muscle and liver of chicks, the sum of the 13 PBDEs analysed was in the range 580–6040 ng/g lipid and 563–18,800 ng/g lipid, respectively. The calculated ratio (hen muscle to eggs) varied between 0.2 and 1.2 on a lipid basis. By comparing the change in concentration ratio between muscle/eggs and liver/eggs of **BDE-47** and **-99**, the authors suggested that **BDE-99** debromination to **BDE-47** could occur during chicken embryo development. The concentration ratios between muscle/eggs and liver/eggs were 7.4 and 1.7 for **BDE-47**, whereas they were only 1.4 and 0.7 for **BDE-99**.

Fernandes et al. (2019) studied the uptake and tissue distribution of PBDEs (BDE-17, -**28**, -**47**, -**49**, -66, -71, -77, -85, -**99**, -**100**, -119, -126, -**138**, -**153**, -**154**, -**183** and -**209**) from recycled materials used in livestock farming in broiler chickens and laying hens. A control group was exposed to uncontaminated material. The concentrations of PBDEs in the recycled materials varied between 0.27 (recycled wood shavings) and 420 µg/kg (dried paper sludge). The median PBDE concentrations in the muscle tissue were 5.1 µg/kg lipid-based, and 6.1 µg/kg lipid-based in the liver. PBDEs were found in higher concentrations in chicken and egg reared on recycled material compared to the control group.

Hakk et al. (2021) studied the absorption, distribution, metabolism and excretion of **BDE-99**, -**153** and -**209** in laying hens and their transfer into eggs. Animals ($n = 16$) were fed with a single dose of radiolabelled congeners (between 2.85 and 3.85 mg/kg bw for **BDE-99**, -**153** and -**209**, respectively). According to the cumulative excretion (excreta collected for 7 days), the bioavailability was 87%, 79% and 17% for **BDE-99**, -**153** and -**209**, respectively. **BDE-99**, -**153** and -**209** were also measured in breast muscle at 1.2%, 1.9% and 0.2% of the applied dose, while it was 16.7%, 18.0% and 0.4% in thigh muscle, respectively. In adipose tissue, the percentage of the dose retrieved was 25.5%, 13.2% and 0.8% for **BDE-99**, -**153** and -**209**, respectively. The total dose transferred to the yolk represented 12.3%, 23.5% and 2.1% for **BDE-99**, -**153** and -**209**, respectively. The authors measured excretion during the first 24 h, and reported that 27%, 22% and 85% of the **BDE-99**, -**153** and -**209** dose, respectively, was eliminated in 24 h. Phenolic metabolites were detected in excreta (0–24 h) from **BDE-99** dosed chickens. This metabolite was characterised as a tribromophenol indicating an ether cleavage within **BDE-99**.

Li, Luo, et al. (2021) exposed laying hens ($n = 8$) to feed spiked with 300 µg/kg dw of **BDE-47**, -**100**, -85, -**99**, -**153**, -**154**, -**183** and -**209** for 58 days, and studied the concentrations in eggs. The absorption efficiencies of **BDE-47**, -85, -**99**, -**100**, -**153**, -**154** and -**183** were ~ 90% each, and 64% for **BDE-209**. The authors measured the concentrations in ng/g lipid (minimal and maximal concentration for each congener) in muscle (0.78–27), heart (0.91–35), intestine (0.63–30), kidney (1.1–25), abdominal fat (1.1–42), liver (0.6–23), stomach (1.0–30), lung (1.0–28) and ovum (1.3–26). The concentration in eggs ranged from 0.036 to 0.82 ng/g lipid. The authors found that the percentages of **BDE-47**, -85, -**99** and -**100** in eggs were lower than those calculated in the spiked feed, while the percentages of **BDE-153**, -**154**, -**183** and -**209** were higher. The authors calculated maternal transfer ratios for PBDEs (ovum/tissues) for the muscle, abdominal fat, liver, kidney, heart, intestine, stomach and lung (ranging from 0.5 to 2.6, according to the congener and the tissues). Negative correlations ($p = 0.0014$, $r^2 = 0.7874$) were found between the maternal transfer ratios for muscle, heart, lung, stomach and log K_{OW} (with log $K_{OW} > 7$).

Ducks

The study by Yang, Li, et al. (2011) above also examined the liver, brain, pectoral muscle, intestine and mesenteric fat of ducks ($n = 3$) from a rural village exposed to e-waste recycling for years. Similar to what was observed in hens, the sum of **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183** and -**209** was measured in brain (1665 ng/g lipid) but at lowest concentrations among other duck tissues (19,645, 119,324, 19,775, 21,153 and 19,775 ng/g lipid in blood, liver, muscle, intestine and mesenteric fat tissues, respectively).

Liu et al. (2015) examined the liver, muscle, lung and brain tissues of ducks ($n = 100$) from a rural village exposed to e-waste recycling, at different sampling times (0 to 12 months). The PBDE concentrations were 8551.0 ng/g dry weight, 158.40 ng/g ww, 3.4 ng/g ww, 0.14 ng/g dry weight and 42.0 ng/L in sediment, fish, mudsnails, paddy and water, respectively. The authors described a fluctuation in total PBDE concentrations in liver, muscle, lung and brain tissues within 12 months (increased at the 6th month, decreased at the 9th month and then increased at the 12th month). The PBDE concentrations (ng/g lipid) in muscle, liver, lung, brain and fat were 258.0, 377.0, 156.6, 42.2 and 1027, respectively at 3 months. At 6 months, the authors observed an increase in the PBDE concentrations with 13,245, 3014, 5397, 512.5 and 1955 ng /g lipid in muscle, liver, lung, brain and fat. The concentrations in the same tissue were 2178, 854.5, 829.2, 61.45, 4290 ng/g lipid and 4090, 4069, 1120, 128.8, 7020.4 ng/g lipid at 9 and 12 months, respectively.

3.1.1.3.3 | *Pigs*

Li, Yang, et al. (2010) studied the tissue distribution of PBDEs in domestic pigs ($n = 3$) from a region exposed to e-waste recycling. **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183** and -**209** were detected in tissues with the following order (lipid weight basis): liver > muscle > intestine > fat. **BDE-47** was the dominant congener detected and accounted for 48%–70% of the total, followed by **BDE-99** (16%–24%). The concentration of total PBDEs in livers ranged from 54.2 to 60.6 ng/g lipid and in fat ranged from 20.2 to 28.9 ng/g lipid.

Shen et al. (2012) studied the tissue distribution of **BDE-47**, -**100** and -**153** in pigs. The animals ($n = 8$) were fed with capsules containing 1, 10, 100 ng of each congener from week 3 to week 13. Similar distributions were observed between the PBDEs in the different tissues with concentrations in liver, lung and muscle being higher than in kidney and mesentery (liver > muscle = lung > mesentery = kidney).

Fernandes et al. (2019) used recycled materials as fertilisers for the cropland on which the pigs ($n = 12$) were reared. The concentrations of PBDEs in the recycled materials varied between 0.23 (poultry litter ash) and 2536 µg/kg (biosolid). The authors measured the concentration of PBDEs in muscle (0.23 to 0.83 µg/kg lipid) and in liver (0.56 to 2.5 µg/kg lipid) of the pigs. The authors found evidence of uptake from recycled material (e.g. the minimum concentration in the recycled material group was greater than the median concentration of the control group).

3.1.1.3.4 | *Fish and shellfish*

Salmon

Isosaari et al. (2005) studied the transfer of PBDEs (**BDE-28**, **-47**, -66, -71, -75, -77, -85, -**99**, -**100**, -119, -**138**, -**153**, **154**, -**183** and -190) in Atlantic salmon (*Salmo salar*). Adult fish were exposed to feed with three different concentrations of PBDEs (3.24, 5.38 and 6.48 ng/g dry weight) but with the same proportion of congeners, during 15 and 30 weeks. In the lowest dose, the total PBDE concentration measured in whole fish and fillet were constant during the exposure period, in contrast with the two highest doses, where total PBDE concentrations increased during the first 15 weeks. The total PBDE concentrations (ng/g fresh weight) in whole salmon and salmon fillet were 4.4–4.9 (at 15 and 30 weeks, respectively), and 3.5–3.9 (at 15 and 30 weeks, respectively) for the middle dose. For the highest dose, the concentrations were 5.4–5.7 (at 15 and 30 weeks, respectively), and 4.2–4.6 (at 15 and 30 weeks, respectively). The accumulation efficiencies of PBDEs calculated by the authors ranged from 73% to 133%. The PBDE congeners were distributed in fish tissues (preferentially in fillet) according to the lipid content: 42%–59% of the total PBDE intake via feed was distributed to fillet and 36%–53% to the other parts of the fish.

Berntssen et al. (2010, 2011) studied in Atlantic salmon (*Salmo salar*) the relative transfer of PBDEs (defined as 'fillet retention rate', calculated as the percentage of contaminants in the edible part of the fish in relation to the total dose consumed). Fish were fed for 12 months with commercial feed containing 7.3 ng/g of the sum of 7 PBDEs (**BDE-28**, -**47**, -66, -**99**, -**100**, -**153**, -**154**). The authors calculated a 'fillet retention rate' of 42% (between 34% and 49% for the different congeners).

Dietrich et al. (2015) fed juvenile Chinook salmon (*Oncorhynchus tschawytscha*, $n = 140–285$) with different concentrations of PBDEs as individual congeners (**BDE-47** and -**99**) or a mix of congeners (**BDE-47**, -**99**, -**100**, -**153**, -**154**) for 40 days. The overall levels of PBDEs in the food ranged from 0.7 to 1500 ng/g, and included other congeners, such as **BDE-28**, -**49**, -66 and -85, attributed to debromination of other PBDEs. The authors estimated the congener-specific assimilation efficiency, defined as the total mass of the congener in the fish divided by the total mass of the congener fed to the fish over the exposure period. The mean overall assimilation efficiencies varied from 0.32 (**BDE-28**, -**153**) to 0.50 (**BDE-47**, -**99**). For **BDE-49**, the assimilation efficiency was > 1 (4.9) and the authors concluded that it could have arisen from other congeners debrominated to **BDE-49** within the Chinook salmon. Assimilation efficiencies for BDE-66 and -85 were not calculated.

Trout

Kierkegaard et al. (1999) studied the absorption of **BDE-209** through the gastrointestinal tract in rainbow trout (*Oncorhynchus mykiss*). Fish were fed for 16, 49 or 120 days with control or **BDE-209**-treated feed (7.5 to 10 mg/kg bw per day). After 16 days of exposure, the concentration of **BDE-209** in muscle was 3.2 ng/g of fresh weight, but the concentrations decreased significantly after 71 days of depuration. **BDE-47**, -**99**, -**100**, -**153** and -**154** were also measured in both liver and muscle, and their concentration increased with exposure length. These congeners were from debromination of **BDE-209**. The absorption efficiency for **BDE-209** (calculated from **BDE-209** concentrations in muscle and the mean dietary dose of **BDE-209**) was 0.005%. When taking into account the sum of all metabolites produced, the uptake was estimated to be 0.02%–0.13% after 120 days of exposure.

Stapleton et al. (2006) compared the *in vivo* and *in vitro* debromination potential of **BDE-209** by juvenile rainbow trout (*Oncorhynchus mykiss*). Fish were fed with a **BDE-209** concentration in the spiked feed of 939 ± 14 ng/g ww for 5 months. **BDE-209** was concentrated in liver tissue on both a wet and lipid weight basis. The absorption efficiency calculated by the authors for **BDE-209** was 3.2%. The authors found several lower brominated PBDEs (BDE-188, -197, -201, -202, -203, -207 and - 208) which increased in concentration throughout the exposure period.

Tomy et al. (2004) studied the bioaccumulation, half-lives and assimilation efficiencies of 13 PBDEs (**BDE-28**, -**47**, -66, -77, -85, -**99**, -**100**, -**138**, -**153**, -**154**, -**183**, -190 and -**209**) in trout (*Salvelinus namaycush*). Fish were fed with three dietary concentrations (0, 2.5, 5 ng/g per PBDE congener) for 56 days, followed by 116 days of depuration period. The assimilation efficiencies of the PBDEs ranged from 50% to 60%. The half-lives (calculated based on depuration rates) were variable among the congeners and between doses. The authors did not find a clear trend with log K_{ow} or level of bromination. The reported half-lives ranged from 38 days (BDE-190) to 210 days (BDE-77) for the low-dose treatment. In the high-dose treatment, the reported half-lives ranged from 26 days (**BDE-209**) to 346 days (**BDE-47**, -77 and -**183**).

Feng, Xu, Zha, et al. (2010); Feng, Xu, He, et al. (2010) exposed rainbow trout (*Oncorhynchus mykiss*) to **BDE-209** via a single i.p. injection (100 and 500 ng/g) and measured the concentration of **BDE-209** and its metabolites in muscle, liver and blood collected on day 1 and day 28 post injection. The highest **BDE-209** concentrations were found (in the low dose group) in muscle tissues (149 and 128 ng/g ww at 1 and 28 days, respectively), and to a lesser extent in the liver (55.6 and 88.0 ng/g ww at 1 and 28 days, respectively). In the high dose group, **BDE-209** concentrations were 796 and 1687 ng/g ww (at 1 and 28 days, respectively) in muscle, and 228.0 and 226.ng/g ww (at 1 and 28 days, respectively) in liver. **BDE-209** was not detected in the blood samples analysed. The authors found that **BDE-209** was metabolised to debrominated PBDEs and MeO-PBDEs. Among the several lower brominated congeners identified, **BDE-47** was the most frequently detected (in 83.3% of the samples), followed by **BDE-49** and -71 (in 75% of the samples). The levels of the debrominated metabolites in tissues followed the order: liver > blood > muscle. The authors also detected eight MeO-PBDEs metabolites: 5-MeO-BDE-47, 6-MeO-BDE-47, 4'-MeO-BDE-49, 2'-MeO-BDE-68, 5'-MeO-BDE-99, 5'-MeO-BDE-100, 4'-MeO-BDE-101 and 4'-MeO-BDE-103. The levels of the MeO-metabolites in tissues followed the order: blood > muscle > liver. The predicted half-life values indicated that **BDE-209** was eliminated more rapidly in the liver (50 and 17.7 days for 100 and 500 ng/g doses, respectively) than in the muscle (75 and 100 days for 100 and 500 ng/g doses, respectively).

Carp

Stapleton, Letcher, and Baker (2004) exposed carp (*Cyprinus carpio*) to feed spiked with **BDE-99** (400 ng per day per fish) and - **183** (100 ng per day per fish) for 62 days following a depuration period of 37 days. The authors did not detect **BDE-99** in whole body or liver, but some amounts of **BDE-99** were present in the intestinal tissue. According to the authors, **BDE-99** was debrominated to **BDE-47**, distributed in carp tissues and accumulated in whole body tissues throughout the exposure time. **BDE-183** was not detected in whole body and liver tissues during the exposure.

In a similar experiment, Stapleton, Letcher, Li, and Baker (2004) exposed juvenile carp (*Cyprinus carpio*) to a diet spiked with **BDE-28**, -**47**, -**99** and -**153** for 60 days followed by a 40-day depuration period. The authors calculated an assimilation efficiency (defined as the concentration of PBDEs in fish normalised to cumulative exposure during 60-days) of 93%, 20%, 4% and 0% for **BDE-47**, -**28**, -**153** and -**99**, respectively. The biomagnification factors (i.e. the ratio of normalised assimilation rate to depuration rate) ranged from 0.028 for **BDE-153** to 1.36 for **BDE-47**.

The study by Stapleton et al. (2006) above, also reported on the debromination potential of **BDE-209** by common carp (*Cyprinus carpio*). Fish were fed with **BDE-209** spiked in feed at 939 ± 14 ng/g ww for 5 months. The authors found several PBDE congeners formed as a result of debromination of this congener (**BDE-154**, -155, -184, -188, -197, -201, -202, -207, -208) which increased in concentration throughout the exposure period in carp.

Jie et al. (2012) exposed crucian carp (*Cyprinus auratus*) in a tank containing three concentrations of BDE-15 (0, 10, 100 µg/L) for 50 days. The authors found that BDE-15 was well absorbed by the carp, and rapidly accumulated in tissues (gill and liver).

Zeng et al. (2012) investigated the gastrointestinal absorption of PBDEs in common carp (*Cyprinus carpio*). Fish were fed feed spiked with three PBDE technical products; a PentaBDE, an OctaBDE and a DecaBDE at 100, 120 and 150 µg per day per fish, respectively. Fish were fed at a rate of 1% of their body weight per day and were sacrificed after 20 days of exposure. The congener profile of the PentaBDE was dominated by **BDE-99**, -**47** and -**100** (46.7, 31.1, 7.5%, respectively), of OctaBDE by **BDE-183**, -197, -207, -196 and -**153** (36.9, 19.8, 11.5, 8.3 and 5.6%, respectively), and of DecaBDE by **BDE-209** and -206 (95.2 and 4.0%, respectively). By comparing the concentration of PBDEs between spiked feed and faeces, the authors estimated

the gastrointestinal absorption. Tri- to pentaBDEs had higher absorption rates (ratio faeces/feed: 1.4–1.9) than hexa- to decaBDEs (ratio faeces/feed: 1.6–6.5). The authors analysed OH-PBDEs and 11 congeners were detected (2'-OH-BDE-28, 3'-OH-BDE-28, 6-OH-BDE-47, 3-OH-BDE-47, 5-OH-BDE-47, 4'-OH-BDE-49, 4-OH-BDE-42, 6'-OH-BDE-99, 5'-OH-BDE-99, 3-OH-BDE-154 and 6-OH-BDE-140) in the serum of fish exposed to PentaBDE. For DecaBDE exposed fish, no OH-PBDEs were detected. The authors also analysed for 17 MeO-PBDEs in the fish serum and none was detected.

Fuhai et al. (2014) exposed crucian carp (*Carassius auratus*) with feed spiked with **BDE-153** for 28 days. **BDE-153** was measured at concentrations of 0.358–3.85 ng/g, 2.36–21.0 ng/g, 11.0–53.8 ng/g, 7.95–79.0 ng/g and 2.6–808 ng/g in the muscle, gill, liver, brain and bile tissues during the 28-day exposure, respectively. The authors also observed that the concentrations of **BDE-153** increased gradually in the gill, liver, brain and bile tissues reaching maximum levels at 14 days of exposure. Several metabolites (4-OH-BDE-49, 6-OH-BDE-47, 2,4-DBP and 2,4,6-TBP) were identified and were present in bile, brain, liver and muscle.

Zhao, Zhang, et al. (2014) studied the distribution and bioaccumulation of two OH-PBDEs (2-OH-BDE-68 and 4-OH-BDE-90) in common carp (*Cyprinus carpio*). Fish were exposed via the water to three concentrations, 0.04, 0.4 and 4 ng/mL for 2-OH-BDE-68, and 0.06, 0.6 and 6 ng/mL for 4-OH-BDE-90 for 30 days followed by a 60-day depuration period. The maximum concentrations (ww) of the two OH-PBDEs were in the range of 17.9–214.9 ng/g in liver, 9.3–84.4 ng/g in kidney and 4.1–29.1 ng/g in muscle, respectively. BCF values ranged from 4.8 to 299.2 ng/mL for 2-OH-BDE-68 and from 5.8 to 162.1 ng/mL for 4-OH-BDE-90. Concentrations of the two OH-PBDEs were found highest in liver, and lowest in muscle in all three exposure treatments. During the depuration period, the concentrations of the two OH-PBDEs decreased in fish tissues. The depuration rates (elimination rate constant) were in the ranges of 0.032–0.071 per day in liver, 0.033–0.045 per day in kidney and 0.027–0.075 per day in muscle.

Sole

Munschy et al. (2010, 2011) studied the accumulation, elimination and metabolism of **BDE-28**, -**47**, -**99**, -**100**, -**153** and -**209** in common sole (*Solea solea*) exposed to spiked feed for 84 days, followed by a depuration period of 5 months. The authors measured all congeners administered in the muscle and liver of the exposed sole. The apparent assimilation efficiencies of **BDE-28**, -**47**, -**99**, -**100** and -**153** were in the range of 10%–16%, whereas **BDE-209** had a lower value of 1.4%. The authors detected debrominated metabolites (**BDE-49**, pentaBDE; tetraBDE). Metabolism of **BDE-99** (debromination) may lead to **BDE-49**, although **BDE-49** could also be a metabolite of **BDE-153** by debromination. In the second part of the study, the authors identified OH-metabolites (4-OH-BDE-49 and 4-OH-BDE-101) which accumulated in fish plasma. Other metabolites (MeO-PBDEs) were also found to accumulate in fish plasma.

In a similar experiment by the same authors, Munschy et al. (2017) studied the distribution and bioaccumulation of PBDEs and their debrominated metabolites in various organs/tissues of adult common sole (*Solea solea*). The authors observed different apparent assimilation efficiencies and debromination pathways in sole according to the PBDE congeners. BMF were calculated and ranged from 1.73 (**BDE-100**) to 0.013 (**BDE-209**). The distribution was the carcass (50 to 80% of the PBDEs) followed by skin (6%–13%), and muscle (7%–16%). The transfer value of PBDEs and their metabolites from female gonads to eggs was > 1.

Other fish species

Mhadhbi et al. (2014) investigated the bioconcentration, elimination and biotransformation of **BDE-47** in juvenile turbot (*Psetta maxima*). Fish were exposed via the water to **BDE-47** at different concentrations (0.001, 0.1, 0.3, 1 µg/L) for 16 days. After the exposure period, the fish were transferred into clean water. The **BDE-47** concentrations in whole body of the fish during the exposure period increased and for all concentrations. The average tissues concentrations of **BDE-47** ranged from 6.91 to 1635 ng/g ww during the exposure period, and from 47.97 to 1294 ng/g ww during the depuration period (according to the different concentrations of exposure). The estimated BCF, calculated as the aqueous uptake rate constant divided by the elimination rate, ranged from 11,415 to 33,105 L/kg, whereas the half-life ranged from 36 to 106 days. The authors also identified and reported debromination of **BDE-47** to -**28**.

Blanco, Martinez, et al. (2011) evaluated the PBDE levels in farmed turbot (*Psetta maxima*), and the contribution of the feeding (containing 2.35–4.76 ng/g of PBDEs) in the overall levels of PBDEs found in fish fillets. **BDE-47**, -**49**, -**99**, -**100**, -**154** and -**209** accounted for 90%–97% of total PBDEs in turbots. It was reported that about 30% of total PBDE intake via feed was retrieved in the turbot fillets. The authors calculated the BMF (based on lipid-normalised concentrations in fish and in feed) that was > 1 for all for all the detected congeners, except for **BDE-209** for which it was 0.72.

Burreau et al. (2000) studied the distribution of [^{14}C]-labelled **BDE-47** in pike (*Esox lucius*) tissue. Fish were exposed via the diet and examined 9, 18, 36 and 65 days after exposure. The absorption efficiency of **BDE-47** was 96% as analysed by scintillation counting. The whole-body autoradiography results showed that radioactivity was present in the entire body of the pike, and was detectable in lipid rich tissues after 65 days following exposure. In a previous experiment, Burreau et al. (1997) had reported absorption efficiency values of 90% for **BDE-47**, and of 60% and 40% for **BDE-99** and **BDE-153**, respectively.

Kuo et al. (2010) exposed lake whitefish (*Coregonus cupleaformis*) fed with **BDE-209** at concentrations 0, 0.1, 1 and 2 mg/kg feed for 30 days. In the dose group 0.1 µg/g of **BDE-209**, the authors did not find a significant difference compared to the control group regarding the concentration of PBDEs (**BDE-47**, -**99**, -**100**, -**153**, -**154**, -196, -197, -207, -208, -**209**) in the

liver and carcass. In the dose groups 1 and 2 µg/g, the concentrations increased in liver for BDE-206, -207, -208 and -**209**. The authors supposed that BDE-206 was the major debrominated metabolite of **BDE-209**.

Mussels

Drouillard et al. (2007) investigated the elimination rate coefficients for 10 PBDE congeners in mussels (*Elliptio complanate*). Mussels were exposed via water to **BDE-47**, -**99**, -**100**, -**138**, -**153** and -**183** for 18 days followed by a depuration period of 120 days. Based on a toxicokinetic model, calculated elimination rate coefficients were in the range of 0.006 (for **BDE-153**) to 0.041 (for BDE-15).

3.1.1.3.5 | *Toxicokinetic models (for transfer)*

Bhavsar et al. (2008) developed a multichemical fish model to assess the kinetic of 13 PBDE congeners (**BDE-28**, -**47**, -66, -77, -85, -**99**, -**100**, -**138**, -**153**, -**154**, -**183**, -190, -**209**) in juvenile lake trout (*Salvelinus namaycush*). The model, when calibrated to experimental laboratory data, provided estimates of half-lives, gut absorption efficiencies and various transport rates of 13 major PBDEs in this fish species.

3.1.1.3.6 | *Summary on transfer*

From the available studies on the transfer of PBDEs from feed to food of animal origin, accumulation of PBDEs mainly occurred in liver and fat tissues in laying hens, broilers, ducks, cows, pigs and fish. In laying hens, transfer to eggs was also described. The transfer of PBDEs from feed to milk has been described in cows, goats and reindeer.

In lactating goats, **BDE-47** and **-99** were retained in the liver and fat tissues. In pigs, PBDE concentrations seemed to be higher in adipose tissue than in muscle and liver (based on lipid weight).

In chicken, most of the **BDE-47** dose was reported to be retained in body fat.

In Atlantic salmon, PBDE accumulation was high in fillet, with around half of the consumed PBDE retained in fillet. Also, among the PBDEs, individual congeners have different accumulation patterns. Debromination of PBDEs is an important factor in the retention of PBDEs. The predominant congeners found in fish seem to be the result of direct absorption of the parent PBDEs to which they were exposed, as well as debromination from congeners such as **BDE-209**, -**99** or-**183** into lower brominated congeners such as **BDE-47**.

3.1.1.4 | *Levels in human tissues*

3.1.1.4.1 | *Human milk*

The previous Opinion on PBDEs (EFSA CONTAM Panel, 2011b) summarised the occurrence data in human milk published in the literature until 2011. The number of congeners analysed differed from study to study. While all studies reported on the occurrence of **BDE-47**, **-99**, **-100** and **-153**, fewer studies covered **BDE-28**, **-154** and **-183**, and only seven studies reported **BDE-209** concentrations in human milk samples from European countries. Some papers reported additional congeners. While the average concentrations of the predominant PBDE congeners, in particular **BDE-47**, were comparable across various European countries, the individual contamination differed considerably due to the wide concentration ranges of several congeners.

Table 10 summarises the occurrence data on PBDEs in human milk from European mothers published in the open domain since the previous EFSA Opinion on PBDEs. The table includes those 10 PBDE congeners that were included in the Commission Recommendation 2014/118/EU on the monitoring of BFRs in food. Although the data were published between 2011 and 2021, most of the samples were collected between 2010 and 2011. Only a few studies reported on human milk samples collected after 2011. As in the previous Opinion, the number of PBDE congeners analysed differs widely. Besides the eight PBDEs considered in the previous Opinion as of primary interest, other PBDE congeners that were often included are BDE-66, -71 and -85. **BDE-49** and **-138** which are also included in the above Commission Recommendations are only seldomly reported in human milk. Generally, **BDE-47** and **-153** showed the highest mean or median concentration, with values ranging from 0.02 to 2.8 and from 0.02 to 1.0 ng/g lipid, respectively, followed by **BDE-99** with mean values ranging from < 0.01 to 1.0 ng/g lipid. The CONTAM Panel noted the high concentration of **BDE-209** in the human milk samples from the Netherlands (Čechová et al., 2017), which amounted to more than 80% of the mean sum of the eight PBDEs. This share is substantially higher than the contribution of **BDE-209** to the sum of PBDEs analysed in the other human milk surveys.

Since 1987, WHO (in cooperation with the United Nations Environment Programme (UNEP)) conducted several coordinated surveys on the occurrence of various POPs in human milk. These surveys were not primarily intended to compare levels of POPs among countries, but rather to examine levels within countries over time. Therefore, strict protocols had to be followed with respect inter alia to selection of donors, location and time of sampling, storage and pooling of samples (generally 1 pool consisted of 50 individual samples), and shipping of the samples to the laboratory (WHO, 2007). To ensure consistency in the analytical measurements, from the third survey onwards except for PFAS all samples were analysed by one laboratory, i.e. the EURL for Halogenated POPs in Feed and Food. The results of these surveys on PBDEs in European pooled human milk samples, conducted between 2001 and 2019 are given in Table 11 (Schächtele et al, see Documentation

provided to EFSA). Besides the lipid content, the table shows the levels of **BDE-28**, -**47**, -**49**, -**99**, -**100**, -**138**, -**153**, -**154**, -**183** and -**209**. **BDE-49** and -**209** were only analysed in the human milk samples collected in 2016 and 2019. If more than one pool within one sampling period in a given country was analysed, the medians of the respective results were reported. Generally, **BDE-47** and **-153** showed the highest concentrations, followed by **BDE-99** and -**100**. In contrast, **BDE-28**, **-138, -154** and **-183** were only determined close to the LOQ. However, there were some distinct differences in the PBDE contamination between human milk pools from different countries, in particular for **BDE-47** which showed a range of 0.18–4.6 ng/g lipid, with usually higher concentrations in the pools collected in the early 2000s. This observation was substantiated in the case where human milk pools were collected in one country at various time periods. In general, the samples collected at later date had lower concentrations than the earlier ones. However, the low number of samples does not allow derivation of a general time trend for this observation.

The next paragraphs will focus on those studies on human milk where not only levels on PBDEs are reported, but other aspects are also considered, such as temporal trends and other influencing factors on the body burden. Correlations among different tissues are described in **Section 3.1.1.4.4**.

Rovira et al. (2022) measured a wide range of environmental pollutants, including **BDE-28**, -**47**, -**99**, **-100**, **-153** and **-154** in human milk from Spanish mothers ($n = 60$; age: 34 ± 5 years). Milk samples were collected in case of exclusive breastfeeding between 2016 and 2019 at different periods of lactation: < 1-month-old ($n = 22$), 1–6 months old ($n = 29$) and >6–9 months old ($n = 9$). The detection rates for PBDEs varied depending on the specific congener with percentages ranging between 5% for **BDE-154** and 100% for **BDE-47**. Median concentrations were reported to be 0.01, 0.1, < 0.01, 0.1, 0.3 and < 0.01 ng/g lipid for **BDE-28**, **-47**, **-99**, **-100**, **-153** and -**154**, respectively. The mean concentration for the sum of the six PBDE congeners was given as 0.84 ± 0.74 ng/g lipid. These levels were lower than concentrations found some 10–15 years before in human milk from the same study area. Statistical analyses showed no significant differences ($p < 0.05$) between PBDE levels in human milk and BMI, age, citizenship, food consumption, and use of personal care products of the mothers.

Antignac et al. (2016) analysed human milk samples from French (collected 2011–2014), Danish (collected 1997–2002) and Finnish (collected 1997–2002) women for PBDEs and a number of other POPs. The concentrations of the sum of **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154** and -**183** were found to be similar for milk from Danish women (range: 1.2–111.1; median: 4.9 ng/g lipid) and Finnish (range: 1.5–19.0; median: 5.2 ng/g lipid), but around 3-fold lower than for milk from French women (range: 0.5–15.3; median: 1.5 ng/g lipid). The lower levels in the French samples may be due to the later observation time and a decline of the PBDE levels due to the introduction of legal restrictions in Europe in the 2000s. A statistical evaluation of the results showed no significant correlations between PBDEs and HBCDDs, and between the age of the mother and the respective PBDE content.

Croes et al. (2012) analysed 84 individual human milk samples and one pooled sample collected in rural communities in East and West Flanders and Flemish Brabant in 2009–2010 for several POPs, including eight PBDEs (**BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183** and -**209**). The results were comparable to the concentrations measured in the pooled Belgian sample collected in 2006 for the WHO/UNEP field study. The authors reported that the tetra- and pentaBDE congeners increased with increasing body mass index (BMI) of the mothers ($p = 0.01$ for **BDE-47**, $p = 0.02$ for **BDE-99** and $p = 0.02$ for **BDE-100**).

Several publications reported PBDE concentrations in human milk from women from several non-European countries. Generally, PBDE concentrations in human milk from women in the USA were higher, in particular for **BDE-47**, compared to human milk from women in European countries (Guo et al., 2016; Hartle et al., 2018). In contrast, PBDE concentrations in human milk samples from South Korea were similar to results from European samples (Lee et al., 2013; Shin et al., 2016). Müller et al. (2016) analysed 95 colostrum samples collected in 2012 from healthy, primiparous mothers living in Northern Tanzania for **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183** and further BFRs. The sum of the seven PBDEs analysed ranged from < LOD to 785 ng/g lipid, with **BDE-47**, -**99**, -**100** and -**153** being the dominating congeners which may suggest recent and ongoing exposure to commercial PentaBDE at the time of sample collection. A multiple linear regression model revealed that mothers eating clay soil/Pemba during pregnancy had significantly higher levels in human milk of **BDE-47**, -**99**, -**100** and -**153** than mothers who did not eat clay soil/Pemba.

In their review, Shi et al. (2018) summarised occurrence data on PBDEs in Chinese human milk and compared the results with levels found in other regions of the world. Two Nation Human Milk Surveys were conducted in 2007 (24 pooled human milk samples from 12 provinces) and 2011 (32 pooled human milk samples from 16 provinces). While the levels for tri- to heptaBDEs in 2007 ranged from 0.85 to 2.97 ng/g lipid, with mean and median levels of 1.58 and 1.49 ng/g lipid, respectively, the concentrations in the 2011 samples ranged from 0.3 to 4.0 ng/g lipid, with mean and median levels of 1.5 and 1.3 ng/g lipid, respectively. A comparison of the two study results indicated that the concentrations for the sum of tri- to heptaBDEs were comparable. However, significant differences of **BDE-47**, -**99** and -**100** were observed between the two studies ($p < 0.01$), with average reductions of 45%, 48% and 46% from 2007 to 2011, respectively. In contrast, for **BDE-183** an increase of 56% was observed in the average concentration from 2007 to 2011 ($p = 0.07$). In the 2011 survey, **BDE-209** was analysed for the first time, and levels ranged from 0.276 to 2.06 ng/g lipid, with mean and median levels of 0.799 and 0.566 ng/g lipid, respectively. The authors concluded that **BDE-209** became the predominant congener in total PBDE levels in human milk, after the restriction of PentaBDE and OctaBDE in China. Improper recycling of e-waste can be a source of elevated PBDE concentrations in human tissues, as shown by Li, Tian, et al. (2017). The authors analysed human milk samples from 25 women who did not directly participate in e-waste recycling operations, but lived for more than 20 years adjacent to e-waste recycling sites in a village in China. The results were compared with respective concentrations in human milk from a control group of 25 women who did not live around the e-waste recycling sites. The sample collection was done in 2012–2013 and the analysis comprised the eight PBDE congeners considered of primary

interest. The median sum of PBDEs in the human milk samples of the women who lived adjacent to the e-waste recycling sites was found to be 19.5 ng/g lipid (range: 7.89–90.6). These concentrations were significantly higher than those in the control group ($p < 0.05$) where the median sum of PBDEs was 3.88 ng/g lipid (range: 1.87–22.0). In both groups, the highest contribution to the sum of PBDEs came from **BDE-209** and -**153**.

Tang and Zhai (2017) performed a systematic review on the global distribution of PBDEs in human milk, cord blood (see **Section 3.1.1.4.2**) and placenta (see **Section 3.1.1.4.3**). The review finally included 117 papers. To assess the PBDE levels in human milk, cord blood and placentas, the authors summarised the available results of PBDE congener in these matrices during 1996–2016 globally. Overall, the median concentration of the sum of PBDEs in human milk ranged from 0.57–117, 0.07–6.3 and 2.99–54.5 ng/g lipid in Asia, Europe and North America, respectively. In China, studies showed high PBDE body burden in local residents due to primitive e-waste recycling. The levels of PBDE differed markedly among regions and exhibited different time trends. PBDEs in human milk reached a peak at around 2006 worldwide. In addition to concentration and time trends, the congener profiles of PBDEs show regional differences. **BDE-47** generally made the highest contribution to the total amount of PBDEs, followed by **BDE-153** and -**99**. **BDE-209** was also detected as the major congener in other studies. **BDE-47** accounted for 54% of congeners in Asia, 59% in Europe and 57% in North America. However, the relative proportions of **BDE-47** differed widely in different studies, especially in Asia and Europe. A compilation of PBDE levels in human milk from non-European countries can be found in Annex C (Table C.1).

Temporal trends in human milk

Temporal trends of PBDE levels in human milk from first-time mothers in Uppsala were published for the time period 1996–2006 by Lignell et al. (2009). During the 11 years, decreasing temporal trends were observed for **BDE-47** and **-99**, whereas **BDE-100** showed no change, and **BDE-153** concentrations increased. In a follow-up study, Gyllenhammar et al. (2021) analysed human milk samples from 2007 to 2017 from the same area to study whether the temporal trend continued at the same rate. **BDE-47**, -**99**, -**100** and -**153** were measured between 1996 and 2017, and **BDE-209** between 2009 and 2017. **BDE-47** and -**153** showed the highest mean concentrations, 1.5 and 0.63 ng/g lipid respectively. For **BDE-99** and **-100**, 20% and 44% of the samples were < LOQ, respectively. For **BDE-209** only 19% of the samples had concentrations > LOQ. PBDE concentrations < LOQ were used for human milk samples from 2009 to 2016. These reported PBDE concentrations, adjusted for concentrations in blank samples, were used instead of half the LOQ to improve the power of the statistical analyses. Before temporal trend analysis by linear regression of logged values, the measured concentrations in the human milk samples were adjusted for potential confounding factors, i.e. age of the mother, pre-pregnancy BMI, weight gain during pregnancy, weight loss after delivery and education level. Temporal trends of **BDE-47**, **-99** and **-100** showed decreasing levels between 1996 and 2016 with adjusted mean rates of –6.5% –14% per year. No significant trend was observed for **BDE-153** for the whole study period, but a change point was observed around the year 2004 with an increasing trend before and a decreasing trend after that year. For **BDE-209**, no significant trend was observed between 2009 and 2017.

Wemken et al. (2020) analysed 16 pools from 92 Irish primiparas sampled between 2016 and 2018 for eight PBDEs (**BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183** and -**209**). Human milk sampling and donor recruitment were comparable with the previous study of Pratt et al. (2013) in order to facilitate elucidation of possible time trends for BFRs in human milk from Irish women. Using a *t*-test, the authors compared the concentrations of individual PBDEs in individual pools of the two studies and noted that the levels of **BDE-47**, **-99**, **-100** and **-153** in the pools collected between 2016 and 2018 were significantly lower ($p < 0.05$) compared to the respective concentrations in the pools collected in 2011 (Pratt et al., 2013). **BDE-209** concentrations did not differ between the two studies. Due to the LODs for **BDE-154** and **-183** in the 2016–2018 pools exceeding the concentrations measured for these congeners in the 2011 pools, it was not possible to perform a meaningful statistical trend analysis.

Based on scientific literature published between 1995 and 2011, Fång et al. (2015) performed a global review on spatial and temporal trends of the Stockholm Convention POPs, including PBDEs in human milk. In general, the reported levels of **BDE-47** were much higher in the human milk samples from the USA compared to the rest of the world. The concentrations in the USA milk samples were rather uniform, with mean values at 35–40 ng/g fat, but with levels reaching as high as 73 ng/g fat. The levels of **BDE-209** were higher in the USA than those reported in the rest of the world. The concentrations of **BDE-47** in human milk in Europe (~ 1–2 ng/g fat) were generally higher compared to the levels in Asia and the Pacific region and Africa, but lower than in the USA. A common global trend, whether the PBDE levels in human milk decline or increase, could not be observed, as the concentrations were predominantly dependent on the length and extent of use of the technical products in the respective area, the surveillance time and the date of ban or legal restriction of the BFRs.

Based on literature published during 2000–2019, Meng et al. (2020) conducted a systematic meta-analysis on the global distribution and trends of PBDEs in human milk and blood (see also **Section 3.1.1.4.2**). The review comprised 44 studies on human milk which included about 3300 participants from 19 countries. On a global scale, total concentrations ranged from 0.38 to 85.6 (median: 3.22) ng/g lipid in human milk. The PBDE concentrations in human milk showed a non-normal distribution ($p < 0.05$) which may indicate different local contamination, manufacture and use of the PBDE containing technical products. **BDE-47**, -**153** and -**209** were the dominant congeners in human milk, representing 29.5, 21.9 and 21.9% of the total PBDEs, respectively. Total PBDE concentrations in human milk differed significantly ($p < 0.05$) among North America, Asia and Europe. Although the maximum concentrations of several congeners were determined in Asia, the median concentrations of all selected congeners, excluding **BDE-183** and -**209**, were significantly higher in North America (all

at $p < 0.05$). While **BDE-47**, **-99**, **-100** and **-153** were the main PBDE contributors in human milk in North America (representing 60.6%, 12.4%, 10.0% and 9.20% of the total PBDE concentration, respectively), in Asia and Europe **BDE-47**, **-153** and **-209** were the main congeners found in human milk. There was no significant difference in the median concentrations of total PBDEs between 2000–2009 and 2010–2015. However, in the two periods, slight decreases in milk PBDE concentrations were observed for Asia, Europe and North American regions.

Zhao and Shi (2021) analysed 105 human milk samples collected in 2018 from Beijing/China for eight PBDEs (**BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**, **-183** and **-209**), three HBCDD isomers and TBBPA, and compared the results with data from investigations performed in the same area in 2004 and 2011. Of the PBDEs measured in the samples collected in 2018, **BDE-153** showed the highest median level of 0.39 ng/g lipid, followed by **BDE-209** with a median concentration of 0.28 ng/g lipid. By comparing the results of the study performed in 2018 with those of Beijing human milk surveys conducted in 2014 and 2011, the contamination of TBBPA and HBCDD increased steadily from 2011 to 2018, whereas that of PBDEs decreased sharply during this period. The authors concluded that the production and consumption of BFRs in China have shifted from PBDEs to other brominated flame retardants.

In summary, the results on PBDEs in human milk seem to be dependent on the type, length and extent of use of the various technical products in the respective area, the surveillance time, the date of the legal restrictions of PBDEs and the impact of potential contamination sites. The influence of these parameters hampers the derivation of a general global time trend on PBDE concentrations in human milk based on the data reported in the scientific literature.

Human milk data from European countries point to a steady decline of **BDE-47** and **-99** which are the predominant congeners in the technical product PentaBDE since the late 1990s. Levels of **BDE-153**, one of the predominant congeners in the technical product OctaBDE seem to decrease in human milk samples from European countries since around 2005/2010. Time trend data on **BDE-209** concentrations in human milk from European countries are inconclusive as shown in surveys conducted between 2009 and 2018.

TABLE 10 Concentrations of PBDEs in **human milk samples** from European countries.

Country Year	*N*	Mean [median] concentration (ng/g lipid)													
		BDE-28	**BDE-47**	**BDE-49**	**BDE-99**	**BDE-100**	**BDE-138**	**BDE-153**	**BDE-154**	**BDE-183**	**BDE-209**	**Other PBDEs analysed**	**Sum of congeners**	**Lipid %**	**Reference**
Belgium 2009–2010	84	< LOQ	[0.16]	NA	[0.06]	[0.06]	NA	[0.29]	[0.07]	< LOQ	0.65	–	–	4.4% (median)	Croes et al. (2012)
France 2011–2014	96	0.04	0.43	NA	0.10	0.10	NA	0.54	0.03	0.05	0.21	–	Sum 8 PBDEs: 1.47	2.8% (median)	Antignac et al. (2016)
Ireland 2016–2018	16	< 0.06	0.64	NA	< 0.2	< 0.2	NA	0.78	< 0.12	< 0.3	2.8	–	Sum 7 PBDEs (w/o **BDE-209**): 1.4	3.47% (median)	Wemken et al. (2020)
Ireland 2010	109	NR	1.11	NR	0.27	0.31	NR	1.00	NR	NR	0.77	BDE-33, -37, -66, -119, -155, -197, -202, -206, -207, -208	Sum 19 PBDEs: 4.12	–	Pratt et al. (2013)
Moldova 2009	50	0.035	0.415	NA	0.104	0.113	NA	0.095	0.003	NA	NA	BDE-17	–	4.7%	Tirsina et al. (2017)[a]
2015		0.049	0.755	NA	0.552	0.163	NA	0.219	0.049	NA	NA		–	4.1%	
The Netherlands 2011–2014	116	0.017	0.197	NA	0.083	0.059	NA	0.483	[0.025]	[0.047]	5.8	BDE-66, -85	–	3.8% (median)	Čechová et al. (2017)
Slovakia 2011–2012	37	[0.063]	0.017	NA	0.069	0.041	NA	0.119	0.022	0.035	NA	BDE-66, -85	–	4.0% (median)	
Slovenia 2008–2014	50	0.074	0.660	NA	0.166	0.160	NA	0.371	0.020	0.023	NA	NA	Sum 7 PBDEs: 1.23	NR	Runkel et al. (2021)
Spain 2012	20	NR	NR	NA	NR	NR	NR	NR	NR	NR	NA	BDE-66, -71, -75, -77, -85, -119, -190	Sum 15 PBDEs: 1.25	1.0–7.0%	Schuhmacher et al. (2013)
Spain 2016–2019	60	0.02	0.2	NA	0.1	0.1	NA	0.4	0.02	NA	NA	–	–	3.2% (median)	Rovira et al. (2022)
Sweden 1996–2017	164–405[b]	0.10	1.5	NA	0.33	0.30	< LOD	0.63	0.09	0.07	0.10[c]	BDE-66	–		Gyllenhammar et al. (2021)
Sweden 2010	30	[0.04]	[0.46]	NA	[0.07]	[0.13]	0	[0.45]	[0.05][d]	[0.01]	[0.06]	BDE-66	Sum 10 PBDEs: [1.50]	NR	Darnerud et al. (2015), Lignell, Aune, Glynn, et al. (2013)
Sweden 2009–2010	2[e]	0.003	0.031	NA	< 0.006	0.006	NA	0.02	NA	NA	0.01	BDE-197, -206, -207, -208	Sum 6 PBDEs[f]: 66	3%	Sahlström, Sellström, De Wit, Lignell, and Darnerud (2015a)
UK 2010	25	NR	NR	NA	NR	NR	NA	NR	NR	NR	0.25	–	Sum tri–hexaBDEs: 5.0	3.5% (median)	Tao et al. (2017)
UK 2014–2015	10	NR	NR	NA	NR	NR	NA	NR	NR	NR	< 0.22	–	Sum tri–hexaBDEs: 5.8	4.1% (median)	

(Continues)

TABLE 10 (Continued)

Country Year	*N*	Mean [median] concentration (ng/g lipid)												Lipid %	Reference
		BDE-28	BDE-47	BDE-49	BDE-99	BDE-100	BDE-138	BDE-153	BDE-154	BDE-183	BDE-209	Other PBDEs analysed	Sum of congeners		
UK 2011–2012	6	0.09	1.92	0.03	0.88	0.64	0.07	1.01	0.07	0.05	0.52	BDE-17, -66, -71, -77, -85, -119, -126	–	1.0%–5.0%	Bramwell et al. (2014), Bramwell, Harrad, et al. (2017)
UK 2010–2011	120	NA	2.30	NA	1.04	NA	NA	0.48	NA	NA	0.08	–	–	2.3%–4.3%	Harrad and Abdallah (2015)
UK 2010	35	NA	2.80	< 0.05	0.69	0.38	NA	0.91	0.21	NA	0.25	BDE-85	–	1.3%–4.2%	Abdallah and Harrad (2014)

Abbreviations: NR, not reported; NA, not analysed; LOQ, limit of quantification; w/o, without.

[a]Samples analysed within the framework of the WHO/UNEP monitoring programme.

[b]Varying number of samples per congener.

[c]Data collection 2009–2017.

[d]Sum of BDE-154 + BB-153.

[e]Two pooled samples corresponding to 30 individual human milk samples each.

[f]Sum of **BDE-28**, -**47**, -**153**, -207, -208 and - **209**.

TABLE 11 PBDEs in human milk pools from various European countries as analysed in the frame of the WHO/UNEP coordinated studies between 2001 and 2019.

			Concentration (ng/g lipid)										
Country	**Year**	**Lipid (%)**	**BDE-28**	**BDE-47**	**BDE-49**	**BDE-99**	**BDE-100**	**BDE-138**	**BDE-153**	**BDE-154**	**BDE-183**	**BDE-209**	**Other PBDEs analysed**
Austria	2016	4.1	0.03	0.41	0.01	0.13	0.13	< 0.01	0.55	0.01	0.05	0.88	BDE-15, -17, -66, -71, -75, -77, -85, -119, -126, -190, -196, -197, -203, -206, -207, -208
Belgium	2015	3.6	0.03	0.36	NA	0.11	0.10	< 0.01	0.44	0.01	0.03	NA	
Belgium	2006	3.2	0.06	0.89	NA	0.22	0.21	< 0.01	0.49	0.02	0.05	NA	
Belgium-Median	2002	–	0.08	0.85	NA	0.21	0.20	< 0.01	0.66	0.02	0.02	NA	
Bulgaria	2014	3.9	0.02	0.27	NA	0.08	0.08	0.01	0.15	0.01	0.04	NA	
Bulgaria	2001	4.6	0.06	0.29	NA	0.12	0.06	< 0.01	0.16	0.04	< 0.01	NA	
Croatia	2014	4.0	0.02	0.22	NA	0.07	0.08	< 0.01	0.24	0.01	0.03	NA	
Croatia	2001	3.4	0.06	0.99	NA	0.31	0.20	0.01	0.30	0.05	0.01	NA	
Cyprus	2006	3.6	0.04	0.64	NA	0.19	0.18	< 0.01	0.31	0.02	0.07	NA	
Czech Republic	2019	NR	0.01	0.23	< 0.01	0.06	0.06	< 0.01	0.22	0.01	0.03	0.09	
Czech Republic	2014	3.8	0.02	0.34	NA	0.09	0.08	< 0.01	0.21	0.01	0.02	NA	
Czech Republic	2006	3.5	0.05	0.71	NA	0.15	0.12	< 0.01	0.18	0.01	0.07	NA	
Czech Republic	2001	4.3	0.04	0.41	NA	0.09	0.08	< 0.01	0.11	0.01	0.01	NA	
Finland-Median	2007	–	0.15	2.09	NA	0.55	0.38	0.01	0.82	0.04	0.02	NA	
Finland	2001	3.5	0.32	3.00	NA	0.49	0.40	< 0.01	0.61	0.05	0.02	NA	
Georgia	2014	4.0	0.02	0.31	NA	0.09	0.07	< 0.01	0.12	0.01	0.02	NA	
Georgia	2009	4.8	0.02	0.26	NA	0.10	0.07	< 0.01	0.11	< 0.01	< 0.01	NA	
Germany-Median	2019	–	0.01	0.22	0.01	0.08	0.06	< 0.01	0.38	0.01	0.02	0.11	
Germany-Median	2002	–	0.12	2.03	NA	0.76	0.34	0.01	0.79	0.04	0.03	NA	
Hungary	2006	4.1	0.03	0.35	NA	0.11	0.07	< 0.01	0.27	0.01	0.07	NA	
Hungary	2001	5.0	0.03	0.32	NA	0.11	0.07	< 0.01	0.18	0.01	0.01	NA	
Ireland	2019	NR	0.04	0.56	0.01	0.13	0.18	< 0.01	0.82	0.01	0.03	0.17	
Ireland-Median	2001	–	0.21	4.59	NA	1.20	0.79	0.01	1.00	0.07	0.07	NA	
Italy	2001	3.1	0.09	1.14	NA	0.50	0.26	0.01	0.66	0.08	0.01	NA	
Lithuania	2015	3.4	0.04	0.39	NA	0.10	0.12	< 0.01	0.27	0.01	0.02	NA	
Luxembourg	2006	3.5	0.09	1.31	NA	0.25	0.26	< 0.01	0.66	0.02	0.05	NA	
Luxembourg	2002	3.5	0.12	1.54	NA	0.29	0.30	< 0.01	0.67	0.03	0.03	NA	
Moldova	2015	4.1	0.05	0.75	NA	0.55	0.16	0.01	0.22	0.05	0.04	NA	
Moldova	2009	4.7	0.04	0.42	NA	0.10	0.11	< 0.01	0.10	< 0.01	0.05	NA	
The Netherlands	2014	3.0	0.03	0.49	NA	0.13	0.16	< 0.01	0.74	0.02	< 0.07	NA	
The Netherlands	2001	3.1	0.12	1.15	NA	0.50	0.32	0.02	1.26	0.05	0.03	NA	
Norway	2001	2.9	0.10	1.27	NA	0.42	0.32	< 0.01	0.49	0.04	0.04	NA	
Romania	2014	3.7	0.02	0.20	NA	0.08	0.12	< 0.01	0.33	0.02	< 0.09	NA	
Romania	2001	3.6	0.03	0.51	NA	0.17	0.09	< 0.01	0.22	0.04	< 0.01	NA	
Russia	2001–2002	3.8	0.05	0.31	NA	0.11	0.08	< 0.01	0.18	0.04	< 0.01	NA	
Slovak Republic	2019	NR	0.01	0.18	< 0.01	0.04	0.07	< 0.01	0.17	0.01	0.02	0.31	
Slovak Republic	2006	3.2	0.02	0.32	NA	0.07	0.06	< 0.01	0.18	0.03	0.18	NA	
Slovak Republic	2001	4.1	0.03	0.37	NA	0.11	0.09	0.02	0.19	0.04	0.01	NA	
Spain	2002	3.9	0.06	1.25	NA	0.42	0.27	< 0.01	0.57	0.04	0.01	NA	
Sweden	2019	NR	0.02	0.29	0.01	0.12	0.08	< 0.01	0.45	0.01	0.01	0.11	
Sweden	2007	2.9	0.15	2.12	NA	0.39	0.47	< 0.01	1.13	0.03	0.09	NA	
Sweden	2001	2.9	0.17	1.50	NA	0.43	0.30	0.01	0.69	0.07	0.01	NA	
Switzerland	2016	4.2	0.03	0.42	0.01	0.09	0.12	< 0.01	0.36	0.01	0.04	NA	
Ukraine	2001	3.7	0.05	0.54	NA	0.14	0.11	< 0.01	0.15	0.03	< 0.01	NA	

Abbreviations: NA, not analysed; NR, not reported.

3.1.1.4.2 | *Human blood*

The previous Opinion on PBDEs (EFSA CONTAM Panel, 2011b) summarised the occurrence data in human serum and blood published in the literature until 2011. The eight BDE congeners **BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**, **-183** and **-209** were found to be the congeners most frequently analysed in these studies. **BDE-47** followed by **BDE-153** were the two most predominant congeners, with median concentrations ranging from 0.16 to 7 ng/g fat and from 0.021 to 3.7 ng/g fat, respectively among the different studies. When analysed, **BDE-209** was the most predominant congener (median values ranging from 0.77 to 37 ng/g fat). Some studies focused on specific sub-groups of population considered at higher risk, such as populations with a high seafood intake or with a high intake of fish from a PBDE-contaminated lake. In the population with high seafood intake, **BDE-47**, **-153** and **-209** showed the highest levels in serum of mothers and 7-year-old children. In occupational studies, the highest concentrations were found in serum from electronic waste dismantlers compared to other occupational groups, such as computer clerks and hospital cleaners. In the electronic dismantler group **BDE-183** was the most abundant congener while in the other two groups **BDE-47** showed the highest concentrations.

Table 12 summarises the occurrence data on PBDEs in human blood from European individuals published in the open domain since the previous Opinion (EFSA CONTAM Panel, 2011b). As noted in the section on human milk, the number of PBDE congeners analysed varies widely between the different studies. Matrices analysed are either serum or plasma which are evaluated together in this assessment. Most studies focused on the body burden of the general population. Some surveys examined the impact of specific food intake on the PBDE levels in the blood of the cohort. Others investigated the weight-loss-induced changes on the PBDE levels in blood of obese patients, the correlation between PBDE concentrations in mother/child pairs or the ratio between PBDE levels in human milk and blood. The PBDE levels in human blood showed wide concentration ranges depending on country and year of sample collection. Generally, **BDE-47**, **-99**, **-153** and **-100** showed the highest mean/median concentrations with values ranging from 0.05–3.85, 0.03–2.29, 0.33–1.96 and 0.01–0.85 ng/g lipid, respectively. In some studies, **BDE-209** was the major contributor with mean/median ranges from 0.68–3.3 ng/g lipid, probably due to the phasing out of PentaBDE and OctaBDE in the 2000s and its replacement by DecaBDE.

The following paragraphs describe in more detail studies that include the levels in blood together with additional information, such as influence of consumption habits, temporal trends, matched samples of mothers and toddlers, and others. Correlations among different tissues are described in **Section 3.1.1.4.4**.

Hausken et al. (2014) investigated the effect of salmon consumption on the PBDE levels in blood and adipose tissue of volunteer consumers. Outpatients with different metabolic disorders consumed 380 g of farmed Atlantic salmon fillets or 60 g of salmon oil for 15 weeks, and the results were compared with a control group. Concentrations of 10 PBDEs (**BDE-28**, **-47**, -66, **-99**, **-100**, -119, **-138**, **-153**, **-154**, **-183**) were measured in salmon fillets, salmon oil capsules, plasma and abdominal fat biopsies from patients before and after intervention. The mean concentrations for the sum of PBDEs in plasma before and after intervention were 3.81 and 3.97 ng/g lipid, respectively for the salmon group, and 4.92 and 4.81 ng/g lipid, respectively for the control group. After 15 weeks of salmon consumption no significant changes in concentrations of PBDE in samples of human plasma and abdominal fat were observed. The authors stated that the interpretation of the study was limited by a relatively large inter-individual variation in the concentrations of the measured congeners, probably due to the heterogeneity in the study populations age and pretrial dietary habits.

Dirtu et al. (2013) investigated the dynamics of seven PBDEs and several other halogenated contaminants in an obese population during weight loss. Serum samples from obese individuals were taken before patients lost weight and after 3, 6 and 12 months. Samples were also collected from a matched lean control population. Only for **BDE-47**, **-100** and **-153** a detection frequency of more than 50% was found. While the median (range) body weight of the patients decreased from 109.8 kg (73–197.4) to 87.8 kg (57–142) after 12 months, the concentration of the PBDE sum increased from 0.98 ng/g lipid (0.72–1.36) to 1.48 ng/g lipid (0.9–2.4). The median (range) concentrations of the most abundant **BDE-47** and **-153** increased from 0.35 ng/g lipid (0.25–0.60) to 0.50 ng/g lipid (0.20–0.80) and from 0.33 ng/g lipid (0.22–0.52) to 0.65 ng/g lipid (0.39–1.0), respectively after 12 months. Similar results were reported by Rantakokko et al. (2015) as referenced by Jansen et al. (2017).

Jansen et al. (2018) analysed serum samples that were collected between 2012 and 2014 from 63 patients before and 1 year after bariatric surgery for **BDE-47**, **-99**, **-100**, **-153** and **-209** as well as other POPs. **BDE-47** and **-153** were detected in 81% and 70%, and 14% and 52% of the samples, respectively before surgery and 1 year after surgery. The detection frequency of the other PBDE congeners was ≤ 1%. As the measured levels were all close to the LOD and thus considered with higher uncertainty, the PBDEs were not included in the further statistical analysis.

Fénichel et al. (2021) studied the kinetics and characteristics of the release of persistent pollutants from adipose tissues during drastic weight loss after bariatric surgery. They screened 100 morbidly obese patients (73 women including 53 of childbearing age and 27 men) before and 3, 6 and 12 months after bariatric surgery for serum concentrations of six PBDEs (**BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**) and various other POPs. Mean initial body weight was higher in men (132 kg) than in women (107 kg) with a mean weight loss 1 year after surgery (40 kg for men vs. 32.1 kg for women) similar in percentage (30%) in both sexes. All PBDE congeners showed a sustained increase following bariatric surgery after 12 months: the sum of the six PBDEs (median) increased from 0.65 to 1.31 ng/g lipid in women, and from 0.90 to 1.97 ng/g lipid in men, respectively. In the group of women of childbearing age, the median sum of the six PBDEs analysed increased from 0.60 to 1.26 ng/g lipid.

Sugeng et al. (2017) systematically reviewed the literature on toddler exposure to BFRs. Studies were only included in their review if BFRs were measured in or on children (e.g. serum, urine or body wipe samples). Furthermore, the study

population had to include children aged between 8 and 24 months old and measurements had to be taken within this age range. Five studies that were retrieved included PBDEs. Most samples were collected between 2006 and 2009, with one study covering serum samples from USA toddlers which were sampled in 2011–2012. **BDE-47** was found to be the main congener in serum from USA toddlers, whereas **BDE-209** was the most abundant congener in the study performed in Sweden. The PBDE concentrations in the USA study (Jacobson et al., 2016) were a factor of 8–20 higher than those reported in the Swedish study (Sahlström et al., 2014).

Sahlström et al. (2014) analysed matched serum samples collected in 2009–2010 from 24 Swedish mothers (24–40 years old) and their toddlers (11–15 months of age) for 12 PBDEs (**BDE-28**, -**47**, -**99**, -**100**, -**153**, -196, -197, -203, -206, -207, -208 and -**209**), and several other BFRs. The median concentrations of individual PBDEs ranged from 0.036 (**BDE-28**) to 0.95 (**BDE-153**) ng/g lipid in mothers, and from 0.057 (**BDE-28**) to 1.5 (**BDE-209**) ng/g lipid in toddlers, respectively. Serum PBDE concentrations were overall higher in toddlers compared to their mothers, with statistically significant differences for **BDE-47**, -**100**, -207, -208 and -**209**. **BDE-153** in mothers' and toddlers' serum was correlated and concentrations were similar, which implied the same source (including maternal transfer to the child via lactation) and/or exposure route, whereas **BDE-209** in mothers' and toddlers' serum was not correlated and toddlers had a higher serum concentration compared to their mothers, which implied that toddlers were more exposed to **BDE-209** via another exposure route, such as ingestion of house dust (Sahlström et al., 2014).

Tang and Zhai (2017) performed a systematic review on the global distribution of PBDEs in cord blood, human milk and placenta (see also **Section 3.1.1.4.1** for human milk and **Section 3.1.1.4.3** for placenta) based on occurrence data from 1996–2016. Overall, the median total PBDE levels in cord blood ranged from 0.65 to 89, 0.96 to 17 and from 38.4 to 100 ng/g lipid in Asia, Europe and North America, respectively. The highest concentration of 100 ng/g lipid for the sum of nine PBDEs in cord blood was detected in Canada. PBDE levels in cord blood obtained from e-waste sites in China were generally higher than those obtained from other regions in Asia and Europe. Similar to human milk, **BDE-47** was mostly the dominant congener, accounting for up to 52% of the total amount of PBDEs, followed by **BDE-153**.

Based on literature published during 2000–2019, Meng et al. (2020) conducted a systematic meta-analysis on the global distribution of PBDEs in human blood and milk (see also **Section 3.1.1.4.1** regarding human milk). The review comprised 63 studies on human blood which included ~ 14,000 participants from 15 countries. On a global scale, total PBDE concentrations in human blood ranged from 0.79–613 ng/g lipid (median: 31.6). The concentrations showed a non-normal distribution ($p < 0.05$) which may indicate different local contamination, manufacture and use of the PBDE containing technical products. The concentrations of PBDEs in blood in different population subgroups varied, e.g. total concentration in occupationally exposed populations was 2.39 times higher than that in the general populations ($p < 0.05$). The occupational population mainly included workers engaged in the poorly controlled recycling and/or disposal of e-waste, or residents living in and around the e-waste recycling sites. The review also reported that total PBDEs concentration of blood in children were ~ 8.31 and 7.30 times higher than that in pregnant women and umbilical cords, respectively. Children are more likely to be exposed to indoor dust and specific products that contain high concentrations of PBDEs due to extended periods of playing, mouthing behaviour and frequent hand-to-mouth contact. A comparison of the concentrations of the eight PBDE congeners considered in the review in blood revealed that across all population groups, the median concentration of **BDE-47** was highest, followed by **BDE-153** and **-209**, which were all significantly higher than the concentrations of the other five congeners (all at $p < 0.05$). However, the concentrations of individual PBDEs in different populations varied. For example, the concentrations of **BDE-153**, -**154**, -**183** and -**209** in the blood of those with occupational exposure, especially those involved in poorly controlled e-waste recycling where significantly higher concentrations were found compared to those of the general population ($p < 0.05$). An appraisal of the geographical distribution of PBDEs in human blood showed that the highest concentration was observed in North America, being one-fold and seven-fold higher compared to Asia and Europe, respectively. The review indicated that the concentrations and contamination patterns of PBDEs in blood samples from Asia, Europe and North America differed clearly, reflecting that the exposure to PBDEs varied among the three regions because of the difference in the production and use of these chemicals (Meng et al., 2020). A compilation of PBDE levels in human blood from non-European countries can be found in Annex C (Table C.2).

A comprehensive review conducted by Arvaniti and Kalantzi (2021) addressed the determinants of PBDEs and other flame retardants in blood in non-occupationally exposed individuals based on surveys and questionnaire data. Overall, the authors concluded that there was epidemiological evidence for a significant association ($p < 0.05$) among human exposure and demographic factors, as well as a significant correlation between exposure to flame retardants and behavioural and environmental factors. The published studies demonstrated that age, gender, housing characteristics, electrical and electronic equipment and mouthing behaviour (in children) played a leading role in human exposure to PBDEs and other flame retardants. However, an appraisal of the various determinants indicated that the conclusions were often inconsistent, as the PBDE concentrations in human blood were either associated in a positive or negative way with the respective determinants. Moreover, several studies showed no correlation. The authors noted that their review revealed some methodological differences between studies and that most of the studies had a relatively small population size (< 100), resulting in low levels of statistical power.

Temporal trends in human blood

Darnerud et al. (2015) analysed 36 pooled serum samples from Swedish first-time mothers for several PBDEs and HBCDDs. A total of 413 individual serum samples were collected between 1996 and 2010, and each pool consisted of 5–25 individual

samples (approx. three pools per year). In addition, the authors studied serum/human milk correlations for PBDE levels in 30 paired samples from individual mothers (see **Section 3.1.1.4.4** on Correlations). The mean serum level of **BDE-209** (1.3 ng/g lipid) was highest of all studied PBDE congeners, followed by **BDE-47** and -**153**. While the levels of **BDE-47**, -**99** and -**100** decreased significantly in pooled serum between 1996 and 2010, no significant temporal trend for **BDE-209** during the study period was observed. When an outlier with a very high level was omitted from the statistical analysis, a significant increasing trend was observed for **BDE-153**.

In their systematic meta-analysis on PBDEs in human blood, Meng et al. (2020) did not only focus on the global distribution, but also on time tends. On a global scale, the contribution of **BDE-47**, the most abundant congener, to total concentration of PBDEs in blood was lower in 2010–2016 than that in 2000–2009, although the difference was not statistically significant ($p > 0.05$). In contrast, the contribution of **BDE-209** to the total concentration of PBDEs in blood increased from 37.4% in 2000–2009 to 51.4% in 2010–2016; however, the increase was also not statistically significant ($p > 0.05$).

Porta et al. (2021) investigated changes in serum concentrations of various POPs, including **BDE-28**, **-47**, -85, -**99**, -**100**, -**153**, -**154** and -**183** in Barcelona from 2006 to 2016. Seven of the eight PBDEs were detected in ≤ 7.5% of individuals both in 2006 and 2016, while only **BDE-153** was found in 24% of the participants sampled in 2016. Due to the low number of positive results, a temporal trend of PBDE concentrations in blood could not be derived.

In conclusion, data on time trends of PBDEs in human blood are sparse and are hampered by a low number of positive results. Moreover, it should be mentioned that not always the same matrix, being either serum or plasma, was analysed and in many cases it was not reported whether the participants fasted before their blood sampling which could have an influence on the results. The limited available data point to a steady decline for **BDE-47** and -**99** since the late 1990s. Due to lack of recent data, a temporal trend for the occurrence of **BDE-209** in human blood across European countries cannot be reliably deduced.

TABLE 12 Concentrations of PBDEs in **human blood samples** from European countries.

			Mean [median] concentration (ng/g lipid)												
Country Year	**Matrix**	***N***	**BDE-28**	**BDE-47**	**BDE-49**	**BDE-99**	**BDE-100**	**BDE-138**	**BDE-153**	**BDE-154**	**BDE-183**	**BDE-209**	**Other PBDEs analysed**	**Sum of congeners**	**Reference**
Austria 2008–2011	Adults, children, blood	150	NR	NR	NR	NR	NR	NA	8.0 ng/L	NR	NR	NA	BDE-66, -77, -85, -118, -126, -139, -181, -196, -197, -203	–	Hohenblum et al. (2012)
Belgium 2015	Adults, serum	274	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	5-OH-BDE-47, 6-OH-BDE-47, 5′-OH-BDE-99	–	Dufour et al. (2017)
Belgium 2009–2013	Obese adults, serum	Control: 44	NR	Control: [0.31	NA	NR	NR	NA	[0.64]	NR	NR	NA	–	Sum 7 PBDEs: [1.33]	Dirtu et al. (2013)
		Obese: 151	NR	Baseline: [0.35] Weight loss treatment: 3 months: [0.41] 6 months: [0.38] 12 months: [0.50]	NA	NR	NR	NA	Baseline: [0.33] Weight loss treatment: 3 months: [0.50] 6 months: [0.50] 12 months: [0.65]	NR	NR	NA	–	Sum 7 PBDEs: Baseline: [0.98] Weight loss treatment: 3 months: [1.17] 6 months: [1.30] 12 months: [1.48]	
Belgium 2010–2011	Obese adolescents, serum	Before treatment: 94	NA	[0.43]	NA	NR	< LOQ	NA	< LOQ	NR	NR	NA	–	Sum 7 PBDEs: [0.63]	Malarvannan et al. (2018)
Czech Republic 2019	Adults, serum	274	NR	Spring: 1.38 Autumn: 1.65	NR	NR	NR	NA	NR	NR	NR	Spring: < 1.5–459 Autumn: < 1.5–618	BDE-37, -66, -77, -85, -196, -197, -203, -206, -207		Poláchová et al. (2021)[c]
Czech Republic 2015	Adults, serum	300	< LOQ	Range: < LOQ–5.44	NA	Range: < LOQ–9.46	Range: < LOQ–3.85	NA	Range: < LOQ–6.44	< LOQ	Range: < LOQ–5.18	Range: < LOQ–2693	BDE-66, -85, -196, -197, -203, -206, -207	–	Sochorová et al. (2017)
Czech Republic 2015	Adults, serum	38	NA	Range: < LOQ–1.83	NA	Range: < LOQ–5.60	NA	NA	Range: < LOQ–1.63	NA	NA	Range: < LOQ–67.8	BDE-196, -197	–	Svarcová et al. (2019)
Denmark 2011	Mothers, blood	143	0.21	2.68	NA	1.85	0.58	NA	1.96	NA	NA	NA	–	–	Knudsen et al. (2017)
	Children, blood	116	0.24	3.85	NA	2.29	0.85	NA	1.39	NA	NA	NA	–	–	
France 2013–2014	Adult women, serum	87	[0.02]	[0.18]	NA	[0.04]	[0.07]	NA	[0.48]	[0.02]	[0.09]	[0.68]	–	Sum 7 PBDEs (w/o **BDE-209**): [0.95]	Ploteau et al. (2016)
France 2014–2016	Adults, serum	742	NR[b]	0.24	NA	0.05	0.07	NA	0.78	NR[b]	NR[b]	1.20	BDE-15, -17, 25, -33, -66, -85	–	Fillol et al. (2021)
	Children, serum	243	< LOQ	[0.28]	NA	[0.07]	[0.08]	NA	[0.36]	< LOQ	< LOQ	[1.48]		–	
Germany 2013	Adults, blood	42	NA	[0.08]	NA	[0.12]	0.10	NA	[1.28]	NR	0.09	[1.76]	–	Sum 6 PBDEs (w/o **BDE-209**): [3.81]	Fromme et al. (2016)
Germany 2013	Adults, blood	70	[0.020]	[0.384]	NA	[0.163]	[0.134]	NA	[0.972]	[0.023]	[0.115]	NA	BDE-17, -66, -85	–	Fromme et al. (2015)

(Continues)

TABLE 12 (Continued)

Country Year	Matrix	*N*	Mean [median] concentration (ng/g lipid)												Reference
			BDE-28	**BDE-47**	**BDE-49**	**BDE-99**	**BDE-100**	**BDE-138**	**BDE-153**	**BDE-154**	**BDE-183**	**BDE-209**	**Other PBDEs analysed**	**Sum of congeners**	
The Netherlands 2015	Adults, serum	38	NR	[1.6]	NA	Min–max: LO[d]–2.7	Min–max: LOD[d]–6.9	NA	[3.1]	NA	NA	NA	–	–	van den Dungen et al. (2016)
Norway 2013–2015	Obese adults, serum	63	NA	Min–max: < LOD[a]–7.5	NA	Min–max: < LOD–< LOD	Min–max: < LOD–8.5	NA	Min–max: < LOD–7.6	NA	NA	NA	–	–	Jansen et al. (2018)
Norway 2013	Adults, serum	61	< LOD	1.7	0.42	1.6	0.58	NA	1.5	0.41	< LOD	3.3	BDE-35, -66, -85, -182, -196, -197, -203, -206, -207, -208	Sum 19 PBDEs: 13	Tay et al. (2019)
Norway 2012	Adults, serum	46	[0.33]	[0.49]	NA	[0.13]	[0.14]	NA	[0.82]	[0.07]	[0.09]	NA	–	Sum 7 PBDEs: [2.3]	Cequier et al. (2015)
Norway 2010–2011	Children, plasma	99	0.1	1.8	NA	0.3	0.01	NA	0.7	0.02	NA	NA	–	–	Caspersen et al. (2016)
Norway NR	Adults, plasma	Control group: 6	NR	NR	NA	NR	NR	NR	NR	NR	NR	NA	BDE-66, -119	Sum 10 PBDEs: 4.92	Hausken et al. (2014)
		Salmon intake: 17	NR	NR	NA	NR	NR	NR	NR	NR	NR	NA		Sum 10 PBDEs: 3.81	
Romania 2017–2018	Adults, serum	121	< LOD	[0.1]	NA	< LOD	< LOD	NA	< LOD	< LOD	< LOD	NA	BDE-85	[0.1]	Luzardo et al. (2019)
Slovenia 2008–2014	Adults, plasma	33	< 0.001 [0.28]	0.007 [6.00]	NA	0.002 [1.4]	< 0.001 [0.63]	NA	< 0.001 [0.25]	NR	NR	NA	–	Sum of 7 PBDEs: 0.011 [9.20]	Runkel et al. (2021)
Sweden 2010–2011	Adults, serum	170	[0.028]	[0.49]	NA	[0.29]	[0.21]	[0.008]	[1.2]	[0.28]	[0.066]	[0.95]	BDE-66	–	Bjermo et al. (2017)
Sweden 2010	Adults, serum	30	[0.06]	[0.36]	NA	[0.05]	[0.18]	[0]	[0.72]	[0.12]	[0.04]	[0.90]	BDE-66	Sum 10 PBDEs: [2.80]	Darnerud et al. (2015), Lignell, Aune, Glynn, et al. (2013)
Sweden 2009–2010	Mothers, serum	24	[0.036]	[0.56]	NA	[0.078]	[0.10]	NA	[0.95]	NA	NA	[0.68]	BDE-196, -197, -203, -206, -207, -208	Sum 12 PBDEs: [4.5]	Sahlström et al. (2014)
	Toddlers, serum		[0.057]	[1.3]	NA	[0.22]	[0.28]	NA	[1.2]	NA	NA	[1.5]		Sum 12 PBDEs: [8.9]	

Abbreviations: NR, not reported; NA, not analysed; LOQ, limit of quantification; yo, years old.

[a]LOD min–max: 0.002–0.008.

[b]Geometric mean was not calculated because of a large amount of left-censored biomarker levels (% quantification < 60%) (Fillol et al., 2021).

[c]**BDE-49**, -66, -85, -**100**, -**154**, -**183** were detected in 0%–7% of the samples. **BDE-99** and -**153** were detected in 5%–33% of the samples. **BDE-28** and -206 were not detected in any of the samples (Poláchová et al., 2021).

[d]LOD: 0.01 (ng/g ww).

3.1.1.4.3 | *Other human tissues*

The previous Opinion on PBDEs (EFSA CONTAM Panel, 2011b) summarised the occurrence data in other human tissues, such as adipose tissue, liver and placenta published in the literature until 2011. In adipose tissue, **BDE-153** and -**47** were the predominant congeners with mean/median ranges of 1.0–2.5 and 0.6–6 ng/g lipid, respectively. A similar profile was observed for liver samples. In placenta, **BDE-47** was the predominant congener with median concentrations ranging from 0.32 to 0.77 ng/g fat, followed by **BDE-153** with median concentrations ranging from 0.20 to 0.44 ng/g fat. Besides the above mentioned 'non-related' samples, the former Opinion on PBDEs also summarised studies that were carried out in paired mother/child samples, such as maternal serum, adipose tissue and umbilical cord serum, in order to assess prenatal exposure and exposure via human milk.

Table 13 summarises occurrence data on PBDEs in human tissues other than human milk and blood from European individuals published in the open domain since the previous Opinion (EFSA CONTAM Panel, 2011b). The studies have focused on the analysis of PBDEs in adipose tissue, greater omentum, placenta, faeces, meconium, hair, semen and brain. Some of these studies are described below in more detail, in particular if they analyse factors that have an impact on the body burden. Correlations among different tissues are described in **Section 3.1.1.4.4**.

Woods et al. (2012) investigated the long-lasting effects of **BDE-47** exposure in a genetically and epigenetically susceptible mouse model. Brain samples of **BDE-47** exposed dams were analysed for **BDE-47** and compared with a random sampling of 24 human postmortem brain samples with no known neurologic disorders ($n = 24$, mean (SD) age, 26 (16.5) years). **BDE-47** could be detected in 13 of the 24 human brain samples at a median concentration of about 25 ng/g lipid (range: about 10–100 ng/g lipid, with one highest observation at about 170 ng/g lipid).[26]

Hausken et al. (2014) investigated the effect of salmon consumption on the PBDE levels in blood (see details in **Section 3.1.1.4.2**) and adipose tissue of the respective test persons. The mean level for the sum of the 10 PBDEs in the abdominal fat of the salmon group at the start was 4.2 ng/g lipid. After 15 weeks of salmon consumption no significant changes in concentrations of PBDE levels in samples of abdominal fat were observed. The authors stated that the interpretation of the study was limited by a relatively large interindividual variation in the levels of the measured congeners, probably due to the heterogeneity in the study populations age and pretrial dietary habits.

Perrot-Applanat et al. (2021) analysed **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183**, -**209** and a number of further POPs in greater omentum samples from 32 patients (16 men and 16 women). The pilot study included 14 patients with diffuse-gastric cancer, 10 patients with other cancers (ovary or colon) that had metastasised in the peritoneal cavity and 8 patients operated for non-cancer diseases serving as a control. The patients were matched for age, body mass index and further major factors that may have an influence on the body burden with lipophilic POPs. While **BDE-209** was significantly higher ($p = 0.005$) in patients with diffuse cancer compared to the control group, no statistical significant differences could be determined for the other measured PBDEs.

Ruis et al. (2019) analysed **BDE-28**, -**47**, -**99** and -**153** concentrations in 10 fetal and maternal sides of human placentas. The results indicate that the measured PBDEs accumulate on the fetal side of the placenta (see **Section 3.1.1.2.2**.).

Sahlström et al. (2015b) investigated the feasibility of using faeces as a non-invasive matrix to estimate serum concentrations of PBDEs and other BFRs in toddlers for biomonitoring purposes. In their study, faeces samples from 22 toddlers were analysed for **BDE-28**, -**47**, -**99**, -**100**, -**153**, -196, -197, -203, -206, -207, -208 and -**209**. The objective of this study was not only to determine PBDE concentrations in faeces, but also to compare the concentrations to results in matched serum samples from the same toddlers and to study possible associations between the two matrices (see also **Section 3.1.1.4.4**). Except **BDE-28**, -**99** and -**100**, all other PBDEs could be determined in the faeces samples. The median (range) concentrations in these samples ranged from 0.055 (< 0.019–0.48) ng/g lipid for BDE-196 to 18 (4.2–575) ng/g lipid for **BDE-209**.

Tang and Zhai (2017) performed a systematic review on the global distribution of PBDEs in placenta, human milk and cord blood (see also **Section 3.1.1.4.1** for human milk and **Section 3.1.1.4.2** for cord blood) based on occurrence data from 1996–2016. The median concentration for the sum of PBDEs ranged from 0.32 to 32.3, < LOD–2.31 and < LOD–17.6 ng/g lipid in Asia, Europe and North America, respectively. PBDE levels in placenta samples from the USA (median: 17.6 ng/g lipid) and an e-waste site of China (median: 32.3 ng/g lipid) were higher than those in samples from Europe (median: 1.9 ng/g lipid) and Japan (median: 0.32 ng/g lipid). In the group of tetra- to octaBDEs, **BDE-47** and -**153** were the predominant congeners. In some studies, the PBDE content was dominated by **BDE-209**, which accounted for ~ 50% of the total PBDE amount. In conclusion, **BDE-47**, -**153** and -**209** played a major role in the proportion of total PBDE congeners in placentas.

In a pilot study, Yu et al. (2018) investigated associations between PBDE exposure from house dust and human semen quality at an e-waste area in South China (see also **Section 3.1.3**). The analyses comprised **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183** and -**209**. The geometric mean levels in house dust from the 32 participants ranged from 1.58 (**BDE-28**) to 2576 (**BDE-209**) ng/g. Excluding congeners with a detection frequency of < 50%, the mean values of **BDE-28**, -**47** and -**153** in semen of the 32 participants were 5.02 ± 4.99, 6.75 ± 5.61 and 7.36 ± 6.62 pg/g, respectively. A statistical analysis showed that the levels of **BDE-28**, -**47** and -**153** in semen samples of the study group were higher than those of the control group ($p < 0.05$). Statistically significant positive correlations were found for **BDE-28**, -**47** and -**153** between concentrations in house dust and paired semen samples.

[26]The data in the original study were presented as a Figure. The CONTAM Panel used PlotDigitizer to extract the underlying numerical data.

Genuis et al. (2017) investigated the elimination of five PBDE congeners (**BDE-28**, -**47**, -**99**, -**100**, -**153**) in the three body fluids: blood, urine and perspiration. Twenty participants provided respective samples for PBDE analysis. The median levels **BDE-28**, -**47**, -**99**, -**100** and -**153** found in blood were 0.77, 16.0, 1.33, 1.90 and 5.10 ng/g lipid, respectively. In perspiration, the corresponding median levels were substantially lower, being 0.02, 0.61, 0.63, 0.15 and 0.09 ng/g perspiration. In urine, the parent PBDE congeners could not be detected. The data showed that **BDE-47** and -**99** were most effectively excreted into perspiration. Excretion rates for each congener were also observed to differ between perspiration induction interventions. In this sample, participants who induced perspiration through exercise excreted the greatest proportion of **BDE-28**; those who used infrared sauna excreted the most **BDE-100**; and those who used steam sauna to induce perspiration excreted the most **BDE-153**.

In the past years several studies have been published on the determination of PBDEs in other matrices which do not require an invasive sample collection, such as hair. The following paragraphs, which do not claim to be complete, illustrates some approaches.

Appenzeller and Tsatsakis (2012) reviewed the state of the art at the time of publication in human hair analysis for the detection of PBDEs and other POPs associated with environmental and occupational exposure. The review focused on specific topics, such as analytical sensitivity and sample pre-treatment, and concluded that hair may be a relevant biomarker of exposure to be used in epidemiological studies.

Król et al. (2014) analysed hair and dust samples from 12 house-holds from Northern Poland for the presence of eight PBDEs (**BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183** and -**209**). Before extraction of the analytes, the hair samples were not pretreated. The concentrations in the hair samples ranged from < LOD–25 ng/g. **BDE-209** was reported to be the predominant congener. For the sum of the eight PBDE congeners median and mean sums were determined as 14 and 17 ng/g (range: < LOD–33), respectively. In non-dyed hair the sum of PBDEs was higher than in dyed hair. The authors suggested that hair treatment may reduce adsorptive properties of hair with the consequence that compounds may not be adsorbed or can be easily released from hair. Similar distributions of PBDE congeners in both dust and human hair were found. The positive correlation between concentrations of selected PBDE congeners in dust and hair indicated that human hair may provide some valuable information regarding exposure to PBDEs through dust.

Between 2013 and 2015, Iglesias-González et al. (2020) collected hair samples from 142 French children originating from different geographical areas (urban and rural) and analysed the samples for five PBDEs (**BDE-47, -99, -100, -153, -154**) and various other pollutants. While the median values of the analysed PBDEs were < LOD (0.6–1.3 pg/mg), the highest concentrations of 92.9, 195.9, 37.0, 24.2, 13.4 pg/mg were found for **BDE-47**, **-99**, **-100**, **-153** and -**154**, respectively. The authors concluded that the results of their study support the relevance of hair for the biomonitoring of exposure.

Kucharska et al. (2015) investigated the hypothesis whether externally adsorbed and internally deposited PBDEs in hair could be distinguished. For this, hair samples collected from one volunteer were exposed under controlled conditions to standards containing **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154** and -**183** to mimic external contamination. All congeners were found to be transferred onto the hair surface. Except for **BDE-153** and -**183**, levels of all congeners were increased in the hair samples after the maximum exposure time of 10 days. The highest value was observed for **BDE-28** which was positively correlated with the exposure time. Various washing procedures to remove the PBDEs from the hair surface were investigated. Results indicated that there is no washing medium able to entirely and exclusively remove external contamination of hair. Thus, it was not possible to distinguish external from internal exposure. Therefore, the authors suggested that unwashed hair could be used as a biomarker of human exposure as it integrates internal and external exposure.

Hair was also analysed for PBDEs in samples from non-European countries as indicated in the following two studies. Malarvannan, Isobe, et al. (2013) demonstrated that PBDEs can be detected in human hair when they analysed paired human milk and scalp hair samples collected in 2008 from 30 women from the Philippines. From these, 20 women lived near a dumpsite and 10 in a non-dumpsite. The authors carefully removed external contamination (e.g. fine soil particles and dust) on the hair before analysis. Samples were subsequently dried in an oven at 40°C for 12 h, and cut into pieces of 2 mm. BDE-15, -**28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183**, -196, -197, -207 and -**209** were measured in both matrices. The concentrations of the sum of the congeners in human scalp hair samples varied widely, from 21 to 170 ng/g hair, with a mean of 71 ng/g hair. Among the PBDE congeners analysed, **BDE-209** was the dominant congener, closely followed by **BDE-47**, -**99**, -206 and -207, contributing respectively 16%–82%, 2–41%, 1–24%, 1–15% and 1–10% to the total PBDEs content. The study did not find any associations between the levels of PBDEs measured in human milk and hair.

Peng et al. (2020) investigated the occurrence of seven PBDEs (**BDE-28/**33, -**47**, -**99**, -**100**, -**153**, -**154**) in hair from 204 Chinese women living in the urban areas of Baoding and Dalian, and from 311 pregnant French women. Sample collection was performed in 2016 and 2011, respectively. The detection frequencies of the PBDEs in the Chinese and French hair samples were between 0 and 11%, and 4–57%, respectively. Except for **BDE-47** in the French samples, all median concentrations of the other samples in the two cohorts were < LOD. The highest concentration of 14.8 pg/mg was found for **BDE-99** in the Chinese samples. In the French cohort, the highest concentration was also found for **BDE-99** at a value of 396 pg/mg.

Tang et al. (2022) investigated the changes of several POPs, including **BDE-47**, -**99**, -**100**, -**153**, -**154**, -**183** and -**209** in hair samples collected from the same area in China between 2009 and 2019. The median levels in hair for **BDE-209** were 33.8 (2009, $n = 31$), 34.0 (2011, $n = 35$), 133 (2015, $n = 31$), 10.1 (2016, $n = 42$) and 2.61 (2019, $n = 37$) ng/g. The respective median sum of the seven PBDEs in the five sampling years amounted to 45.5, 70.0, 147, 17.5 and 3.55 ng/g. The authors concluded that the significant decline ($p = 0.05$) of the PBDE levels in hair since 2015 is due to the strict e-waste disposal regulation implemented in 2015 in this area.

Annex C (Table C.3) lists further studies on the determination of PBDEs in hair from non-European countries.

TABLE 13 Concentration of PBDEs in human tissues other than human milk and blood from European countries.

Country Year	Matrix	*N*	Mean [median] (ng/g lipid) BDE-28	BDE-47	BDE-49	BDE-99	BDE-100	BDE-138	BDE-153	BDE-154	BDE-183	BDE-209	Other PBDEs analysed	Sum of PBDEs	Reference
Belgium 2009–2012	Visceral fat, Adult M, F	52	[0.04]	[0.63]	NA	[0.21]	[0.21]	NA	[0.88]	[0.45]	[0.13]	NA	–	–	Malarvannan, Dirinck, et al. (2013)
	s.c. fat, Adults M, F	52	[0.06]	[0.47]	NA	[0.22]	[0.23]	NA	[0.92]	[0.50]	[0.16]	NA			
France 2013–2015	Omental adipose tissue, Adults M, F	32 (8 controls, 14 diffuse-gastric cancer patients, 10 other tumours patients)	Controls: [0.016]	Controls: [0.151]	NA	Controls: [0.038]	Controls: [0.074]	NA	Controls: [0.847]	Controls: [0.015]	Controls: [0.178]	Controls: [1.860]	–	Sum 7 PBDEs (w/o **BDE-209**): Controls: [1.346]	Perrot-Applanat et al. (2021)
			Difuse-gastric cancer: [0.016]	Difuse-gastric cancer: [0.165]	NA	Difuse-gastric cancer: [0.047]	Difuse-gastric cancer: [0.076]	NA	Difuse-gastric cancer: [2.141]	Difuse-gastric cancer: [0.019]	Difuse-gastric cancer: [0.219]	Difuse-gastric cancer: [5.014]		Difuse-gastric cancer: [2.627]	
			Other cancers: [0.009]	Other cancers: [0.075]		Other cancers: [0.022]	Other cancers: [0.067]		Other cancers: [1.831]	Other cancers: [0.021]	Other cancers: [0.289]	Other cancers: [2.755]		Other cancers: [2.392]	
Norway NR	Adipose tissue, Adults M, F	12 (Control)	NR	3.28	NA	NR	NR	NR	NR	NR	NR	NA	BDE-66, -119	Sum 10 PBDEs: 4.18	Hausken et al. (2014)
		12 (Salmon intake)	NR	2.70	NA	NR	NR	NR	NR	NR	NR	NA		Sum 10 PBDEs: 3.59	
France 2013–2014	Parietal adipose tissue, Adults F	99	[0.03]	[0.32]	NA	[0.09]	[0.12]	NA	[1.12]	[0.03]	[0.18]	[1.82]	–	Sum 7 PBDEs (w/o **BDE-209**): [10.64]	Ploteau et al. (2016)
	Omental adipose tissue, Adults F	51	[0.03]	[0.34]	NA	[0.08]	[0.12]	NA	[1.20]	[0.02]	[0.19]	[2.75]		Sum 7 PBDEs (w/o **BDE-209**): [1.97]	
Sweden 2009–2010	Faeces, Toddlers	22	< LOD	[0.41]	NA	< LOD	< LOD	NA	[0.23]	NA	NA	[18]	BDE-196, -197, -203, -206, -207, -208	–	Sahlström et al. (2015b)
Germany NR	Placenta	5	0.001[a]	0.018[a]	NR	0.010[a]	0.002[a]	NR	0.004[a]	0.001[a]	0.025[a]	0.098[a]	BDE-7, -10, -15, -17, -30, -66, -71, -77, -85, -119, -126, -139, -140, -156, -171, -180, -184, -191, 196, -197, -201, -203, -204, -205, -206, -207, -208	–	Li, Benker, et al. (2020)
Spain 2016–2017	Placenta	88	NR	NR	NR	NR	NR	NA	NR	NR	NA	NA	–	Sum 7 PBDEs: 8.6	Fernández-Cruz (2020)
	Meconium	53	NR	NR	NR	NR	NR	NA	NR	NR	NA	NA		Sum 7 PBDEs: 0.29	
France 2013–2015	Hair, Children M, F	150	NA	[< 1.00]	NA	[< 0.60]	[< 0.94]	NA	[< 0.15]	[< 1.28]	NA	NA	–	–	Iglesias-González et al. (2020)
France 2011	Hair, Adults F	311	0.26 pg/mg[b]	16 pg/mg	NA	38.5 pg/mg	5.5 pg/mg	NA	14.7 pg/mg	7.72 pg/mg	NA	NA	BDE-33	–	Peng et al. (2020)
Poland 2012	Hair, Adults M, F	12	[0.40]	[0.40]	NA	[0.21]	< LOD	NA	< LOD	< LOD	< LOD	[9.5]	–	Sum 8 PBDEs: 14	Król et al. (2014)

Abbreviations: s.c., subcutaneous; NA, not analysed; LOD, limit of detection; NR, not reported; M, male; F, female.

[a]Results in fresh weight basis.

[b]Reported as sum of **BDE-28** and -33.

3.1.1.4.4 | *Correlation between different human tissues*

Lignell, Aune, Glynn, et al. (2013) and Darnerud et al. (2015) investigated correlations between human milk and blood serum concentrations of **BDE-28**, -**47**, -66, -**99**, -**100**, -**138**, -**153**, -**154**, -**183** and -**209** in paired samples from 30 first-time mothers, and evaluated whether the PBDE concentrations in human milk were a good indicator of maternal body burden and possibly also of prenatal exposure of the infant. In human milk, **BDE-153** showed the highest median concentration (0.45 ng/g lipid), followed by **BDE-47** and -**100**. In blood serum, **BDE-209** showed the highest median concentration (0.90 ng/g lipid), followed by **BDE-153** and **-47**. Using determined concentrations < LOQ, the median levels of the sum of the 10 PBDEs in blood serum (2.8 ng/g lipid) was about two times higher than the median level in human milk (1.5 ng/g lipid). While Pearson's correlation coefficients for **BDE-28**, -**47**, -**100** and -**153** between human milk and serum ranged from 0.83 to 0.98, the correlations for **BDE-154**, -**183** and -**209** were weaker (0.38–0.66). Correlations for BDE-66, -**99** and -**138** were not calculated as the concentrations were < LOQ. The median serum/milk quotients ranged from 0.83 (**BDE-47**) to 17 (**BDE-209**), with quotients around 1 for tri- to pentaBDEs congeners and increasing quotients with increasing degree of bromination. The results were similar to the data published by Mannetje 't et al. (2012), who reviewed five studies on PBDEs and other POPs in paired serum and human milk samples. In their study, the mean serum/human milk quotients ranged from 0.70 for **BDE-47** and -**100**, to 25 for **BDE-209**.

Butryn et al. (2020) assessed the partitioning profiles of PBDEs and OH-PBDEs in 48 paired human milk and serum samples collected in 2007, and evaluated the relationship between variants in cytochrome P450 2B6 (CYP2B6) genotype and PBDE and OH-PBDE accumulation in humans see **Section 3.1.1.2.3**). The study comprised the following PBDEs and OH-PBDEs: **BDE-28, -47, -49, -85, -99, -100, -153, -154, -183**, 3'-OH-BDE-28, 4-OH-BDE-42, 3-OH-BDE-47, 5-OH-BDE-47, 6-OH-BDE-47, 4'-OH-BDE-49, 2'-OH-BDE-68, 6-OH-BDE-82, 6-OH-BDE-85, 6-OH-BDE-87, 4-OH-BDE-90, 5'-OH-BDE-99, 6'-OH-BDE-99 and 4'-OH-BDE-101. The geometric mean (GM) concentrations of PBDEs in serum and milk samples were similar (43.4 and 52.9 ng/g lipid, respectively). The concentrations of the OH-PBDEs were substantially lower in both matrices. Moreover, it was found that the OH-PBDEs were primarily retained in serum (GM = 2.31 ng/g lipid), compared to milk (GM = 0.045 ng/g lipid).

Vizcaino et al. (2014) investigated the transfer of 14 PBDE congeners and other POPs between mother and fetus by measuring 308 maternal serum samples, their respective umbilical cords and 50 placental tissues from a mother–infant cohort representative of Spanish general population. In general, the adjusted lipid-basis concentrations were higher in maternal serum than in cord serum and placenta. The concentrations of most pollutants between maternal serum and cord serum and between maternal serum and placenta were significantly correlated. The authors concluded that prenatal exposure to some PBDEs, such as **BDE-99** and -**209** is much higher than it could be anticipated from the composition of maternal serum.

Sahlström et al. (2015a) analysed two human milk pools collected from 30 mothers each in 2009 and 2010, respectively within a study to compare estimated intakes of eight PBDEs (**BDE-28, -47, -99, -100, -153**, -197, -207, -208, -**209**) along with other BFRs via diet and dust to internal concentrations in a Swedish mother-toddler cohort (see also **Section 3.3.3** on non-dietary exposure). The concentrations were similar in both milk pools. **BDE-47** was the predominant congener in the milk pools at a concentration of 31 pg/g whole weight. The lipid-based concentrations of the PBDEs in the human milk samples were compared to their respective lipid-based concentrations in the serum of a subset of 24 women. While the concentrations of tri- to pentaBDEs were higher in the human milk compared to serum, the concentrations of **BDE-153** and nona- to decaBDEs were lower. The concentration of BDE-197 was found to be similar in both matrices.

Tang and Zhai (2017) performed a systematic review on the global distribution of PBDEs in human milk, cord blood and placenta (see **Section 3.1.1.4.1** for human milk, **Section 3.1.1.4.2** for cord blood and **Section 3.1.1.4.3** for placenta) based on occurrence data from 1996–2016. In paired human milk and cord blood samples, a few studies have revealed significant correlations between these two tissues. Several studies have indicated that smaller PBDE molecules are transferred more efficiently to human milk, and that larger PBDEs are more likely to accumulate in cord blood. Results contradicting this trend in human milk and cord blood were reported; while one study found that cord blood contained higher contributions of **BDE-153** and -**154** among total PBDEs compared with human milk samples, other studies have reported a decrease in transport with an increasing degree of bromination.

Varshavsky et al. (2021) examined PBDE levels in matched maternal serum, placenta and fetal liver tissues ($n = 180$) collected between 2014 and 2016) during mid-gestation among a geographically, racially/ethnically and socially diverse population of pregnant women from Northern California and the Central Valley to characterise maternal-fetal PBDE exposures among potentially vulnerable groups. The PBDE analysis comprised the following congeners: (BDE-17, -**28, -47**, -66, -85, -**99, -100, -153, -154, -183**, -196, -197, -201, -202, -203, -206, -207, -208 and -**209**). A detection frequency threshold of more than 50% was applied for five PBDE (**BDE**-**47**, -**99**, -**100**, -**153** in all biological tissues; **BDE**-**28** in placenta and fetal liver only). Population characteristics and maternal–fetal PBDE levels were compared using censored Kendall's tau correlation and linear regression. PBDEs were commonly detected in all matrices. Before lipid adjustment, wet-weight levels of the four PBDE congeners were highest in the fetal liver ($p < 0.001$), whereas median PBDE levels were significantly higher in maternal serum than in the fetal liver or placenta after lipid-adjustment ($p < 0.001$). The authors also found evidence of racial/ethnic disparities in PBDE exposures (Non-Hispanic Black > Latina/Hispanic > Non-Hispanic White > Asian/Pacific Islander/Other; $p < 0.01$), with non-Hispanic Black women showing higher levels of **BDE-100** and -**153** compared to the referent group (Latina/Hispanic women). In addition, participants living in Fresno/South Central Valley had 34% (95% CI: –2.4 to 84%, $p = 0.07$) higher wet-weight levels of **BDE-47** than residents living in the San Francisco Bay Area. PBDEs were widely detected and differentially distributed in maternal–fetal compartments. Non-Hispanic Black pregnant women and women

from Southern Central Valley geographical populations may be more highly exposed to PBDEs. The authors conclude that further research is needed to identify sources that may be contributing to differential exposures and associated health risks among these vulnerable populations.

Kim, Bang du, et al. (2012) investigated the relationship between umbilical cord blood, maternal blood and human milk concentrations of PBDEs in South Korean. The levels of seven PBDEs (**BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183**) were measured in 21 paired samples. The total mean ± SD PBDEs concentrations in the umbilical cord blood, maternal blood and human milk were 10.7 ± 5.1 ng/g lipid (range: 2.28–30.94), 7.7 ± 4.2 ng/g lipid (range: 1.8–17.66) and 3.0 ± 1.8 ng/g lipid (range: 1.08–8.66), respectively. **BDE-47** (45%–73% of total PBDEs) was observed to be present dominantly in all samples, followed by **BDE-153**. A strong correlation was found for major PBDE congeners between human milk and cord blood or maternal blood and cord blood samples.

Yu, Li, et al. (2021) collected 32 paired human samples of maternal serum, umbilical cord serum and placentas. The authors measured the concentrations of 12 PBDE congeners (BDE-17, -**28**, -**47**, -66, -85, -**99**, -**100**, -**138**, -**153**, -**154**, -**183**, -190) in placenta (sum 12 PBDEs = 0.09–3.92 ng/g lipid), maternal serum (0–13.7 ng/g lipid) and umbilical cord serum samples (0.04–17.4 ng/g lipid). The authors found a significant linear relationship ($p = 0.01$) between umbilical cord serum and maternal serum for the total concentrations of PBDEs, with a linear slope of 0.46 ($R^2 = 0.33$). The authors calculated the umbilical cord-maternal serum median concentrations ratios for only three congeners with values of 0.54, 1.0 and 0.62 for **BDE-28**, -**47** and -**153**, respectively.

Tang and Zhai (2017) performed a systematic review on the global distribution of PBDEs in placenta, human milk, cord blood and placenta (see also **Section 3.1.1.4.1** for human milk, **Section 3.1.1.4.2** for cord blood and **Section 3.1.1.4.3** for placenta) based on occurrence data from 1996–2016. Four studies evaluated paired human milk and placental samples, and significant positive correlations between the two matrices were found in only one study that collected five sets of milk and placentas from an e-waste site in China. The study also reported similar congener profiles for milk and placentas, and no relationship was observed in the control group in their or other studies. A strong and positive correlation between placentas and cord blood for the sum of PBDEs and most PBDE congeners was found. The placental transfer of highly brominated PBDEs, such as BDE-196 and -197 was greater than that of **BDE-47**, which according to the authors might be due to the greater lipophilicity and affinity for binding with plasma proteins.

Matovu et al. (2021) collected paired human samples of placenta and cord blood samples ($n = 30$) in 2018 from primiparous mothers living in Kampala/Uganda, and analysed these for 24 tri- to decaBDE congeners. The median (range) levels of the sum of PBDEs were 7.11 (0.25–30.9) ng/g lipid in placental tissues, and 11.9 (1.65–34.5) ng/g lipid in cord blood serum. **BDE-209** was the dominant congener in both matrices, contributing 40.5% and 51.2% to the sum of PBDEs in placenta and cord blood, respectively. Statistical analysis showed no significant difference between the levels of PBDEs in cord blood and placenta samples ($p = 0.665$). Non-significant associations were observed between the sum of PBDEs in maternal placenta and maternal age, household income, pre-pregnancy BMI and beef/fish consumption. The authors suggest that this is due to ongoing exposure to PBDEs through multiple sources, such as dust from indoor/outdoor environments and ingestion of other foods. Based on absolute concentrations, the extent of transplacental transport was greater for congeners with nine and 10 bromines (**BDE-209**, -206 and -207) than for lower ones, such as **BDE-47**, which according to the authors suggest alternative transplacental transfer mechanisms besides passive diffusion.

Zhang, Cheng, et al. (2021) reviewed studies on internal exposure levels of various POPs, including PBDEs in placenta, and both maternal and umbilical cord sera. There were substantial variations in transplacental transfer efficiencies obtained for individual PBDE congeners, with average umbilical cord: maternal serum concentration rates ranging between 0.76 and 1.67. The ratios for certain congeners varied widely. For example, reported lipid-adjusted ratios for **BDE-209** ranged from 0.5 to 2.88. In addition, a higher range of transfer efficiency values was reported for **BDE-209** compared with PBDEs with fewer bromine atoms. Reported placental: maternal serum concentration ratios were lower than corresponding umbilical cord: maternal serum concentration ratios, except for **BDE-183**. This indicated that PBDE accumulation was lower in placental tissue than in umbilical cord blood. However, the findings were based on sparse available data and more information is needed for deeper analysis.

Fernández-Cruz et al. (2020) evaluated the prenatal exposure to seven PBDEs (**BDE-28**, -**47**, -77, -97, -**100**, -**153**, -**154**) and other POPs using meconium and placenta as non-invasive biological samples. A total of 88 placenta and 53 meconium samples were collected in Ourense (Spain) at the delivery and after birth from mothers and their infants. The sum of PBDEs (mean, range) in placenta was given as 8.6 (< LOD–45) ng/g lipid. For meconium, the respective concentrations were reported as 0.29 (< LOD–3.2) ng/g lipid. While in placenta the main contributors to the sum of PBDEs were **BDE-47** (23%), -**100** (18%), -**99** (15%), -**28** (13%) and -**154** (12%), the predominant congeners in meconium were **BDE-47** (40%), -**28** (17%), -**154** (15%), -**153** (13%) and -**99** (8%). Thus, the presence of PBDEs in meconium confirms the transplacental transfer of these compounds. The statistical evaluation of the data indicated that the PBDE accumulation in placenta samples increased with weight increment during pregnancy and parity of the mother.

Björvang, Vinnars, et al. (2021) measured the concentrations of three PBDEs (**BDE-47, -99** and **-153**) along with a number of other POPs in maternal serum, placenta and fetal tissues (adipose tissue, liver, heart, lung and brain) in 20 pregnancies that ended in stillbirth at gestational weeks 36–41. In most of the samples the PBDEs could not be detected above the LOQ. A 100% detection frequency was only found for **BDE 47** and **-153** in fetal adipose tissue with median (range) concentrations of 63.3 (21.09–264.73) and 103.67 (31.55–865.9) pg/g ww, respectively. It is striking that the PBDEs were detected in the fetal adipose tissue even in cases where the compounds were not detected in the maternal serum and placenta. Consequently, maternal serum and placenta may underestimate actual fetal exposure.

Malarvannan, Dirinck, et al. (2013) analysed PBDEs in paired visceral fat and subcutaneous abdominal fat samples collected in 2010–2012 from 52 obese individuals in Belgium. The study included **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154** and -**183**. The levels and the patterns of PBDE distribution in both tissue depots were not significantly different. The median (range) sum of PBDEs in visceral and subcutaneous fat were 2.6 (1.0–13) ng/g lipid and 2.7 (0.8–14) ng/g lipid, respectively. **BDE-153** was the dominant congener, followed by **BDE-47**, -**154**, -**100** and -**99**. The PBDE concentrations in the fat samples did not correlate with the age of the patients.

In their study, Ploteau et al. (2016) aimed to characterise the internal exposure levels of PBDEs and other POPs in a set of 113 adult French women, within three biological compartments, i.e. omental adipose tissue, parietal adipose tissue and serum. The analysis comprised **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183** and -**209**. The median (range) concentrations of **BDE-209** in parietal adipose tissue, omental adipose tissue and serum were 1.8 (0.55–103) ng/g lipid, 2.8 (0.80–10.8) ng/g lipid and 0.68 (0.08–20.11) ng/g lipid, respectively. For the sum of the other seven analysed PBDEs, the median (range) concentrations in the three matrices were 2.1 (0.73–10.6) ng/g lipid, 1.97 (0.81–10.8) ng/g lipid and 0.95 (0.47–8.2) ng/g lipid, respectively. The correlation between the concentrations measured in parietal vs. omental adipose tissue was found strongly significant ($p < 0.0001$). While the correlation between the concentrations determined in serum and parietal adipose tissue were significant for PCDD/Fs and PCBs, they were less clear for PBDEs for which the ratio between circulating and storage compartment was in favour of the adipose tissue.

Deshmukh et al. (2020) studied associations of 17 PBDEs (BDE-17, -**28**, -**47**, -**49**, -66, -71, -77, -85, -**99**, -**100**, -119, -126, -**138**, -**153**, -**154**, -**183**, -**209**) and a number of other POPs with body mass index (BMI) and changes in their concentration following bariatric surgery. Subcutaneous fat, visceral fat and liver tissue samples were collected from 106 patients undergoing Roux-en-Y gastric bypass surgery for weight loss or patients who were undergoing abdominal surgery for nonbariatric reasons. After adjustments for age and gender and corrections for multiple testing ($p < 0.007$), BMI was not statistically associated with the 17 PBDEs. In a group of 10 individuals resampled up to 5 years after bariatric surgery and substantial weight loss, the concentrations of brominated compounds including PBDEs increased significantly with weight loss in subcutaneous fat.

Sahlström et al. (2015b) investigated the feasibility of using faeces as a non-invasive matrix to estimate serum concentrations of PBDEs and other BFRs in toddlers for biomonitoring purposes. In their study, faeces samples from 22 toddlers were analysed for **BDE-28**, -**47**, -**99**, -**100**, -**153**, -196, -197, -203, -206, -207, -208 and -**209**. The objective of this study was not only to determine PBDE concentrations in faeces, but also to compare the concentrations to results in matched serum samples from the same toddlers and to study possible associations between the two matrices (see **Section 3.1.1.4.3** on Other human tissues). Tetra- to octaBDE concentrations were significantly higher in serum compared to faeces with **BDE-153** having the highest mean difference between the sample matrices. **BDE-209** was found in significantly higher concentrations in faeces compared to serum. Significant correlations (Pearson's, $\alpha = 0.05$) between congener-specific concentrations in faeces and serum were found for all BDEs except BDE-197 and -203. The authors concluded that the faeces-serum associations found can be used to estimate serum concentrations of tetra- to decaBDEs from faeces concentrations and enable a non-invasive sampling method for biomonitoring PBDEs in toddlers.

Chen, Niu, et al. (2018) investigated the relationship between **BDE-209** exposure and thyroid hormones in occupational workers of a DecaBDE manufacturing plant by analysing serum and urine levels of **PBDEs**, and serum thyroid hormones in 72 workers (see also **Section 3.1.3**). Serum concentrations of **BDE-209** ranged from 67.4 to 109,000 ng/g lipid, with a median of 3420 ng/g lipid, contributing to 93.1% of the total PBDEs. The median **BDE-209** level in urine was determined as 1.31 ng/mL. The concentration of **BDE-209** in urine was highly correlated with that in the serum ($r^2 = 0.440$, $p < 0.001$), indicating that urine may be a good non-invasive biomonitoring medium of **BDE-209** body burden in occupational workers.

Zhao, Liu, and Pang (2021) performed a meta-analysis to investigate whether hair can be used as a non-invasive biomarker of human exposure to PBDEs. For this, they reanalysed the data from cross-sectional human studies to investigate correlations between the concentrations of **BDE-28**, -**47**, -**99**, -**100** and -**209** in hair and serum. The sample sizes in these studies ranged from 160 to 249. Significant positive relationships for the five PBDE congeners were found, and the results of the sensitivity analysis showed that the conclusion remains the same regardless of whether a fixed-effects model or random-effects model is used. The authors conclude that hair may be a promising biomarker for biomonitoring human exposure to several PBDE congeners within a certain detection range, which should be explored by studies with larger sample sizes.

In summary, a number of studies tried to derive correlations for PBDEs between different human matrices. In some studies, the conclusions were hampered by a high number of left-censored data in specific matrices, other studies revealed conflicting results. Correlations were found between PBDE levels in human milk and blood with median serum/milk ratios ranging from around 0.7–0.8 for **BDE-47** to around 17–25 for **BDE-209**, with quotients around 1 for tri- to pentaBDEs and increasing quotients with increasing degree of bromination. Strong correlations were also found for predominant PBDE congeners between human milk and cord blood or maternal blood and cord blood. Limited data on PBDEs in matched faeces/serum indicate that the faeces/serum associations found can be used to estimate serum concentrations for tetra- to decaBDEs from faeces concentrations which could enable a non-invasive sampling to biomonitor PBDEs in toddlers. It is noteworthy that one study determined PBDEs in fetal adipose tissue of stillborn babies even in cases where the compounds were not detected in the maternal serum and placenta which is an indication that maternal serum and placenta may underestimate the actual fetal exposure.

3.1.1.4.5 | *Levels of PBDE metabolites in human samples*

Data on metabolites of PBDEs in human samples are mostly related to the determination of OH-PBDEs. However, these compounds can also be synthesised naturally by marine organism, especially through the symbiosis of sponges with bacteria (Schmitt et al., 2021, see also **Section 1.3.3**). A number of naturally occurring OH-PBDEs, such as 6-OH-BDE-47 and 2-OH-BDE-68 have been structurally identified with the common feature that the hydroxy group is attached to one of the *ortho*-positions in the PBDE structure (EFSA CONTAM Panel, 2011b; Schmitt et al., 2021). The hydroxyl group in the metabolites formed from the synthetically produced PBDEs can be located not only in the -*ortho*, but also in the *meta*- or *para*-position to the bridge between the two rings. Where 2- or 6-OH-BDE is found, it is almost impossible to distinguish whether the compounds are naturally occurring or are biotransformation products from PBDEs used as flame retardants. This is especially true for cohorts with high seafood consumption.

Appendix D (Table D.1) summarises data on OH-, MeO-PBDEs and brominated phenols (whether produced as metabolites of PBDEs or directly by biota), reported in the last two decades from European and non-European countries. Recently generated data on PBDE metabolites in human samples from European countries are scarce (Dufour et al., 2017; Meijer et al., 2008). Dufour et al. (2017) analysed several phenolic organohalogenated compounds including three OH-PBDEs in human serum from 274 people aged from 18–76 years old living in Belgium. While 5-OH-BDE-47 was not detected in any sample (LOD = 2.3 pg/mL), the detection frequency for 5′-OH-BDE-99, and 6-OH-BDE-47 were very low (2.2%, 2.6%, respectively). The highest concentrations for these two OH-PBDEs were 8.2 and 4.5 pg/mL, respectively. The detection frequencies for 2,4,6-TBP and 2,3,4,6-tetrabromophenol were 63.8% and 11.8%, respectively with median (max) levels of 57.3 (1277) and < LOQ (51.1) pg/mL. In contrast, 2,3,6-TBP and 2,4,5-TBP could not be detected in any sample at LOQs of 2.4 and 5.0 pg/mL, respectively. The congener profile for bromophenols was largely dominated by 2,4,6-TBP which is in accordance with findings from non-European studies. However, the concentrations in the Belgium samples were lower than in samples of occupational exposed workers or Asian cohorts with high seafood consumption. The authors note that 2,4,6-TBP has different likely sources including the TBBPA synthesis (as an intermediate). Exposure through seafood consumption has also been suggested as the main exposure way based on its known natural production by some marine organisms and its previous detection in fish.

Almost all studies that report recent data on OH-PBDEs in humans are coming from non-European countries, often in connection with occupational exposure in polluted environments, such as waste disposal sites or e-waste dismantling areas.

Li, Tian, et al. (2017) analysed human milk samples from 25 women who did not directly participate in e-waste recycling operations, but lived for more than 20 years adjacent to e-waste recycling sites in a village in China. The sample collection was done in 2012–2013 and the analysis comprised besides the eight PBDEs (**BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183** and -**209**), also the eight OH-PBDEs (3-OH-BDE-47, 2′-OH-BDE-68, 6-OH-BDE-47, 4′-OH-BDE-49, 4-OH-BDE-42, 6′-OH-BDE-99, 4-OH-BDE-90, 6-OH-BDE-85) in the analysis of the human milk samples. All OH-PBDEs analysed, even in the human milk sample with the highest PBDE concentration, were < LOD.

In their review, Wei et al. (2021) summarised published data on OH-PBDEs in human tissues. Various congeners of OH-PBDEs have been detected in maternal and cord serum, placenta, human milk and urine. Most of the data were generated from populations living in non-European countries, especially China and the USA. The concentrations of OH-PBDEs are closely related to the sampling population and sites. Occupational exposure to PBDEs, such as working at an e-waste dismantle site, may result in higher levels of OH-PBDEs in human bodies than those living in ordinary places. This was shown in a study with five e-waste dismantling workers from China where the highest total concentration of OH-PBDEs in serum was found at 896 ng/g lipid. While the sum of the seven dominant PBDE congeners (BDE-193, -197, -203, -206, -207, -208, -**209**) in the serum of the workers ranged from 12.3 to 267 ng/g lipid (with **BDE-209** making up around 80% of the total), the sum of the three dominant OH-metabolites (6-OH-BDE-196, 6-OH-BDE-199 and 6′-OH-BDE-206) were determined at concentrations from 44.7 to 896 ng/g lipid, respectively. The levels of OH-PBDEs found in the electronic waste dismantling workers were similar or even higher than their precursors. **MeO-PBDE** metabolites could not be identified in the study (Ren et al., 2011). The results of this study are different from other *in vivo* and *in vitro* studies, especially with low brominated PBDE congeners which indicate smaller concentration ratios (generally < 1%) between OH-PBDE metabolites and their precursors (Wiseman et al., 2011).

Zhang, Cheng, et al. (2021) reviewed reported internal exposure levels of PBDEs, OH-PBDEs and varies other POPs in placenta, and both maternal and umbilical cord sera. They also summarised data on the transplacental transfer and placental distribution characteristics of each class of compounds. Concentrations of OH-PBDEs in paired maternal and umbilical cord sera were investigated in six of the studies covered in the review. In five of the studies, levels in cord serum samples were found to be higher than to, or equal to, levels in corresponding maternal serum samples. For example, median wet weight-based umbilical cord: maternal serum values of 1.1 and 1.78 for 5-OH-BDE-47 have been obtained from analyses of 69 and 20 sets of samples from San Francisco and Cincinnati in the USA, respectively. It was also reported that fetal concentrations of 6-OH-BDE-47 and 5-OH-BDE-47 exceeded the concentrations measured in maternal serum. Most studies have reported higher wet weight-based concentrations of OH-PBDEs in cord blood than in maternal blood. These results indicate that OH-PBDEs, which are more hydrophilic than the lipophilic parent PBDE compounds, traverse the placental membrane more readily than the parent compounds.

Ho et al. (2015) studied the correlation between levels of PBDEs in human blood plasma and those of the corresponding bromophenols conjugates in human urine. Concentrations of 17 PBDEs, 22 OH-PBDEs, 13 MeO-PBDEs and 3 bromophenols

in plasma collected from 100 voluntary donors in Hong Kong were measured. Geometric mean concentration of the sum of PBDEs, OH-PBDEs, MeO-PBDEs and bromophenols in human plasma were 4.45, 1.88, 0.42 and 1.59 ng/g lipid, respectively. Concentrations of glucuronide and sulfate conjugates of 2,4-DBP and 2,4,6-TBP measured by direct LC–MS/MS in paired samples of urine were found in all of the parallel urine samples, in the range of 0.08–106.49 µg/g creatinine.

Feng, Xu, et al. (2016) studied bromophenols as potential exposure markers for human biomonitoring of PBDEs in human urine. The analytical method comprised 19 bromophenols with detection limits of 23 pg/mL. The method was applied in a pilot study and 2-bromophenol, 4-bromophenol, 2,4-DBP and 2,4,6-TBP as the predominant analytes were detected in human urine samples collected from the general population at mean (SD) concentrations of 2.10 (1.58), 3.46 (2.35), 0.66 (0.2) and 2.35 (0.91) µg/g creatinine (corresponding to volumetric concentrations of 2.04 (4.33), 7.55 (8.40), 0.65 (0.90) and 5.57 (4.05) µg/L urine), respectively. The authors also determined the bromophenols in deconjugated form, and the results showed only the conjugated (glucorinated) form could be identified in the human urine samples. The authors concluded that the determination of bromophenols in urine may be an alternative to the traditional analytical approaches, e.g. analysis of PBDEs in serum and human milk, to measure human body burden of PBDEs.

In summary, based on the data on PBDE metabolites reported in the last two decades from European and non-European countries, most of the studies deal with OH-PBDEs and bromophenols, with only a few studies reporting on MeO-PBDEs. A wide variety of metabolites were determined with different congener profiles, presumably due to the source and extent of exposure. Although some recent studies have shown that 6-OH-BDE-47 and 2,4,6-TBP seem to be major contributors to the sum of OH-PBDEs and bromophenols in human matrices, a general conclusion regarding predominant metabolites cannot be derived from the data shown in Appendix D. In addition, it may be difficult to decide whether these two compounds are metabolites of parent PBDEs or are the result of exposure to naturally generated substances.

3.1.1.5 | *Kinetic modelling*

PBK models in experimental animals

Emond et al. (2010, 2013) developed rat and mouse PBK models for **BDE-47**.

The rat model included eight compartments: blood, brain, liver, adipose tissue, kidney, placenta, fetus and rest of the body. The model was built to predict **BDE-47** tissue concentrations in both male and female (pregnant and non-pregnant) rats. Data from Emond et al. (2010) and Sanders et al. (2006) were used to calibrate and to evaluate the model (same studies but other set of data). In conclusion, the model showed adequate estimation, e.g. simulation/measured ratio within a factor 2, for adipose tissue, blood, kidney, fetus and liver concentration.

The mouse model included seven compartments: blood, brain, adipose tissue, kidney, liver, gastrointestinal tract and rest of the body (without placenta and fetus compartment). This mouse model was built to predict **BDE-47** tissue concentrations and its elimination in faeces and urine, and to evaluate the role of transporters for **BDE-47**. Data from the literature were used to calibrate (by optimisation) the model. Data from Staskal et al. (2005) were used to evaluate the model prediction (excretion). According to the authors, refinement of this model is needed, involving more mechanistic studies in the elimination of **BDE-47** in adult mice. However, the model is able to predict accurately the cumulative excretion of **BDE-47** (urinary and faeces) after oral administration, and the kinetic profile in adipose tissues, liver, brain, kidney and blood in mice.

PBK models in humans

Song et al. (2016) developed a PBK model for **BDE-47** in humans, based on the Emond et al. (2010, 2013) model, by changing the rat into human parameters. The objective was to study the association between **BDE-47** and the timing of menarche. According to the authors, their PBK model can be used to quantify the potential bias in epidemiological studies in associations with serum **BDE-47** levels and the timing of menarche. However, the authors do not describe how the model was calibrated, nor how it was validated from independent data. This makes it difficult to use this model for a risk assessment according to WHO recommendations (IPCS, 2009).

Lorber and Toms (2017) developed a simple toxicokinetic model for **BDE-47** to estimate the infant body burdens following breastfeeding or formula feeding. Pooled serum samples were obtained for half years increments ($n = 4$), from birth (0–3 month) until 4 years, and analysed. Information on infant feeding practices (breastfeeding or formula feeding) for infants who provided these samples were not reported. For the intakes from breastfeeding, the authors assumed a linear decline in milk levels (50% after 6 months and another 50% for the second 6 months of breastfeeding). The predicted infant body burdens of **BDE-47** (breastfed and/or formula fed) was compared with observed average infant serum concentrations of **BDE-47**. They found that their model underpredicted the serum concentration: the serum concentration predicted ranged between 2 to 5 ng/g lipid, while the observed concentration was 20 ng/g lipid. To explain this disparity between predictions and observations, the authors suggested different hypotheses (internal debromination of higher-brominated PBDEs, inaccurate model parameter such as elimination constant, additional exposure pathways via dust ingestion). In conclusion, the CONTAM Panel considers that this toxicokinetic model is not appropriate for studying the impact of breastfeeding on levels in infants.

Shin et al. (2018) studied the prenatal contribution to the body burden of **BDE-47** in young children after birth. For this purpose, they collected the median concentration of **BDE-47** from umbilical cord blood in 108 neonates in South Korea. Simulation was made by PBK modelling to estimate the disposition of **BDE-47** in body from birth to 5 years. The prenatal exposure was the input dose in the PBK model. For simulation of total body burden up to 5 years, the authors considered house dust, babyfood

and human milk consumption, as postnatal exposure. The model was initially developed by Emond et al. (2010, 2013) for rats and was extrapolated to humans by taking in account modifications of physiological and anatomical parameters. Nevertheless, the performance of the model (validation step) in predicting **BDE-47** exposure in humans was not demonstrated. This makes it difficult to use this model for a risk assessment according to WHO recommendations (IPCS, 2009).

Zhang, Hu, et al. (2022) developed two oral PBPK human models for **BDE-209** (considering enterohepatic circulation or not). These models have been evaluated according to the WHO recommendation (WHO/IPCS, 2010). The structure (compartments) of the models was built according to the PBPK model of **BDE-47** previously described by Song et al. (2016). For model calibration, the authors used data (estimated oral intakes of **BDE-209** and measured serum concentrations of **BDE-209**) from 26 participants (Chinese subjects). These human data were used to estimate specific parameters of **BDE-209** for humans, e.g. tissue-plasma partition coefficients. For validation, the authors used biomonitoring data from China where oral intakes of **BDE-209** were estimated. In conclusion, the authors provide a full description of their models: calibration, validation and evaluation (sensitivity and uncertainty analysis). Both models predicted the distribution of **BDE-209** in blood for human exposure to **BDE-209** via dietary and dust ingestion in less than a two-fold difference compared to the estimated intake. These two models have been developed specifically for the Chinese adult population, nevertheless they could be applied to the European population. More interesting, their models provide a more precise value of the half-life of **BDE-209** in humans, e.g. between 15 and 18 days.

3.1.2 | Toxicity in experimental animals

This section provides an overview of the toxicity data in experimental animals described in the previous EFSA Opinion on PBDEs (EFSA CONTAM Panel, 2011b) with the new data published since then.

Several studies were identified in which the experimental animals were exposed to PBDEs together with other BFRs and/or other POPs (Allais et al., 2020; Berger et al., 2014; Berntsen et al., 2021; Dianati et al., 2017; Ernest et al., 2012; Gouesse et al., 2021; Hansen et al., 2019; Johanson et al., 2020; Khezri et al., 2017; Lefevre et al., 2016; Mailloux et al., 2014, 2015; Myhre et al., 2021; Tung et al., 2016, 2017). The CONTAM Panel did not consider these studies informative for the hazard characterisation of PBDEs and thus these studies were not considered in this Opinion.

The presence of trace amounts of brominated dioxins and furans (PBDD/Fs) has been reported in PBDE technical products used as test substances in the toxicity studies (Bondy et al., 2013; Dunnick, Shockley, Pandiri, Kissling, Gerrish, Ton, Wilson, Brar, Brix, Waidyanatha, Mutlu, & Morgan, 2018; Hanari et al., 2006; Kodavanti et al., 2010). No information on the presence of such impurities in individual congeners has been identified. Therefore, this was taken into account in the uncertainty analysis (see **Section 3.5**). Information about the purity and the nature of the impurities present in the test substances is provided in the Tables describing the studies, when provided by the authors.

3.1.2.1 | *Acute toxicity studies*

In the previous EFSA Opinion, no information was available on the acute toxicity of any specific PBDE congener (FAO/WHO, 2006; EFSA CONTAM Panel, 2011b). The available data on the technical products of PBDEs showed low acute toxicity with oral LD_{50} values in rats between 2640 and 6200 mg/kg bw for PentaBDE, > 5000 mg/kg bw for OctaBDE and > 2000 mg/kg bw for DecaBDE (ECB, 2001, 2002, 2003, see EFSA CONTAM Panel, 2011b).

No new studies have been identified since the previous Opinion.

3.1.2.2 | *Repeated dose toxicity studies*

In the previous Opinion (EFSA CONTAM Panel, 2011b) it was concluded that the main targets in sub-chronic and chronic toxicity studies in rats and mice for a variety of PBDE congeners and PBDE technical products were the liver, and the thyroid hormone, nervous, reproductive and immune systems.

The sections below provide, by toxicological endpoint and for each PBDE congener or technical product, a brief summary of the effects reported in the previous Opinion, a summary of the effects reported in the new studies identified in the open literature since then, and an overall summary of all the evidence available.

The details of the studies considered in the previous Opinion can be found in EFSA CONTAM Panel (2011b). The details of the new studies published since then are provided in Appendix E (Tables E.1, E.2, E.3, E.4 and E.5 for **BDE-47**, **-99**, **-209**, other PBDE congeners (BDE-3 and -15) and PBDE technical products (e.g. DE-71), respectively).

3.1.2.2.1 | *Effects on the liver*

Studies considered in the previous EFSA assessment

The previous EFSA Opinion (EFSA CONTAM Panel, 2011b) reported no effects on the liver after exposure to **BDE-47**, **-99**, **-153** and **-209**, other than effects on liver enzymes. Induction of enzymes of hepatic drug metabolism, such as CYPs and UDP-glucuronosyltransferases (UGTs), was observed after exposure to these congeners (Sanders et al., 2005; van der Ven, van de Kuil, Leonards, et al., 2008; Richardson et al., 2008; Albina et al., 2010; Bruchajzer et al., 2010).

For the technical product DE-71, the major effects observed in rats and mice after oral exposure for 3 to 90 days were liver enlargement (Dunnick & Nyska, 2009; van der Ven, van de Kuil, Verhoef, et al., 2008; Zhou et al., 2001) and histopathological changes, mainly centrilobular hepatocellular hypertrophy and vacuolisation (Dunnick & Nyska, 2009; van der Ven, van de Kuil, Verhoef, et al., 2008). Induction of enzymes of hepatic drug metabolism was also observed after exposure to DE-71 (Kuiper et al., 2008; Zhou et al., 2001) and in addition, a loss of apolar retinoids (e.g. retinol and retinylesters), normally stored in the liver, was noted in rats after 28 days exposure to DE-71 (Öberg et al., 2010; van der Ven, van de Kuil, Verhoef, et al., 2008).

It was also reported that treatment of pregnant rats with DE-71 from GD6 to PND12 or PND18 induced hepatomegaly in pups at PND12, PND18 or PND31 (Ellis-Hutchings et al., 2006). Also, in the study by Dunnick and Nyska (2009), increases in absolute liver weight and hepatocellular hypertrophy appeared at doses ≥ 5 mg DE-71/kg bw per day in a 90-day rat study. Hepatocellular vacuolisation appeared in male rats at 50 mg/kg bw per day. In mice, increases in liver weight appeared at 50 mg/kg bw per day.

Studies published since the previous EFSA assessment

Since the publication of the previous Opinion, short-term studies reporting on liver effects have been identified for **BDE-47**, **-99**, **-209**, for other individual PBDEs (BDE-15) and for PBDE technical products (DE-71, PentaBDE and OctaBDE). Details of these studies are provided in Appendix E Table E.1 for **BDE-47**, Table E.2. for **BDE-99**, Table E.3 for **BDE-209**, Table E.4 for BDE-15 and Table E.*5* for technical products).

BDE-47

Exposure by gavage of adult female mice to **BDE-47** for 28 days induced liver toxicity, e.g. increased incidence of vacuolation and pyknotic nuclei in hepatocytes and lymphocytic infiltration in periportal areas at 0.45 mg/kg bw per day (Maranghi et al., 2013). In **male rats**, increased absolute liver weight and centrilobular hepatocyte hypertrophy, changes in serum clinical chemistry and microsomal enzyme induction were seen after 5 days exposure at ≥ 48.5 mg/kg bw per day (Shockley et al., 2020) as well as lipid accumulation/steatosis at doses ≥ 0.03 mg/kg bw per day after 12 weeks exposure (Zhang, Yu, et al., 2017).

Exposure of male rat pups to doses ≥ 15 mg/kg bw per day during gestation and lactation, and also directly from PND12–21 resulted in similar changes: increased absolute and relative liver weight, increased incidences of centrilobular hepatocytes hypertrophy and fatty changes (Dunnick, Shockley, Pandiri, Kissling, Gerrish, Ton, Wilson, Brar, Brix, Waidyanatha, Mutlu, & Morgan, 2018). In another study, no changes in absolute liver weight were reported in male mouse pups examined on PND21 and PNW20 after exposure of their mothers to **BDE-47** at 0.2 mg/kg bw per day from GD8 to PND21 (Khalil, Parker, Mpanga, et al., 2017). Hepatic steatosis was reported in male mouse pups exposed to **BDE-47** at ≥ 0.002 mg/kg bw per day from GD6-PND21 (Wang, Yan, et al., 2018).

BDE-99

Only one new study was identified on the liver effects of **BDE-99**, reporting increases in oxidative stress markers (CAT and SOD) in the liver of rat offspring exposed during gestation and lactation (GD6–PND21) to 1 and 2 mg **BDE-99**/kg bw per day (Blanco et al., 2014).

BDE-209

Exposure by gavage of adult male rats to **BDE-209** for 28 days resulted in increased relative liver weight at 1000 mg/kg bw per day, however decreases were observed at 2000 and 4000 mg/kg bw per day (Curčić et al., 2015). Changes in serum clinical chemistry were also noted. Histopathological changes (such as inflammation, increased number of mitoses and polymorphonuclear cell infiltration) were induced at the two highest doses, and edema of hepatocytes, mild hyperemia and small focal haemorrhages were observed at 1000 mg/kg bw per day (Curčić et al., 2015).

In another study, increases in liver weight (absolute and relative), changes in clinical chemistry and extensive liver damage (e.g. inflammation, necrosis) were also reported at ≥ 50 mg/kg bw per day after 28 days (Sun, Wang, Liang, et al., 2020). An increase in liver malondialdehyde (MDA) levels and a marked decrease in SOD activities was also reported at these doses. The NOAEL was 5 mg/kg bw per day.

Changes in serum clinical chemistry were also reported in rats exposed for 90 days at 100 mg/kg bw per day (Wang et al., 2010). Hepatocellular spotty necrosis and perivasculitis in the liver were reported in female rats exposed to **BDE-209** by gavage for 20 days at 100 mg/kg per day (Yang et al., 2014). Hepatomegaly and clear histopathological changes (such as focal infiltration of inflammatory cells) were observed in the liver of female mice exposed for 2 years to 400 mg **BDE-209**/kg bw per day (Feng et al., 2015).

Increases in absolute liver weight were observed in mice exposed for 8 weeks to 500 mg/kg bw per day (Che et al., 2021). At 20, 100 or 500 mg/kg bw per day, severe histopathological changes: focal infiltration of inflammatory cells and necrotic degeneration were reported. There were also significant increases in aspartate aminotransferase (AST) (all doses) and ALT (at highest dose) concentrations in serum. In addition, dose-dependent increases of pro-inflammatory factors, TNFα and

IL-1β and reduction of anti-inflammatory factors IL-4, IL-6 and IL-10 were noted. There was a dose-related increase in apoptosis (Che et al., 2021). The LOAEL was 20 mg/kg bw per day.

Significant increases in liver weight were reported in male rat pups (absolute at 10 and 1000 mg/kg feed and relative at ≥ 10 mg/kg feed), and in females rat pups (absolute and relative at 1000 mg/kg feed) exposed during gestation and lactation (maternal dose of 0.7 mg/kg bw per day and 66.3 mg/kg bw per day, respectively) (Fujimoto et al., 2011). Diffuse cell hypertrophy was observed at ≥ 100 mg/kg feed (maternal dose of 7.0 mg/kg bw per day). The maternal dose of 0.7 mg/kg bw per day was the LOAEL for the offspring.

Significant absolute and relative liver weight increases were reported in male rat pups exposed to **BDE-209** by gavage at 600 mg/kg bw per day from PND10 to PND42 and hepatocellular fatty degeneration and vascular degeneration, inflammatory foci and necrosis were observed at 300 and 600 mg/kg bw per day (Lee et al., 2010[27]). Thus, the NOAEL was 100 mg/kg bw per day.

Other individual PBDE congeners

One study was identified on the liver effects of BDE-15, reporting increased relative liver weight, swelling of the hepatic cells, inflammation, vacuolisation and hepatocellular hypertrophy in male mice exposed to BDE-15 for 28 days at 1.2 mg/kg bw per day, the only dose tested (Zhang et al., 2014).

PBDE technical products

After exposure of F344/*N* rats by gavage to DE-71 for 14 weeks dose-related increases in serum cholesterol concentrations were observed at ≥ 36 mg/kg bw per day as well as statistically significant increases in liver weight (absolute and relative), hepatocellular hypertrophy and activities of liver enzymes at ≥ 3.6 mg/kg bw per day (NTP, 2016). Increased incidences of hepatocyte cytoplasmic vacuolisation was also seen at 36 mg/kg bw per day in males and at 71 and 357 mg/kg bw per day in both sexes. The NOAEL was 0.007 mg/kg bw per day. In B6C3F1 mice after 14 weeks exposure, statistically significant increases in absolute and relative liver weights as well as hepatocellular hypertrophy were noted at 36 mg/kg bw per day in males, and at 71 and 357 mg/kg bw per day in both sexes. Significant increased incidences of hepatocytes necrosis were observed in both sexes and increased incidences of hepatocyte cytoplasmic vacuolisation in males at 357 mg/kg bw per day. Statistically significant increases in liver enzymes activities were reported at ≥ 3.6 mg/kg bw per day (NTP, 2016). The NOAEL was 3.6 mg/kg bw per day based on hepatocellular hypertrophy and effects on liver weight.

After 2-year exposure in mice, centrilobular hepatocellular hypertrophy (both sexes, from 2.1 mg/kg bw per day), eosinophilic foci (in females at 21 and 71 mg/kg bw per day), clear cell foci (males at 21 mg/kg bw per day), fatty changes (females at 21 and 71 mg/kg bw per day), focal necrosis (males at 21 mg/kg bw per day) ang Kupffer cell pigmentation (from 2.1 mg/kg bw per day) were reported (NTP, 2016). The LOAEL was 2.1 mg/kg bw per day.

Increased absolute and relative liver weight, centrilobular hepatocellular hypertrophy and fatty changes were observed on PND22 in male pup Wistar Han rats exposed via the dams during GD6–PND21 and also by direct gavage on PND12–21 to DE-71 at 15 and 50 mg/kg bw per day. In addition, an increased trend of serum cholesterol levels and increased mitoses in hepatocytes were noted in pups exposed at ≥ 0.1 mg/kg bw per day. No effects were observed on the levels of triglycerides (Dunnick, Shockley, Pandiri, Kissling, Gerrish, Ton, Wilson, Brar, Brix, Waidyanatha, Mutlu, & Morgan, 2018). The LOAEL was 0.1 mg/kg bw per day based on cholesterol increases observed at this dose level.

Significantly increased absolute and relative liver weights were noted at 36 mg DE-71/kg bw per day in males and females F1 Wistar Han rats exposed by gavage during gestation and lactation (GD6–PND21) and thereafter from PND12–PND21 and for an additional 13 weeks. At this dose, significantly increased incidences of centrilobular and midzonal hepatocyte hypertrophy and hepatocyte cytoplasmic vacuolation were also seen in both sexes, and significantly increased incidence of fatty changes in the liver in males (Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Recio, et al., 2018; NTP, 2016). The NOAEL was 10.7 mg/kg bw per day. In a follow-up study, the F1 animals were exposed for an additional 2 years; the following effects were reported: centrilobular hepatocellular hypertrophy (both sexes, from 2.1 mg/kg bw per day), eosinophilic foci and fatty changes (both sexes at 10.7 and 36 mg/kg bw per day), nodular and oval cell hyperplasia (females at 36 mg/kg bw per day). Cholangiofibrosis occurred in three females at 36 mg/kg bw per day (Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Recio, et al., 2018; NTP, 2016). The LOAEL was 2.1 mg/kg bw per day.

Exposure of F0 male and female rats by gavage to DE-71 for 21 weeks before mating, during mating, gestation, lactation and F1 postweaning until PND42 resulted in effects on liver weight: increased absolute and relative liver weight was observed in male F0 rats at 25 mg/kg bw per day, while in F1 males only increased absolute liver weight was observed at this dose, and increased relative liver weight at 5 and 25 mg/kg bw per day (Bondy et al., 2013). In F0 females, absolute liver weight was increased at 5 and 25 mg/kg bw per day and relative liver weight was not significantly altered by treatment. Increased absolute and relative liver weight was observed in female F1 rats at 5 and 25 mg/kg bw per day. Hepatocellular hypertrophy was seen in male and female F0 and F1 rats at 25 mg/kg bw per day, and in F0 M at 5 mg/kg bw per day, consistent with microsomal enzyme induction (Bondy et al., 2013). The NOAEL was 0.5 mg/kg bw per day.

[27]This study was cited in the previous EFSA assessment on PBDEs (EFSA CONTAM Panel, 2011b) and it is included in the current assessment to provide insight into additional observations by the study authors not reported in the previous Opinion.

Liver enlargement was noted on PND23 in male and female rats exposed by gavage to 30 mg DE-71/kg bw per day from PND5 to PND22 (de-Miranda et al., 2016). This effect did not persist on PND70 or PND120. Statistically significant increases of liver EROD and PROD activities were also reported.

Feeding DE-71 to female rats from GD1 to PND21 resulted in increased relative liver weight in dams at 30 mg/kg bw per day, and increased absolute and relative liver weight at 3 and 30 mg/kg bw per day in the offspring on PND21 (Bowers et al., 2015). On PND105, increased relative liver weight was still seen at 30 mg/kg bw per day and increased absolute and relative liver weight was observed in males at PND250. Increased activities of xenobiotic metabolising enzymes were seen in dams at 30 mg/kg bw per day and in offspring at 3 and 30 mg/kg bw per day. Increased liver EROD was also noted at 0.3 mg/kg bw per day in offspring on PND21. The NOAEL was 0.3 mg/kg bw per day based on changes in liver weight.

In another study, female mice were exposed by feeding DE-71 on cornflakes from 4 weeks before conception until weaning of the pups at PND21 (Kozlova et al., 2020). Dams and female offspring were then kept on a normal diet until the offspring were 4 months of age. There was a slight increase in relative liver weight in the dams at 0.1 mg/kg bw per day and an increase of the absolute liver weight in offspring at 0.1 and 0.4 mg/kg bw per day. The LOAEL was 0.1 mg/kg bw per day.

Pregnant Wistar dam rats were exposed by gavage to 0, 20, 40 or 60 mg DE-71/kg bw per day from GD7 to PND14 (study 1) or to 0, 40 or 60 mg DE-71/kg/day from GD7 to PND16 (study 2). Dam liver weights (absolute and relative) were increased dose-dependently in all exposure groups on PND14 in study 1 (~ 20% in high dose). On PND27, in study 2, liver weights were similar between groups. Offspring liver weights were markedly increased (up to ~ 50%), particularly on PND16 (study 2). By PND27 the increase was less pronounced, demonstrating some recovery after exposure ceased. There was an increased severity of hypertrophy and vacuolation of hepatocytes with increasing dose in offspring on PND16. Hypertrophy of hepatocytes was localised to the centrilobular areas. No microvesicular vacuolation was observed (Ramhøj et al., 2022). The LOAEL was 20 mg/kg bw per day.

Increases in relative liver weight were observed in rats exposed by gavage for 28 days to ≥ 40 mg PentaBDE/kg bw per day. Dose-related increases in liver GSH concentration and glutathione reductase activity in serum were reported from 8 mg/kg bw per day. Increased MDA concentration was seen at 200 mg/kg bw per day. There were also dose-related and time dependent decreases in total antioxidant status (TAS) in serum and increased serum ALT and AST levels. Fatty degeneration was observed at 200 mg/kg bw per day (Bruchajzer et al., 2010[28]). In addition, a dose-dependent increase in ALA-S activity and an increased concentration of total porphyrins were observed. A dose-dependent increase in urine excretion of total porphyrins was also noted. The disturbed synthesis of porphyrins greatly affects the function of heme-containing proteins-hemoproteins (Bruchajzer, 2011). The LOAEL was 2 mg/kg bw per day.

Impaired redox homeostasis, indicated by increased levels of reduced (GSH) and oxidised (GSSG) glutathione and increased concentration of MDA in the liver and reduced TAS in serum, were reported in rats exposed by gavage for 7 or 28 days to OctaBDE at doses ≥ 0.4 mg/kg bw per day (Bruchajzer et al., 2014). Increased activity of glutathione S-transferase (GST) was also noted in the liver. The LOAEL was 0.4 mg/kg bw per day. In another study by the same authors, administration of OctaBDE by gavage to female rats at 0, 2, 8, 40 and 200 mg/kg bw per day for 7, 14, 21 or 28 days affected heme biosynthesis and the levels of porphyrins (Bruchajzer et al., 2012). Lower aminolevulinic acid synthase (ALA-S) and aminolevulinic acid dehydratase (ALA-D) activity were observed in the liver. In addition, increased concentrations of high carboxylated porphyrins were found from the lowest dose. In urine, there were dose-dependent and time-dependent increased concentrations and excretion of total porphyrins. The LOAEL was 2 mg/kg bw per day.

Overall summary of the effects on the liver

In summary, repeated dose exposure of rodents to **BDE-47**, **-209**, -15 and DE-71 induced effects in the liver, e.g. increased liver weight, centrilobular hepatocyte hypertrophy, lymphocytic infiltration in periportal areas, lipid accumulation/steatosis, changes in serum clinical chemistry, microsomal enzyme induction. Similar effects, including also inflammation and necrosis, were seen in offspring exposed via the dams during gestation and/or postnatally until weaning. Increases in oxidative stress markers were noted in the liver of rat offspring exposed in utero and during lactation to **BDE-99**.

For **BDE-47**, the LOAEL for adult mice based on histopathological effects was 0.45 mg/kg bw per day (Maranghi et al., 2013), and for adult rats based on lipid accumulation/steatosis was 0.03 mg/kg bw per day (Zhang, Yu, et al., 2017). The NOAEL for offspring mice exposed in utero and during lactation based on hepatic steatosis and injury was 0.002 mg/kg bw per day (Wang, Wu, et al., 2018) and the NOAEL for offspring rats exposed in utero, during lactation and directly from PND12–21, based on increased absolute and relative liver weight and hepatocellular hypertrophy was 0.1 mg/kg bw per day (Dunnick, Shockley, Pandiri, Kissling, Gerrish, Ton, Wilson, Brar, Brix, Waidyanatha, Mutlu, & Morgan, 2018).

For **BDE-209**, the NOAEL for adult rats based on increase in relative liver weight and liver damage was 5 mg/kg bw per day (Sun, Wang, Liang, et al., 2020). The maternal dose of 0.7 mg/kg bw per day was the LOAEL for offspring rats exposed in utero and during lactation (Fujimoto et al., 2011).

For BDE-15, the LOAEL for adult mice was 1.2 mg/kg bw per day based on hepatocellular hypertrophy and histopathological effects (Zhang et al., 2014).

For the technical product DE-71, the NOAEL (14 weeks exposure) based on increased absolute and relative liver weight and hepatocellular hypertrophy was 0.007 mg/kg bw per day for adult rats (NTP, 2016) and 3.6 mg/kg bw per day for adult

[28]This study was cited in the previous EFSA assessment on PBDEs (EFSA CONTAM Panel, 2011b) and it is included in the current assessment to provide insight into additional observations by the study authors not reported in the previous Opinion.

mice (NTP, 2016). For adult mice exposed for 2 years, the LOAEL based on histopathological findings (such as fatty changes and focal necrosis) was 2.1 mg/kg bw per day (Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Recio, et al., 2018; NTP, 2016). The LOAEL for offspring rats exposed in utero, during lactation and for 2 years postweaning was 2.1 mg/kg bw per day based on histopathological effects (hepatocellular hyperthrophy) (Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Recio, et al., 2018; NTP, 2016).

Repeated administration of PentaBDE caused fatty degeneration in the liver, and had a porphyrogenic effect. Effects on the heme biosynthesis and the levels of porphyrins are also induced by OctaBDE.

3.1.2.2.2 | *Effects on the thyroid hormone system*

Studies considered in the previous EFSA assessment

In its previous Opinion the CONTAM Panel concluded that the data available at the time provided convincing evidence that PBDEs affect the thyroid hormone homeostasis (EFSA CONTAM Panel, 2011b). Exposure of rats to **BDE-47**, **-99**, **-209** or DE-71 during gestation or postnatally caused reduction of serum T4 (total T4, TT4) and sometimes triiodothyronine (TT3) levels. It was concluded that changes in enzymes of hepatic xenobiotic metabolism and in the binding of thyroid hormones to transthyretin seemed to play a key role in the decrease in serum T4 observed in rodents.

For **BDE-47**, exposure of rats or mice by gavage for 14 days resulted in decreases in TT4 and free T4 (FT4) levels at doses of ≥ 18 mg/kg bw per day (Hallgren et al., 2001; Hallgren & Darnerud, 2002; Darnerud et al., 2007). Four-day exposure of female mice at 100 mg/kg bw per day resulted in a decrease in serum TT4 (Richardson et al., 2008). Exposure of rats by gavage to this congener during gestation (GD6) resulted in histologic and morphometric changes in the thyroid at doses of 0.14 mg/kg bw (occasional follicular cyst formation, multiple areas of degenerated follicular epithelium, detachment of thyroid follicular epithelial cells, which can be found in the colloid) and 0.7 mg/kg bw (mild cyst formation). No changes were noted in thyroid weight (Talsness et al., 2008). Decreases in TT4 were observed in rat offspring exposed by i.v. (GD15–PND20) to 0.02 and 0.2 mg **BDE-47**/kg bw per day during gestation and lactation (GD15–PND20), and decreases in FT4 were observed at 0.2 mg/kg bw per day (Suvorov et al., 2009).

For **BDE-99**, no changes in TT3, TT4 and FT4 were seen after 45 days in rats exposed to a single dose of this congener at 0.6 or 1.2 mg/kg bw (Alonso et al., 2010). No statistically significant change in TT4 levels were seen in dams or offspring after exposure of mice during gestation and lactation (GD4–PND17) to 452 mg/kg bw per day (Skarman et al., 2005) or from GD6–PND21 to 18 mg/kg bw per day (Branchi et al., 2005). However, decreased TT4 levels were observed on PND1 in rat dams exposed during gestation (GD6) to 0.06 mg/kg bw and in their offspring on PND22 at 0.3 mg/kg bw (Kuriyama et al., 2007).

For **BDE-209**, after 28 days gavage exposure of rats to this congener, increases in circulating TT3 levels were noted in females at 60 mg/kg bw per day. No effect was observed on TT3 in males or on TT4 in both sexes (van der Ven, van de Kuil, Leonards, et al., 2008). Exposure of rats to 320 mg/kg bw per day during gestation (GD6–18) caused reduction of TT4 levels in female offspring and increases in serum thyroid-stimulating hormone (TSH) levels in male and female offspring on PND42 (Kim et al., 2009), whereas decreases of TT3 levels were observed in mice exposed at ≥ 10 mg/kg bw per day (Tseng et al., 2008). In rats exposed postnatally (PND10–PND42) to **BDE-209**, decreases in TT3 were noted from 100 mg/kg bw per day, and increases in TSH were observed at doses of 300 and 600 mg/kg bw per day. Follicular degeneration in the thyroid gland (slightly enlarged colloid in a few acini, dose-dependent transformation of cuboidal epithelium into squamous epithelium, multiple areas of degenerated follicular epithelium and slight attenuation of follicular epithelium) was also observed at these doses and increase in thyroid weights was seen at 600 mg/kg bw per day (Lee et al., 2010[27,29]). The LOAEL was 100 mg/kg bw per day.

Postnatal exposure (PND2–PND15) of mice to 6 and 20 mg **BDE-209**/kg bw per day resulted in dose-dependent non-statistically significant decrease of TT4 level in males (Rice et al., 2007). The LOAEL was 6 mg/kg bw per day.

For the technical product DE-71, decreased levels of TT4 and FT4 were reported in female mice exposed for 14 days to 18, 36 or 72 mg/kg (Fowles et al., 1994) and decreased levels of TT4 were noted in rats after 4 days exposure to ≥ 30 mg/kg bw per day as well as decreased TT3 levels at ≥ 100 mg/kg bw per day (Zhou et al., 2001). The same authors reported that exposure of rats from GD6 to PND21 to 1, 10 and 30 mg DE-71/kg bw per day caused a significant decrease in TT4 levels in dams on GD20 and PND22 (at 30 mg/kg bw per day), in fetuses on GD20 (two highest doses), and in pups on PND4 and PND14 (two highest doses), with recovery by PND36 (Zhou et al., 2002). The NOAEL was 1 mg/kg bw per day.

Age and dose-dependent decreased TT4 was observed after exposure by gavage of pregnant rats to 1.7, 10.2 and 30.6 mg DE-71/kg bw per day from GD6 to PND21, whereas the levels of TT3 remained unchanged (Szabo et al., 2009). The NOAEL was 1.7 mg/kg bw per day. In a similar study, exposure of rats to 18 mg/kg bw per day from GD6 to PND18 resulted in a decrease in TT4 levels in dams on PND19 and in pups on PND18 with full recovery by PND31. Increased TSH levels were also observed in dams (Ellis-Hutchings et al., 2006).

Following exposure of juvenile rats to DE-71 (males: PND23–PND53, females: PND22–PND41), TT4 levels were decreased in females at 30 and 60 mg/kg bw per day and at 3, 30 and 60 mg/kg bw per day in males. TT3 levels were decreased and TSH levels increased at 30 and 60 mg/kg bw per day on PND31 in males only. Decreased colloid area and increased follicular cell heights were observed in the thyroid of males and females at 60 mg/kg bw per day on PND20 and 31 (Stoker et al., 2004).

[29]This study was cited in the previous EFSA assessment on PBDEs (EFSA CONTAM Panel, 2011b) and it is included in the current assessment to provide insight into additional observations by the study authors not reported in the previous Opinion.

Studies published since the previous EFSA assessment

Since the publication of the previous Opinion, new studies reporting on effects on the hypothalamus-pituitary-thyroid axis have been identified for **BDE-47**, **-209** and PBDE technical products (DE-71). No new studies have been identified for **BDE-99**.

BDE-47

Three studies were reported in adult mice or rats. Cellular debris was seen in the thyroid follicular cell lumen of mice exposed orally (feed) to **BDE-47** at 0.45 mg/kg bw per day for 28 days (Maranghi et al., 2013). Significant decreases in TT4 and TT3 levels were reported in male rats exposed by gavage for 5 days to 48.5 and 485 mg **BDE-47**/kg bw per day (Shockley et al., 2020). The NOAEL was 4.85 mg/kg bw per day. There was a statistically significant decrease in plasma TT4 at 0.86 mg/kg bw per day in adult male rats exposed by gavage to **BDE-47** for 8 weeks and a statistically significant dose-related decrease in TT3 and increase in reverse T3 (rT3) at doses ≥ 0.026 mg/kg bw per day (Wang, Zhu, et al., 2020). The NOAEL was 0.0009 mg/kg bw per day.

Several studies were performed in offspring of mice or rats and these are described below.

Dose-related decreases in TT3 and TT4 levels were observed on PND22 in male and female Wistar Han rat pups exposed during gestation and lactation (from GD6 to PND21) and by direct gavage from PND12–21 to **BDE-47** at doses of 0.1, 15 and 50 mg/kg bw per day (Dunnick, Shockley, Pandiri, Kissling, Gerrish, Ton, Wilson, Brar, Brix, Waidyanatha, Mutlu, & Morgan, 2018). Decreased TT4 levels were also observed in the dams on PND22. The decrease in TT4 were generally greater in pups than in the dams. There was also a significant dose-related increased trend in TSH levels in male and female pups. The NOAEL was 0.1 mg/kg bw per day.

Small but statistically significant decreases in TT4 were noted on PND 21 in male mice offspring exposed during gestation and lactation (GD6-PND21) to 0.2 mg **BDE-47**/kg bw per day. The NOAEL was 0.002 mg/kg bw per day (Wang, Yan, et al., 2018). No changes in TT3, FT3, TT4 and FT4 were reported in male pups exposed by gavage to 10 mg **BDE-47**/kg bw on PND10 (Costa et al., 2015). Decreased TT4 levels were noted in 2 months rat pups exposed by gavage on PND10 to **BDE-47** at 5 mg/kg bw. No effects were noted at 1 and 10 mg/kg bw (He et al., 2011).

After exposure of female rats by gavage to 0, 0.1, 1.0 and 10 mg **BDE-47**/kg bw per day from 10 days before mating, throughout gestation and lactation, until weaning of the pups on PND21, offspring were observed on PND88 (Li, Gao, et al., 2020). In females, decreased relative thyroid weights were observed at 1.0 and 10 mg/kg bw per day and decreased serum TT3 and TT4 levels at doses ≥ 0.1 mg/kg bw per day. Smaller and immature thyroid follicular cells (unorganised arrangement of thyroid follicular cells and replacement by increased connective tissue) were seen, as well as cell detachment and loss in some disturbed follicles. The LOAEL was 0.1 mg/kg bw per day. The number of TUNEL positive cells was highly increased in 1.0 and 10 mg/kg bw per day when compared to untreated control rats, suggesting enhanced DNA fragmentation, a characteristic feature of apoptosis. In males, increased TT3 levels at 1.0 and 10 mg/kg bw per day but no effect on TT4 levels were reported by Li, Gao, et al. (2020).

Dose-dependent reductions in TT3 and TT4 levels were seen in rat dams administered ≥ 3.2 mg **BDE-47**/kg feed from GD1 to PND14 (corresponding to a dose of ~ 0.4 mg/kg bw per day using a conversion factor of 0.12[30]) on PND1, in neonates on PND7, and both in dams and neonates at PND14 (Wang, Liu, et al., 2011).

Male and female rats were exposed by gavage to 0, 0.1, 1.0, 10 mg **BDE-47**/kg bw per day from 10 days prior to mating, until weaning of offspring on PND21. In the treated dams, there was a significant increase in TT3 levels at the two highest doses and in TT4 levels at all doses. Changes in thyroid follicle structure (expanded thyroid follicles and hyperplastic epithelial cells and shed cell remnants filled in the exhausted follicular lumen) were also observed (Li, Liu, et al., 2018). The LOAEL was 0.1 mg/kg bw per day.

BDE-209

Four studies were reported in adult mice or rats. Significant decreases in TT4 and FT4 levels were reported at 1000 and 2000 mg/kg bw per day in male rats exposed by gavage for 28 days to **BDE-209**, and significant decreases in FT3 and TT4; FT3, TT4 and FT4; and TT3 at 1000, 2000 and 4000 mg/kg bw per day, respectively (Curčić et al., 2012). Increased TT3 and TT4 levels were reported in male rats exposed by gavage to doses ≥ 10 mg **BDE-209**/kg bw per day for 90 days (Wang, Wang, et al., 2011).

Abnormal structures in the thyroid (smaller follicular cavities, disordered follicular epithelial cells) were observed at ≥ 5 mg/kg bw per day in male rats exposed by gavage to **BDE-209** for 28 days (Wang et al., 2019). Increased height of follicular epithelial cells was observed at 5 mg/kg bw per day, as well as swelling and vacuolation of part of the follicular cells. At 50 mg/kg bw per day, a small amount of mast cells infiltrated in the follicular stroma and edema was widely seen in follicular epithelial cells. A few exfoliated epithelial cells were observed. At 500 mg/kg bw per day, swelling was observed in a large number of epithelial cells as well as more exfoliated epithelial cells and mast cells. Moreover, focal necrosis was seen. Dose-dependent decreased average colloid area was also reported. In addition, significant decreases in

[30]In the absence of specific factors for the conversion of the concentrations in feed into doses per kg bw per day for developmental studies, the conversion has been done using a factor of 0.12 for rats assuming a subacute study duration (EFSA, 2012).

TT3, TT4, FT3 and FT4 levels were noted at 500 mg/kg bw per day and increased TSH and thyrotropin-releasing hormone (TRH) levels in treated groups. Significant decreases in FT3 levels were reported at 50 mg/kg bw per day. The LOAEL was 5 mg/kg bw per day based on histopathological changes in the thyroid.

Significant reductions in serum levels of TT3 and TT4 were reported at 950 mg/kg bw per day in male mice exposed to **BDE-209** by gavage for 35 days. The NOAEL was 750 mg/kg bw per day (Sarkar et al., 2016).

Regarding studies in offspring, male and female rat **pups** were exposed to **BDE-209** via the dams during gestation (GD10–20) and lactation (PND1–20) (Fujimoto et al., 2011) (see **Section 3.1.2.2.1** for details). Increased absolute and relative thyroid weights were observed in the dams on PND20 at doses ≥ 10 mg/kg feed (statistically significant at 10 and 1000 mg/kg feed. In male pups, significant decreases in TT3 (on PND20) and TT4 (on PNW11) levels were seen at 1000 mg/kg feed, as well as increased absolute thyroid weights at 100 mg/kg feed on PND20. Diffuse follicular hypertrophy was observed in male pups at 1000 mg/kg feed and in females at 10 and 1000 mg/kg feed. On PNW11, cases of follicular cell hypertrophy were seen in males from 10 mg/kg feed and one case in females at 100 and 1000 mg/kg feed. The maternal dose of 10 mg/kg feed (0.7 mg/kg bw per day) was the LOAEL for the offspring.

Significant reduction of TT3 and TT4 levels were reported in male pups of mice exposed to **BDE-209** via their mothers during lactation (PND1–28) at 500 or 700 mg/kg bw per day. Reduction of TT3 and TT4 levels were also noted in the dams (Sarkar et al., 2018).

Female mice were exposed during gestation (GD7–9 to GD15) to **BDE-209** (Chi et al., 2011). Dose-related decreases in TT3 and TT4 levels were observed in their offspring, statistically significant at 2500 mg/kg bw per day and at 1500 and 2500 mg/kg bw per day, respectively. The NOAEL was 750 mg/kg bw per day based on TT4 decreases.

Mixtures of specific congeners

In the study by Ruis et al. (2019), rats were orally dosed with a mixture of PBDEs (**BDE-28**, -**47**, -**99**, -**100**, -**153** and - **209**, composition not specified) in a total dose of 105.3 mg/kg bw per day or a vehicle control during gestation (GD6–15). TT3 levels in the dosed dams were significantly increased relative to controls at GD14/15 but not at GD12/13. In the placental tissues, there were significant differences in TT3 and TT4 based on tissue location (e.g. fetal vs. maternal). There was a significant decrease in TT3 levels in the fetal placental tissue relative to the maternal placental tissue for all control and exposed groups. There was also a significant decrease in TT4 levels in the fetal placental tissue relative to the maternal placental tissue in control females on GD12/13. TT3 levels in the maternal and fetal placenta significantly differed from one another based on the GD of the fetus. There was a significant increase in TT3 levels in exposed female fetus on GD12/13.

PBDE technical products

In adult animals, after 14 weeks exposure of male and female F344/N rats by gavage to DE-71, dose-related decreases in TT4 level on days 4, 25 and 93 were reported in males and females at ≥ 3.6 mg/kg bw per day (NTP, 2016). Increases in serum TSH concentrations were noted in females at ≥ 71 mg/kg bw per day (on day 25 and at 14 weeks) and in males at 357 mg/kg bw per day at 14 weeks. Increased incidences of thyroid gland follicle hypertrophy were also seen in females at ≥ 36 mg/kg bw per day and at 357 mg/kg bw per day in both sexes (NTP, 2016). The NOAEL was 0.007 mg/kg bw per day.

In B6C3F1/N mice exposed by gavage for 2 years to DE-71, significantly increased incidences of thyroid follicle hypertrophy were observed in males at 2.1 mg DE-71/kg bw per day and in females at 21 and 71 mg/kg bw per day (Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Recio, et al., 2018; NTP, 2016).

Several studies reported effects in offspring of mice or rats.

Male and female rats were exposed by gavage to DE-71 at 0, 0.5, 5 and 25 mg/kg bw per day for 21 weeks (Bondy et al., 2013). Then, F0 rats were mated and exposure continued throughout breeding, pregnancy, lactation and postweaning until pups were PND42 (F1 generation). Significant decreases in TT4 levels were noted in F0 males at 5 and 25 mg/kg bw per day and in females at 25 mg/kg bw per day. Decreased TT3 and TT4 levels were also seen in F1 males and females at 25 mg/kg bw per day. The NOAEL was 0.5 mg/kg bw per day based on decrease TT4 in F0 males.

Female rats were exposed by gavage to DE-71 from GD6 until PND21, and their offspring analysed till PND60 (Kodavanti et al., 2010[27,30]). In the dams, decreases in TT4 levels were noted on PND22 at 10.2 and 30.6 mg/kg bw per day. Increased serum TSH levels were also seen (statistically significant at 30.6 mg/kg bw per day). In male and female offspring, dose- and age-dependent decreases in circulating TT4 level were reported between PND4 and PND21 from 10.2 mg/kg bw per day. This effect was no longer apparent in males on PND60, but TT4 levels in females were elevated compared to controls. In the offspring, serum TSH levels increased during postnatal development. On PND60, increased serum TSH levels was reported in males, and decreased levels in females. The NOAEL was 1.7 mg/kg bw per day.

Decreased TT4 levels on PND23, were reported in male and female rats exposed by gavage on PND5–22 to 30 mg DE-71/kg bw per day. No effects were observed on PND70 or PND120 (de-Miranda et al., 2016).

Female rats were exposed to 60 mg DE-71/kg bw per day from GD1.5 through lactation and F1 pups were sacrificed on PND21 or outbred at ~ 80 days of age. F1 females were sacrificed on GD14.5 or at 5 months of age. F1 males were sacrificed at 5 months of age. Increased relative thyroid weight was reported in F1 rats at 5 months (Blake et al., 2011). Female rats were fed

[31]This study was cited in the previous EFSA assessment on PBDEs (EFSA CONTAM Panel, 2011b) and it is included in the current assessment to provide insight into additional observations by the study authors not reported in the previous Opinion.

with DE-71 from GD1 to PND21 (Bowers et al., 2015). Decreased TT3 and TT4 levels were observed in the dams at 30 mg/kg bw per day, and in the offspring at 3 and 30 mg/kg bw per day. These effects were transient and returned to normal on PND50. In addition, significant increases in TSH serum levels were observed on PND21 at 30 mg/kg bw per day. Increased epithelial cell height of the thyroid follicles was also reported on PND21 at 30 mg/kg bw per day. The NOAEL was 0.3 mg/kg bw per day.

Exposure by gavage of male and female rat pups from GD6 to PND21 to DE-71 resulted in reduction of TT4 levels at doses ≥ 2.85 mg/kg bw per day on PND7 and PND21, and at doses ≥ 5.7 mg/kg bw per day on PND14. The maximum reduction was seen on PND21 after exposure to 34.3 mg/kg bw per day (Miller et al., 2012). The NOAEL was 0.96 mg/kg bw per day.

Exposure by gavage of male rat pups from GD6 to PND21 to DE-71 resulted in reduction of TT4 and FT4 at 10 and 30 mg/kg bw per day. Reduction of TT4 was also observed in the dams at the same doses and in FT4 at 30 mg/kg bw per day (Bansal et al., 2014). The NOAEL was 1 mg/kg bw per day.

Pregnant female rats were exposed by gavage from GD6 to PND21 to DE-71. In male offspring exposed to 30.6 mg/kg bw per day plasma T4 and T3 levels were reduced on PND21 and recovered to control levels by PND60 when TSH levels were elevated (Shah et al., 2011). The NOAEL was 1.7 mg/kg bw per day.

Female rats were exposed by gavage 28 days before breeding, during gestation and lactation to DE-71. There was a decrease in TT4 levels in treated offspring at 5.7 and 11.4 mg/kg bw per day on PND21 (Poon et al., 2011). The LOAEL was 5.7 mg/kg bw per day.

In female Wistar Han rats exposed by gavage from GD6 to PND21 to DE-71 and thereafter their offspring from PND12–PND21, dose-related decreases in TT3 and TT4 levels were observed on PND22 in male and female pups from doses of 0.1 mg/kg bw per day (Dunnick, Shockley, Pandiri, Kissling, Gerrish, Ton, Wilson, Brar, Brix, Waidyanatha, Mutlu, & Morgan, 2018). Decreased TT4 levels were also observed in dams on PND22. The decreases in TT4 were generally greater in the pups than in the dams. Significant dose-related trend in TSH levels were also noted in pups after DE-71 exposure (increased serum TSH levels in males at 15 and 50 mg/kg bw per day and in females at 50 mg/kg bw per day. Significantly increased incidences of follicle hypertrophy were seen in both sexes at 50 mg/kg bw per day (Dunnick, Shockley, Pandiri, Kissling, Gerrish, Ton, Wilson, Brar, Brix, Waidyanatha, Mutlu, & Morgan, 2018). The LOAEL was 0.1 mg/kg wb per day. In a follow-up study, F1 rats were exposed for an additional 2-year at 0, 2.1, 10.7 and 36 mg/kg bw per day). Significant increases in the incidences of follicle hypertrophy were reported in the 36 mg/kg bw per day males and females afer 3 months (interim sacrifice) (NTP, 2016). After 2-year exposure, there was a significant increased incidence of thyroid folliular hypertrophy in males at doses ≥ 2.1 mg/kg bw per day and in females at 10.7 and 36 mg/kg bw per day and a significant increased incidence of thyroid follicular cell hyperplasia in females at 36 mg/kg bw per day (Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Recio, et al., 2018; NTP, 2016). The LOAEL was 2.1 mg/kg bw per day.

In the study by Ramhøj et al. (2022) previously described in **Section 3.1.2.2.1**, in which pregnant Wistar rats were exposed by gavage to 0, 20, 40 or 60 mg DE-71/kg bw per day from GD7 to PND14 (study) or to 0, 40 or 60 mg DE-71/kg bw per day from GD 7 to PND 16 (2d. study), DE-71 significantly reduced serum TT4 and TT3 levels in both dams and offspring without a concomitant upregulation of TSH. On GD15, dam TT4 (studies 1 and 2) and TT3 levels (study 2) were dose-dependently reduced by DE-71 exposure. In study 2, there was no statistically significant effect on TSH concentration, albeit the values appeared more variable at 60 mg/kg bw per day compared to controls. In offspring, all doses of DE-71 markedly reduced postnatal TT4 concentrations to 25%–45% of control levels (study 1). On PND16 and PND27, TT3 levels were reduced to ~ 75%–85% of controls (study 2). DE-71 exposure was discontinued on PND16, but there was only slow recovery in TT4 and TT3 levels between PND16 and PND27. There was no effect on thyroid weight in the dams on PND27 nor in female pups on PND16 or in male pups on PND27. In male pups, no changes in the follicular epithelium, follicular morphology, stroma or c-cells were evident in thyroid glands on PND16. However, a dose-dependent increase in minimal vacuolation of follicular colloid was noted (statistically significant higher incidence at 60 mg/kg bw per day, study 2) (Ramhøj et al., 2022) The LOAEL was 20 mg/kg bw per day.

Overall summary of the effects on the thyroid hormone system

In summary, exposure of rats to **BDE-47**, **-209** or DE-71 resulted in increased thyroid weight, changes in thyroid hormone homeostasis and of the follicle structure in adult rats. Reductions of TT3 and/or TT4 levels with increased serum TSH levels in some cases were also observed in offspring exposed via the dams during gestation and lactation.

The lowest LOAELs for **BDE-47** were 0.026 mg/kg bw per day for adults based on decreased TT3 levels (Wang, Zhu, et al., 2020), and 0.1 mg/kg bw per day for offspring based on reduced TT3 and TT4 levels (Li, Gao, et al., 2020).

Reduced TT4 levels were observed in pregnant rats exposed during gestation to 0.06 mg **BDE-99**/kg bw per day, and in offspring exposed to 0.3 mg/kg bw per day (Kuriyama et al., 2007).

In studies with **BDE-209**, increases in absolute and/or relative thyroid weight, diffuse follicular hypertrophy and degeneration of the follicular epithelium were noted in rat offspring exposed via the dams during gestation and/or postnatally. The lowest LOAEL for **BDE-209** was 0.7 mg/kg bw per day for adults based on increased thyroid weight, and offspring based on follicular cell hypertrophy (Fujimoto et al., 2011).

Increased incidence of follicular cell hypertrophy was seen in offspring exposed to 36 mg DE-71/kg bw per day via the dams during gestation, lactation and for an additional 13 weeks postweaning (NTP, 2016). The lowest LOAELs for DE-71 were 3.6 mg/kg bw per day for adults based on decreases in TT4 levels (NTP, 2016), and 0.1 mg/kg bw per day for offspring based on decreases in TT3 and TT4 levels (Dunnick, Shockley, Pandiri, Kissling, Gerrish, Ton, Wilson, Brar, Brix, Waidyanatha, Mutlu, & Morgan, 2018).

3.1.2.2.3 | *Effects on lipid and sugar metabolism*

Studies considered in the previous EFSA assessment

The studies available at the time of the previous EFSA Opinion on PBDEs (EFSA CONTAM Panel, 2011b) indicated that exposure to **BDE-47** or **-99** via injection routes (*i.v.* and *s.c.*) affected lipid and glucose metabolism (Ceccatelli et al., 2006; Suvorov et al., 2009; Suvorov & Takser, 2010).

Studies published since the previous EFSA assessment

Since the publication of the previous Opinion, studies reporting on metabolic effects following oral exposure have been identified for **BDE-47**, **-209** and the PBDE technical product DE-71. No oral toxicity studies have been identified for **BDE-99**. Details of these studies are provided in Appendix E (Table E.1 for **BDE-47**, Table E.3 for **BDE-209** and Table E.5 for technical products).

BDE-47

McIntyre et al. (2015) exposed post-weaning mice by oral gavage to 0 or 1 mg/kg bw per day of **BDE-47** and found no effect on glucose tolerance, insulin sensitivity, liver somatic index or white adipose tissue. Adult male rats were orally administered **BDE-47** at 0, 0.001, 0.03 and 1 mg/kg bw per day for 8 weeks (6 days per week) (Zhang, Li, Liu, et al., 2016). After the treatment there was a shallow but dose-dependent increase fasting glucose (significant at all doses), but there was no change serum insulin. No effects were found on serum cholesterol or triglyceride concentrations. Microvesicular steatosis was observed in liver sections of rats treated with 1 mg/kg bw per day of **BDE-47** but not at lower doses. Effects on sugar metabolism was supported by transcriptomics analysis of the liver, which was carried out on rats exposed to 0.03 mg/kg bw per day and the control. Within the list of 1049 genes differentially regulated by the treatment, the Gene Ontology Terms 'glucose transport', 'positive regulation of glucose transport' and 'regulation of glucose transport' were significantly enriched (FDR < 0.01) and Type 1 diabetes mellitus was the most enriched KEGG pathway ($p < 10^{-10}$).

Metabolic effects in mice included decreased body weight following **BDE-47** exposure from GD6 to PND21 (LOAEL of 0.2 mg/kg bw per day, NOAEL of 0.002 mg/kg bw per day; Wang, Wu, et al., 2018), reduced serum triglycerides and an increase in liver triglycerides (exposure from partuition to PND21 and examined at 10 months of age; Khalil et al., 2018). Serum triglycerides were reduced in pups at 10 months of age after exposure to **BDE-47** via dams (from GD8 to parturition) with a LOEL of 1 mg/kg bw per day (Khalil et al., 2018). Both gestational and postnatal exposures increased the liver/serum triglyceride ratio at 10 months (Khalil et al., 2018). Feeding a high-fat diet appeared to exacerbate metabolic effects of **BDE-47** (Wang, Yan, et al., 2018).

BDE-209

Alimu et al. (2021) reported that body weights of adult male C57BL/6 mice exposed to 800 and 1000 mg/kg bw per day for 60 days were significantly increased on days 45 and 60 and this was associated with an increased weight of adipose tissues at the end of the experiment on day 60. **BDE-209** exposure resulted in dose-dependent increase in liver weight, which was significant at all doses. The CONTAM Panel noted that the reporting of the duration and route of exposure was unclear.

Increased serum triglycerides along with reduced high-density lipoprotein was also reported in adult male mice after oral exposure for 28 days to **BDE-209** with an LOEL of 7.5 mg/kg bw per day (Zhu et al., 2019). Alimu et al. (2021) reported similar results after exposure of adult male mice for 60 days, but with LOEL of 300 mg/kg bw per day for both these endpoints. Increased blood or serum glucose was observed in studies with rats and mice after oral exposure to **BDE-209** but the effect level varies vastly between studies with the LOEL being 0.05 mg/kg bw per day in one study with adult male rats (8 weeks exposure; Zhang, Sun, et al., 2013), 500 mg/kg bw per day in a study with 6 week old male rats (4 weeks exposure; Sun, Wang, Liang, et al., 2020), 75 mg/kg bw per day in a study in adult male mice (4 weeks exposure; Zhu et al., 2019) and 600 mg/kg bw per day in another mice study (60 days exposure; Alimu et al., 2021).

For serum fasting insulin, a rat study reported reduced insulin concentrations with a LOEL of 1 mg/kg bw per day (Zhang, Sun, et al., 2013), a mouse study showed increased serum insulin in mice at doses of 25 and 75 mg/kg bw per day (Zhu et al., 2019), and another mouse study at doses of 450 mg/kg bw and above (Alimu et al., 2021). Feeding a high-fat diet appeared to exacerbate metabolic effects of **BDE-209**, with increased fasting blood glucose observed in male mice fed a high-fat diet while exposed to 0.005 mg/kg bw per day of **BDE-209** from five to 20 weeks of age (Yanagisawa et al., 2019).

PBDE technical products

One study found that exposure of weanling male rats to 14 mg DE-71/kg bw per day for 28 days reduced serum fasting glucose and triglycerides (Cowens et al., 2015) while another study using the same strain, dose and exposure duration, but slightly older animals (1 month) found no effect (Nash et al., 2013). There was also no effect on blood fasting glucose in female mice exposed for 7 weeks (including during pregnancy and lactation) to DE-71 at doses up to 0.4 mg/kg bw per day (Kozlova et al., 2020). A daily dose of 14 mg/kg bw had also no effect on serum fasting insulin in rats (Nash et al., 2013).

Plasma insulin was reduced in adult female mice exposed to 0.4 mg/kg bw per day but there was no effect on their insulin sensitivity (Kozlova et al., 2020).

Increased glucose tolerance and reduced insulin sensitivity were found in female mice at 4 months of age exposed during gestation and lactation to DE-71 via their dams with LOEL for both effects of 0.1 mg/kg bw per day (Kozlova et al., 2020). Absolute liver size was increased in the perinatally exposed mice at a dose of 0.4 mg/kg bw per day (Kozlova et al., 2020).

Overall summary of effects on lipid and sugar metabolism

In summary, the studies available at the time of the previous EFSA Opinion on PBDEs indicated that exposure to **BDE-47** or **-99** via injection routes affected lipid and glucose metabolism (EFSA CONTAM Panel, 2011b). Studies published since the previous EFSA Opinion tend to support that these compounds induce metabolic effects following oral exposure.

These include decreased body weight following **BDE-47** exposure (LOAEL of 0.2 mg/kg bw per day; Wang, Yan, et al., 2018), and changes in liver and serum lipids, serum glucose and serum insulin levels. However, almost all these variables show contradictory results when comparing studies, even those using the same test substance. Serum triglycerides were reduced in pups after exposure to **BDE-47** via dams with a LOEL of 1 mg/kg bw per day; Khalil et al., 2018).

Increased fasting serum glucose was observed after exposure to **BDE-209** with a lowest NOEL of 0.01 mg/kg bw per day observed in mice fed a high-fat diet (Yanagisawa et al., 2019).

Increased glucose tolerance and reduced insulin sensitivity were found in mice exposed to DE-71 via their dams with LOEL for both effects of 0.1 mg/kg bw per day (Kozlova et al., 2020).

3.1.2.2.4 | *Other effects*

Studies considered in the previous EFSA assessment

No information on other effects was reported in the previous Opinion.

Studies published since the previous EFSA assessment

Since the publication of the previous Opinion, short-term studies reporting on effects other than those reported in the liver, in the thyroid and sex hormone systems and metabolic effects have been identified for **BDE-209** and PBDE technical products (DE-71). Details of these studies are provided in Appendix E (Table E.3 for **BDE-209** and Table E.5 for technical products).

BDE-209

Exposure of male rats to 0, 100, 300 and 600 mg **BDE-209**/kg bw per day from PND10 to PND42 induced significant increases in absolute and relative adrenal weights at 600 mg/kg bw per day (Lee et al., 2010[27,32]).

Maternal exposure of offspring rats to 0, 10, 100 or 1000 mg **BDE-209**/kg feed via the dams during gestation and lactation (GD10–PND20) induced on PND20 decreases in absolute kidney weights in males at 100 mg/kg feed (22.8 mg/kg bw per day) and increased cytoplasmic eosinophilia in cortical proximal tubular epithelia in males and females (statistically significant in males from 100 mg/kg feed and in females from 10 mg/kg feed (2.4 mg/kg bw per day) (Fujimoto et al., 2011).

Male rats were exposed by gavage for 28 days to 0, 31.25, 62.5, 125, 250 and 500 mg **BDE-209**/kg bw per day (Milovanovic et al., 2018). Serum creatinine was increased, while results obtained for serum urea were inconclusive. Relative kidney weight was not affected by **BDE-209**. Kidney reduced glutathione was elevated but not at the highest dose, while SOD activity was not changed after **BDE-209** treatment. Levels of thiobarbituric acid reactive substances (TBARS) were increased at 125 mg/kg bw per day and above, and total -SH groups were decreased in all exposure groups. The LOAEL was 31.25 mg/kg bw per day.

Serious edema in the kidney was reported in female rats exposed to **BDE-209** by gavage for 20 days at 100 mg/kg bw per day (Yang et al., 2014).

Male adult rats exposed by gavage to 0, 1000, 2000 and 4000 mg **BDE-209**/kg bw per day for 28 days showed statistically significant, but not dose-related, decreases in RBC count (Curčić et al., 2017). There were also dose-related increases in WBC (statistically significant at the two highest doses) and statistically significant, but not dose-related, decreases in PLT count at all doses. The LOAEL was 1000 mg/kg bw per day.

In male rats exposed by gavage for 28 days to 0, 5, 50 and 500 mg **BDE-209**/kg bw per day, heart and abdominal aorta morphological and ultrastructural lesions were observed (Jing et al., 2019). In the heart, congestion of intermuscular capillaries with mild disorganisation were seen at 5 and 50 mg/kg bw per day and severe fibre disorganisation with focal haemorrhagic areas between the muscle bundles, and nuclear condensation or dissolution and myocyte swelling at 500 mg/kg bw per day. In the aorta, dose-related increased disarray of elastin networks in the medial layer was observed at the two highest doses. BDE-209 causes a series of dose-related ultrastructure lesions in cardiomyocytes.

[32]This study was cited in the previous EFSA assessment on PBDEs (EFSA CONTAM Panel, 2011b) and it is included in the current assessment to provide insight into additional observations by the study authors not reported in the previous Opinion.

Serum creatine kinase (CK) and lactate dehydrogenase (LDH) were dose-dependently increased with significance at 5 mg/kg bw per day. Lipid peroxidation (MDA) was dose-dependently increased with significance at 5 mg/kg bw per day, and antioxidant enzyme activity changes. The LOAEL was 5 mg/kg bw per day.

Exposure by gavage of female mice for 2 years to 800 mg **BDE-209**/kg bw every second day (400 mg/kg bw per day) resulted in extensive inflammation of the lung with perivascular and interstitial cellular infiltrates accompanied by thickening of the alveolar walls and the destruction of the alveolar septa (Feng et al., 2015). In the heart, cardiac myocytes appeared swollen with faintly stained cytoplasm. In the kidney, there was also tubular degeneration and dilation, tubular cast formation, shrunken glomeruli with widening of the urinary space and focal infiltrates of inflammatory cells.

PBDE technical products

There is some evidence that exposure during gestation and lactation (GD6-PND21) by gavage of rats to 1.7 or 30.6 mg DE-71/kg bw per day alter cardiovascular reactivity and osmoregulatory responses to physiological activation (hyperosmotic treatment) in late adulthood (14–18 months). Greater (dose-related) systolic blood pressure responses were measured in exposed animals at 3 h hyperosmotic injection compared to pretreatment baseline (Shah et al., 2011).

Female Wistar Han rats were exposed from GD6 to PND21 by gavage to DE-71 at doses of 0, 3, 15 and 50 mg/kg bw per day. At PND4 all litters were culled to 3 males and 3 females per litter. Pups started on direct dosing from PND12 to PND21. At PND22 the pups were assigned to the two-year study and were dosed 5 days per week (at 0, 2.1, 10.7 and 36 mg/kg bw per day). Hydronephrosis in the kidney was noted in males at 10.7 mg/kg bw per day, and in males and females at 36 mg/kg bw per day. Significantly increased incidence of thymus atrophy, forestomach epithelial hyperplasia, atrophy and cytoplasmic vacuolisation of the parotid salivary gland, focal hyperplasia of the adrenal cortex and preputial gland duct ectasia were also observed in males at 36 mg/kg bw per day. In addition, there was a significant increase in the incidence of chronic active inflammation of the prostate in males at 10.7 and 36 mg/kg bw per day (Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Recio, et al., 2018; NTP, 2016).

B6C3F1/N mice were exposed by gavage for 2 years (5 days per week) to DE-71 at 0, 3, 30 and 100 mg/kg bw (0, 2.1, 21 and 71 mg/kg bw per day). In the forestomach, significantly increased incidence of epithelial hyperplasia was observed in males at 21 and 71 mg/kg bw per day and in females at 71 mg/kg per day and inflammation was seen in males at 21 and 71 mg/kg bw per day. In addition, significantly increased incidence of diffuse adrenal cortex hypertrophy occurred in males and females at 71 mg/kg bw per day (Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Recio, et al., 2018; NTP, 2016).

Overall summary of other effects

In addition to the main targets, some studies in rats or mice exposed to **BDE-209** described effects on the kidney (LOAEL: 22.8 mg/kg bw per day), the heart, (LOAEL: 5 mg/kg bw per day) the adrenal gland (LOAEL: 600 mg/kg bw per day) and haematological effects (LOAEL: 1000 mg/ kg bw per day).

Regarding technical products, one study showed that exposure during gestation and lactation of rats to DE-71 altered cardiovascular reactivity and osmoregulatory responses (Shah et al., 2011). Hydronephrosis in the kidney was noted in F1 rats exposed to DE-71 for 2 years (in males at 10.7 mg/kg bw per day, and in males and females at 36 mg/kg bw per day) (NTP, 2016). Effects on thymus, forestomach, parotid salivary gland, adrenal cortex and preputial gland were also observed in males at 36 mg/kg bw per day. In addition, there was a significant increase in the incidence of chronic active inflammation of the prostate in males. In mice exposed for 2 years to DE-71, forestomach hyperplasia and adrenal cortex hypertrophy was reported.

3.1.2.3 | *Developmental and reproductive toxicity studies*

Studies considered in the previous EFSA assessment

At the time of the previous Opinion, the CONTAM Panel identified a number of developmental and reproductive studies on **BDE-47**, **-99**, **-209** and PBDE technical products (DE-71) (EFSA CONTAM Panel, 2011b).

Administration of **BDE-47** to rats by gavage of doses of 0.14 and 0.7 mg/kg bw during gestation (GD6) showed effects on female offspring reproductive organs: decrease ovarian weight at the lowest dose and alterations in folliculogenesis at the highest dose (Talsness et al., 2008).

Administration of **BDE-99** to rats by gavage of single doses of 0.06 or 0.3 mg/kg bw on GD6 resulted in female reproductive tract changes in the F1 generation apparent at adulthood (altered mitochondrial morphology in the ovaries). Mating of the F1 females with untreated males resulted in increased resorption rates (Talsness et al., 2005). The LOAEL was 0.06 mg/kg bw per day. Skeletal anomalies were observed in two animals of the F2 generation from two different litters following dosing at 0.3 mg/kg bw. Impaired spermatogenesis (decrease in sperm and spermatic counts on PND140) was also observed at the same doses (Kuriyama et al., 2005). It was reported that prenatal exposure to **BDE-99** modified the expression of oestrogen target genes and their regulation by endogenous oestrogens (Ceccatelli et al., 2006). Decreases in circulating sex steroids oestradiol and testosterone were noted at weaning and adulthood in rats exposed from GD10 to GD18 to 1 mg **BDE-99**/kg bw per day (Lilienthal et al., 2006).

Administration of **BDE-209** to rats by gavage during gestation (GD0–19) did not cause reproductive or developmental effects at doses up to 1000 mg/kg bw per day (Hardy, 2002). Changes in sperm parameters (velocity of motion and sperm count) were reported in mice exposed at 1500 mg/kg bw from PND21 to PND70 with a NOEL of 500 mg/kg bw (Tseng et al., 2006). Decreased epididymis weight and increased weight of seminal vesicle/coagulation gland were observed in male rats exposed to **BDE-209** by gavage for 28 days. BMD modelling indicated that these effects occurred at doses of ≥ 1 mg/kg bw per day but no NOAEL or LOAEL was presented or could be identified (van der Ven, van de Kuil, Leonards, et al., 2008[33]).

Regarding PBDE technical products, in rats gavaged with DE-71 at 0, 3, 30 and 60 mg/kg bw per day from PND23 to PND53 in males or from PND22 to PND41 in females, seminal vesicle and ventral prostate weights were reduced at 60 mg/kg bw per day, while testes and epididymal weights were not affected (Stoker et al., 2004). A delay in preputial separation was noted at ≥ 30 mg/kg bw per day. In females, a delay in vaginal opening was observed at 60 mg/kg bw per day. The NOAEL was 3 mg/kg bw per day. DE-71 tested in adult rats by gavage in a 28-day toxicity test, induced dose-dependent decreased epididymis, seminal vesicles and prostate weighs as well as sperm head deformities (van der Ven, van de Kuil, Verhoef, et al., 2008[33,34]). No NOAEL or LOAEL was presented. Significant increases in luteinizing hormone (LH) were reported in male rats exposed for 3 days to 60 mg DE-71/kg bw per day (Stoker et al., 2005).

The CONTAM Panel noted in the previous Opinion that the reproduction and developmental toxicity studies showed that in general fetuses were more sensitive to PBDEs than mothers. Although it is known that maternal toxicity can influence fetal ossification (Khera, 1983), the fetal effects, e.g. increased number of resorptions, delayed/reduced ossification, oedema, reduced fetal weight, increase number of fetal variants, seemed to appear at lower doses than those indicative of maternal toxicity (EFSA CONTAM Panel, 2011b).

Studies published since the previous EFSA assessment

Since the publication of the previous Opinion, developmental and reproductive studies have been identified for **BDE-47**, -**99**, **-209**, **-3** and PBDE technical products (DE-71). Details of these studies are provided in Appendix E (Table E.1 for **BDE-47**, Table E.2 for **BDE-99**, Table E.3 for **BDE-209**, Table E.4 for BDE-3 and Table E.5 for technical products). New studies reporting on effects on the sex hormone system have been identified for **BDE-47**, -**99**, -**209** and - 3. No new studies have been identified on PBDE technical products.

BDE-47

Dietary exposure of juvenile female mice to **BDE-47** at 0.45 mg/kg bw per day for 28 days resulted in significantly elevated concentrations of serum testosterone as well as higher testosterone/oestradiol ratios (Maranghi et al., 2013).

Huang, Cui, et al. (2015) showed effects on the testes of adult rats exposed by gavage for 8 weeks to **BDE-47** at 0.03, 1 and 20 mg/kg bw per day, with a dose-related decrease in relative tubular epithelial thickness and increased apoptotic germ cells (early leptotene spermatocytes) as well as impaired mitochondrial function. The NOAEL was 0.001 mg/kg bw per day.

Changes in the normal cellular organisation of the seminiferous epithelium were observed in male rats exposed by gavage for 8 weeks to **BDE-47** at 0.001, 0.03 and 1 mg/kg bw per day. Increased numbers of multinucleated giant cells in the lumen were observed at the two highest doses and abundant vacuolar spaces in the seminiferous epithelium at the highest dose. Decreased numbers of spermatids and daily sperm production (observed at 1 mg/kg bw per day) as well as decreased testosterone levels were also observed (at all doses) (Zhang, Zhang, et al., 2013). The LOAEL was 0.001 mg/kg bw per day.

In male rats exposed by gavage to **BDE-47** at 0.03 and 20 mg/kg bw per day for 12 weeks, changes in the normal cellular organisation of the seminiferous epithelium were seen in treated animals (Zhang, Yu, et al., 2017). At the highest dose, **BDE-47** significantly increased the numbers of multinucleated giant cells that arose from spermatocytes and aborted meiosis. Abundant vacuolar spaces were also noted in the seminiferous epithelium. Dose-dependent reduction of testosterone concentration was noted (Zhang, Yu, et al., 2017). The LOAEL was 0.03 mg/kg bw per day.

After administration by gavage of **BDE-47** to male rats for 14 days, significantly increased serum testosterone levels and decreased LH level were noted at 0.4 mg/kg bw per day. No effect was observed on oestradiol level or on serum FSH levels (Li, Li, et al., 2021). The NOAEL was 0.2 mg/kg bw per day.

In mice exposed by gavage for 30 days to **BDE-47** at 0.0015, 0.045 and 30 mg/kg bw per day, decreased sperm motility and lower capacitated sperm rates were reported relative to pre-incubation values (Wang et al., 2013). At the two highest doses complete germ cell loss was observed in some seminiferous tubules that had a Sertoli cell-only phenotype. According to the authors, this may result from increased apoptosis. The Panel noted limitations in the data reporting and in the statistical analysis performed. Therefore no reliable LOAEL could be determined.

Male mice were administered 0, 1.5, 10 and 30 mg **BDE-47**/kg bw per day by gavage, 6 days per week for 6 weeks (0, 1.3, 8.6 and 25.7 mg/kg bw per day). Degeneration and necrosis of the spermatogenic cells in the testes was noted at the highest dose, accompanied by seminiferous epithelium thinning. BDE-47 caused sperm reductions in the epididymal lumens at 8.6 and 25.7 mg/kg bw per day. Spermatic granulomas were observed at 8.6 mg/kg bw per day and spermatic granulomas

[33]The authors of the study provided only benchmark doses at the lower confidence bound (BMDL) of the effects observed.

[34]The authors of the study provided only benchmark doses at the lower confidence bound (BMDL) of the effects observed.

accompanied by suppurative inflammation were observed at 25.7 mg/kg bw per day (Xu, Gao, et al., 2021). The NOAEL was 1.3 mg/kg bw per day.

In new-born female rats exposed by gavage on PND10 to **BDE-47** at 1, 5 and 10 mg/kg bw per day, a significant decrease of ovarian coefficient was seen at all doses at the age of 2 months. Thinning of the ovarian granular cell layer and corpus luteum was reported at the two lowest doses, and reduction of the granular cell layer, Graafian follicles and oocytes as well as increased corpus luteum were seen at the highest dose (Wang et al., 2016). The LOAEL was 1 mg/kg bw per day.

Exposure of female rats during gestation until weaning (from GD8 to PND21) to **BDE-47** at 0.2 mg/kg bw per day caused decreases in testes weight and sperm production and motility, and an increase in the percentage of morphologically abnormal spermatozoa in male offspring on PND120 (Khalil, Parker, Brown, et al., 2017).

Exposure of pregnant mice to **BDE-47** for 4 days during gestation (from GD13.5 to GD16.5) resulted in increased rates of stillbirth at ≥ 3.6 mg/kg bw per day, low birth weight and reduction of plasma testosterone and progesterone levels at 36 mg/kg bw per day. Decreased growth hormone peptide expression in the placental tissue extracted at GD17.5 was observed at 3.6 mg/kg bw per day (Zhu et al., 2017). The NOAEL was 0.36 mg/kg bw per day.

Female rats were exposed by gavage to 0, 0.1, 1.0 and 10 mg **BDE-47**/kg bw per day for 10 days before mating, throughout gestation and lactation, till weaning of the pups on PND21 (Li, Gao, et al., 2021). Offspring (4 males and 4 females) were examined on PND88. At the highest dose tested, the following effects were observed in males: increased body weights, decreased relative testis weights, decreased total sperm count and living sperm count, decreased (non-significant trend, non-statistically significant) motile sperm count, sperm density and sperm activity. There was also a lower proportion of sperm with Grade A, significant decreases in sperm curvilinear velocity (VCL), straight-line velocity (VSL) and average path velocity (VAP) and decreased mean amplitude of lateral head displacement (ALH), beat cross frequency (BCF), linearity (LIN) and wobble (WOB). Significant influences straightness (STR) and mean angular displacement (MAD) and significant declines in count, motility and density of linear motile sperm (LM). The LOAEL was 0.1 mg/kg bw per day.

BDE-99

Degeneration of gonadal system histology was reported in male rats exposed by gavage to **BDE-99** at 120 mg/kg bw per day for 5, 15, 30 or 45 days. No changes were observed after 5 days. On day 15, increased testicular weight, and damaged sperm in seminiferous tubules were observed. On day 30, there were further increases in testicular weight and degeneration of seminiferous epithelium. On day 45, decreased testicular weight, and severe degeneration of seminiferous epithelium were seen. Decreases in serum oestradiol levels after 15 days and further decreases in serum testosterone and oestradiol levels after 30 and 45 days were noted (Yu & Zhan, 2011). The LOAEL was 120 mg/kg bw per day.

A dose-related increase in relative testis weight was reported in male rats exposed by gavage to **BDE-99** at 60, 120 and 180 mg/kg bw per day for 30 days. Degeneration and necrosis in testicular seminiferous tubules, desquamation of seminiferous epithelium and a decrease in spermatozoa (more severe at the high dose) were reported. Statistically significant decreases in serum testosterone and oestradiol concentrations were also noted (Yuan et al., 2012).

Dose-related increases in the total number of fetuses (on GD20) with incomplete or delayed ossification and internal variations were reported in a study where female rats were exposed during GD6–19 to **BDE-99** at 1–2 mg/kg bw per day (Blanco et al., 2012). No external malformations were observed. The NOAEL was 0.5 mg/kg bw per day.

Exposure of mice during gestation (GD1–21) to **BDE-99** induced effects on male reproductive system in male offspring (Zhao, Tang, et al., 2021). Statistically significant decreases in anogenital index (AGD/bw) were observed on PND1, 7, 21 and 35. Dose-related increased incidence of cryptorchidism were reported as well as decreases in testicular weight and testicular organ coefficient in treated groups on PND35. There were also reduction and nuclear fragmentation of spermatogenic cells at 2 and 20 mg/kg bw per day and short diameter, long diameter and lumen area of seminiferous tubules at 20 mg/kg bw per day were significantly smaller. Significantly lower densities of Leydig cells in the treated groups were noted. In addition, there were reductions in serum testosterone levels in all treated groups and significant increases in serum LH and FSH concentrations at 20 mg/kg bw per day. However, the ratios of T/LH were found to decrease significantly in all **BDE-99** groups (Zhao, Tang, et al., 2021). The LOAEL was 0.2 mg/kg bw per day.

BDE-209

Exposure of male mice to **BDE-209** at 950 mg/kg bw per day for 35 days resulted in reduction of testis and epididymis weights, degeneration of the seminiferous tubules, specially thinning of the germinal epithelium and marked depletion of germ cells, exfoliation of germ cells and intraepithelial vacuolation (Sarkar et al., 2016). In severe cases, the epithelium consisted of only a layer of Sertoli cells and few spermatogonia. Significant reductions in the diameter of the seminiferous tubules and of the height of the germinal epithelium were also seen as well as significant reductions in the number and viability of spermatozoa in cauda epididymis. Significant reductions in serum testosterone and in the activities of 3β- and 17β-hydroxysteroid dehydrogenase (3β- and 17β-HSD) in testis were reported (Sarkar et al., 2016). The NOAEL was 750 mg/kg bw per day.

Exposure of male rats to 0, 5, 50 and 500 mg **BDE-209**/kg bw per day for 28 days induced reduction of sperm cells and pathological changes in seminiferous tubules: seminiferous epithelium deletion, intraepithelial vacuolation and even cell exfoliation, as well as significant decreases in sperm number, motility and significant increases in sperm malformations (coiled tail, bent neck and irregularly shaped head) at 50 and 500 mg/kg per day (Li, Liu, et al., 2021). There were also

significant increases in MDA content in the testis at the two highest doses and decreases in T-SOD activity at the highest dose. Significant increases in the number of TUNEL-positive cells (indicating apoptosis) per seminiferous tubule were observed at all doses (Li, Liu, et al., 2021). The LOAEL was 5 mg/kg bw per day.

Male rats were exposed by gavage to 0, 5, 50 and 500 mg **BDE-209**/kg bw per day for 28 days (Zhang, Li, et al., 2021). There was a decrease in sperm quality and quantity at 50 and 500 mg/kg bw per day, the spermatocytes layers sparsely arranged and mature sperms in the lumen dramatically decreased; there were also vacuolation of seminiferous tubules and exfoliation of spermatogenic cells. The height of the germinal epithelium was significantly decreased at these doses. The mitochondria were slightly swollen, the cristae mildly fractured and vacuolisation appeared at 5 and 50 mg/kg bw per day; while at 500 mg/kg bw per day, the mitochondria were swollen and vacuolated; the mitochondrial cristae ruptured or even disappeared. At the two highest doses, sperm concentration and motility were significantly reduced and sperm malformations increased resulting in spermatogenesis impairment. Apoptosis of spermatogenic cells was also noted at these doses. The levels of glucose, triglyceride and total cholesterol in testes were negatively correlated with sperm concentration, and triglyceride and total cholesterol levels were negatively correlated with sperm motility, while positively correlated with the sperm malformation rate (Zhang, Li, et al., 2021). The NOAEL was 5 mg/kg bw per day.

No effect on placental histology was noted in rats after gestational exposure (GD0–21) to **BDE-209** at 1, 5 and 10 mg/kg bw per day. Significant reduction of birth weight of the offspring was reported at 5 and 10 mg/kg bw (Du et al., 2015). The NOAEL was 5 mg/kg bw per day.

Pregnant mice were exposed by gavage to 0, 2, 20 or 200 mg **BDE 209**/kg bw per day from GD0–18 (Zhao et al., 2022). Statistically significant decreases in placental weight (all doses), impaired placental vascular development (at the highest dose) and induced placental apoptosis (at all doses) were observed. The LOAEL was 2 mg/kg bw per day.

Female mice were exposed by gavage to **BDE-209** at 0, 150, 750, 1500 and 2500 mg/kg bw per day from GD7/9 to GD16. Increased rates of post-implantation loss (at 3 highest doses) and resorptions (at 2 highest doses) were seen, as well as a dose-related decreased rate of live fetuses/litter (statistically significant at the highest dose) (Chi et al., 2011). Decreased placenta weight was noted at the highest dose. Fetotoxicity was also observed: dose-related decreased brain, liver and heart weights (statistically significant at the highest dose) and decreased fetal weight at the 3 highest doses (Chi et al., 2011). The NOAEL was 150 mg/kg bw per day.

Gestational exposure (GD0–17) of female mice to **BDE-209** at 10, 500 and 1500 mg/kg bw per day resulted in pathological lesions in the testes (mainly in interstitial cells and/or seminiferous tubules), severe vacuolation, sperm morphological abnormalities and loss of spermatozoa and spermatids in their male offspring, specially at the highest dose. Significant reduction in anogenital distance (AGD) and index were also reported at 1500 mg/kg bw per day (Tseng et al., 2013). The LOAEL was 10 mg/kg bw per day based on moderate vacuolation of the interstitial cells.

Exposure of female mice by gavage to **BDE-209** at 500 and 700 mg/kg bw per day during lactation (PND1–28) caused testicular and epididymal toxicity, decreases in number and motility of spermatozoa, decreases in sperm viability, increases in the number of morphologically abnormal spermatozoa, reduction of sialic level in the epididymis in male offspring on PND42. Decreased mating and fertility index as well as litter size were reported in exposed animals (Sarkar et al., 2019).

Exposure of female mice by gavage to **BDE-209** at 500 and 700 mg/kg bw per day during lactation (PND1–28) caused decreased testis, seminal vesicle and prostate weights in male pups on PND42. Effects on testicular histopathology (increased % of affected seminiferous tubules with centrally displaced germ cells, thinning of the germinal epithelium, intraepithelial vacuolation, exfoliation of germ cells, absence of lumen and disorganisation of germ cells), decreased germ cell proliferation and steroidogenesis were observed. A significantly decreased number of Leydig cells was noted at 500 mg/kg bw per day and a lesser non-significant decrease at the highest dose (Sarkar & Singh, 2018).

Sarkar et al. (2018) also tested male offspring on PND1 and PND28. **BDE-209** caused a reduction in testis weight on PND28. It affected testicular histopathology, steroidogenesis and germ cell dynamics: significant reduction of the diameter of the seminiferous tubules, non-uniform degeneration changes in the seminiferous tubules (decreases in the number of spermatogonia and spermatocytes, lumen not properly developed, few round spermatids and in some cases multinucleated giant cells) at doses ≥ 500 mg/kg bw per day.

Exposure of female mice by gavage to **BDE-209** at 500 and 700 mg/kg bw during lactation (PND1–PND28) affected steroidogenesis (decreased activity of 3β- and 17β-HSD in testis) and induced significant reductions in serum and intratesticular levels of testosterone in male pups on PND28, PND42 and PND75 (Sarkar et al., 2018; Sarkar & Singh, 2017, 2018, 2021).

In a follow-up study in mice, male offspring exposed to **BDE-209** at 500 and 700 mg/kg bw per day during lactation from PND1–28 were tested on PND75 (Sarkar & Singh, 2021). Significant decrease of the absolute and relative testis, epididymis, seminal vesicle and prostate weights were noted. There were modifications of the testis histoarchitecture: multinucleated giant cells were common in the majority of degenerate seminiferous tubules, there was a significant decrease of the height of the germinal epithelium in seminiferous tubules and several seminiferous tubules showed degenerative changes (disorganisation of germ cells, intraepithelial vacuolation and thinning of germinal epithelium). Statistically significant decrease in sperm count, motility and viability were also reported. The number of PCNA-positive cells significantly decreased as well as the proliferation index. There were also significantly decreased testicular activities of SOD and catalase (Sarkar & Singh, 2021).

Zhai et al. (2019) studied the effects on male offspring on PND35 (adolescents) and PND105 (adults) after gavage exposure of female mice during gestation and lactation (GD7 to PND21) to **BDE-209** at 100, 300 and 500 mg/kg bw per day. Significant decreases in body weight were observed at both times of exposure as well as significant decreases in testis weight at the two highest doses and in epididymis weight at all 3 doses. Histopathological lesions were seen in the testis

at the two highest doses (vacuolations in spermatogonia, spermatocytes and Leydig cells, disturbed array of germ cells, slightly reduced layers of germ cells, exaggeration of intracellular space). Premature spermatid loss was noted at the low dose and absence of spermatids in the majority of tubules at 300 mg/kg bw per day. Fewer efferent ductules were noted at the two high doses on PND105. Ultrastructural changes in blood-testis barrier were also shown. Vacuolated or swollen mitochondria, pyknotic nuclei and marginal chromatin were seen in exposed F1 mice, as well as absence of spermatozoa. However, there was no effect on breeding success of F1 adults. The LOAEL was 100 mg/kg bw per day.

Female Sprague–Dawley rats were exposed to 0 and 1000 mg/kg bw per day in the diet from 5 weeks of age to delivery (Zhao et al., 2017). The females were mated with untreated males at 8 weeks of age. Pregnant rats were sacrificed on GD7, GD13 and GD19 (6 females per group). No difference in the number of fetuses in each rat on GD19 or in the number of pups in each litter on PND1 were observed between the treated and control groups. Pup birth weight was statistically significantly lower in the exposed group than in the control group.

Pregnant female rats (3/group) were treated by gavage from GD0 to birth with 5 mg **BDE-209**/kg bw per day (Hsu et al., 2021). On PND21, three male offspring were randomly selected from each litter. After normal feeding up to 70 days old, one of the three male F1 offspring from each litter was randomly selected to mate with a normal female rat and breed the F2 generation. Untreated and non-littermate females and males aged 70 days from the F1 generation control or **BDE-209** lineages were bred to obtain the F2 generation offspring. The F2 generation rats were bred to obtain the F3 generation offspring. Significant decreases in body weight were noted on PND25, 31, 34, 37, 40 and 58 in the F1 generation, PND28 in the F2 generation and PND31, 40 and 43 in the F3 generation. Significant decrease was also reported in the F1 rats on PND84. There was no effect on the weight of testes, epididymis, seminal vesicles and ventral prostate. Significant decreases in anogenital distance were observed on PND25, 49, 52, 67 and 70 in the F1 generation, PND37 and 40 in the F2 generation, and PND31, 34, 52, 55, 64, 67 and 70 in the F3 generation. There were significant decreases in sperm count of the F1 and F2 generations and a significant reduction in the sperm motility of the F1 offspring. A reduction of the normal morphology rates of the testis was observed in the offspring of the F2 and F3 generation and increases in the percentage of spermatozoa with bent tails in all generations (F1–F3). There were also significant increases in the frequency of multiple abnormal spermatozoa in the third generation. Significant decreases in serum testosterone levels in the F3 generation were reported. There were no apparent morphological differences including the spermatogenesis, structure of testis, morphology of lumens and seminiferous tubules, between the control and exposed groups.

Pubertal male Sprague–Dawley rats were exposed by gavage to 0, 5, 50 and 500 mg **BDE-209**/kg bw per day for 28 days and the intracavernous pressure/mean arterial pressure ratio was used to assess the erectile response. Erectile dysfunction was observed at the two highest doses. Exposure to these doses induced fibrosis in the corpus cavernosum and decreased endothelial nitric oxide synthase (eNOS) expression. In the high dose group, the expression of testosterone significantly decreased. The expression levels of caspase-3 in the cavernosum were significantly increased in all treatment groups, indicating apoptosis (Zhou et al., 2022). The LOAEL was 5 mg/kg bw per day.

Other individual PBDE congeners

Three studies were identified for BDE-3.

No effects were observed on testis and epididymal weights or on Leydig cells or Sertoli cells numbers after postnatal exposure (PND35–56) of male rats to BDE-3 at 50, 100 and 200 mg/kg bw per day. However, decreased Leydig cells size (cytoplasmic size) was reported. Dose-dependent decreases in testosterone were observed from 50 mg/kg bw per day (statistically significant at 200 mg/kg bw per day). No effect on serum LH and FSH levels were noted (Chen, Dong, et al., 2018).

Dose-dependent decreases in sperm count were observed in male mice exposed by gavage for 6 weeks to BDE-3 at 1.5, 10 and 30 mg/kg bw per day. Increased rate of tail folding sperm was also reported. Slight decrease in germ cells in seminiferous tubules occurred in 4 males (out of 6) at the highest dose and decreases in mature sperm in epididymis in 3 males (out of 6) at the highest dose with cellular debris in lumen and inflammatory cell infiltration in epididymal interstitium appearing in one male (Wei et al., 2018). The LOAEL was 0.015 mg/kg bw per day.

In the study Li, Ma, et al. (2021) in which pregnant female rats were exposed by gavage from GD12 to GD21 to 0, 50, 100 and 200 mg BDE-3/kg bw per day, there was no effect on the birth rate, pup number per dam or percent male/female sex ratio of fetuses. No effect on body weight of male fetuses was noted. Significant reduction of serum testosterone levels was noted in male pups at doses ≥50 mg/kg bw per day. A reduction in the anogenital distance was observed at 100 and 200 mg/kg bw per day. There was also a reduction of the fetal Leydig cell number at 200 mg/kg bw per day without effect on fetal Leydig cell cluster frequency and Sertoli cell number. The LOAEL was 50 mg/kg bw per day.

PBDE technical products

In the NTP, 2016 study in which male and female B6C3F1 mice were exposed for 14 weeks (5 days per week) by gavage to 0, 0.01, 5, 50, 100 and 500 mg DE-71/kg bw (0, 0.007, 3.6, 36, 71 and 357 mg/kg bw per day), decreased absolute testis weight as well as significantly increased incidence of abnormal residual bodies were noted at 357 mg/kg bw per day. Significantly decreased left cauda epididymis weight and sperm motility were also seen at 71 mg/kg bw per day (not examined at 357 mg/kg bw per day due to high mortality). The NOAEL for effects on reproductive organs was 36 mg/kg bw per day.

In B6C3F1/N mice exposed by gavage for 2 years (5 days per week) to DE-71 at 0, 3, 30 and 100 mg/kg bw (0, 2.1, 21 and 71 mg/kg bw per day), there was a significant increase in the incidence of the testis germinal epithelium atrophy at

71 mg/kg bw (Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Recio, et al., 2018; NTP, 2016). The NOAEL for effects on reproductive organs was 21 mg/kg bw per day.

In male and female F344/N rats exposed for 14 weeks (5 days per week) by gavage to 0, 0.01, 5, 50, 100 and 500 mg DE-71/kg bw (0, 0.007, 3.6, 36, 71 and 357 mg/kg bw per day), fewer total spermatids per testis and significantly decreased sperm per gram of testis were seen at 71 and 357 mg/kg bw per day, and significantly decreased sperm motility at 357 mg/kg bw per day. In addition, significantly increased incidences of hypospermia, decreased epididymis and cauda epididymis weights, significantly decreased sperm per cauda and sperm per gram of cauda were seen at 357 mg/kg bw per day. All 357 mg/kg bw per day females failed to cycle and remained in persistent diestrus throughout the examination period (NTP, 2016). The NOAEL for effects on reproductive organs was 36 mg/kg bw per day.

Exposure of female rats by gavage to DE-71 at 0, 1.7, 10.2 and 30.6 mg/kg bw per day from GD6 to PND21 resulted in decreased body weight in female pups at the two highest doses (PND29–58) and at the lowest dose (PND56–58). There was also a decrease in anogenital distance and a delay in preputial separation in male pups at the highest dose. Effects on developmental scores were reported on PND21 (Kodavanti et al., 2010[27,35]). The LOAEL was 1.7 mg/kg bw per day.

Female Wistar Han rats were exposed by gavage from GD6–PND21 to 0, 3, 15 and 50 mg DE-71/kg bw per day and thereafter their offspring from PND12–PND21 and for an additional 13 weeks. Significantly increased absolute testis weight was seen at 50 mg/kg bw per day (NTP, 2016). In a follow-up study, at PND22 the pups were assigned to a two-year study and were dosed 5 days per week (0, 2.1, 10.7 and 36 mg/kg bw per day). Significant increase in the incidence of chronic active inflammation of the **prostate** was observed in males at 10.7 and 36 mg/kg bw per day (Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Recio, et al., 2018; NTP, 2016). The NOAEL for effects on reproductive organs was 2.1 mg/kg bw per day.

Overall summary of the developmental and reproductive effects

In summary, exposure of adult rats or mice to PBDEs affects both male and female reproductive systems. Maternal exposure to these compounds during gestation and/or lactation causes reproductive toxicity in offspring which are more sensitive than adults.

Repeated exposure of male rats and mice to **BDE-47**, **-99** and **-209** resulted in decreases in serum testosterone and oestradiol levels. In two studies with **BDE-47** an increase in serum testosterone was however observed. In female mice exposed to **BDE-47**, significantly elevated concentrations of serum testosterone as well as higher testosterone/oestradiol ratio were noted.

Repeated exposure of male adult rats or mice to **BDE-47** by gavage resulted in effects on the testes with changes in the organisation of the seminiferous tubules, germ cell loss, increased numbers of multinucleated giant cells, and decreased numbers of spermatids and daily sperm production. Effects were also observed on sperm motility. The lowest LOAEL for apical effects for **BDE-47** was 0.03 mg/kg bw per day based on effects on the testes (Huang, Cui, et al., 2015; Zhang, Zhang, et al., 2013; Zhang, Yu, et al., 2017). Exposure of pregnant rats during gestation and lactation until weaning caused adverse effects on male offspring: decreases in testes weight, sperm production and motility. The lowest LOAEL was 0.2 mg/kg bw per day (Khalil, Parker, Brown, et al., 2017). Effects on reproductive organs of female offspring (decreased ovarian weight and alteration of folliculogenesis) are also described in rats exposed during gestation (GD6). The LOAEL was 0.14 mg/kg bw (Talsness et al., 2008).

Degeneration of gonadal system histology (time-related changes in testicular weights, damaged sperm, degeneration of seminiferous tubule epithelium, a decrease in spermatozoa) was shown in male rats after repeated exposure to **BDE-99**. Administration to pregnant rats on GD6 resulted in female reproductive tract changes in the F1 generation apparent at adulthood. The LOAEL was 0.06 mg/kg bw (Talsness et al., 2005). Exposure of pregnant mice during gestation resulted in changes in male reproductive organs: decreases in anogenital index, increases in incidence of cryptorchidism, effects on Leydig cells and spermatogenic cells and on sex hormone levels. The LOAEL was 0.2 mg/kg bw per day (Zhao, Tang, et al., 2021). Incomplete or delayed ossification and internal variations were also observed in fetuses exposed during gestation (Blanco et al., 2012), and impaired spermatogenesis in male offspring.

Adverse effects on the male reproductive organs (decreased testis and epididymis weights, degeneration of seminiferous tubules, decreased germ cell proliferation, decreased sperm count and viability, as well as increases in sperm malformations) were reported after repeated exposure of male rats or mice to **BDE-209**. Exposure during gestation and/or lactation resulted in the same types of adverse effects in male offspring, resulting in decreased mating and fertility index and litter size. The lowest LOAEL was 5 mg/kg bw per day (Li, Liu, et al., 2021). **BDE-209** affected testicular histopathology, steroidogenesis and germ cell dynamics. Embryotoxicity (post-implantation loss, resorptions and decreases in live fetuses/litter) occurred in mice exposed to ≥ 750 mg **BDE-209**/kg bw per day during gestation (Chi et al., 2011). In addition, a significant reduction in anogenital distance was reported at 1500 mg/kg bw per day in mice exposed during gestation (Tseng et al., 2013).

Maternal exposure of rats or mice to **BDE-99** and **-209** affected steroidogenesis (decrease in the activities of 3β- and 17β-HSD in testis) and induced significant reductions in serum and intratesticular levels of testosterone at weaning and adulthood. The LOAEL for **BDE-99** was 1 mg/kg bw per day. This was based on decreases in circulating sex steroids oestradiol

[35]This study was cited in the previous EFSA assessment on PBDEs (EFSA CONTAM Panel, 2011b) and it is included in the current assessment to provide insight into additional observations by the study authors not reported in the previous Opinion.

and testosterone at weaning and adulthood in rats exposed from GD10-18 (Lilienthal et al., 2006). The LOAEL for **BDE-209** was 500 mg/kg bw per day, based on significant reductions in serum testosterone and in the activities of 3β- and 17β-hydroxysteroid dehydrogenase (Sarkar et al., 2018; Sarkar & Singh, 2017, 2018, 2021).

Regarding other individual congeners, decreases in germ cells and sperm count were reported in male mice exposed to BDE-3. The lowest LOAEL was 1.5 mg/kg bw per day (Wei et al., 2018). It was also shown that in utero exposure to BDE-3 blocks the development of fetal rat testis. A reduction in the anogenital distance was observed at ≥ 100 mg/kg bw per day (Li, Ma, et al., 2021). BDE-3 exposure of rats during gestation or postnatally induced reduction of testosterone levels in male offspring. The LOAEL was 50 mg/kg bw per day (Li, Ma, et al., 2021).

For PBDE technical products, repeated exposure of adult rats or mice to DE-71 affected also the male reproductive organs with decreased testis and epididymis weights, sperm count and motility and increased testis germinal atrophy. The lowest LOAEL was 71 mg/kg bw per day (NTP, 2016). There was also a decrease in anogenital distance and a delay in preputial separation in male pups exposed in utero and during lactation until weaning at 30.6 mg/kg bw per day (Kodavanti et al., 2010). Postnatal exposure of rats affected the reproductive organs in males at doses ≥ 30 mg/kg bw per day, and in females (delay in vaginal opening) at 60 mg/kg bw per day (Stoker et al., 2004). Significant increases in LH, non-significant increase in testosterone, androstenedione and oestrone were reported in male rats exposed for 3 days to 60 mg DE-71/kg bw per day (Stoker et al., 2005).

3.1.2.4 | *Immunotoxicity studies*

Studies considered in the previous EFSA assessment

In the previous Opinion (EFSA CONTAM Panel, 2011b) it was stated that PBDEs might exert toxic effects to the immune system resulting in reduced resistance to infections by microorganisms. Only a few experimental studies on immunotoxicity in which contamination of the test substance with PBDD/Fs had been controlled were identified.

A single exposure of mice to Bromkal 70-5DE or **BDE-99** (20 mg/kg bw) did not affect susceptibility to CBV3 infection (Lundgren et al., 2007a, 2007b, 2009).

Immunotoxic effects were observed after 8 weeks exposure of ranch mink to DE-71 at 0.457 or 0.777 mg/kg bw per day (Martin et al., 2007).

Increased respiratory syncytial virus (RSV) titres were seen in offspring of dams exposed to DecaBDE at 3300 mg/kg bw per day from GD10 to PND21 (Watanabe et al., 2010).

Studies published since the previous EFSA assessment

Since the publication of the previous Opinion, short-term studies reporting on effects on the immune system have been identified for **BDE-47** and **-209**, and PBDE technical products (DE-71, PentaBDe and DecaBDE). No new studies have been identified for **BDE-99**.

Details of these studies are provided in Appendix E (Table E.1 for **BDE-47**, Table E.3 for **BDE-209**, Table E.4 for BDE-3 and Table E.5 for technical products).

BDE-47

Gavage exposure of juvenile female mice to 0.45 mg **BDE-47**/kg bw per day resulted in a significant increase in follicular hyperplasia in the spleen with germinal centre development and lymphocyte infiltration involving the red pulp in the spleen. In the thymus the presence of lymphocyte apoptosis and Hassal's bodies was reported (Maranghi et al., 2013).

BDE-209

Exposure of mice by gavage up to 10 months to **BDE-209** at 4, 40 and 400 mg/kg bw per day resulted in reduced leukocytes, decreased cytokine (IFN-c, IL-2 and TNF-a) production and lower CD8 T-cell proliferation (Zeng et al., 2014). Only minimal effects on other components of the haematopoietic system were seen. Significantly lower numbers of monocytes were observed in the peripheral blood of exposed mice after 1 or 2 months. After 7 months of exposure, lower amount of cytokines IFN-c and IL-2 were produced by the CD8 T cells in the peripheral blood from mice exposed to 400 mg/kg bw per day compared controls. Moreover, after 27 months exposure, the splenic CD8 T cells from these exposed mice produced much less IFN-c and IL-2 than the controls. Long-term **BDE-209** exposure decreased the polyfunctional CD8 T-cell population in adult mice. It was also observed that in mice exposed to 400 mg/kg bw per day at month 7, the numbers of both effector memory CD8 T cells and central memory cells from the peripheral blood were reduced. Lower numbers of antigen-specific CD8 T cells were observed after immunisation with recombinant *Listeria monocytogenes* expressing ovalbumin (rLm-OVA) and the OVA-specific CD8 T cells had reduced functionality (Zeng et al., 2014). The LOAEL was 4 mg/kg bw per day.

Exposure by gavage of female mice for 2 years to 400 mg **BDE-209**/kg bw per day resulted in a significant decrease in numbers of splenic nodules. The distinction between the white pulp and the red pulp was blurry. A large number of megakaryocytes was found in the red pulp, which was characteristic of extramedullary haematopoiesis (Feng et al., 2015).

Impaired proliferation and cytokine (IFN-γ, IL-2 or TNF-α) production of CD4 T cells were observed in mice exposed by gavage to 400 mg **BDE-209**/kg bw per day for 10 months, accompanied by increased T regulatory cells in the blood. Furthermore, weaker antigen-specific CD4 T-cell responses to *L. monocytogenes* infection in the exposed mice was observed, suggesting decreased resistance to exogenous pathogens (Feng, Zeng, et al., 2016).

Exposure of male rats by gavage to **BDE-209** for 28 days, induced inflammation characterised by the upregulation of key inflammatory mediators including IL-1 beta, IL-6, IL-10 and tumour necrosis factor alpha (TNF-α) at doses ≥ 5 mg/kg bw per day (Jing et al., 2019). Additionally, **BDE-209** led to endothelial dysfunction, as evidenced by the endothelin-1 (ET-1) and intercellular adhesion molecule-1 (ICAM-1). The LOAEL was 5 mg/kg bw per day.

Increases of inflammatory cytokines TNF–α and IL-6 levels were observed in rats exposed by gavage to **BDE-209** for 28 days to 50 and 500 mg/kg bw per day (Sun, Wang, Liang, et al., 2020). The NOAEL was 5 mg/kg bw per day.

Oral dosing of male mice with **BDE-209** at 200 mg/kg bw per day for 28 days resulted in damage to the intestinal morphology and barrier function, intestinal oxidative stress and inflammation accompanied by a marked decrease in body weight gain (Shaoyong et al., 2021).

Female mice were exposed by gavage to **BDE-209** from PND56 to PND76, and examined on PND77 and on PND98 after a 21-day recovery period (Liao et al., 2021). On PND77, decreases in WBC (statistically significant at 400 mg/kg bw per day) and lymphocyte percentage (statistically significant at ≥ 40 mg/kg bw per day) were noted, as well as increases in the levels of AST (statistically significant from 4 mg/kg bw per day), but not alkaline phosphatase (ALP) or alanine transaminase (ALT). There were dose-dependent decreases in relative spleen weight at 40 and 400 mg/kg bw per day and in thymus weight at 400 mg/kg bw per day. Significant increases in IgG (at 4 and 40 mg/kg bw per day) and IgM (400 mg/kg bw per day) levels were reported on PND77. Dose-dependent significantly decreased splenic lymphocyte proliferation was observed. At 400 mg/kg bw per day, there was inhibition of IFN-γ secretion and increased IL-4 secretion, whereas IL-10 secretion was induced at all doses in a dose-dependent manner. The phagocytic index (α) was significantly decreased at 400 mg/kg bw per day. Significant increases in MDA levels were measured in the liver and spleen (40 and 400 mg/kg bw per day), and the thymus (400 mg/kg bw per day) on PND77. Significant decreases in SOD activities in liver and spleen (40 and 400 mg/kg bw per day), thymus (400 mg/kg bw per day) were measured. Most of the effects had returned to control levels on PND98. However, only partial reversibility was noted for promotion of IL-4 and IL-10 and the effects on MDA and SOD activities were still significant at 400 mg/kg bw per day on PND98. Furthermore there was a dose-related increase in IgA at all doses on PND98, which was not seen on PND77 (Liao et al., 2021). The LOAEL was 4 mg/kg bw per day.

PBDE technical products

Regarding DE-71, in the study by Bondy et al. (2013), adult rats were exposed to 0, 0.5, 5 and 25 mg DE-71/kg bw per day for 21 weeks. F0 rats were bred and exposure continued through gestation, lactation and postweaning. F1 pups were weaned and exposed daily by gavage from PND22 to PND42. On PND42, half of the F1 rats were assessed for toxicological changes, and the remaining F1 rats were challenged with the T-dependent antigen keyhole limpet hemocyanin (KLH) and immune function was assessed on PND56. In spleen from exposed rats, the area occupied by B cells declined while the area occupied by T cells increased. However, cellular and humoral immune responses to KLH challenge were not altered (Bondy et al., 2013). The LOAEL was 5 mg/kg bw per day.

After exposure by gavage of mice for 28 days to DE-71, peripheral blood monocyte numbers were decreased at doses up to 1.8 mg/kg bw per day, but not at 3.6 mg/kg bw per day (Fair et al., 2012). Mitogen-stimulated T- and B-cell proliferation was increased and splenic lymphocyte proliferation was induced at 3.6 mg/kg bw per day. At this dose, NK cell activity was decreased, however, no alterations were noted in thymic T-cell populations or in SRBC-specific-IgM production. The numbers of splenic $CD4^+CD8^+$ cells were decreased at 0.018, 0.18 and 3.6 mg/kg bw per day (Fair et al., 2012). The LOAEL was 0.018 mg/kg bw per day.

Exposure by gavage of male and female B6C3F1 mice for 14 weeks to 0, 0.007, 3.6, 36, 71, 357 mg DE-71/kg bw per day result in significant increased incidence of thymus atrophy in males at 357 mg/kg bw per day (NTP, 2016).

When male and female F344/N rats were exposed to DE-71 for the same time and dose regime, decreased absolute thymus weight was noted at 357 mg/kg bw per day in males and decreased absolute and relative thymus weight at ≥ 36 mg/kg bw per day in females and thymus atrophy was reported in females at 357 mg/kg bw per day (NTP, 2016).

Female Wistar Han rats were exposed by gavage from GD6–PND21 to 0, 3, 15 and 50 mg DE-71/kg bw per day and their offspring were also dosed by direct gavage from PND12–PND21 and for an additional 13 weeks or 2 years. Significantly decreased absolute thymus weight was reported in females at 36 mg/kg bw per day (NTP, 2016).

In female mice orally exposed to PentaBDE at 0, 50, 100 and 200 mg/kg bw per day from GD0 to PND21, a significantly decreased absolute and relative spleen weight of the dams was reported at 100 and 200 mg/kg bw per day (Hong et al., 2010). At these doses, there was also a statistically significant decrease in absolute and relative spleen and thymus weights in the offspring on PND21, as well as a reduction of the number of splenocytes and thymocytes. The decrease in splenocytes and thymocytes was not statistically significant in the dams. Splenic T-cell proliferation in dams and PND21 offspring exposed to PentaBDE was increased (specially at 200 mg/kg bw per day). There was no significant difference in

splenic B-cell proliferation in all treatment groups. The percentage of total T-cells, T helper cells and T cytotoxic cells in splenocytes of PND21 offspring exposed to PentaBDE was slightly increased (Hong et al., 2010). The NOAEL was 50 mg/kg bw per day.

In the same study, oral exposure of female mice to DecaBDE at 0, 500, 2500 and 12,500 mg/kg bw per day from GD0 to PND21, resulted in a decrease in the relative distribution of B cells and an increase in the percentage of macrophages in dams and a decrease in PND21 offspring (Hong et al., 2010). The percentages of white blood cells (WBC) and neutrophils increased in dams exposed to DecaBDE (statistically significant at 500 mg/kg bw per day). The LOAEL was 500 mg/kg bw per day.

Overall summary of the effects on the immune system

In summary, PBDEs exerted toxic effects to the immune system that may result in reduced resistance to infections by microorganisms.

For **BDE-47**, morphological changes in the spleen and thymus were reported in juvenile mice at 0.45 mg **BDE-47**/kg bw per day, the only dose tested (Maranghi et al., 2013).

BDE-209 exposure specifically affected peripheral immune cells and this effect was not due to overt toxicity. Exposure of mice to **BDE-209** for up to 10 months resulted in reduced leucocytes (monocytes), decreases in cytokine production and lower CD8-T and CD4-T cells proliferation as well as weaker antigen-specific responses to Listeria infection, and exposure for 2 years resulted in morphological changes in the spleen. Exposure of rats to **BDE-209** induced morphological changes in the gastrointestinal tract, impaired barrier function and inflammation characterised by the upregulation of inflammatory mediators including interleukins. Postnatal exposure (PND56–76) of mice to 400 mg/kg bw per day, decreased splenic and thymus weight. The lowest LOAEL was 4 mg/kg bw per day based on reduction of leukocytes, decreases of cytokine production and lower CD8-T cell proliferation (Zeng et al., 2014).

Studies on immunotoxicity of other congeners were not identified.

For PBDE technical products, DE-71 was found to alter splenic lymphocyte populations but not cellular or humoral immune responses in rat pups exposed via the dams during gestation, lactation and postweaning. Thymus atrophy was reported in rats and mice exposed for 14 weeks to DE-71. The lowest LOAEL for immune effects of DE-71 was 0.018 mg/kg bw per day (based on decreased splenic $CD4^+CD8^+$ cells) (Fair et al., 2012).

It has also been shown that PentaBDE has an impact on the immune system of adult mice and on the development of the immune system of their offspring, with a NOAEL of 50 mg/kg bw per day (Hong et al., 2010). The potential of DecaBDE to affect the immune system is less clear.

3.1.2.5 | *Neurotoxicity studies*

This section provides a brief summary of the effects reported in the previous Opinion, a summary of the effects reported in the new studies identified in the open literature since then, and an overall summary of all the evidence available. The details of the studies considered in the previous Opinion can be found in EFSA CONTAM Panel (2011b). The details of the new studies published since then are provided in Appendix E (Table E.6).

Studies considered in the previous EFSA assessment

In its previous Opinion (EFSA CONTAM Panel, 2011b), the CONTAM Panel concluded that exposure of rodents to PBDE congeners during development can cause neurobehavioural effects, such as alterations in learning and memory, habituation, spontaneous behaviour, locomotor activity and anxiety. Data were available for **BDE-47**, **-99**, **-153**, **-183**, -203 and -206, **-209** and some technical products, produced in non-standard studies with differing dosing and testing protocols. Because of the differing protocols, it is not possible to distinguish differing effects of the congeners, however most studies indicate potential for developmental neurobehavioural effects.

For **BDE-47**, a number of studies were available involving a single administration to neonatal mice or rats with neurobehavioural testing in adulthood (Eriksson et al., 2001; Gee & Moser, 2008; He et al., 2009; Kuriyama et al., 2004). One study involved administration to pregnant rats on GD6 followed by testing of the offspring from PND35 to PND80. One study involved repeat dosing of mice through mating, gestation and lactation with neurobehavioural testing of the adult offspring (Ta et al., 2011). Of these studies, the CONTAM Panel calculated a $BMDL_{10}$ of 0.309 mg/kg bw (309 µg/kg bw) from the data on locomotion in the study of Eriksson et al. (2001) and converted it to a body burden of 0.232 mg/kg bw (232 µg/kg bw), which was used as the Reference Point in the risk characterisation.

For **BDE-99**, there were also several studies involving a single administration to neonatal mice or rats with neurobehavioural testing in adulthood (Eriksson et al., 2001, 2002; Viberg et al., 2004a, 2004b). One single administration study was available in which pregnant rats were dosed on GD6 and the offspring were tested for locomotion on PND36 and PND71 (Kuriyama et al., 2005). Two studies involved repeated oral dosing of mouse dams from GD6 to PND21, with neurobehavioural testing of the offspring at various times (Branchi et al., 2002, 2005). Three studies involved repeated oral or s.c. dosing of mouse or rat dams for varying periods followed by testing of the juvenile or adult offspring (Cheng et al., 2009; Lichtensteiger et al., 2004; Lilienthal et al., 2006). One study involved administration of much lower doses of **BDE-99** (0.00015–0.015 mg/kg bw per day) to adult rats for 90 days with no reported neurobehavioural effects (Daubié et al., 2011).

The CONTAM Panel conducted dose–response modelling on the data from the single administration studies in mice and rats and selected the $BMDL_{10}$ of 0.012 mg/kg bw (12 μg/kg bw) calculated from the data on total activity in mice in the study of Eriksson et al. (2001)[36] which was converted to a body burden of 0.009 mg/kg bw (9 μg/kg bw) for use as the Reference Point in the risk characterisation.

One study was available for each of **BDE-153**, **-183**, -203 and -206, also involving a single administration to neonatal mice resulting in neurobehavioural changes in adulthood. For **BDE-153** the CONTAM Panel conducted dose–response modelling on the data from the single administration study in mice of Viberg, Fredriksson, and Eriksson (2003), and selected the $BMDL_{10}$ of 0.083 mg/kg bw (83 μg/kg bw) calculated from the data on total activity, which was converted to a body burden of 0.062 mg/kg bw (62 μg/kg bw) for use as the Reference Point in the risk characterisation for **BDE-153**. No risk characterisation could be performed for the **BDE-183**, -203 and - 206 due to the lack of dose–response data.

For **BDE-209**, two studies with single administration to neonatal mice or rats, and two studies with repeated oral administration to mice from PND2 to PND15 were available with neurobehavioural testing at various ages (Rice et al., 2007, 2009; Viberg, Fredriksson, & Eriksson, 2003; Viberg et al., 2007). The CONTAM Panel conducted dose–response modelling on the data from the single administration studies in neonatal mice, which showed neurobehavioural effects in tests conducted at 2, 4 or 6 months, and selected the $BMDL_{10}$ of 1.7 mg/kg bw (1700 μg/kg bw) calculated from the data on total activity in the study of Viberg et al. (2007), which was used as the Reference Point in the risk characterisation.

Two studies were available for the technical PBDE product DE-71 (Dufault et al., 2005; Kodavanti et al., 2010), and were not used in risk characterisation of PBDE congeners.

Studies published since the previous EFSA assessment

Since the previous assessment, a number of studies on neurobehavioural effects have been identified for **BDE-47**, **-99**, **-209** and PBDE technical products (DE-71, DecaBDE). No new oral behavioural studies were available for **BDE-153**, **-183**, -203 and -206.

These new studies again used differing dosing and testing protocols and most indicate potential for similar neurobehavioural effects to those observed previously. For details on the available studies see Appendix E (Table E.6).

BDE-47

Thirteen new studies were identified regarding the neurotoxicity of **BDE-47**. Eight studies were performed in mice and five in rats. Four studies consisted of a repeated exposure to **BDE-47** in adult animals, one in rats (Yan et al., 2012) and three in mice (Li, Ma, et al., 2021; Zhuang et al., 2017, 2018). Three studies reported a significant reduction in the spatial learning and memory performances, two at the single level of dose tested (20 mg/kg bw per day for 30 days, Zhuang et al., 2017, 2018) and one at the three levels of doses administered (0.1, 0.5 or 1 mg/kg bw per day, Yan et al., 2012). The last study (Li, You, & Wang, 2021) reported histological alterations in hippocampus that remain inadequate to determine a clear dose–response relationship with the doses used (1, 10 or 100 mg/kg bw per day, 56 days).

Two studies consisted of an acute administration of **BDE-47** at PND10 to the dams at several doses ranging 0–30 mg/kg bw (Gee et al., 2011) or 0–10 mg/kg bw (He et al., 2011). Gee et al. (2011) reported a statistically significant increase in dopamine levels in the cortex, regardless of age, in the 10 mg/kg bw groups, but not at 1 and 30 mg/kg bw. A significant dose–response impairment of learning and memory abilities was reported by He et al. (2011) at all doses administered (1, 5 and 10 mg/kg bw).

Three studies consisted of a repeated exposure to **BDE-47** during gestation and lactation (Haave et al., 2011; Kim, Colon, Chawla, Vandenberg, & Suvorov, 2015; Li, You, & Wang, 2021). A single level of dose was used in two studies: 0.2 mg/kg bw (Kim, Colon, Chawla, Vandenberg, & Suvorov, 2015) or 50 mg/kg bw (Li, You, & Wang, 2021). Results reported increases in the level of anxiety (Kim, Colon, Chawla, Vandenberg, & Suvorov, 2015) and repetitive behaviours (Li, You, & Wang, 2021), correlated with a significant reduction of the social preference (Li, You, & Wang, 2021), suggesting both the potent ability of **BDE-47** to induce the emergence of mild autistic-like behaviours. The third study (Haave et al., 2011) reported a discrete increase in the latency of the righting reflex in animals exposed to the highest level of dose (0.227 mg/kg bw per day).

Four studies consisted of a continuous exposure to **BDE-47** during a preconceptual period, the gestation and the lactation (Koenig et al., 2012; Li, Ma, et al., 2019; Qiu et al., 2022; Woods et al., 2012).

Dam exposure was started 10 days (Li, Ma, et al., 2019; Qiu et al., 2022) or 4 weeks (Koenig et al., 2012; Woods et al., 2012) before mating until PND21 with **BDE-47** levels of dose ranging from 0.1–10 mg/kg bw per day (Li, Ma, et al., 2019; Qiu et al., 2022) or 0.03–1.0 mg/kg bw per day (Koenig et al., 2012; Woods et al., 2012). **BDE-47** tissue levels were assessed in dams (blood, brain, fat and milk) and pups (whole fetus, blood and brain) at GD15, PND1, 10 and 21 (Koenig et al., 2012). **BDE-47** perinatal exposure was reported to impair the spatial learning and memory performances measured in a Barnes maze for 4 consecutive days at the adult age (8 weeks) only at the first session of testing with all doses used (Koenig et al., 2012). The same protocol of exposure to **BDE-47** was shown to impair the distress call of pups at PND8, 10 and 16 in males and females, sociability at PND40 and 72 in females, and spatial learning and memory performances at PND56 also in females (Woods et al., 2012).

[36]This was wrongly cited as Viberg et al. (2004b) in Table 40 of the EFSA CONTAM Panel (2011b).

However, these last results were not presented for individual doses and are unable to be used for the risk assessment study of **BDE-47**. The study from Li, Ma, et al. (2019) reported a reduction in spatial learning and memory performances at all doses administered (0.1, 1.0 or 10.0 mg/kg bw per day, 10 days before mating until PND21).

Finally, the study from Qiu et al. (2022) that applied the same protocol of exposure as used by Li, Ma, et al. (2019), showed at the adult stage (PND88) in the open-field an increase in the level of activity of the animals early dosed with 1.0 and 10 mg/kg bw per day, and a significant reduction in the distance travelled in the central part of the maze. At the same time, the time spent in the central area was significantly reduced, but non dose related.

BDE-99

Four new studies were identified, one performed in mice (Hallgren et al., 2015) and three in rats (Bellés et al., 2010; Blanco et al., 2013; Zhao, Cheng, et al., 2014). One study was done in adult animals whereas the other three were performed in developing mice or rats.

The study from Bellés et al. (2010)[37] was performed in adult male rats orally dosed (gavage) with 0.6 or 1.2 mg/kg bw per day of **BDE-99** for 45 days and reported a transient impairment in locomotor coordination and self-reactivity but not in other neurobehavioural testing. The single administration study in neonatal mice from Hallgren et al. (2015) reported significant changes in the spontaneous locomotor activity measured in mice aged of 2 months orally administered at PND10 at a dose of 12 mg/kg bw.

The last two studies (Blanco et al., 2013; Zhao, Cheng, et al., 2014) were two repeat dose studies with dosing of rat dams during gestation and lactation and neurobehavioural testing of the offspring early after weaning at PND21 and the end of exposure. **BDE-99** was administered orally (gavage) in both studies, at a dose of 0, 1 or 2 mg/kg bw per day from GD6 to PND21 (Blanco et al., 2013), or 0–0.2 mg/kg bw per day from GD1 to PND21 (Zhao, Cheng, et al., 2014). Both studies reported a lack of effects on learning and memory performances and locomotor activity. A reduction in the level of anxiety (with the potential to adversely affect adaptation to stressful situations) was reported in rat offspring at PND22 at highest dose of **BDE-99** (2 mg/kg bw per day, Blanco et al., 2013). Based on these effects on anxiety (Blanco et al., 2013), a LOAEL of 2 mg/kg bw per day with a NOAEL of 1 mg/kg bw per day were found in pups early exposed to **BDE-99** during gestation and lactation (GD6–PND21).

BDE-209

Ten new studies were reported for **BDE-209** since the previous Opinion, five in rats (Chen, Li, et al., 2014; Li, Wang, et al., 2017; Sun et al., 2017; Wang, Wang, et al., 2011; Xiong et al., 2018) and six in mice (Buratovic et al., 2014; Feng et al., 2015; Heredia et al., 2012; Markowski et al., 2017; Qian et al., 2021; Wang and Dai, 2022). Five studies were performed in young and/or adult animals for a period of exposure ranging from 2 to 3 weeks or months to 2 years. The other 6 studies were done in developing rats or mice including pre- or post-natal period alone, or both.

Two studies (Chen, Li, et al., 2014; Sun et al., 2017) consisted of a gestational exposure of rats to **BDE-209**. Repeated gavage administration to rats from GD1 to PND25 resulted in dose-related impaired learning in a Morris water maze test commencing on PND25, which was statistically significant at 30 and 50 mg/kg bw per day, but not at 10 mg/kg bw per day (Chen, Li, et al., 2014). Repeated gavage administration at 10 and 20 mg/kg bw per day to pregnant rats from GD1 to GD21 resulted in impaired learning and memory in a Morris water maze test conducted over PND28–32. The NOAEL was 5 mg/kg bw per day (Sun et al., 2017).

The exposure of mice during gestation and lactation (GD0–PND21) at 225 and 900 mg/kg bw per day of **BDE-209** resulted in impaired spatial learning and memory ability in the offspring tested on PND21–26, with histopathological changes in the hippocampi at the high dose (Qian et al., 2021).

Postnatal exposure to **BDE-209** was also shown to induce delayed learning and memory disturbances. The study from Buratovic et al. (2014) reported the ability of a single oral administration of **BDE-209** by gavage at 1.5, 6.3 and 14.6 mg/kg bw per day on PND3 to mice pups to impair in a dose-dependent manner spontaneous behaviour (including locomotion, rearing and total activity) of animals of 2 and 4 months of age when placed in a novel environment, and to alter the spatial learning and memory abilities of mice tested at age 5 and 7 months in a Morris water maze only at the two highest doses. Significant changes in the same behavioural tasks were reported in animals challenged for their cholinergic susceptibility with both cholinergic agents paraoxon or nicotin.

Neonatal rats daily administered by gavage with **BDE-209** from PND5 to 10 at doses of 0, 1, 10 and 20 mg/kg bw per day were tested for their learning and memory abilities starting on PND70 (Li, Wang, et al., 2017). Dose-related impaired spatial learning and memory was observed in the Morris water maze at all dose levels. Impaired working and reference memory were decreased at the two higher doses in an eight-arm radial maze.

Dosing of neonatal mice via a micropipette at 20 mg/kg bw per day (the only dose tested) from PND1–21 resulted in deficits in grip strength, motor activity and learning in the animals tested on PND250, with lesser effects on females compared to the males (Markowski et al., 2017).

[37]This study was cited in the previous EFSA assessment on PBDEs (EFSA CONTAM Panel, 2011b) and it is included again in the current assessment to provide insight into additional observations by the study authors not reported in the previous Opinion.

Mice of 3 weeks of age were daily administered with **BDE-209** for 28 days at doses of 0, 50 and 100 mg/kg bw per day and their learning and memory performances assessed during the last week of treatment. Impaired learning and memory performances were reported in the Morris Water Maze at both doses whereas no significant changes were observed in the two-object recognition test (Wang and Dai, 2022).

In adult animals, gavage dosing of 3-month-old mice for 15 days at 20 mg/kg bw per day (only dose tested) resulted in reduced arousal, increased indicators of anxiety and impaired learning in a spatial memory task only during the first probe trial (Heredia et al., 2012). Gavage administration of **BDE-209** to 3-week-old male rats for 90 days at 0, 10 and 50 mg/kg bw per day did not result in consistent signs of anxiety nor activity in an open-field test (Wang, Wang, et al., 2011).

When 11-week-old male rats were dosed by gavage for 30 days at 250, 500 and 1000 mg/kg bw per day and then 7 days later were tested in a Morris water maze, there was a dose-related impairment of spatial learning and memory, with a NOAEL of 250 mg/kg bw per day (Xiong et al., 2018). Administration of **BDE-209** to adult female mice by gavage at 800 mg/kg bw per day on alternate days for 2 years resulted in decreased number of neurons and neuronal degeneration in the hippocampus, a structure in the brain that plays an important role in spatial learning and memory (Feng et al., 2015). The authors reported behavioural abnormalities in mice at 6 months of age, but did not provide details of the methodology or results.

PBDE technical products

Four new studies were available for the technical PBDE product DE-71, with varying PBDE composition. Dosing of rats at 0, 0.3, 3.0 and 30 mg/kg bw per day from GD1 to PND21 with a product containing predominantly **BDE-47** and **-99** led to small transient changes in motor activity and startle responses, but no effect on learning and memory or anxiety (Bowers et al., 2015). The NOAEL was 3 mg/kg bw per day. Two other studies were conducted with a DE-71 technical product containing predominantly tetra- and pentaBDEs, but with no specific information on the congener composition. No effects on learning and attention were observed in male rats dosed at 0, 5 and 15 mg/kg bw per day from PND6 to PND12 and tested from PND40–95 (Driscoll et al., 2012). Dosing of neonatal rats at 30 mg/kg bw per day (only dose tested) from PND5 to PND22 resulted in a reference memory deficit in females, but no effect on motor activity or working memory in either sex (de-Miranda et al., 2016). In a recent study with a DE-71 product containing predominantly **BDE-47**, **-99** and **-100**, and dosing of mice through mating, gestation and lactation, effects on memory were reported at 0.1 mg/kg bw per day, and in some tests also at 0.4 mg/kg bw per day (Kozlova et al., 2021).

A developmental neurotoxicity study complying with OECD TG 426 and GLP was conducted with a composite of three commercial DecaBDE products, containing 97.51% **BDE-209** (Biesemeier et al., 2011). No neurobehavioural changes were observed in detailed clinical observations, startle response, learning and memory, motor activity or in neuropathological or morphometric measurements when female rats were dosed by oral gavage at dose levels of 1, 10, 100 and 1000 mg/kg bw per day from GD6 to PND21. The Panel notes that the Biel swim maze was used to test the animals for their spatial learning and memory performances. The lack of effects observed may be due to the use of this maze, whereas most of the studies identified used the Morris water maze for testing. Performance in the Morris water maze is considered to be more sensitive compared to the Biel swim maze; the first allows to study the spatial learning and memory performance of the animals based on both distal visual cues (allocentric memory) and non-spatial strategies (egocentric memory), whereas the Biel swim maze explores only the egocentric spatial abilities of the animals (mapping navigation) (Akaike et al., 1994; Paul et al., 2009).

Overall summary on neurotoxicity

In summary, all individual PBDE congeners and technical products that have been tested showed evidence of neurobehavioural effects in rats and mice, such as alterations in locomotion and spontaneous activity, anxiety and learning and memory abilities. The study protocols were mostly non-standard, with different dosage regimens and behavioural tests performed at different life stages.

The data indicated that effects are seen at lower doses when tests are performed in adulthood following early exposure including only gestation or lactation, or both, than with dosing or testing at other life stages.

For **BDE-47**, the lowest LOAEL among the different studies was 0.03 mg/kg bw per day in mice, based on impaired learning when faced for the first time with the maze (Koenig et al., 2012).

For **BDE-99**, the lowest LOAEL was 0.06 mg/kg bw following a single administration on GD6 in rats, based on increased locomotor activity in 71 day-old animals early exposed through the dam (Kuriyama et al., 2005). The lowest LOAEL used for the previous assessment of **BDE-99** was 0.8 mg/kg bw by single administration to pregnant mice at GD10 based on the significant reduction of total activity of offspring tested at 2 and 4 months of age during the first 20 min of testing (Eriksson et al., 2001).

One study was conducted on **BDE-153** (Viberg, Fredriksson, & Eriksson, 2003) which provided a NOAEL of 0.45 mg/kg bw per day (LOAEL of 0.9 mg/kg bw per day) in mice, based on total activity.

The only studies available on **BDE-183, -203** and **-206** (Viberg et al., 2006), each only used one dose level, and therefore do not provide information on the dose–response relationships.

For **BDE-209**, the lowest LOAEL was 1 mg/kg bw per day in rats, based on impaired spatial learning and memory (Li, Wang, et al., 2017). In contrast, a developmental neurotoxicity study conducted according to OECD TG 426 with technical

DecaBDE material containing 97.51% **BDE-209** revealed no neurobehavioural changes in detailed observations, including startle response, learning and memory tests, or in motor activity, neuropathological or morphometric measurements, at maternal doses up to 1000 mg/kg per day (Biesemeier et al., 2011). It has to be noted that this last study used a lower sensitive paradigm to test the spatial learning and memory performances (Biel swimming maze) whereas the more recent studies considered in the present Opinion referred to Morris water maze whose methodology and performances are widely established.

In addition, the CONTAM Panel noted the systematic review of Dorman et al. (2018) that reported a meta-analysis of six developmental animal PBDE neurotoxicity studies using the Morris water maze and showed a significant alteration of learning and memory performances in PBDE-exposed animals with low heterogeneity. Such outcomes were selected because they paralleled the cognitive-related issues evaluated in a systematic review of human studies (Lam et al., 2017). Details of this review are also described in NASEM (2017). Taking into account a risk of bias, the review concluded that there was a 'moderate' level of evidence that exposure to **BDE-47**, **-99** and **-209** affects learning performances. For the other PBDEs assessed (**BDE-153**, -203 and -206, and the technical product DE-71) and for the memory and attention endpoints, the evidence was 'low' or 'very low'.

3.1.2.6 | *Genotoxicity studies*

Studies considered in the previous EFSA assessment

The available studies evaluated in the previous EFSA assessment (EFSA CONTAM Panel, 2011b) indicated that PBDEs do not induce gene mutations (in *S. typhimurium* reverse mutation tests, *S. cerevesiae* or mammalian cells *in vitro*). Some studies indicated that PBDEs (**BDE-47**, -**49**, -**99**, -**138**, -**209** and 6-OH-BDE-47 and 4-OH-BDE-49) can cause DNA damage and chromosomal aberrations through the induction of reactive oxygen species (ROS).

Studies published since the previous EFSA assessment

Since the publication of the previous Opinion, genotoxicity studies have been identified for BDE-1, -12, -32, **-47**, -**49**, -**99**, -**100**, -**138**, **-153, -154, -209**, for PBDE technical products (DE-71, PentaBDE and OctaBDE), as well as for PBDE metabolites.

Details of the *in vitro* studies are provided in Table 14 ordered by type of assay. For completeness, this table also shows the *in vitro* mammalian cell studies considered in the previous assessment. Details of the *in vivo* assays are reported in Table 15.

BDE-47

BDE-47 was negative in reverse gene mutation assays in *S*. typhimurium in presence or absence of S9 mix (NTP, 2016; Pereira et al., 2016).

BDE-47 was positive in a gene recombination assay in Chinese hamster cells (Helleday et al., 1999[38]).

Positive results have been reported in *in vitro* Comet assays in human neuroblastoma cells (Gao et al., 2009; He et al., 2010; Pellacani et al., 2012), human HepG2 cells (Pereira et al., 2016; Saquib et al., 2016; Wang, Zou, et al., 2012), human acute monocytic leukaemia cells (Wang, Wang, et al., 2020), primary rat hippocampal neurons (He, He, Wang, Xia, Xu, Zhang, & Chen, 2008) and human bronchial epithelial 16HBE cells (Montalbano et al., 2020). A negative result was reported in human liver L02 cells (An, Yin, et al., 2011). Pellacani et al. (2012) showed that the single strand breaks induced by **BDE-47** in human neuroblastoma cells were secondary to induction of oxidative stress.

BDE-47 was positive in a micronucleus test in human neuroblastoma cells SHSY5Y (expressing xenobiotic-metabolising CYP enzymes (He, He, Wang, Xia, Xu, & Chen, 2008; He et al., 2010), and negative in HepG2 cells (Pereira et al., 2016; Song et al., 2021). It is also positive in V79 cells expressing CYP enzymes (Song et al., 2021).

Chromosomal aberrations were induced in chicken isogenic DT40 cells (deficient in one of the major DNA damage repair mechanisms) (Ji et al., 2011).

In addition, increases in double strand breaks have been measured in a test for Ser-139 phosphorylated H2AX (γ-H2AX) in human bronchial epithelial 16HBE cells and in chicken isogenic DT40 cells (Ji et al., 2011; Montalbano et al., 2020).

In vivo exposure by gavage of **BDE-47** was negative in a micronucleus test in peripheral blood of mice, in a Pig-a gene mutation assay in mice as well as in a *Gpt* gene mutation assay (in liver and germ cells) in mice (You et al., 2018).

BDE-49

BDE-49 was positive in a chromosomal aberration test in chicken isogenic DT40 cells as well as in a γH2AX assay in human bronchial epithelial 16HBE cells (Ji et al., 2011).

[38]The study by Helleday et al. (1998) was not reported in the previous Opinion and it is thus described under studies published since the previous assessment.

BDE-99

BDE-99 was negative in reverse gene mutation assays in *S*. Typhimurium in presence or absence of S9 mix (NTP, 2016; Pereira et al., 2016).

Positive results have been reported in *in vitro* Comet assays in human HepG2 cells (Pereira et al., 2016), in human bronchial epithelial 16HBE cells (Montalbano et al., 2020).

It was negative in a micronucleus test in HepG2 cells (Pereira et al., 2016).

Chromosomal aberrations were induced in chicken isogenic DT40 cells (deficient in one of the major DNA damage repair mechanism) (Ji et al., 2011).

In addition, increases in double strand breaks have been measured in γ-H2AX test in human bronchial epithelial 16HBE cells and in chicken isogenic DT40 cells (Ji et al., 2011; Montalbano et al., 2020).

BDE-100

Few studies were also performed with **BDE-100** showing negative results in Ames tests with and without S9 mix and in a micronucleus test in human HepG2 cells (Pereira et al., 2016) and positive results in a Comet assay in human HepG2 cells (Pereira et al., 2016).

BDE-138

BDE-138 was positive in a chromosomal aberration test in chicken isogenic DT40 cells as well as in a γH2AX assay in human bronchial epithelial 16HBE cells (Ji et al., 2011).

BDE-153

BDE-153 was negative in reverse gene mutation assays in *S*. Typhimurium in presence or absence of S9 mix (NTP, 2016; Pereira et al., 2016).

Positive results have been reported in *in vitro* Comet assays in human HepG2 cells (Pereira et al., 2016).
It was negative in a micronucleus test in HepG2 cells (Pereira et al., 2016).

BDE-154

Negative results were reported on **BDE-154** in Ames tests with and without S9 mix and in a micronucleus test in human HepG2 cells (Pereira et al., 2016) and positive results in a Comet assay in human HepG2 cells (Pereira et al., 2016).

BDE-209

BDE-209 was negative in reverse gene mutation assays in *S*. Typhimurium in presence or absence of S9 mix (Pereira et al., 2016).

It was positive in an *in vitro* Comet assay in human colon carcinoma cells (Curčić et al., 2014), in human HepG2 cells (Pereira et al., 2016), in human neuroblastoma cells (Pellacani et al., 2012), in human bronchial epithelial 16HBE cells (Montalbano et al., 2020).

It was negative in a micronucleus test in HepG2 cells (Pereira et al., 2016).

Pellacani et al. (2012) showed that the single strand breaks induced by **BDE-209** in human neuroblastoma cells were secondary to induction of oxidative stress.

Chromosomal aberrations were induced in chicken isogenic DT40 cells (deficient in one of the major DNA damage repair mechanisms) (Ji et al., 2011).

In addition, increases in double strand breaks have been measured in γ-H2AX test in human bronchial epithelial 16HBE cells, in chicken isogenic DT40 cells and in HepG2 cells (Ji et al., 2011; Montalbano et al., 2020; Yuan, Che, et al., 2021).

In vivo, **BDE-209** was negative after dietary exposure in a micronucleus test in mouse bone marrow and in a gene mutation assay (in liver) in mice (Takasu et al., 2017).

After exposure by gavage of pregnant mice, **BDE-209** induced significant sperm chromatin DNA damage (DNA denaturation induction and increased DNA fragmentation index) in male offspring (Tseng et al., 2013).

Other individual PBDE congeners

BDE-1 and BDE-12 were positive in a gene recombination assay in Chinese hamster cells (Helleday et al., 1999).

BDE-32 was reported to be positive in an *in vitro* Comet assay in HepG2 cells (Saquib et al., 2016).

PBDE Technical products

DE-71 was negative in reverse gene mutation assays in *S*. Typhimurium in presence or absence of S9 mix (NTP, 2016). It was also negative in *in vivo* micronucleus tests (peripheral blood and bone marrow) in mice exposed by gavage for 3 months (up to 500 mg/kg bw per day) or once daily for 3 days (up to 1500 mg/kg bw per day) (NTP, 2016).

DecaBDE was negative in a gene mutation test (mouse lymphoma L5178Y $TK^{+/-}$) in presence or absence of S9 mix and in a chromosomal aberration test in CHO cells in presence or absence of S9 mix (NTP, 1986).

In an *in vivo* Comet assay, no increase in strand breaks have been reported in spermatozoa of rat exposed to a complex BFR mixture during 70 days of three commercial PBDE products (52.1% DE-71, 0.4% DE-79 and 44.2% **BDE-209**) and HBCDDs (3.3%) (Ernest et al., 2012).

PBDME metabolites

6-OH-BDE-47 or 6-MeO-BDE-47 gave positive results in *in vitro* Comet assays (An, Li, et al., 2011; Saquib et al., 2018), in a *in vitro* micronucleus test (An, Li, et al., 2011) and in a chromosomal aberration test in chicken isogenic DT40 cells (Ji et al., 2011). Positive results were also reported in a γH2AX assay in human bronchial epithelial 16HBE cells (Ji et al., 2011).

2-OH-BDE-47 and 2-OH-BDE-85 were negative in a Comet assay in human H295R adrenocortical carcinoma cells (Song et al., 2009).

4-OH-BDE-49 was positive in a chromosomal aberration test in chicken isogenic DT40 cells as well as in a γH2AX assay in human bronchial epithelial 16HBE cells (Ji et al., 2011).

Synthetic PBDE-quinones, with no more than one Br substituent on the quinone ring, have been investigated for covalent binding to DNA and formation of DNA adducts. Huang, Li, et al. (2015) and Lai et al. (2011c) synthesised di- and tri-PBDE-quinones[25,39] from the reaction of phenol or bromophenol with bromobenzoquinones. Adduct formation was reported when deoxynucleosides or calf thymus DNA were treated with these synthetic PBDE-quinones. In further experiments, exposure of HeLa cells to one of these PBDE-quinones[40] resulted in increased induction of single (Comet assay) and double strand breaks (γ-H2AX assay), increased micronucleus frequency and the induction of 8-OHdG foci (Dong et al., 2018; Liu et al., 2021). The same authors reported the formation of adducts when metabolites of 6′-OH-BDE-17 produced via microsomal-mediated metabolism, were incubated with deoxyguanosine, horseradish peroxidase and H_2O_2 (Lai, Lu, Gao, et al., 2011). The authors speculated this could be attributed to PBDE-quinones (see **Section 3.1.1.1.3**). However, formation of PBDE-quinones has not been demonstrated either *in vitro* or *in vivo*, and DNA adducts from PBDE metabolites have only been demonstrated using sub-cellular systems and it is not clear if these adducts are identical to DNA adducts produced by synthetic PBDE quinones.

Overall summary on Genotoxicity

In summary, *in vitro*, negative results were obtained in Ames tests for several PBDE congeners, and also for **BDE-47** and **-209** in *in vivo* gene mutation assays. **DecaBDE** was negative in a gene mutation test and in a chromosomal aberration test.

Positive micronucleus tests were observed in SH-SY5Y cells (expressing xenobiotic-metabolising CYP enzymes) after exposure to **BDE-47**. However, negative results were reported for **BDE-47**, **-99**, **-100**, **-153**, **-154** and **-209** in HepG2 cells. **BDE-47** was also positive in V79 cells expressing CYP enzymes.

Induction of micronuclei was shown *in vitro* in cells expressing xenobiotic-metabolising CYP enzymes (human neuroblastoma cells or V79) exposed to **BDE-47** but not in HepG2 cells. Two metabolites, 6-OH-BDE-47 and 6-MeOH-BDE-47, were also positive for induction of micronuclei *in vitro*. *In vivo*, negative results were obtained in micronucleus tests in peripheral blood and bone marrow with **BDE-47**, **-209** and DE-71. The CONTAM Panel noted that while the micronucleus tests do not show evidence of toxicity to the bone marrow, systemic exposure is evident from toxicokinetics (see **Section 3.1.1**) and from systemic toxicity (see **Section 3.1.2**) and thus these are lines of evidence of bone marrow exposure to the test substance, according to the recommendations of the EFSA Scientific Committee (2017b).

In vitro tests indicate that some PBDEs (**BDE-47**, **-99**, **-100**, **-153**, **-154** and **-209**) can cause DNA damage (single and double strand breaks). Positive results were also reported for hydroxylated or methoxylated metabolites of **BDE-47** and **-49** in Comet assays.

There is evidence that PBDEs can induce DNA damage via an indirect mechanism of action involving, i.e. reactive oxygen species (ROS). This was demonstrated for **BDE-47** and **-209** by the induction of DNA strand breaks along with the increase of 8-OHdG or the presence of DNA strand breaks along with oxidative stress markers (increases in ROS production and MDA content, decreases in SOD, GSH and GSH-Px activities). It was also shown that in a comet assay carried out in the presence of FPG there was an increase in DNA strand breaks. These DNA lesions may be related to ROS production and purine oxidation (see also **Section 3.1.4** on MOA).

Although there is evidence of genotoxicity *in vitro* for some congeners, there was no evidence for *in vivo* genotoxicity. The CONTAM Panel concluded that the 10 congeners considered in the Opinion are not genotoxic *in vivo*.

[39]2-(2′,4′-Bromophenoxyl)-benzoquinone, 2-Phenoxyl-6-bromo-benzoquinone, 2-(2′-Bromophenoxyl)-6-bromo-benzoquinone, 2-(2′,4′-Bromophenoxyl)-6-bromo-benzoquinone, 2-(2′,4′,6′-Bromophenoxyl)-6-bromo-benzoquinone.

[40]2-(2′,4′-Bromophenoxyl)-benzoquinone.

TABLE 14 *In vitro* genotoxicity studies on PBDEs considered in the previous Opinion and published since the previous EFSA risk assessment.

Type of test	Experimental test system	Test substance(s)	Exposure conditions	Result	Comments	Reference
Reverse gene mutation assay (Ames test)	*S.* Typhimurium TA98, TA100	**BDE-47** **BDE-99** **BDE-100** **BDE-153** **BDE-154** **BDE-209** Purity: 100% Solvent: DMSO	0.025–10 μg/plate +/– S9 mix Pre-incubation test	Negative with and without S9 mix **Negative**	–	Pereira et al. (2016)
Reverse gene mutation assay (Ames test)	*S.* Typhimurium TA98, TA100, TA102	**BDE-47** **BDE-99** **BDE-153**	**BDE-47**: 0–10,000 μg/plate **BDE-99**: 0–10,000 μg/plate **BDE-153**: 0–5000 μg/plate +/– S9 mix of rat Pre-incubation test	**Negative**	No cytotoxicity. Precipitation occurred at the higher doses of most trials. Adequate positive controls used gave the expected positive results	NTP (2016), Zeiger et al. (1992)
Reverse gene mutation assay (Ames test)	*S.* Typhimurium TA98, TA100, TA102, TA1535 and TA1537, and *E. coli* strain WP2 *uvr*A/pKM101	DE-71	0, 100, 333, 1000, 3333, 10,000 μg/plate +/– S9 mix of rat and hamster Pre-incubation test	**Negative**	No cytotoxicity. Precipitation occurred at the higher doses of most trials. Adequate positive controls used gave the expected positive results	NTP (2016), Zeiger et al. (1987)
Gene recombination assay	Chinese hamster SPD8 and Sp5 cell lines	BDE-1 BDE-12 **BDE-47** Solvent: DMSO	SPD8 assay: BDE-1: 0, 5, 10, 20, 30 μg/mL BDE-12: 0, 5, 10, 20 μg/mL **BDE-47**: 0, 10, 20, 30, 40 μg/mL Sp5 assay: BDE-1: 0, 10, 20, 30, 40 μg/mL BDE-12: 0, 5, 15, 25, 35 μg/mL **BDE-47**: 0, 10, 20, 40 μg/mL Exposure: 24 h	SPD8 assay: increases in recombination frequency with all compounds at the highest dose. Sp5 assay system: increases in recombination frequency with BDE-1 and BDE-12 at the highest dose. **Positive**	–	Helleday et al. (1999)
Gene mutation assay	Mouse lymphoma L5178Y $TK^{+/-}$	DecaBDE Negative control: DMSO Positive controls: EMS (–S9), 3-methylcholanthrene (+S9)	0, 7, 8, 9, 10 μg/mL +/– S9 mix of rat Exposure: 4 h	**Negative**	–	NTP (1986)
Chromosomal aberration	CHO cells	DecaBDE Negative control: DMSO Positive controls: MMC (–S9) and CP (+S9)	50, 100, 250, 500 μg/mL +/– S9 mix of rat –S9: 8–10 h exposure, harvesting 2–3 h later +S9: 2 h exposure, harvesting 8–10 h later	**Negative**	–	NTP (1986)

TABLE 14 (Continued)

Type of test	Experimental test system	Test substance(s)	Exposure conditions	Result	Comments	Reference
Comet assay	Human neuroblastoma cells (SH-SY5Y)	**BDE-47** Solvent: DMSO *N*-acetylcysteine	0, 1, 5, 10 μM Corresponding to: 0, 0.49, 2.43, 4.86 μg/mL Exposure: 24 h	Statistically significant increase in % DNA in tail and olive tail moment at the two highest concentrations **Positive** Increase in 8-OHdG after exposure to 10 μM and return to control level when coexposure with *N*-acetylcysteine Statistically significant increase in ROS level at 10 μM Decrease ROS level when coexposure with *N*-acetylcysteine	–	Gao et al. (2009)
Comet assay (alkaline)	Human L02 cells (liver cell line)	**BDE-47** Negative control: DMSO Positive control: B(a)*P* (50 μmol/L, 2 h)	5, 10 μmol/L Corresponding to: 2.4, 4.9 μg/mL Exposure: 24 h	Non-statistically significant slight increase (dose-related) in tail moment. **Considered negative**	No effect on the cell proliferation or survival *N*-acetyl cysteine could partly inhibit the DNA strand break induced by **BDE-47**	An, Yin, et al. (2011)
Comet assay (alkaline)	HepG2 cells (human liver hepatocellular carcinoma)	**BDE-47** BDE-32 Purity: 99.99% Negative control: acetonitrile Positive control: EMS	25, 50, 100 nM Corresponding to: **BDE-47**: 0.01, 0.02, 0.05 μg/mL BDE-32: 0.01, 0.02, 0.04 μg/mL Exposure: 3 or 6 days	Statistically significant increase in DNA damage (olive tail moment, tail length and tail intensity) **Positive**	Cytotoxicity: Significant decrease in cell viability in MTT assay. Concentration and time-dependent reduction in cell viability in NRU assay	Saquib et al. (2016)
Comet assay (alkaline)	Human hepatoma cell line HepG2	**BDE-47** Negative control: DMSO Positive control: **BDE-47** (50 μM) for 24 h	10^{-10}, 10^{-9}, 10^{-8} M Corresponding to: 0.0005, 0.005, 0.05 μg/mL Exposure: 24 h Or 10^{-10}, 10^{-9} or 10^{-8} M for 24 h followed by 50 μM **BDE-47**	No increase in DNA damage (% tail DNA) after low dose exposure Statistically significant increase in DNA damage after exposure to 50 μM **BDE-47** **Positive** Lower increase in cells pretreated with low doses of **BDE-47**	–	Wang et al. (2012)
Comet assay (alkaline)	Human acute monocytic leukaemia (THP-1)	**BDE-47** Purity 99.5% Negative control: DMSO Estimation of % tail DNA	0, 5, 20, 40, 60, 80, 100 μg/mL Exposure 1 h	Statistically significant increase in DNA damage from 40 μg/mL **Positive**	–	Wang, Wang et al. (2020)

(Continues)

TABLE 14 (Continued)

Type of test	Experimental test system	Test substance(s)	Exposure conditions	Result	Comments	Reference
Comet assay (alkaline)	Primary rat hippocampal neurons	**BDE-47** Purity: 100% Solvent: DMSO Positive control: none	0, 2.06, 20.6, 41.2 μM Corresponding to: 1, 10, 20 μg/mL Exposure: 24 h	Statistically significant concentration-related increase in tail DNA **Positive** Statistically significant increase in ROS level and MDA content at the highest concentration Statistically significant decrease in GSH, GSH-Px and SOD at all concentrations Statistically significant increase in percentage of apoptosis, and LDH leakage rate at the highest dose	–	He, He, Wang, Xia, Xu, Zhang, and Chen (2008)
Comet assay (alkaline)	Human neuroblastoma cells (SH-SY5Y)[b]	**BDE-47** Purity: 100% Solvent: DMSO Positive control: MMC	0, 1, 2, 4, 8 μM Corresponding to: 0, 0.5, 1.0, 1.9, 3.9 μg/mL Exposure: 24 h	Concentration-dependent significant increases in the olive tail moment (OTM) and statistically significant increase in % tail DNA at 8 μM **Positive**	Decreases in cell viability at concentrations from 4 μM Increased LDH leakage, and induction of cell apoptosis from 4 μM Concentration-dependent increase in ROS formation from 2 μM	He, He, Wang, Xia, Xu, and Chen (2008)
Comet assay (alkaline)	Human neuroblastoma cells (SH-SY5Y)[b]	**BDE-47** Purity: 100% Solvent: DMSO Positive control: MMC	0, 2, 4, 8 μM Corresponding to: 0, 1.0, 1.9, 3.9 μg/mL Exposure: 24 h	Concentration-dependent significant increases in the olive tail moment (OTM) and in % tail DNA at two highest concentrations. **Positive**	**BDE-47** at a concentration of 8 μM decreased slightly cell viability compared to the control	He et al. (2010)
Comet assay (alkaline)	Human hepatoma cell line HepG2	**BDE-47** **BDE-99** **BDE-100** **BDE-153** **BDE-154** **BDE-209** Purity: 100% Solvent: DMSO Positive control: H_2O_2	0, 0.1, 0.5, 1.0, 5.0, 10.0, 25 μM Corresponding to: **BDE-47**: 0, 0.2, 0.5, 2.4, 4.9, 12.1 μg/mL **BDE-99**: 0, 0.3, 0.6, 2.8, 5.6, 14.1 μg/mL **BDE-100**: 0, 0.3, 0.6, 2.8, 5.6, 14.1 μg/mL **BDE-153**: 0.1, 0.3, 0.6, 3.2, 6.4, 16.1 μg/mL **BDE-154**: 0.1, 0.3, 0.6, 3.2, 6.4, 16.1 μg/mL **BDE-209**: 0.1, 0.5, 1.0, 4.8, 9.6, 24.0 μg/mL Exposure: 4 h	Statistical increase of % tail DNA with all substances (two highest concentrations for **BDE-47**, -**99**, -**154** and three highest concentrations for **BDE-100**, -**153**, from 1 μM for BDE-209) **Positive**	Viability test: > 90%	Pereira et al. (2016)

TABLE 14 (Continued)

Type of test	Experimental test system	Test substance(s)	Exposure conditions	Result	Comments	Reference
Comet assay (alkaline)	Human neuroblastoma cell line SK-*N*-MC cells	**BDE-47** **BDE-209** Solvent: DMSO	0, 5, 10, 20 µmol/L Corresponding to: **BDE-47**: 0, 2.4, 4.9, 9.7 µg/mL **BDE-209**: 0, 4.8, 9.6, 19.2 µg/mL Exposure: 4 h or 24 h	Concentration-related statistical increase in DNA damage (% tail DNA) after 4 h and 24 h exposure. **BDE-47** is more potent than **BDE-209** (about 2-fold) **Positive**	Cytotoxicity: concentration-dependent decrease in cell viability after 24 h exposure (effects were small and non-statistically significant), viability always > 70%	Pellacani et al. (2012)
Comet assay (alkaline) Fpg test	Human neuroblastoma cell line SK-N-MC cells	**BDE-47** **BDE-209** Solvent: DMSO	0, 20 µmol/L Corresponding to: **BDE-47**: 9.7 µg/mL **BDE-209**: 19.2 µg/mL Exposure: 4 h or 24 h	Evidence that DNA damage were secondary to induction of oxidative stress **BDE-47** and -**209** induce purine oxidation (8-oxoG) particularly after short-term treatment (4 h exposure). BDE-47 is more potent than BDE-209 **Positive**	–	Pellacani et al. (2012)
Comet assay (alkaline)	16HBE cells (SV40 large T antigen-transformed cell line from normal human bronchial epithelial cells) and NHBE cells (primary normal human bronchial epithelial cells)	**BDE-47** **BDE-99** **BDE-209** Solvent: DMSO	0.1 µM Corresponding to: **BDE-47**: 0.05 µg/mL **BDE-99**: 0.06 µg/mL **BDE-209**: 0.10 µg/mL Exposure: 72 h	Statistically significant increase of Olive Tail Moment in both 16HBE and pNHBE cells. **Positive**	–	Montalbano et al. (2020)
Comet assay (alkaline)	Human colon carcinoma cell line (SW 480)	**BDE-209** Purity: 98% Solvent: DMSO Positive control: H_2O_2	2.5, 5, 10 µg/mL (corresponding to 2.5, 5, 10 µM) Exposure: 24 h	Two higher concentrations of **BDE-209** induced a significant increase of tail intensity **BDE-209** caused slight to moderate changes in tail length **Positive**	The two higher **BDE-209** concentrations caused significant decreases in cell survival of ~ 20% and 40%, respectively	Curčić et al. (2014)
Comet assay (alkaline)	Human H295R adrenocortical carcinoma cells	2-OH-BDE-47 2-OH-BDE-85 Solvent: DMSO Positive control: none	0, 2, 6, 10, 20 µM Corresponding to: 2-OH-BDE-47: 0, 1, 3, 5, 10 µg/mL 2-OH-BDE-85: 0, 1.2, 3.5, 5.8, 11.6 µg/mL Exposure: 12 h	No increase in % tail DNA **Negative**	Cytotoxicity: Inhibition of cell proliferation at concentrations < 10 µM Concentration-related cell death at ≥ 10 µM	Song et al. (2009)

(Continues)

TABLE 14 (Continued)

Type of test	Experimental test system	Test substance(s)	Exposure conditions	Result	Comments	Reference
Comet assay (alkaline)	Human H295R adrenocortical carcinoma cells	2-OH-BDE-47 2-OH-BDE-85 Solvent: DMSO Positive control: H_2O_2	10 μM +/- DNA repair inhibitors hydroxyurea (10 mM) and cytosine arabinoside (1.8 mM). Corresponding to: 2-OH-BDE-47: 5 μg/mL 2-OH-BDE-85: 5.8 μg/mL Exposure: 24 h	Without repair inhibitors: negative With repair inhibitors: increase in % tail DNA similar to control	–	Song et al. (2009)
Micronucleus assay	Human neuroblastoma cells (SH-SY5Y)	**BDE-47** Purity: 100% Solvent: DMSO Positive control: MMC	0, 1, 2, 4 μM Corresponding to: 0, 0.5, 1, 1.9 μg/mL Exposure: 24 h	Statistical increases in MN frequency at 4 μM Statistical increases in MNBNC and NPBs (nucleoplasmic bridges) frequencies at 2 and 4 μM **Positive**	Decreases in cell viability at 4 μM. Concentration-dependent decrease in NDI (nuclear division index) (statistically significant from 2 μM)	He, He, Wang, Xia, Xu, and Chen (2008)
Micronucleus assay	Human neuroblastoma cells (SH-SY5Y)	**BDE-47** Purity: 100% Solvent: DMSO Positive control: MMC	0, 2, 4, 8 μM Corresponding to: 0, 1, 1.9, 3.9 μg/mL Exposure: 24 h	Statistical increases in MN frequency in cells treated with **BDE-47** (8 μM) Statistical increases in MNBNC frequency at 4 and 8 μM **Positive**	**BDE-47** at a concentration of 8 μM decreased slightly cell viability compared to the control DNA-protein crosslinks were determined via quantification of DNA crosslinked with protein Significant increase in DPC observed after exposure to **BDE-47**	He et al. (2010)
Micronucleus assay	Human hepatoma cell line HepG2	**BDE-47** **BDE-99** **BDE-100** **BDE-153** **BDE-154** **BDE-209** Purity: 100% Solvent: DMSO Positive control: MMS	0, 0.1, 0.5, 1.0, 5.0, 10.0, 25 μM Corresponding to: **BDE-47**: 0, 0.2, 0.5, 2.4, 4.9, 12.1 μg/mL **BDE-99**: 0, 0.3, 0.6, 2.8, 5.6, 14.1 μg/mL **BDE-100**: 0, 0.3, 0.6, 2.8, 5.6, 14.1 μg/mL **BDE-153**: 0.1, 0.3, 0.6, 3.2, 6.4, 16.1 μg/mL **BDE-154**: 0.1, 0.3, 0.6, 3.2, 6.4, 16.1 μg/mL **BDE-209**: 0.1, 0.5, 1.0, 4.8, 9.6, 24.0 μg/mL Exposure: 20 h Harvesting: 26–28 h after exposure	None of the PBDEs increased the micronucleus frequency. **Negative**	No cytotoxicity observed	Pereira et al. (2016)

TABLE 14 (Continued)

Type of test	Experimental test system	Test substance(s)	Exposure conditions	Result	Comments	Reference
Micronucleus assay	V79-Mz cells[c] + different cell lines expressing xenobiotic-metabolising enzyme	**BDE-47** Purity: 98% Solvent: DMSO	0, 5, 10, 20, 40 and 80 μM Exposure 6h (+18h recovery) Exposure 24h	V79 Mz: equivocal (marginal increase MN frequency at 80 μM) V79-hCYP1A2: equivocal V79-hCYP1A1: inactive V79-hCYP2B6, V79-hCYP3A4-hOR and V79-hCYP2E1-hSULT1A1: positive Induction of MN only at 40 μM (HD) in V79-Mz and V79-hCYP1A2 Induction of MN (concentration-related) in V79-hCYP3A4-hOR and V79-hCYP2E1-hSULT1A1		Song et al. (2021)
Micronucleus assay	HepG2 cells	**BDE-47** Purity: 98% Solvent: DMSO	10, 14, 20, 28 and 40 μM Exposure: 48 h	Negative	Midly cytotoxic	Song et al. (2021)
Comet assay	HepG2 cells (Human liver hepatocellular carcinoma)	6-OH-BDE-47 Negative control: acetonitrile Positive control: EMS	10, 25, 50 nM Corresponding to: 0.005, 0.01, 0.03 μg/mL Exposure: 24 h	Dose-related statistically significant increase in DNA damage (olive tail moment, tail length and tail intensity) **Positive**	Cytotoxicity: statistically significant decrease cell survival at two highest concentrations after 3 or 6 days of exposure in MTT assay and at the 3 concentrations in NRU assay	Saquib et al. (2018)
Comet assay (alkaline)	Human hepatoma cell line HepG2	6-OH-BDE-47 6-MeO-BDE-47 Purity: > 98% Solvent: DMSO	Comet assay: 0, 0.1, 0.2, 0.5, 1.0, 2.0 and 5.0 μM Corresponding to: 6-OH-BDE-47: 0.05, 0.10, 0.25, 0.50, 1.00, 2.51 μg/mL 6-MeO-BDE-47: 0.05, 0.11, 0.26, 0.53, 1.06, 2.64 μg/mL Exposure: 24 h Cell proliferation: 0, 0.1, 0.2, 0.5, 1.0, 2.0, 5.0 μM Corresponding to: 6-OH-BDE-47: 0.05, 0.10, 0.25, 0.50, 1.00, 2.51 μg/mL 6-MeO-BDE-47: 0.05, 0.11, 0.26, 0.53, 1.06, 2.64 μg/mL	Increased tail lengths and tail moments in 6-OH-BDE-47 and 6-MeO-BDE-47 treatment groups (from 1.0 μM) compared with the control. Both chemicals could cause DNA single strand breaks in a dose-dependent manner. **Positive** Inhibition of cell proliferation. Concentration-dependent increase in apoptosis. Marked cell cycle block with 6-OH-BDE-47 (0.5 μM)	Marked inhibition of proliferation of HepG2 with 6-OH-BDE-47 Significant increase intracellular ROS levels (GSH depletion and increase SOD level)	An, Li, et al. (2011)
Micronucleus assay	Human hepatoma cell line HepG2	6-OH-BDE-47 6-MeO-BDE-47 Purity: > 98% Solvent: DMSO	0, 0.1, 0.5, 2.0 μM Corresponding to: 6-OH-BDE-47: 0, 0.05, 0.25, 1.00 μg/mL 6-MeO-BDE-47: 0, 0.05, 0.26, 1.06 μg/mL) Exposure: 24 h	Dose-related increases in the numbers of micronuclei were observed following treatment with 6-OH-BDE-47 or 6-MeO-BDE-47 (more marked with OH) **Positive**	Marked inhibition of proliferation of HepG2 Significant increase intracellular ROS levels (GSH depletion and increase SOD level)	An, Li, et al. (2011)

(Continues)

TABLE 14 (Continued)

Type of test	Experimental test system	Test substance(s)	Exposure conditions	Result	Comments	Reference
Chromosomal aberration assay[a]	Chicken isogenic DT40 mutants each defective in one of the major DNA damage repair mechanisms REV3$^{-/-}$	**BDE-47** **BDE-49** **BDE-99** **BDE-138** **BDE-209** 6-OH-BDE-47 4-OH-BDE-49 Solvent: DMSO	200 µM +/- N-acetylcysteine Corresponding to: **BDE-47**: 97.2 µg/mL **BDE-49**: 97.2 µg/mL **BDE-99**: 113 µg/mL **BDE-138**: 129 µg/mL **BDE-209**: 192 µg/mL 6-OH-BDE-47: 100 µg/mL 4-OH-BDE-49: 100 µg/mL) Exposure: 48 h	Significant increases in the number of chromosomal aberrations **Positive** 6-OH-BDE-47 was more potent than **BDE-47** (may be related to the fact that 6-OH-BDE-47 may cause more oxidative stress than **BDE-47**)	50 mitotic cells/conc	Ji et al. (2011)
γ-H2AX (detection of double strand breaks)	Chicken isogenic DT40 mutants each defective in one of the major DNA damage repair mechanisms REV3$^{-/-}$	**BDE-47** **BDE-49** **BDE-99** **BDE-138** **BDE-209** 6-OH-BDE-47 4-OH-BDE-49 Solvent: DMSO	200 µM Corresponding to: **BDE-47**: 97.2 µg/mL **BDE-49**: 97.2 µg/mL **BDE-99**: 113 µg/mL **BDE-138**: 129 µg/mL **BDE-209**: 192 µg/mL 6-OH-BDE-47: 100 µg/mL 4-OH-BDE-49: 100 µg/mL Exposure: 1 h	Significant increases γ-H2AX foci/cell in REV3$^{-/-}$ after exposure to **BDE-47**, **-49** and 6-OH-BDE-47 and 4-OH-BDE-49 compared to wildtype **Positive**	200 cells/sample	Ji et al. (2011)
γ-H2AX foci (detection of double strand breaks)	16HBE cells (SV40 large T antigen-transformed cell line from normal human bronchial epithelial cells)	**BDE-47** **BDE-99** **BDE-209** Solvent: DMSO	0.1 µM Corresponding to: **BDE-47**: 0.05 µg/mL **BDE-99**: 0.06 µg/mL **BDE-209**: 0.10 µg/mL Exposure: 72 h	Increase γH2AX foci by all congeners **BDE-47** induces a higher number of γH2AX foci, than **BDE-99** and -**209** **Positive**	–	Montalbano et al. (2020)
γ-H2AX foci (detection of double strand breaks)	HepG2 cells	**BDE-209** Solvent: DMSO	Exposure 24 h	Increase gH2AX foci/nucleus **Positive**		Yuan, Che, et al. (2021)
Comet assay (alkaline)	HeLa cells	**Synthesised PBDE-Quinone** [2-(2′,4′-Bromophenoxyl)-benzoquinone] Solvent: DMSO Positive control: H_2O_2	5 µM Exposure: 6 h	Significant increase in olive tail moment **Positive**	Cell viability (CCK-8 assay): synthesised PBDE-Quinone (0–20 µM) for 6, 12 or 24 h. Concentration-related decrease viability from 5 µM at all time points and at 2.5 µM at 24 h (about 85% cell viability at 5 µM at 6 h) Synthesised PBDE-Quinone exposure lead to ROS accumulation	Dong et al. (2018)
8-OHdG Assay	HeLa cells	**Synthesised PBDE-Quinone** [(2-(2′,4′-Bromophenoxyl)-benzoquinone] Solvent: DMSO Positive control: H_2O_2	5 µM Exposure: 6 h	Significant increase in 8-OHdG. **Positive**	–	Dong et al. (2018)

TABLE 14 (Continued)

Type of test	Experimental test system	Test substance(s)	Exposure conditions	Result	Comments	Reference
Micronucleus test	HeLa cells	**Synthesised PBDE-Quinone** [2-(2′,4′-Bromophenoxyl)-benzoquinone] Solvent: DMSO Positive control: H_2O_2	Exposure: 6 h	Significant increase in MN frequency **Positive**	–	Dong et al. (2018)
γ-H2AX foci	HeLa cells	**Synthesised PBDE-Quinone** [2-(2′,4′-Bromophenoxyl)-benzoquinone] Solvent: DMSO Positive control: H_2O_2	Exposure: 6 h	**Positive** Significant increase in γ-H2AX foci	–	Dong et al. (2018)
Comet assay (alkaline) and γ-H2AX	Murine BV2 microglia cells	**Synthesised PBDE-Quinone** [2-(2′,4′-Bromophenoxyl)-benzoquinone] Solvent: DMSO Positive control: no	0, 5, 10 μM Exposure: 24 h	**Positive** Clear increase in olive tail moment in a concentration-dependent manner Synthesised PBDE-Quinone increased the γ-H2AX formation in the nucleus in a concentration-dependent manner compared with the control group This indicates significant DNA strand breaks	–	Liu et al. (2021)

Abbreviations: CP, cyclophosphamide; DMSO, dimethyl sulfoxide; EMS, ethyl methanesulfonate; GSH, glutathione; GSH-Px, glutathione peroxidase; HC, high concentration; LDH, lactic dehydrogenase; MMC, methylmethcathinone; MMS, methyl methanesulphonate; MDA, malondialdehyde; SOD, superoxide dismutase. ROS, reactive oxygen species.

[a]Analysis of CA was limited to the 11 autosomal macrochromosomes and the Z chromosome in giemsa-stained metaphase cells.

[b]Cells expressing xenobiotic-metabolising CYP enzymes (CYP1A1, 2E1, 2D6 and 3A4). Cyt P450 enzymes (CYP) may catalyse the metabolism of PBDE leading to the production of metabolites such as OH-PBDE. And UDP-glucuronosyltransferases (UGTs).

[c]Parental cell line deficient in the activities of CYPs, sulfotransferases (SULTs).

TABLE 15 *In vivo* genotoxicity studies on PBDEs published since the previous EFSA risk assessment.

Type of test Experimental test system	Test substance	Exposure conditions	Result	Comments	Reference
Chromosomal aberrations Sprague–Dawley rats Observation of bone marrow of adults and offspring at weaning	DecaBDE (77.4% **BDE-209**, 21.8% nonaBDEs, 0.8% octaBDEs)	0, 3, 30, 100 mg/kg bw per day Dietary exposure during 90 days prior to mating as well as during mating, gestation and lactation. Examination at necropsy	Cytogenetic examination of bone marrow cells taken at necropsy from the femur of the treated parental animals as well as from the neonates at weaning showed no increase in cytogenetic aberrations when compared with controls	Minimal reporting of methods and results. No table with results	Norris et al. (1975)
Micronucleus test (peripheral blood) M 57BL/6J *gpt* delta mice	**BDE-47** Negative control: solvent Positive control: BαP	0, 0.0015, 1.5, 10, 30 mg/kg bw per day Gavage 6 days per week for five consecutive weeks Examinations: before exposure, 2.5 and 5 weeks after first exposure	**Negative**	No obvious signs of toxicity or effects on body weight gain[a]	You et al. (2018)
Pig-a Gene mutation assay M 57BL/6J *gpt* delta mice	**BDE-47** Negative control: solvent Positive control: BαP	0, 0.0015, 1.5, 10, 30 mg/kg bw per day Gavage 6 days per week, for 5 consecutive weeks Examinations: before exposure, 2.5 and 5 weeks after first exposure	**Negative** (MF in Pig-a gene)	No obvious signs of toxicity or effects on body weight gain[a] The RET% in peripheral blood of the **BDE-47**-treated groups showed a dose-dependent increase at 5 weeks after the first treatment	You et al. (2018)
gpt Gene mutation assay (in liver and germ cells from seminiferous tubules) M 57BL/6J *gpt* delta mice	**BDE-47** Negative control: solvent Positive control: BαP	0, 1.5, 30 mg/kg bw per day Gavage 6 days per week for six consecutive weeks	**Negative**	No obvious signs of toxicity or effects on body weight gain	You et al. (2018)
Flow cytometry DNA damage in sperm Pregnant CD-1 mice treated (5/group). Male offspring observed	**BDE-209** Purity: 99% Vehicle: corn oil	0, 10, 500, 1500 mg/kg bw per day Gavage once daily GD0–17 Observation: day 71	Significant sperm chromatin DNA damage. DNA denaturation induction and increased DNA fragmentation index in the sperm chromatin structure analysis **Positive**	Hydrogen peroxide, which was increased in sperm cells, may have been involved in induction of oxidative DNA damage	Tseng et al. (2013)
Micronucleus test (in bone marrow) B6C3F1 *gpt* delta mice	**BDE-209** Negative control: diet Positive control/EMS (gavage)	0, 25,000, 50,000 ppm in diet (corresponding to 0, 5000, 10,000 mg/kg bw per day)[b] For 4 weeks	**Negative**	No effect on PCE frequency. Significant increases (dose-related) in absolute and relative liver weights. Centrilobular hepatocellular hypertrophy in the livers of treated mice, demonstrating systemic toxicity. No significant changes in final body weights	Takasu et al. (2017)

TABLE 15 (Continued)

Type of test Experimental test system	Test substance	Exposure conditions	Result	Comments	Reference
Gene mutation assay (in liver) B6C3F1 *gpt* delta mice	**BDE-209** Negative control: diet Positive control/EMS (gavage)	0, 25,000, 50,000 ppm in diet (corresponding to 0, 5000, 10,000 mg/kg bw/day)[b] For 4 weeks	**Negative**	No significant changes in final body weights Significant increases (dose-related) in absolute and relative liver weights Centrilobular hepatocellular hypertrophy in the livers of treated mice, demonstrating systemic toxicity	Takasu et al. (2017)
Micronucleus test (peripheral blood) B6C3F1/N mice (M and F)	DE-71 Negative control: corn oil Positive control: none	0, 0.01, 5, 50, 100, 500 mg/kg bw per day Gavage, 5 days per week for 3 months	No increases in the frequencies of micronucleated NCE. **Negative**	No significant change in %PCE. Decreased survival at the top dose and decrease in bodyweight in M at high dose and in F from 100 mg/kg bw per day Clear signs of systemic toxicity	NTP (2016), MacGregor et al. (1990)
Micronucleus test (peripheral blood and bone marrow) B6C3F1/N mice (M)	DE-71 Negative control: corn oil Positive control: cyclophosphamide	0, 312.5, 625, 1250 mg/kg bw per day Gavage, once daily for 3 days Harvesting of peripheral blood and bone marrow 24 h after last treatment	Peripheral Blood: No increases in micronucleated NCE or PCE Bone marrow: No increases in micronucleated PCE **Negative**	No significant change in % PCE	NTP (2016); Witt et al. (2008)
Comet assay (alkaline) Spermatozoa (frozen sperm samples) Adult Sprague–Dawley male rats (5/group)	Complex BFR mixture of three commercial brominated diphenyl ethers (52.1% DE-71, 0.4% DE-79 and 44.2% **BDE-209**) and HBCDDs (3.3%) Negative control: corn oil	0, 0.02, 0.2, 2, 20 mg/kg per day Dietary, 70 days	Measurement of tail length, % tail DNA and tail extent moment (tail length/fraction of tail DNA) **Negative** (no increase in single or double strand breaks)	Toxicity: significant increase in the weights of the kidneys and liver, induction of CYP1A and CYP2B P450 hepatic drug–metabolising enzymes Thyroid toxicity at 20 mg/kg bw per day No effect on reproductive organ weights, serum testosterone levels, testicular function or sperm DNA integrity	Ernest et al. (2012)

Abbreviations: BαP, Benzo(α)pyrene; EMS, ethyl methanesulfonate; F, female; GD, gestational day; M, male; NCE, normochromatic erythrocyte; PCE, polychromatic erythrocytes; RET %, % of reticulocyte.

[a]The CONTAM Panel noted that while the micronucleus tests do not show evidence of toxicity to the bone marrow, systemic exposure is evident from toxicokinetics (see **Section 3.1.1**) and from systemic toxicity (see **Section 3.1.2**) and thus these are lines of evidence of bone marrow exposure to the test substance, according to the recommendations of the EFSA Scientific Committee (2017b).

[b]The conversion of the concentrations in feed into doses per kg bw per day has been done using a factor of 0.2 for mice assuming a subacute study duration (EFSA Scientific Committee, 2012).

3.1.2.7 | *Carcinogenicity studies*

Studies considered in the previous EFSA assessment

In the previous EFSA assessment (EFSA CONTAM Panel, 2011b), there were no long-term toxicity/carcinogenicity studies available for individual PBDE congeners or technical PBDE products, with the exception of DecaBDE, and no tumour promotion studies were available.

For DecaBDE there was some evidence for an increase in liver adenoma in Fischer 344/N rats and liver adenoma and carcinoma in male B6C3F1 mice (see **Tables 16** and **17**) (NTP, 1986). The technical product DecaBDE tested contained 94%–97% **BDE-209** and other components identified as isomers of nonaBDEs.

TABLE 16 Incidence of tumours in Fisher 344/N **rats** administered DecaBDE (NTP, 1986).

	Males			Females		
Dose (mg/kg bw per day)	**Control**	**1120**	**2240**	**Control**	**1200**	**2550**
Hepatocellular adenoma	1/50	7/50	15/49	1/50	3/49	9/50
Hepatocellular carcinoma	1/50	1/50	1/49	0/50	2/49	0/50
Hepatocellular adenoma or carcinoma	2/50	8/50	15/49	1/50	5/49	9/50
Mononuclear cell leukaemia	30/50	33/50	35/50	14/50	21/50	18/50
Pancreas acinar cell adenoma	0/49	0/50	4/49	NR	NR	NR

Abbreviation: bw, body weight.

Notes: Historical control incidences in 2-year studies by gavage (vehicle: corn oil) at the study laboratory: Liver adenoma or carcinoma: in M: 4% ± 3%, range: 0/50–7/49; in F: 3% ± 3%, range: 0/50–5/50. Mononuclear cell leukaemia: in M: 27% ± 9%, range: 5/50–23/50. Pancreas acinar cell adenoma in M: 0.2% ± 0.6%, range: 0/88–1/47.

TABLE 17 Incidence of tumours in B6C3F1 **mice** administered DecaBDE (NTP, 1986).

	Males			Females		
Dose (mg/kg bw per day)	**Control**	**3200**	**6650**	**Control**	**3760**	**7780**
Hepatocellular adenoma and carcinoma (combined)	8/50	22/50	18/50	8/50	13/50	13/50
Thyroid gland follicular call adenoma and carcinoma (combined)	0/50	4/50	3/50	1/50	3/50	3/50

Abbreviation: bw, body weight.

Notes: Historical control incidences in 2-year studies by gavage (vehicle: corn oil) at the study laboratory: Hepatocellular adenoma and carcinoma: in M: 30% ± 8%, range: 7/50–29/50; F: NR. Thyroid gland follicular call adenoma and carcinoma: in M: 1.7%–2.0%, range: 0/50–3/42; in F: NR.

DecaBDE has been classified by IARC as Group 3 (not classifiable as to its carcinogenicity to humans) (IARC, 1990).

Studies published since the previous EFSA assessment

Since the previous EFSA assessment, a study in rats and mice both exposed to DE-71 (**BDE-99**: 42%, **BDE-47**: 36%, **BDE-100**: 10%, **BDE-154**: 4%, **BDE-153**: 3%, BDE-85: 2%, PBDD/Fs were identified as impurities at approx. 7×10^{-6}% by weight) has been identified (NTP, 2016; Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Recio, et al., 2018) (for details on the study design see **Appendix E**, Table E.5).

Female Wistar Han rats were exposed from GD6 to PND21 by gavage to DE-71 at doses of 0, 3, 15 or 50 mg/kg bw per day. At PND4 all litters were culled to 3 males and 3 females per litter. Pups started on direct dosing (as above) from PND12 to PND21. At PND22 the pups were assigned to the two-year study and were dosed 5 days per week (0, 2.1, 10.7 and 36 mg/kg bw per day).

A positive trend in liver tumours was noted in both male and female rats (see Table 18). There were positive trends in the incidence of hepatocellular adenoma or carcinoma combined in males and hepatocholangioma, hepatocellular adenoma or hepatocellular carcinoma (combined) in males. In females, there were positive trends in the incidence of hepatocholangioma, hepatocellular adenoma, hepatocellular carcinoma, hepatocellular adenoma or carcinoma combined, and hepatocholangioma, hepatocellular adenoma or carcinoma combined. The incidence of these combined lesions was significantly increased in the highest dose groups. In addition, in females two cholangiocarcinomas were observed in females at the highest dose. Incidence of cholangiofibrosis occurred in three females at the highest dose. With regard to putative preneoplastic liver lesions, the incidences of eosinophilic liver foci were elevated significantly at 10.7 and 36 mg/kg bw per day in male and female rats.

A statistically significant increased incidence of thyroid follicular cell adenoma was observed in males at the highest dose as well as a significantly increased incidence of thyroid follicular cell hyperplasia (considered as potentially pre-neoplastic

lesions) in females at the highest dose. A significant statistical increased incidence of adenomas of the pars distalis of the pituitary gland was also observed in males at the highest dose.

In female rats, there were increased incidence of uterine stromal polyps or stromal sarcoma in the treated groups which were statistically significant in the 2.1 and 10.7 mg/kg bw per day groups. In addition, squamous metaplasia of the uterus and squamous hyperplasia of the cervix were noted at the two highest doses. Two polyps were also reported in the vagina at the highest dose (Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Recio, et al., 2018; NTP, 2016). These were considered as potentially pre-neoplastic lesions.

TABLE 18 Incidence of tumours and pre-neoplastic effects in Wistar Han **rats** administered DE-71 (Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Recio, et al., 2018; NTP, 2016).

	Males				Females			
Dose (mg/kg bw per day)	**Control**	**2.1**	**17**	**36**	**Control**	**2.1**	**17**	**36**
Hepatocholangioma	NR	NR	NR	NR	0/50	0/49	0/50	8/47
Hepatocellular adenoma	NR	NR	NR	NR	3/50	2/49	8/50	16/47
Hepatocellular carcinoma	NR	NR	NR	NR	0/50	0/49	1/50	6/47
Hepatocellular adenoma or carcinoma combined	3/49	2/50	4/50	9/50	3/50	2/49	8/50	17/47
Hepatocholangioma, hepatocellular adenoma or hepatocellular carcinoma (combined)	3/49[a]	2/50	4/50	11/50	3/50[b]	2/49	8/50	21/47
Cholangiocarcinoma	NR	NR	NR	NR	0/50[c]	0/49	0/50	2/47
Eosinophilic liver foci	3/49	3/50	12/50	15/50	NR	NR	NR	NR
Thyroid follicular cell adenoma	1/45[d]	3/45	2/48	6/46	NR	NR	NR	NR
Thyroid follicular cell adenoma or carcinoma	1/45[e]	5/45	3/48	6/46	NR	NR	NR	NR
Thyroid follicular cell hyperplasia	NR	NR	NR	NR	1/45	5/49	4/47	6/42
Adenomas of the pars distalis of the pituitary gland	19/49[f]	12/49	22/50	35/50	NR	NR	NR	NR
Uterine stromal polyps or sarcoma	NR	NR	NR	NR	4/50[g,h]	12/50	12/50	9/49

Abbreviation: bw: body weight.

Note: Historical control incidences in 2-year studies by gavage (vehicle: corn oil) at the study laboratory.

[a]Hepatocholangioma, hepatocellular adenoma or hepatocellular carcinoma (combined) in M: 3.1% ± 4.3%, range: 0%–6%.

[b]Hepatocholangioma, hepatocellular adenoma or hepatocellular carcinoma (combined) in F: 4% ± 2.8%, range: 2%–6%.

[c]Cholangiocarcinoma in F: 0%.

[d]Thyroid follicular cell adenoma in M: 4.1% ± 2.7%, range: 2%–6%.

[e]Thyroid follicular cell adenoma or carcinoma in M: 0%.

[f]Pituitary gland adenoma in M: 40.4% ± 2.3%, range: 39%–42%.

[g]Uterine stromal polyp in F: 5% ± 1.4%; range: 4%–6%.

[h]Uterine stromal sarcoma in F: 0%.

The non-neoplastic effects are described in **Section 3.1.2.2** and in the tables in Appendix E.

B6C3F1/N mice were exposed by gavage for 2 years (5 days per week) to DE-71 at 0, 3, 30 and 100 mg/kg bw (0, 2.1, 21 and 71 mg/kg bw per day). Incidences of hepatocellular adenomas were significantly increased in males at all doses and in females at the two highest doses (Table 19). Incidence of hepatocellular carcinomas were increased at the two highest doses in males and at the highest dose in females and incidence of hepatoblastoma was increased in males at 21 mg/kg bw per day (Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Recio, et al., 2018; NTP, 2016).

TABLE 19 Incidence of tumours in B6C3F1/N **mice** administered DE-71 (Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Recio, et al., 2018; NTP, 2016).

	Males				Females			
Dose (mg/kg bw per day)	**Control**	**2.1**	**21**	**71**	**Control**	**2.1**	**21**	**71**
Hepatocellular adenoma	23/50[a]	35/50	49/50	40/50	5/50[b]	7/49	32/50	46/49
Hepatocellular carcinoma	18/50[c]	15/50	30/50	45/50	4/50[d]	2/49	6/50	27/49
Hepatocellular adenoma or carcinoma (combined)	31/50[e]	40/50	49/50	47/50	8/50[f]	8/49	33/50	47/49
Hepatoblastoma	1/50[g]	1/50	16/50	5/50	NR	NR	NR	NR
Hepatocellular adenoma, carcinoma or hepatoblastoma (combined)	31/50[h]	40/50	49/50	47/50	NR	NR	NR	NR
Eosinophilic liver foci	NR	NR	NR	NR	3/50	2/49	16/50	15/49

Abbreviation: bw, body weight.

Note: Historical control incidences in 2-year studies by gavage (vehicle: corn oil) at the study laboratory.

[a]Hepatocellular adenoma in M: 56% ± 6.7%; range: 46%–64%.

[b]Hepatocellular adenoma in F: 22.3% ± 10.5%; range: 10%–39%.

[c]Hepatocellular carcinoma in M: 35% ± 9.8%; range: 22%–44%.

[d]Hepatocellular carcinoma in F: 10% ± 5.1%; range: 4%–18%.

[e]Hepatocellular adenoma or carcinoma (combined) in M: 73.3% ± 6.3%; range: 62%–78%.

[f]Hepatocellular adenoma or carcinoma (combined) in F: 28.3% ± 10.2%; range: 16%–40%.

[g]Hepatoblastoma in M: 3.3% ± 2.4%; range: 0%–6%.

[h]Hepatocellular adenoma, carcinoma or hepatoblastoma (combined) in M: 73.7% ± 6.1%; range: 62%–78%.

With regard to putative preneoplastic liver lesions, female mice exhibited significantly increased incidences of eosinophilic foci at 21 and 71 mg/kg bw per day, and in males, clear cell foci were increased significantly at 21 mg/kg bw per day.

Treatment-related non-neoplastic lesions are described in **Section 3.1.2.2** and in Appendix E (Table E.5).

Overall summary on carcinogenicity

In summary, individual PBDE congeners have not been tested for carcinogenicity. There was an increase in liver adenoma in Fischer 344/N rats and in liver adenoma and carcinoma in male B6C3F1 mice exposed to DecaBDE (NTP, 1986). The CONTAM Panel noted that the doses administered were very high. The Panel also noted that the technical product DecaBDE tested contained 94%–97% **BDE-209** and thus, the results of this study are also relevant to **BDE-209**.

According to the NTP report, there is clear evidence of carcinogenic activity of DE-71 in male and female Wistar Han rats based on increased incidence of hepatocholangioma, hepatocellular adenoma or hepatocellular carcinoma (combined). In males, increased incidences of thyroid gland follicular cell adenoma and increased incidences of pituitary gland (pars distalis) adenoma were also considered to be related to exposure as well as the occurrence of cholangiocarcinoma of the liver in females. The incidences of stromal polyp or stromal sarcoma (combined) of the uterus may have been related to treatment. The LOAEL was 2.1 mg/kg bw per day. There is clear evidence of carcinogenic activity of DE-71 in male B6C3F1/N mice based on increased incidences of hepatocellular adenoma, hepatocellular carcinoma and hepatoblastoma, and in female B6C3F1/N mice based on increased incidence of hepatocellular adenoma and hepatocellular carcinoma. The NOAEL was 2.1 mg/kg bw per day.

It is unclear if one or more congeners present in the technical product are responsible for the effects observed.

3.1.3 | Observations in humans

In the previous EFSA Opinion on PBDEs (EFSA CONTAM Panel, 2011b), studies assessing the association between exposure to PBDEs and thyroid hormone disruption, neurodevelopmental effects, cancer, diabetes and metabolic syndrome and effects on fertility or offspring were assessed. The CONTAM Panel concluded at that time that '*Most epidemiological studies suggested an association between PBDEs and (sub)clinical hyperthyroidism, but two studies (Herbstman et al., 2008; Yuan et al., 2008) showed an association with (sub)clinical hypothyroidism. In a few studies (Gascon et al., 2011; Herbstman et al., 2010; Roze et al., 2009) effects on neuropsychological functioning were associated with exposure to PBDEs. Overall, epidemiological results were inconsistent and it was noted that exposure to other halogenated contaminants could have interfered with the outcome of these studies*'.

Since then, a number of epidemiological studies assessing the association between exposure to PBDEs and the endpoints discussed in the previous Opinion plus a large number of others have become available. The assessment of this rapidly evolving evidence base poses challenges but also provides an opportunity to reflect on potential PBDE effects across different human populations with different exposure sources, timing of exposure assessment and exposure levels.

In the current Opinion, the individual studies were grouped according to toxicological endpoints, i.e. thyroid function and disease, neurotoxicity, lipid and sugar metabolism (including diabetes and obesity), cardiovascular effects, effects on

male and female reproduction, birth outcomes, effects on the immune system and inflammation, cancer and other endpoints. The number of endpoints where more than one study was available was small and endpoint definitions often differed from study to study. To accommodate this complexity, interrelated endpoints were discussed together. Moreover, the epidemiological studies have been conducted in subjects/cohorts exposed to PBDEs at various life stages under different exposure conditions. Such factors may influence the adverse endpoints reported and are discussed in detail.

The main source of exposure has been dietary in the general population. Studies assessing occupational exposure, such as chemical workers or exposure related to living in the proximity of e-waste or BFR production areas, were also captured and discussed accordingly.

PBDE congeners and sums thereof were investigated in a non-harmonised way in the individual studies. Contrary to animal studies, the PBDE exposure in human studies cannot be controlled and the exposure mixture is of unknown composition. The studies identified assessed a variety of PBDE congeners. We approached this multilevel exposure matrix by first capturing all the examined congeners (eventually detected or not) and then by putting more emphasis to the ones considered as of primary interest in the previous Opinion (**BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183**, -**209**) as well as **BDE-49** and -**138** (see **Section 1.2**).

Finally, within each toxicological endpoint, studies of various designs, sample sizes and population characteristics were available. Given the wealth of the available evidence and the fact that prospective studies bear a lower risk for specific sources of bias compared to other study designs, longitudinal (cohort and nested case–control) studies are discussed in detail while the totality of the evidence is presented in the accompanying tables in Annex D (Tables D.1 to D.11).

Given the (very) large number of analyses performed within each study pertaining to different congeners, timing of the exposure assessment, endpoint scales and subscales, and follow-up points, the reporting of the results of each study in the main text could not be exhaustive due to space limitations. Hence, the core study characteristics were presented in brief and then the emerging 'positive' signals discussed. The deliberations related to the risk assessment process reported in the present Opinion are based on the assessment of the totality of the evidence.

3.1.3.1 | *Thyroid function and disease*

In the previous EFSA Opinion on PBDEs, 13 epidemiological studies on thyroid function and disorders thereof were included bearing inconclusive results (EFSA CONTAM Panel, 2011b). Since then, 51 publications corresponding to 45 individual studies were identified assessing the association between levels of PBDEs and any outcome related to thyroid function. Thyroid function was assessed through total triiodothyronine (TT3), free triiodothyronine (FT3), reverse T3 (rT3), total thyroxine (TT4), free thyroxine (FT4), thyroid stimulating hormone (TSH), thyroid-binding globulin (TBG), thyroglobulin antibodies (anti-Tg) and thyroid peroxidase antibodies (anti-TPO) as continuous outcomes in most studies. Only one case control study used a binary 'disease' endpoint (hypothyroidism) (see Table 20).

The evidence base included in the current Opinion consists of 6 cohort studies and 45 cross-sectional studies where the PBDE levels were assessed simultaneously or even later than the outcome ascertainment. The sample size of the included observational studies ranged from 25 to 1089 participants. Six of the evaluated populations came from European countries (Belgium, Denmark, The Netherlands, Norway, Spain, Sweden), four from Canada, 14 from the USA, 23 from China, 3 from South Korea, 1 from Taiwan, and another 1 from Vietnam.

The populations under study were diverse. Twenty-one studies (41%) recruited younger children or adolescents, while the remaining 30 studies assessed adult females ($n = 9$) or mixed ($n = 21$) populations. Female populations mostly represented women in pregnancy. PBDE levels were assessed in serum ($n = 43$), placenta ($n = 2$), human milk ($n = 3$), semen ($n = 1$) and hair/nails ($n = 1$).

In the following paragraphs, the evidence stemming from cohort studies is discussed. Moreover, we describe below the sole study on occupational **BDE-209** exposure (DecaBDE plant) and thyroid function, as well as the results from the NHANES and the Canadian Health Measures Survey (CHMS) studies which, despite their cross-sectional design, provide useful information on the largest populations of predominantly European ancestral origin within the cross-sectional study design group. Further details of these studies can be found in Annex D (Table D.1), as well as for the case–control and remaining cross-sectional studies identified.

TABLE 20 Overview of the epidemiological studies identified on the association between levels of PBDEs and thyroid function and disease.

Reference	Study design	Population studied Matrix analysed	Endpoint
Chevrier et al. (2010). Polybrominated diphenyl ether (PBDE) flame retardants and thyroid hormone during pregnancy	Cross-sectional	Pregnant women Maternal blood	TT4, FT4, TSH
Wang et al. (2010b). Examining the relationship between brominated flame retardants (BFR) exposure and changes of thyroid hormone levels around e-waste dismantling sites	Cross-sectional	Adults e-waste area Serum	TT3, TT4, FT3, FT4, TSH
Zhang, Jiang, et al. (2010). Elevated body burdens of PBDEs, dioxins, and PCBs on thyroid hormone homeostasis at an electronic waste recycling site in China	Cross-sectional	Pregnant women Cord blood	TT3, TT4, TSH
Wan et al. (2010). Hydroxylated polybrominated diphenyl ethers and bisphenol A in pregnant women and their matching foetuses: placental transfer and potential risks	Cross-sectional	Mother–Child pairs Serum	TT4
Chevrier et al. (2011). Prenatal exposure to polybrominated diphenyl ether flame retardants and neonatal thyroid-stimulating hormone levels in the CHAMACOS study	Cohort	Newborns Maternal blood	Neonatal TSH
Stapleton et al. (2011). Associations between polybrominated diphenyl ether (PBDE) flame retardants, phenolic metabolites, and thyroid hormones during pregnancy	Cross-sectional	Pregnant women Serum	TT3, TT4, FT3, FT4, TSH
Han et al. (2011). Correlations of PCBs, DIOXIN, and PBDE with TSH in children's blood in areas of computer E-waste recycling	Cross-sectional	Children e-waste area Blood	TSH
Lin et al. (2011). Negative associations between PBDE levels and thyroid hormones in cord blood	Cross-sectional	Newborns Cord blood	TT4, TT3, FT4, FT3, TSH
Abdelouahab et al. (2011). Polybrominated diphenyl ethers and sperm quality	Cross-sectional	Adults Serum	TT3, TT4, FT3, FT4, TSH
Zota et al. (2011). Polybrominated diphenyl ethers, hydroxylated polybrominated diphenyl ethers, and measures of thyroid function in second trimester pregnant women in California	Cross-sectional	Pregnant women Serum	TSH, FT4, TT4
Eggesbø et al. (2011). Associations between brominated flame retardants in human milk and thyroid-stimulating hormone (TSH) in neonates	Cross-sectional	Newborns Human milk	TSH in neonates
Gascon et al. (2011). Effects of pre and postnatal exposure to low levels of polybromodiphenyl ethers on neurodevelopment and thyroid hormone levels at 4 years of age	Cross-sectional	Children (4 years) Serum	TSH, TT3, FT4
Kiciński et al. (2012). Neurobehavioral function and low-level exposure to brominated flame retardants in adolescents: a cross-sectional study	Cross-sectional	Adolescents Serum	FT3, FT4, TSH
Leijs et al. (2012). Thyroid hormone metabolism and environmental chemical exposure	Cross sectional	Adolescents Serum	TT3, TT4, FT4, TSH, TBG
Shy et al. (2012). Cord blood levels of thyroid hormones and IGF-1 weakly correlate with breast milk levels of PBDEs in Taiwan	Cross-sectional	Newborns Human milk	TT3, TT4, TSH, FT3, FT4[c]
Kim, Kim, et al. (2012). Assessment of impact of internal exposure to PBDEs on human thyroid function-comparison between congenital hypothyroidism and normal paired blood	Cross-sectional	Newborns Serum	FT4, TT3, TSH
Johnson et al. (2013). Associations between brominated flame retardants in house dust and hormone levels in men	Cross-sectional	Adults House dust	FT4, TT3, TSH
Kim et al. (2013). Association between several persistent organic pollutants and thyroid hormone levels in serum among the pregnant women of Korea	Cross-sectional	Pregnant women Serum	FT3, TT3, FT4, TT4, TSH
Abdelouahab et al. (2013). Maternal and cord-blood thyroid hormone levels and exposure to polybrominated diphenyl ethers and polychlorinated biphenyls during early pregnancy	Cohort	Pregnant women Serum	TSH, TT3, TT4, FT3, FT4, TPO-Ab
Bloom et al. (2014). Thyroid hormones are associated with exposure to persistent organic pollutants in aging residents of upper Hudson River communities	Cross-sectional	Adults Serum	TSH, FT4, TT4, TT3
Huang et al. (2014). The human body burden of polybrominated diphenyl ethers and their relationships with thyroid hormones in the general population in Northern China	Cross-sectional	Adults Serum	T3, FT4, TSH
Xu, Lou, et al. (2014). Association of PCB, PBDE and PCDD/F body burdens with hormone levels for children in an e-waste dismantling area of Zhejiang Province, China	Cross-sectional	Children e-waste area Serum	FT3, TT3, FT4, TT4, TSH

TABLE 20 (Continued)

Reference	Study design	Population studied Matrix analysed	Endpoint
Xu, Liu, et al. (2014). Elevated serum polybrominated diphenyl ethers and alteration of thyroid hormones in children from Guiyu, China	Cross-sectional	Children e-waste area Serum	FT3, FT4, TSH[d]
Xu, Lou, et al. (2015). Effects of PCBs and PBDEs on thyroid hormone, lymphocyte proliferation, haematology and kidney injury markers in residents of an e-waste dismantling area in Zhejiang, China	Cross-sectional	Children e-waste area Serum	FT3, FT4, TSH
Eguchi et al. (2015). Residue profiles of organohalogen compounds in human serum from e-waste recycling sites in North Vietnam: Association with thyroid hormone levels	Cross-sectional	Adults e-waste area Serum	TSH, TT3, TT4, FT3, FT4
Vuong et al. (2015). Maternal polybrominated diphenyl ether (PBDE) exposure and thyroid hormones in maternal and cord sera: the HOME Study, Cincinnati, USA	Cohort	Pregnant women Maternal serum	TSH, FT4, TT4, TT3, FT3, TPO-Ab, Tg-Ab
Kim, Park, Kim, Lee, Choi, Choi, Kim, Kim, Moon, et al. (2015). Association between several persistent organic pollutants and thyroid hormone levels in cord blood serum and bloodspot of the newborn infants of Korea	Cross-sectional	Newborns Maternal and umbilical cord blood	FT3, TT3, FT4, TT4, TSH, TSH bloodspot
Shrestha et al. (2015). Perfluoroalkyl substances and thyroid function in older adults	Cross-sectional	Adults Serum	TSH, FT4, TT4, TT3
Allen et al. (2016). PBDE flame retardants, thyroid disease, and menopausal status in U.S. women	Cross-sectional	Adults Serum	'Current thyroid problem'
Leonetti et al. (2016). Brominated flame retardants in placental tissues: associations with infant sex and thyroid hormone endpoints	Cross-sectional	Newborns Placenta	TT4, TT3, rT3, DIO3, SULT activity
Oulhote et al. (2016). Exposure to polybrominated diphenyl ethers (PBDEs) and hypothyroidism in Canadian women	Cross-sectional	Adults Plasma	Hypothyroidism
Lignell et al. (2016). Maternal body burdens of PCDD/Fs and PBDEs are associated with maternal serum levels of thyroid hormones in early pregnancy: a cross-sectional study	Cross-sectional	Pregnant women Human milk	TT3, FT4, TSH, TPO-Ab
Makey, McClean, Braverman, Pearce, He, et al. (2016). polybrominated diphenyl ether exposure and thyroid function tests in North American Adults	Cohort	Adults Serum	TT3, TT4, FT4, TSH, TPO
Jacobson et al. (2016). Serum polybrominated diphenyl ether concentrations and thyroid function in young children	Cross-sectional	Children Serum	TT3, FT3, rT3, T3 uptake, TT4, FT4, TSH, Tg-Ab, TPO-Ab
Zheng et al. (2017). Disruption of thyroid hormone (TH) levels and TH-regulated gene expression by polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), and hydroxylated PCBs in e-waste recycling workers	Cross-sectional	Adults e-waste area Serum	TT3, TT4, FT3, FT4, TSH
Ding et al. (2017). Polybrominated diphenyl ethers (PBDEs) and thyroid hormones in cord blood	Cross-sectional	Newborns Cord blood serum	TSH, TT4, FT4, TT3, FT3
Liu et al. (2017). Association of polybrominated diphenylethers (PBDEs) and hydroxylated metabolites (OH-PBDEs) serum levels with thyroid function in thyroid cancer patients	Cross-sectional	Adults (thyroid cancer patients) Serum	FT4, FT3, TSH
Guo et al. (2018). Association between serum polybrominated diphenyl ethers, new flame retardants and thyroid hormone levels for school students near a petrochemical complex, South China	Cross-sectional	Children Serum	TT3, TT4, FT3, FT4, TSH
Vuong, Braun, et al. (2018). Polybrominated diphenyl ether (PBDE) exposures and thyroid hormones in children at age 3 years	Cohort	Children Maternal and child serum	TT4, FT4, TT3, FT3, TSH
Byrne et al. (2018). Associations between serum polybrominated diphenyl ethers and thyroid hormones in a cross sectional study of a remote Alaska Native population	Cross-sectional	Adults Serum	TSH, TT3, FT3, TT4, FT4
Albert et al. (2018). Exposure to polybrominated diphenyl ethers and phthalates in healthy men living in the greater Montreal area: A study of hormonal balance and semen quality	Cross-sectional	Adults Hair	TSH, FT3, FT4
Chen, Niu, et al. (2018). Disruption of thyroid hormone levels by decabrominated diphenyl ethers (BDE-209) in occupational workers from a deca-BDE manufacturing plant	Cross-sectional	Adults occupational Serum	TSH, TT4, TT3, FT4, FT3, TG-Ab, TPO-Ab
Li, Hernandez-Moreno, et al. (2018). Association of in utero persistent organic pollutant exposure with placental thyroid hormones	Cross-sectional	Newborns Placenta	TT4, TT3, rT3

(Continues)

TABLE 20 (Continued)

Reference	Study design	Population studied Matrix analysed	Endpoint
Cowell et al. (2019). Pre and postnatal polybrominated diphenyl ether concentrations in relation to thyroid parameters measured during early childhood	Cohort	Children Cord blood, blood	TSH, FT4, TT4
Caron-Beaudoin et al. (2019). Exposure to perfluoroalkyl substances (PFAS) and associations with thyroid parameters in First Nation children and youth from Quebec	Cross-sectional	Children Serum	TSH, FT4, Tg
Yu et al. (2019). Polybrominated diphenyl ethers in human serum, semen and indoor dust: Effects on hormones balance and semen quality	Cross-sectional	Adults e-waste area Serum, Semen, Indoor dust	FT3, FT4, TT3, TT4, TSH
Han et al. (2019). Associations between exposure to persistent organic pollutants and thyroid function in a case–control study of East China	Cross-sectional	Adults serum	TT3, FT3, TT4, FT4, TSH
Ji et al. (2019). Associations of prenatal exposures to low levels of polybrominated diphenyl ether (PBDE) with thyroid hormones in cord plasma and neurobehavioral development in children at 2 and 4 years	Cross-sectional	Newborn Cord blood	TSH, TT3, FT3, TT4, FT4
Zhao, Chen, et al. (2020). Polybrominated diphenyl ethers and decabromodiphenyl ethane in paired hair/serum and nail/serum from corresponding chemical manufacturing workers and their correlations to thyroid hormones, liver and kidney injury markers	Cross-sectional	Adults e-waste area Hair, nail	TT4, FT4, TT3, FT3, TSH, TG-Ab, TPO-Ab[a]
Zhao, Yang, et al. (2021). Polybrominated diphenyl ethers in serum from residents living in a brominated flame retardant production area: Occurrence, influencing factors, and relationships with thyroid and liver function	Cross-sectional	Adults e-waste Serum	TT3, TT4, FT3, FT4, TSH, Tg-Ab, TPO-Ab[b]
Hu et al. (2021). Thyroid hormones in relation to polybrominated diphenyl ether and metals exposure among rural adult residents along the Yangtze River, China	Cross-sectional	Adults Serum	FT3, FT4, TSH

Abbreviations: FT3, free T3; FT4, free T3; T3, triiodothyronine; T4, thyroxine; rT3, reverse T3; TSH, thyroid stimulating hormone; TBG, thyroid-binding globulin; DIO3, thyroid hormone-inactivating enzyme type 3 deiodinase; SULT, sulfotransferase enzymes; TPO, thyroid peroxidases; TPO-Ab, Thyroid peroxidase antibodies; Tg, thyroglobulin; Tg-Ab, thyroglobulin antibodies.

[a]Other endpoints studied: Liver and kidney injury markers in serum (TBIL, DBIL, IDBIL, TP, ALB, GLO, A/G, AST, ALT, AST/ALT, BUN, UA, CRE, β2-MG, RBP, Cys-C).

[b]Other endpoints studied: Liver injury biomarkers: AST, ALT, GLO, ALB, TP, DBIL, IBIL, TBIL. Also LDL, HDL, TG, Cholesterol.

[c]Other endpoints studied: IGF-1.

[d]Other endpoints studied: IGF-1, IGFBP-3.

Chen, Niu, et al. (2018) in a small cross-sectional study investigated the relationship between **BDE-209** levels (serum and urine) and thyroid hormones in occupational workers from a DecaBDE manufacturing plant in China ($n = 72$). The range of **BDE-209** levels in serum was 67.4 to 109,000 ng/g lipid (median: 3420 ng/g lipid) and serum **BDE-209** showed a statistically significant positive association with TT4 (per $\log_{10}$ **BDE-209** increase; β: 8.63, 95% confidence interval (CI): 0.90, 16.33) but not with TT3, FT3, FT4, TSH, anti-TG or anti-TPO after adjusting for gender, age, BMI and duration of occupational exposure.

Makey, McClean, Braverman, Pearce, He, et al. (2016) reporting on the North American FLaRE cohort study ($n = 52$; healthy adult office workers; follow-up 18 months) used repeated measures to estimate the associations between serum PBDE concentrations and thyroid hormone profile (TT4, TSH, fT4, TT3, TPO). Although the most prevalent congeners were **BDE-28**, **-47**, **-99**, **-100** and **-153**, **BDE-47** predominated. The geometric mean for the Sum PBDEs was 22 ng/g lipid at baseline. During the short follow-up period there was a statistically significant TT4 decrease per ng/g serum increase in **BDE-47** (−2.6 μg/dL; 95% CI: −4.7, −0.35), **BDE-99** (−7.6 μg/dL, 95% CI: -15, −0.06) and **BDE-100** (−7.8 μg/dL, 95% CI: −14, −1.6). For FT4 (natural log transformed), there was a statistically significant increase per ng/g serum increase in **BDE-153** (0.35 μg/dL, 95% CI: 0.03, 0.67).

Vuong et al. (2015) in the HOME study (birth cohort, USA) assessed the association between PBDE levels at 16-weeks gestation and the thyroid hormone profile at birth (cord blood, $n = 228$). No statistically significant associations were observed except for FT3 (per 10-fold increase of **BDE-28**; $\beta = -0.11$, 95% CI: −0.21, −0.003). The same authors and for the same birth cohort also provided an assessment at a longer follow-up point (3 years) for TSH, TT3, TT4, FT3 and FT4 in children (Vuong, Braun, et al., 2018). After adjusting for potential confounders, prenatal **BDE-47** and Sum PBDEs were both associated with a decrease in TSH. Prenatal **BDE-99** and Sum PBDEs were associated with increased FT3 levels. No statistically significant associations were observed between prenatal PBDEs (maternal serum) and TT4, FT4 or TT3.

Abdelouahab et al. (2013) in a birth cohort in Canada ($n = 260$) investigated the association between maternal blood PBDEs (**BDE-47**, **-99**, **-100**, **-153**) and PCBs in early pregnancy and levels of thyroid hormones (TT4, FT4, TT3, FT3, TSH, TPO-Ab) in maternal (delivery) and umbilical-cord blood. **BDE-47** constituted more than 70% of total PBDEs. **BDE-47** and **-99** were detected in more than 90% of the samples and these two congeners were analysed further. At delivery, associations were observed between decreased maternal TT4 and **BDE-99**, between maternal total T3, FT3 and **BDE-47**, and between maternal total T3, FT3 and Sum PBDEs.

The CHAMACOS Study (birth cohort, USA) evaluated the association between in utero and child PBDE levels (BDE-17, -**28**, -**47**, -66, -85, -**99**, -**100**, -**153**, -**154**, -**183**) and various endpoints at different follow-up points. Chevrier et al. (2011) reporting in that study focused on neonatal TSH (dried blood spots). **BDE-47**, -**99**, -**100** and -**153** were detected in > 97% of the samples and **BDE-47** showed the highest concentration. Thus, the sum of **BDE-47**, -**99**, -**100** and -**153** was used as the primary exposure measure. No statistical associations were found.

The Columbia Center for Children's Environmental Health (CCCEH) is a birth cohort in the USA ($n = 329$; enrolment 2001–2002) that examined the association between prenatal (cord) and childhood (ages 2, 3, 5, 7 and 9 years) plasma PBDE concentrations (**BDE-47**, -**99**, -**100**, -**153**) and various endpoints in African American and Dominican children. Median cord blood concentrations of **BDE-47**, -**99** and -**100** were 11.2, 3.2 and 1.4 ng/g lipid, respectively. Cowell et al. (2019) focused on **BDE-47** measured at birth and in the toddler years (age 2–3 years) and thyroid parameters at 3 and/or 5 years of age (TSH, FT4, TT4). High levels of **BDE-47** during the prenatal period or early childhood were statistically significantly associated with lower TSH levels.

Finally, the two largest cross-sectional studies are described. Allen et al. (2016) investigated the correlation between serum PBDE concentrations (**BDE-47**, -**99**, -**100**, -**153**) and thyroid disease in women from the USA ($n = 1089$, NHANES 2003–2004 cycle, being told by a doctor that they had a thyroid problem), stratified by menopause status. Women in the highest quartile of serum concentrations of **BDE-47**, -**99** and -**100** had increased odds of currently having thyroid disease (**BDE-47**: odds ratio (OR): 1.48, 95% CI: 1.05, 2.09; **BDE-99**: OR: 1.78, 95% CI: 1.16, 2.75; Sum PBDEs: OR: 1.61, 95% CI: 1.1, 2.4) compared to the reference group (1st and 2nd quartiles combined). Of note, all the associations comparing PBDEs Q3 vs. (Q1 + Q2), albeit non-statistically significant, showed an opposite effect direction. Oulhote et al. (2016) ($n = 745$, Canada) estimated the prevalence ratios for hypothyroidism in relation to **BDE-47**, -**99**, -**100** and -**153** and their sum. No statistically significant correlations were observed.

The remaining cross-sectional studies spanned across different sample sizes (median, $n = 95$) and population characteristics; eight studies were related to high exposure settings (occupation in or proximity to e-waste sites) and four studies pertained to European populations (Denmark, Norway, Sweden and The Netherlands). This diverse evidence base was characterised by considerable effect inconsistency and even when assessed at the level of the individual congener and the individual thyroid function biomarker was not able to corroborate the findings of the prospective studies (see details in Annex D, Table D.1).

Regarding studies on PBDE metabolites, five cross-sectional studies investigated the potential effect of OH-PBDEs and biomarkers of thyroid function. Wan et al. (2010) investigated the correlation between 10 OH-PBDE congeners and TT4 levels in pregnant women (maternal serum, $n = 26$, South Korea). Only 6-OH-BDE-47 was detected (mean; maternal serum: 17.5 ± 26.3 pg/g ww, fetal cord blood serum: 30.2 ± 27.1 pg/g ww). No statistically significant findings were reported. Zota et al. (2011) assessed the correlation between OH-PBDEs and biomarkers of thyroid function (TSH, FT4, TT4) in pregnant women ($n = 25$, USA). The median of the Sum OH-PBDEs was 0.084 ng/mL and a statistically significant relationship was found for TSH and 4′-OH-BDE-49 ($\beta = 0.50$; 95% CI, 0.22 to 0.78). Stapleton et al. (2011) addressed the correlation between 4′-OH-BDE-49 and 6-OH-BDE-47 (detected in > 67% of the samples) and five thyroid hormones in pregnant women ($n = 140$, USA). No statistically significant findings were reported for OH-PBDE congeners. Eguchi et al. (2015) examined the association between the OH-PBDE levels in two populations (e-waste recycling site and rural site) in Vietnam ($n = 111$). Significantly higher mean total OH-PBDE concentrations were detected at the reference (160 pg/g) than at the e-waste recycling site (43 pg/g). No statistically significant findings were reported for the OH-PBDE congeners. Finally, Liu et al. (2017) investigated the association between 11 OH-PBDEs and biomarkers of thyroid function in thyroid cancer patients ($n = 33$, China). The levels of Sum OH-PBDEs ranged from 0.01 to 0.46 ng/g lipid, and 6-OH-BDE-47 and 3-OH-BDE-47 were the predominant congeners. Statistically significant correlations were reported for 3-OH-BDE-47 and TSH and FT4. Moreover, there was an inverse association between log 3-OH-BDE-47 and log FT4 ($\beta = -2.49$, 95% CI: −4.19, −0.78), a positive association for TSH levels and log 4′-OH-BDE-49 ($\beta = 0.23$, 95% CI: 0.04, 0.42), as well as positive associations for both log Sum 5 OH-PBDEs ($\beta = 0.33$, 95% CI: 0.07, 0.58) and log Sum OH-PBDEs ($\beta = 0.36$, 95% CI: 0.07, 0.64) and log TSH.

In summary, there is a growing body of epidemiological research in the field of adverse events related to PBDEs levels and thyroid function. However, the currently available evidence for an association is weak and characterised by a small number of prospective studies, generally short follow-up periods, relatively small sample sizes, considerable heterogeneity in the assessed populations, exposures and outcomes, and varying methodological quality. Besides the between-study heterogeneity, the reported associations frequently are characterised by inconsistency in the effect direction between and within studies; for example, there are studies reporting statistically significant increases in TSH and other papers reporting statistically significant increases in FT3, FT4, TT3 or TT4. Congener-wise, the prospective data propose mostly non-replicated statistically significant associations for **BDE-47**, -**99**, -**100** and -**153**; only **BDE-47** and -**99** were inversely statistically significantly associated with TSH and TT3 in two studies. Moreover, statistically significant associations across the whole panel of thyroid function biomarkers were seen for **BDE-47**, and partially for **BDE-99**, but with discordant effect direction in both cases.

Based on the above, the currently available evidence coming from human studies for thyroid function cannot be used for hazard characterisation.

3.1.3.2 | *Neurotoxicity*

In the previous EFSA Opinion on PBDEs, three cohort studies on neurodevelopment were included indicative yet heterogeneous results (EFSA CONTAM Panel, 2011b). Since then, 60 study publications were identified assessing the association between exposure to PBDEs and any outcome related to neurotoxicity (see Table 21).

The evidence base included in the current Opinion consists of 46 cohort study publications (22 studies), 5 case–controls studies and 9 cross-sectional studies where the PBDE exposure was assessed simultaneously or even later than the outcome ascertainment.

The sample size of the included observational studies ranged widely, and the evaluated populations came from European countries, Canada, from the USA, as well as from China and Taiwan. The populations under study were diverse including children, adolescents and the adult population. PBDE exposure was assessed via biomarkers in serum or plasma or human milk.

In **Sections 3.1.3.2.1** and **3.1.3.2.2** the evidence available on developmental neurotoxicity and neurotoxicity in adults, respectively, is presented and discussed, with detailed information about each of the studies provided in Annex D (Table D.2). In **Section 3.1.3.2.3** the main three domains identified, i.e. cognition and intelligence, autism and ADHD, hyperactivity and attention are discussed in more detail.

TABLE 21 Overview of the epidemiological studies identified on the association between levels of PBDEs and neurotoxicity.

Reference[a]	Study design	Population Matrix	Endpoint
Developmental neurotoxicity			
Herbstman et al. (2010). Prenatal exposure to PBDEs and neurodevelopment	Cohort CCCEH	Children (12–48, 72 months) Cord blood	IQ and IQ subscales, general cognition, motor function
Shy et al. (2011). Neurodevelopment of infants with prenatal exposure to polybrominated diphenyl ethers	Cohort	Children Cord blood	General cognition, language, behavioural problems, motor function
Chao et al. (2011). Levels of breast milk PBDEs from Southern Taiwan and their potential impact on Neurodevelopment	Cohort	Children (8, 12 months) Human milk	General cognition, language, behavioural problems, motor function
Hertz-Picciotto et al. (2011). Polybrominated diphenyl ethers in relation to autism and developmental delay: a case–control study	Case–control	Children Child's serum	Autism spectrum disorder
Gascon et al. (2011). Effects of pre and postnatal exposure to low levels of polybromodiphenyl ethers on neurodevelopment and thyroid hormone levels at 4 years of age	Cohort INMA	Children (4 years) Cord blood, child's serum	General cognition, motor function, ADHD, social/emotional development
Gascon et al. (2012). Polybrominated diphenyl ethers (PBDEs) in breast milk and neuropsychological development in infants	Cohort INMA	Children (12–18 months) Colostrum	General cognition, motor function
Mitchell et al. (2012). Levels of select PCB and PBDE congeners in human postmortem brain reveal possible environmental involvement in 15q11-q13 duplication autism spectrum disorder	Case–control	Postmortem brain samples	Autism spectrum disorder
Hoffman et al. (2012). Lactational exposure to polybrominated diphenyl ethers and its relation to social and emotional development among toddlers	Cohort PIN	Children (30 months) Human milk	Social/emotional development
Kiciński et al. (2012). Neurobehavioral function and low-level exposure to brominated flame retardants in adolescents: a cross-sectional study	Cross-sectional	Adolescents (13.6–17 years) Child serum	Exectutive function, task performance, attention/ hyperactivity, motor function
Eskenazi et al. (2013). In utero and childhood polybrominated diphenyl ether (PBDE) exposures and neurodevelopment in the CHAMACOS study	Cohort CHAMACOS	Children (5, 7 years) Maternal serum, child's serum	General cognition, IQ and IQ subscales, ADHD, attention/ hyperactivity, motor function
Cheslack-Postava et al. (2013). Maternal serum persistent organic pollutants in the Finnish Prenatal Study of Autism: A pilot study	Nested case–control FiPS-A	Children Maternal serum	Autism spectrum disorder
Chen, Yolton, et al. (2014). Prenatal polybrominated diphenyl ether exposures and neurodevelopment in U.S. children through 5 years of age: The HOME Study	Cohort HOME	Children (1–5 years) Maternal serum	Cognitive function, IQ, behavioural problems, attention/ hyperactivity, motor function
Adgent et al. (2014). Brominated flame retardants in breast milk and behavioural and cognitive development at 36 months	Cohort PIN	Children (36 months) Human milk	General cognition, visual/spatial development, language, behavioural problems, attention/ hyperactivity, motor function

TABLE 21 (Continued)

Reference[a]	Study design	Population Matrix	Endpoint
Braun et al. (2014). Gestational Exposure to Endocrine-Disrupting Chemicals and Reciprocal Social, Repetitive, and Stereotypic Behaviours in 4-and 5-Year-Old Children: The HOME Study	Cohort HOME	Children (4–5 years) Maternal urine	Autism spectrum disorder, social/emotional development
Gump et al. (2014). Polybrominated diphenyl ether (PBDE) exposure in children: possible associations with cardiovascular and psychological functions	Cross-sectional	Children Blood	Behaviour,task performance, attention/hyperactivity, social/emotional development, aggression/hostility, depression, motor function
Ding et al. (2015). Association between prenatal exposure to polybrominated diphenyl ethers and young children's neurodevelopment in China	Cohort	Children (12, 24 months) Cord blood	General cognition, language, behavioural problems, social/emotional development, motor function
Cowell et al. (2015). Prenatal exposure to polybrominated diphenyl ethers and child attention problems at 3–7 years	Cohort	Children (3–7 years) Cord blood	Attention
Donauer et al. (2015). Prenatal exposure to polybrominated diphenyl ethers and polyfluoroalkyl chemicals and infant neurobehavior	Cohort HOME	Infants (5 weeks) Maternal serum	Infant neurobehaviour
Bruckner-Davis et al. (2015). Neurotoxicant exposure during pregnancy is a confounder for assessment of iodine supplementation on neurodevelopment outcome	Cohort	Children (2 years) Human milk	General cognition, language, behavioural problems, motor function
Sagiv et al. (2015). Prenatal and childhood polybrominated diphenyl ether (PBDE) exposure and attention and executive function at 9–12 years of age	Cohort CHAMACOS	Children (9, 10, 12 years) Maternal serum, child's serum	IQ subscales, executive function, ADHD, attention/hyperactivity
Vuong, Yolton, et al. (2016). Prenatal polybrominated diphenyl ether and perfluoroalkyl substance exposures and executive function in school-age children	Cohort HOME	Children (5, 8 years) Maternal serum	Executive function
Boggess et al. (2016). Mean serum-level of common organic pollutants is predictive of behavioural severity in children with autism spectrum disorders	Cross-sectional[b]	Children (2–9 years) Child's serum	Autism spectrum disorder, behavioural severity
Forns et al. (2016). Novel application of statistical methods for analysis of multiple toxicants identifies DDT as a risk factor for early child behavioural problems	Cohort HUMIS	Children (1, 2 years) Human milk	Behavioural problems
Chevrier et al. (2016). Childhood exposure to polybrominated diphenyl ethers and neurodevelopment at six years of age	Cohort PELAGIE	Children (6 years) Cord blood, dust	IQ, IQ subscales
Przybyla et al. (2016). Cross-sectional study of polybrominated flame retardants and self-reported attention deficit hyperactivity disorder in US youth aged 12–15 (NHANES 2003–2004)	Cross-sectional	Children (12–15 years) Child's serum	ADHD
Lipscomb et al. (2017). Cross-sectional study of social behaviours in preschool children and exposure to flame retardants	Cross-sectional	Children (3–5 years) Passive samplers	Social/emotional development
Lyall et al. (2017). Prenatal serum concentrations of brominated flame retardants and autism spectrum disorder and intellectual disability in the early markers of autism study: a population-based case–control study in California	Nested case–control EMA	Children Maternal serum	Autism spectrum disorder, intellectual disability
Braun et al. (2017). Prenatal environmental chemical exposures and longitudinal patterns of child neurobehavior	Cohort HOME	Children (1–8 years) Maternal serum	General cognition, IQ, behavioural problems, attention/hyperactivity, motor function
Vuong, Braun, Yolton, et al. (2017). Prenatal and postnatal polybrominated diphenyl ether exposure and visual spatial abilities in children	Cohort HOME	Children (8 years) Maternal serum, child's	Spatial development
Vuong, Yolton, Poston, et al. (2017). Prenatal and postnatal polybrominated diphenyl ether (PBDE) exposure and measures of inattention and impulsivity in children	Cohort HOME	Children (8 years) Child's serum	Attention
Vuong, Yolton, Xie, et al. (2017). Childhood polybrominated diphenyl ether (PBDE) exposure and neurobehavior in children at 8 years	Cohort HOME	Children (8 year) Child's serum	IQ, behavioural problems, attention/hyperactivity

(Continues)

TABLE 21 (Continued)

Reference[a]	Study design	Population Matrix	Endpoint
Zhang, Yolton, et al. (2017). Prenatal PBDE and PCB exposures and reading, cognition, and externalising behaviour in children. *Erratum: Environ Health Perspect, 125: 069001*	Cohort HOME	Children (8 years) Maternal serum	IQ, reading skills, behavioural problems, attention/ hyperactivity
Berghuis et al. (2018). Prenatal exposure to persistent organic pollutants and cognition and motor performance in adolescence	Cohort DACE (COMPARE, RENCO)	Adolescents (13–15 years) Maternal serum	IQ, IQ subscales, motor function
Cowell et al. (2018). Associations between prenatal and childhood PBDE exposure and early adolescent visual, verbal and working memory	Cohort	Children (9–14 years) Cord blood, child's plasma	Visual, verbal and working memory, attention
Kim, Eom, et al. (2018). Association between maternal exposure to major phthalates, heavy metals, and persistent organic pollutants, and the neurodevelopmental performances of their children at 1 to 2years of age- CHECK cohort study	Cohort CHECK	Children (13–21 months) Maternal urine, blood, human milk	General cognition, behavioural problems, motor function
Vuong, Yolton, et al. (2018). Childhood polybrominated diphenyl ether (PBDE) exposure and executive function in children in the HOME Study	Cohort HOME	Children (8 years) Child's serum	Executive function
Oulhote et al. (2018). Prenatal exposure to polybrominated diphenyl ethers and predisposition to frustration at 7months: Results from the MIREC study	Cohort MIREC	Children (7 months old) Maternal serum	Behavioural problems
de Water et al. **(2019)**. A preliminary study on prenatal polybrominated diphenyl ether serum concentrations and intrinsic functional network organisation and executive functioning in childhood	Cohort	Children (5 years) Maternal serum	Executive function
Ruel et al. (2019). Prenatal exposure to organohalogen compounds and children's mental and motor development at 18 and 30 months of age	Cohort DACE	Children (18, 30 months) Maternal blood	General cognition, motor function
Lenters et al. (2019). Early-life exposure to persistent organic pollutants (OCPs, PBDEs, PCBs, PFASs) and attention -deficit/hyperactivity disorder: A multi-pollutant analysis of a Norwegian birth cohort	Cohort HUMIS	Children (13 years) Human milk	ADHD
Liang, Vuong, et al. (2019). Childhood polybrominated diphenyl ether (PBDE) serum concentration and reading ability at ages 5 and 8 years: The HOME Study	Cohort HOME	Children (5, 8 years) Child's serum	Reading skill, IQ, Behavioural problems s
Drobná et al. (2019). PBDE serum concentrations and preschool maturity of children in Slovakia	Cross-sectional	Children (6 years) Child's serum	IQ, IQ subscales
Ji et al. (2019). Associations of prenatal exposures to low levels of polybrominated diphenyl ether (PBDE) with thyroid hormones in cord plasma and neurobehavioral development in children at 2 and 4 years	Cohort Shanghai-Minhang	Children (2, 4 years) Cord blood	Behavioural problems, attention/ hyperactivity
Hamra et al. (2019). Prenatal exposure to endocrine-disrupting chemicals in relation to autism spectrum disorder and intellectual disability	Case–control EMA	Children (4–9 years) Maternal serum	Autism spectrum disorder, intellectual disability
Vuong, Xie, et al. (2020). Prenatal exposure to a mixture of persistent organic pollutants (POPs) and child reading skills at school age	Cohort HOME	Children (8 years) Maternal blood	Reading skills
Margolis et al. (2020). Functional connectivity of the reading network is associated with prenatal polybrominated diphenyl ether concentrations in a community sample of 5 year-old children: a preliminary study	Cohort Endocrine Disruption in Pregnant Women: Thyroid Disruption and Infant Development Study	Children (5 years) Maternal serum	Reading skills
Azar et al. (2021). Prenatal exposure to polybrominated diphenyl ethers (PBDEs) and cognitive ability in early childhood	Cohort MIREC	Children (3 years) Maternal plasma	IQ, IQ subscales

TABLE 21 (Continued)

Reference[a]	Study design	Population Matrix	Endpoint
Jedynak et al. (2021). Prenatal exposure to a wide range of environmental chemicals and child behaviour between 3 and 7 years of age – An exposome-based approach in 5 European cohorts	Cohort HELIX	Children (3, 7 years) Maternal blood	Behavioural problems, attention/ hyperactivity
Kalloo et al. (2021). Chemical mixture exposures during pregnancy and cognitive abilities in school-aged children	Cohort HOME	Children (5, 8 years) Maternal serum	IQ, IQ subscales
Solazzo et al. (2021). The association between prenatal concentrations of polybrominated diphenyl ether and child cognitive and psychomotor function	Cohort GESTE	Children (6–8 years) Maternal plasma	IQ subscales, visual/spatial, attention, motor function
Julvez et al. (2021). Early life multiple exposures and child cognitive function: a multi-centric birth cohort study in six European countries	Cohort HELIX	Maternal serum Child's serum	Non-verbal IQ, working memory, attention
Tsai et al. (2021). Analysis of polybrominated diphenyl ethers and lipid composition in human breast milk and their correlation with infant neurodevelopment	Cohort	Children (8, 12 months) Human milk	General cognition, language, behavioural problems, motor function
Maitre et al. (2021). Early-life environmental exposure determinants of child behaviour in Europe: A longitudinal, population-based study	Cohort HELIX	Children (6–11 years) Child's serum	ADHD, behavioural problems, attention/hyperactivity
Hartley et al. (2022). Gestational exposure to polybrominated diphenyl ethers and social skills and problem behaviours in adolescents: The HOME study	Cohort HOME	Children (up to 12 years) Maternal serum	Social/emotional development
Sussman et al. (2022). The relationship between persistent organic pollutants and Attention Deficit Hyperactivity Disorder phenotypes: Evidence from task-based neural activity in an observational study of a community sample of Canadian mother–child dyads	Cohort GESTE	Children (9–11 years) Maternal serum	Inhibitory control performance, executive function, attention/ hyperactivity
Neurotoxicity in adults			
Fitzgerald et al. (2012). Polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs) and neuropsychological status among older adults in New York	Cross-sectional	Adults Serum	Cognitive and motor function, affective state, olfactory function
Su, Goutman, et al. (2016). Association of environmental toxins with amyotrophic lateral sclerosis	Cross-sectional	Adults Blood	ALS
Goutman et al. (2019). High plasma concentrations of organic pollutants negatively impact survival in amyotrophic lateral sclerosis	Cohort	Adults Plasma	ALS
Vuong, Yolton, et al. (2020). Polybrominated diphenyl ethers (PBDE) and poly- and perfluoroalkyl substances (PFAS) exposures during pregnancy and maternal depression	Cohort HOME	Adults Serum	Postpartum depressive symptoms
Mutic et al. (2021). Polybrominated diphenyl ether serum concentrations and depressive symptomatology in pregnant African American women	Cross-sectional	Adults Serum	Antenatal depressive symptoms

Abbreviations: ADHD, attention deficit hyperactivity disorder; ALS, amyotrophic lateral sclerosis; IQ, intelligence quotient.

[a]The study by Nevison (2014) entitled 'A comparison of temporal trends in United States autism prevalence to trends in suspected environmental factors' is an ecological study and thus it is not further considered in the Opinion.

[b]For the statistical analysis, the concentrations of all xenobiotics per individual were pooled into one variable, termed mean xenobiotic body-burden (MXB).

3.1.3.2.1 | *Developmental neurotoxicity*

In this section, the evidence stemming from cohort and nested case control studies is reported in detail across the whole domain of developmental neurotoxicity. The detailed information on the studies is provided in Annex D (Table D.2).

The HOME Study

The Health Outcomes and Measures of the Environment (HOME) Study is a prospective pregnancy and birth cohort conducted in the USA (Cincinnati metropolitan area, Ohio) designed to study the relationship between environmental chemical exposure and children's growth and development. Pregnant women ($n = 468$) were enrolled between March 2003 and February 2006 who delivered live singleton infants. Prenatal exposure assessment was done at around 16 weeks of gestation and postnatal exposure assessment was done at 1, 2, 3, 5 and 8 years of age. Ten PBDEs were measured among other environmental contaminants such as lead, mercury, organochlorine pesticides, PCBs, PFASs and phthalates. The PBDE

congeners analysed in maternal or child's serum were BDE-17, **-28**, **-47**, -66, -85, **-99**, **-100**, **-153**, **-154** and **-183**. Children were followed up at 1, 2, 3, 4, 5, 8 and 12 years of age for neurobehaviour. Fourteen publications report on the results of various associations pertinent to the present Opinion and are described in the following paragraphs.

Braun et al. (2014) investigated the association between gestational levels of seven PBDEs (**BDE-28**, **-47**, -85, **-99**, **-100**, **-153**, **-154**) ($n = 175$) and autistic behaviour at 4 and 5 years (Social Responsiveness Scale, SRS). Fewer autistic behaviours were observed among children born to women with detectable vs. non-detectable concentrations of BDE-85 ($\beta = -3.2$; 95% CI: −5.9, −0.5) for the comparison of detectable vs. nondetectable levels.

Chen, Yolton, et al. (2014) assessed the association between in utero exposure to PBDEs and child cognitive function and behaviour at ages 1 through 5 ($n = 309$, Bayley Scales of Infant Development-II (BSID-II) at ages 1, 2 and 3 years; Wechsler Preschool and Primary Scale of Intelligence-III (WISC-III) at age 5 years; Behavioural Assessment System for Children-2 (BASC-2) annually at ages 2–5 years). A 10-fold increase in prenatal **BDE-47** was associated with a 4.5-point decrease (95% CI: −8.8, −0.1) in Full-Scale IQ and a 3.3-point increase (95% CI: 0.3, 6.3) in the hyperactivity score at age 5 years.

Donauer et al. (2015) assessed the association between prenatal PBDE levels (maternal serum, **BDE-47**, **-99**, **-100**, **-153**) and early infant neurobehavior at 5 weeks of age ($n = 326$ mother/infant pairs, Neonatal Intensive Care Unit Network Neurobehavioral Scale, NNNS). No statistically significant associations were observed.

Vuong, Yolton, et al. (2016) investigated the association between prenatal PBDEs levels (maternal serum, BDE-17, **-28**, **-47**, -66, -85, **-99**, **-100**, **-153**, **-154**, **-183**) and executive function in children ages 5 and 8 years ($n = 256$, parent-rated Behaviour Rating Inventory of Executive Function, BRIEF). Among the large number of analyses performed, a 10-fold increase in **BDE-153** was associated with poorer behaviour regulation ($\beta = 3.23$; 95% CI: 0.60, 5.86). Higher odds of being 'at risk' of a clinically relevant executive function problem (score > 60 in behaviour regulation, OR = 3.92; 95% CI: 1.76, 8.73) or global executive functioning (OR = 2.34; 95% CI: 1.05, 5.23) was observed with increased **BDE-153**.

Braun et al. (2017) assessed the association between prenatal **BDE-47** levels (maternal serum) and neurodevelopment up to 8 years of age ($n = 229$). The included neurodevelopment endpoints pertained to behaviour (BASC-2), mental and psychomotor development (BSID-II) and child cognitive abilities (WPPSI-III, WISC-IV). Among the large number of analyses performed, a statistically significant association was observed only between each 10-fold increase in prenatal **BDE-47** concentration and the risk of having a score ≥ 60 in externalising BASC-2 (2–8 years; risk ratio (RR) = 2.0; 95% CI: 1.1, 3.6).

Vuong, Braun, Yolton, et al. (2017) assessed the association between prenatal and childhood (at 1, 2, 3, 5 and 8 years) PBDE levels and visual spatial abilities at 8 years ($n = 199$, Virtual Morris Water Maze, VMWM). No statistically significant associations were observed between PBDE congeners (**BDE-28**, **-47**, **-99**, **-100**, **-153**) or their Sum and VMWM path length. Regarding VMWM time, a 10-fold increase in **BDE-47**, **-99** and **-100** at 5 years were associated with faster time to complete the Virtual Morris Water Maze by 5.2 s (95% CI: −9.3, −1.1), 4.5 s (95% CI: −8.1, −0.9) and 4.7 s (95% CI: −9.0, −0.3), respectively. Similar findings were noted with **BDE-47** and **-100** at 8 years. Regarding visual space memory retention, 10-fold increases in prenatal **BDE-28**, **-47**, **-99**, **-100**, and Sum 5 PBDEs were significantly associated with a 10.6% (95% CI: 4.5, 16.7), 8.3% (95% CI: 3.0, 13.7), 7.4% (95% CI: 2.4, 12.5), 8.1% (95% CI: 3.4, 12.8) and 8.2% (95% CI: 2.7, 13.8) increase in the total distance, respectively. Prenatal **BDE-28** was significantly associated with more time in the platform quadrant ($\beta = 3.1$ s; 95% CI: 0.7, 5.4). **BDE-100** at 1 year and **BDE-99** at 5 years were associated with improved spatial memory retention, increasing the time in the correct quadrant by ~ 3 s.

Vuong, Yolton, Poston, et al. (2017) examined the association between both prenatal and postnatal (at 1, 2, 3, 5 and 8 years) PBDE levels with attention and impulse control ($n = 214$, Conners' Continuous Performance Test-Second Edition, CPT-II) at 8 years. No statistically significant associations were observed.

Vuong, Yolton, Xie, et al. (2017) assessed the association between repeated estimates of childhood PBDE levels at 1, 2, 3, 5 and 8 years and Full-Scale Intelligence Quotient (FSIQ) and externalising problems at 8 years ($n = 208$, WISC-IV, BASC-2):

- A 10-fold increase in prenatal **BDE-47** was associated with a 4.5-point decrease (95% CI: −8.8, −0.1) in FSIQ at 5 years. At 8 years, assessment via WPPSI-III, WISC-IV and FSIQ showed no statistically significant differences for **BDE-47**.
- A 10-fold increase in **BDE-28** levels at 3 years was associated with a 7.9-point decrease (95% CI: −13.6, −2.3) in FSIQ at 8 years.
- A 10-fold higher **BDE-153** levels at ages 2, 3, 5 and 8 were significantly associated with FSIQ decrements of 5.4-points (95% CI: −10.8, −0.1), 7.7-points (95% CI: −12.5, −2.9), 8.2-points (95% CI: −13.4, −3.0), and 5.6-points (95% CI: −10.8, −0.4), respectively.
- Several PBDE congeners at 8 years were associated with higher concurrent Externalising Problems scores, including **BDE-28** ($\beta = 4.7$; 95% CI: 0.8, 8.6), **BDE-47** ($\beta = 3.4$; 95% CI: 0.004, 6.8), **BDE-153** ($\beta = 4.2$; 95% CI: 0.4, 8.0), and Sum PBDEs ($\beta = 4.3$; 95% CI: 0.4, 8.2); estimates were all for a 10-fold concentration increase.
- Hyperactivity and Aggression scores were higher among children with increased PBDE concentrations at age 8 years, with statistical significance for **BDE-28** and **-153** in relation suspected environmental factors' is an ecological study and thus it is not further considered in the Opinion. to hyperactivity, and **BDE-28**, **-47**, **-99** and Sum PBDEs in relation to aggression. For earlier ages of PBDE exposures, only **BDE-153** at 1 year was associated with Externalising Problems ($\beta = 3.7$; 95% CI: 0.1, 7.2) and Aggression ($\beta = 3.4$; 95% CI: 0.1, 6.8). No association was observed between childhood PBDEs and Conduct Disorder scores.

Zhang, Yolton, et al. (2017) examined the association between prenatal PBDE levels with children's reading skills at ages 5 and 8 years, Full-Scale Intelligence Quotient (FSIQ), and externalising behaviour problems at age 8 years ($n = 239$,

Woodcock–Johnson Tests of Achievement III (WJ-III), Wide Range Achievement Test-4 (WRAT-4) at age 8 years, WISC-IV, BASC-2). An increase of the Sum 4 PBDEs (sum of **BDE-47**, -**99**, -**100**, -**153**) by 10 times was statistically inversely associated with Reading Composite scores (β: −6.2; 95% CI: −11.7, −0.6) and FSIQ (β = −5.3; 95% CI: −10.6, −0.02) at age 8 years.

Vuong, Yolton, et al. (2018) assessed the association between repeated estimates of childhood PBDE serum concentrations (**BDE-28**, -**47**, -**99**, -**100** and -**153**) at 1, 2, 3, 5 and 8 years and executive function at 8 years using the BRIEF (Behaviour Rating Inventory of Executive Function) (n = 208). Three main outcome areas were derived from the BRIEF: global executive composite, behavioural regulation index, metacognition index. Null associations were observed between childhood PBDEs and metacognition index and global executive composite. Statistically significant impairment in behavioural regulation index was observed with a 10-fold increase in **BDE-153** (β = 4.8, 95% CI: 0.8, 8.8) and **BDE-28** at 8 years (β = 4.6, 95% CI: 0.5, 8.7). The association between Sum PBDEs at 8 years and behavioural regulation index was also borderline significant, with an increase of 3.8 points (95% CI: −0.3, 7.9) with a 10-fold increase in Sum PBDE concentrations. Effect modification by child sex was noted between **BDE-153** at 8 years and behaviour regulation index, metacognition index, and global executive composite, with adverse effects observed in males, but not females.

Liang, Vuong, et al. (2019) investigated the association between repeated childhood PBDE levels (annually, year 1 to 5, 8) and reading ability in children at ages 5 and 8 years (n = 230, WJ-III, WRAT-4). No statistically significant associations were observed in the adjusted analyses.

Vuong, Xie, et al. (2020) estimated associations between prenatal levels to multiple contaminants including five PBDEs (**BDE-28**, -**47**, -**99**, -**100**, -**153**) and reading ability at 8 years (n = 161, Wide Range Achievement Test-4 (WRAT-4)) and applied multiple analytical approaches so as to estimate covariate-adjusted associations with individual and their mixtures in multi-pollutant models. In single pollutant analyses, statistically significant inverse associations were observed between prenatal **BDE-47** (β = −6.1, 95% CI −12.0, −0.2), **BDE-100** (β = −6.1, 95% CI −11.4, −0.7) and **BDE-153** (β = −5.3, 95% CI −10.3, −0.3). Multipollutant analyses showed inverse associations between reading scores and **BDE-28**, **-100** and -**153**.

Finally, Kalloo et al. (2021) in a HOME sub-cohort (n = 253) assessed the associations between prenatal chemical mixture exposure profiles (including **BDE-47**) and individual mixture profile components with cognitive abilities (WPPSI-III and WISC-IV) at ages 5 and 8 years as well as mediators thereof. **BDE-47** exposure was not associated with cognitive abilities. Women were further classified into three clusters based on their environmental chemical level profiles. Mean biomarker concentrations were generally highest, intermediate and lowest among women in clusters 1, 2 and 3, respectively. **BDE-47** was included in Cluster 3 where the highest mean concentrations occurred for the sum of parabens, monoethyl phthalate (MEP), Pb, **BDE-47**, perfluorononanoate (PFNA) and cotinine. Children born to women in clusters 1 and 2 had 5.1 (95% CI: −9.4, −0.8) and 2.0 (95% CI: −5.5, 1,4) lower performance IQ scores compared to children in cluster 3, respectively.

Hartley et al. (2022) assessed the association between prenatal PBDE levels (maternal serum) of five PBDEs (**BDE-28**, -**47**, -**99**, -**100**, -**153**) and social skills and problem behaviours in early adolescence (n = 243). At age 12, social skills and problem behaviours scores were assessed using self- and caregiver-report on the Social Skills Improvement System (SSiS). Increased maternal Sum 5 PBDEs levels among males was associated with decreased caregiver-reported Social Skills composite score (β = −10.2, 95% CI: −19.5, −1.0), increased adolescent-reported Problem Behaviours composite score (β = 12.1, 95% CI: 5.4, 18.8), and increased caregiver-reported Problem Behaviours composite score (β = 6.2, 95% CI: 0.7, 11.7). Associations for the individual congeners were similar. There were no statistically significant associations in stratified models among females.

The CHAMACOS Study

The Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) Study is a longitudinal birth cohort study of pesticides and other chemicals among children in a farmworker community from one of the most productive agricultural regions in the USA, the California's Salinas Valley. Pregnant women, predominantly Mexican-American, living in this area were enrolled in 1999–2000 (n = 601) and followed for 19 years assessing children's growth, health and development every 1–2 years. In 2010–2011, the study was expanded by enrolling additional 9-year-old children into the cohort. Prenatal exposure was measured at around 26 weeks of gestation, while postnatal exposure assessment was done at the follow up visits every 1–2 years and until 12 years. Ten PBDE congeners were analysed among other contaminants such as PCBs, organochlorine and organophosphate pesticides. The PBDEs analysed were BDE-17, -**28**, -**47**, -66, -85, -**99**, -**100**, -**153**, -**154** and -**183**. **BDE-47**, -**99**, -**100** and -**153** were detected in > 97% of the samples and **BDE-47** showed the highest concentration. Thus, the Sum 4 PBDEs (sum of **BDE-47**, -**99**, -**100** and -**153**) was used as the primary exposure measure.

Eskenazi et al. (2013) evaluated the association between prenatal (maternal serum) and postnatal (child's serum at 7 years) PBDE levels and neurodevelopment (attention, motor functioning and cognition) at 5 (n = 310) and 7 years of age (n = 323). The Sum 4 PBDEs was used as the primary exposure measure. Neurodevelopment was assessed used an extensive battery of tests as follows:

– At 5 years, attention was evaluated via the Child Behaviour Checklist (CBCL)/1.5–5 (CBCL) including the two scores (Attention Problems scale, Attention Deficit/Hyperactivity Disorder (ADHD) Problems scale), the Conners' Kiddie Continuous Performance Test (K-CPT), the continuous ADHD Confidence Index score. At 7 years, the Conners' ADHD/DSM-IV Scales (CADS) and the Behaviour Assessment System for Children, 2nd edition (BASC), were used. At age 5 years, maternal Sum 4 PBDEs was associated with attention problems reported in the CBCL (adjusted OR (aOR) for a 10-fold increase in Sum 4 PBDEs = 4.6; 95% CI: 0.9, 24.5) and strongly associated with both errors of omission scores and ADHD Confidence Index scores on the K-CPT at 5 years. At child age 7 years, maternal Sum 4 PBDE levels were associated with

maternally reported ADHD Index scores on the CADS ($\beta = 2.9$; 95% CI: 0.7, 5.2), DSM-IV Total scores ($\beta = 2.6$; 95% CI: 0.2, 5.0) and DSM-IV Inattention scale scores ($\beta = 2.2$; 95% CI: 0.0, 4.5). Maternal levels were also related to higher odds of teacher reports of child behaviour problems (aOR = 2.5; 95% CI: 1.1, 6.0). Child sum 4 PBDE levels were associated with more adverse teacher reports on CADS DSM-IV Inattentive, BASC Hyperactivity and BASC Attention Problems scales. Every 10-fold increase in child Sum 4 PBDE levels was associated with 4.5- and 5.5-times higher odds of the child being rated by the teacher as being in the 'moderately or markedly atypical' range on CADS DSM-IV Hyperactive/Impulsive subscale (95% CI: 1.2, 16.6) and DSM-IV Total subscale (95% CI: 1.5, 20.3), respectively.

- Motor function was assessed at ages 5 and 7 years via select subscales of the McCarthy Scales of Children's Abilities, the pegboard Wide Range Assessment of Visual Motor Ability (WRAVMA) test, a finger-tapping task [at 5 years: Behavioural Assessment and Research System (BARS) and at 7 years: Reitan Neuropsychology Laboratory (Tucson, AZ)]. Maternal Sum 4 PBDE levels were associated with poorer performance on the WRAVMA pegboard at both 5 and 7 years, for the nondominant hand.
- Finally, cognitive function was evaluated at 5 years via the PPVT and TVIP, depending on the language and via the Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III). At age 7 years, cognition was evaluated using the Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV, Verbal Comprehension, Perceptual Reasoning, Working Memory, Processing Speed) and a Full-Scale IQ. At age 7 years, maternal Sum PBDEs was associated with significant decrements in WISC Verbal Comprehension IQ. Quartile analysis indicated that the association was primarily driven by a Verbal Comprehension IQ decrement in the highest quartile ($\beta = -6.0$; 95% CI: −11.3, −0.7). Children's Sum 4 PBDEs was also related to Full-Scale IQ at age 7 years ($\beta = -5.6$; 95% CI: −10.8, −0.3) and with Processing Speed IQ.

Sagiv et al. (2015) examined the associations of prenatal and postnatal (at 9 years) PBDEs levels with attention and executive function at ages 9 to 12 years ($n = 301$, CCPT-II, BRIEF, WISC-IV). Geometric means for prenatal and childhood Sum 4 PBDE levels were 26.3 and 63.2 ng/g lipid, respectively. Among the numerous performed analyses, both at age 9 and 12, a 10-fold increase in prenatal Sum 4 PBDE levels was associated with poorer response consistency on the CCPT-II ($\beta = 2.9$; 95% CI: 0.9, 4.8), lower processing speed score (WISC-IV, $\beta = -4.4$; 95% CI: −8.5, −0.3) and poorer working memory on the BRIEF ($\beta = 2.5$; 95% CI: 0.5, 4.4).

The CCCEH Study

The Columbia Center for Children's Environmental Health (CCCEH) is a birth cohort in the USA ($n = 329$; enrolment 2001–2002) that examined the association between prenatal (cord) and childhood (ages 2, 3, 5, 7 and 9 years) plasma PBDE concentrations (**BDE-47**, -**99**, -**100**, -**153**) and neurodevelopment endpoints in African American and Dominican children. Median cord blood concentrations of **BDE-47**, -**99** and -**100** were 11.2, 3.2 and 1.4 ng/g lipid, respectively.

Herbstman et al. (2010) analysed 210 cord blood specimens for possible neurodevelopmental effects in the children at 12–48 and 72 months of age (BSID-II, WPPSI Revised Edition, WPPSI-R). Associations were significant for 12-month Psychomotor Development Index (**BDE-47**), 24-month Mental Development Index (MDI) (**BDE-47, -99 and -100**), 36-month MDI (**BDE-100**), 48-month full-scale and verbal IQ (**BDE-47**, -**99** and -**100**) and performance IQ (**BDE-100**), and 72-month performance IQ (**BDE-100**).

In a subset of the CCCEH cohort ($n = 212$), Cowell et al. (2018) examined the association between prenatal (cord blood) and childhood (ages 2, 3, 5, 7 and 9 years) plasma PBDE concentrations (**BDE-47**, -**99**, -**100**, -**153**) and memory endpoints at ages 9 and 14. Memory was assessed via the Children's Memory Scale (CMS) and its three subscales, the Attention-Concentration Index, the Immediate (i.e. short-term recall) Visual Memory Index and the Immediate Verbal Memory Index. For the Attention Concentration Index, no overall statistically significant associations were observed. Higher exposure was associated with lower scores among girls (**BDE-47** $\beta = -7.55$; 95% CI: −13.87, −1.24, **BDE-99** $\beta = -8.14$; 95% CI: −15.34, −0.93). For Visual Memory Index, no overall statistically significant associations were observed for prenatal or early childhood exposure. However, statistically significant associations were observed for **BDE-47**, -**99** and -**100** exposure measured at ages 7 and 9 years were inversely associated with this domain (i.e. age 9: **BDE-47** $\beta = -5.18$: 95% CI: −9.95, −0.42; **BDE-99** $\beta = -4.90$; 95% CI: −9.47, −0.33; **BDE-100** $\beta = -$-5.24; 95% CI: −10.23, −0.25). For Verbal Memory Index, no statistically significant associations were observed.

The HELIX cohort Study

The Human Early Life Exposome (HELIX) Study includes six European longitudinal birth cohorts from six European countries: Born in Bradford (BiB, UK), Étude des Déterminants Pré et Postnatals du Développement et de la Santé de l'Enfant (EDEN, France), Infancia y Medio Ambiente (INMA, Spain), Kaunas Cohort (KANC, Lithuania), Norwegian Mother, Father and Child Cohort Study (MoBa, Norway) and Mother–Child Cohort in Crete (RHEA, Greece). The HELIX subcohort was established, nested within these cohorts, totalling 1301 mother–child pairs, where biomarkers, omics signatures and child health outcomes were measured at age 6–11 years using standardised common protocols across the cohorts. The child health and developmental outcomes studied include birth outcomes, growth-related and obesity-related outcomes, blood pressure, neurodevelopment and respiratory health. A wide range of contaminants were measured including PCBs, PFASs and 2 PBDEs (**BDE-47** and -**153**).

Jedynak et al. (2021) assessed 47 exposure biomarkers from eight chemical exposure families in maternal blood or urine collected during pregnancy including two PBDEs (**BDE-47**, -**153**) and used the strengths and difficulties questionnaire (SDQ) to evaluate child behaviour between 3 and 7 years of age ($n = 708$). No statistically significant associations were observed for the two PBDE congeners.

In the same study, Julvez et al. (2021) assessed cognition at ages 6 to 11 years through the following domains: fluid intelligence (Raven's Coloured Progressive Matrices test, CPM), attention (Attention Network Test, ANT) and working memory (*N*-Back task) ($n = 1298$). No statistically significant associations for PBDEs were reported.

In another publication, Maitre et al. (2021) evaluated behavioural problems at ages 6 to 11 years using the child behaviour checklist (CBCL) and the Conner's ADHD index ($n = 1287$). No statistically significant associations for PBDEs were reported.

The INMA Study

The INMA Study – Children and the Environment is a prospective-based cohort study in Spain that aims to study the role of environmental pollutants in air, water and diet during pregnancy and early childhood in relation to child growth and development from early fetal life until adolescence. It includes seven birth cohorts: Ribera d'Ebre ($n = 102$), Menorca ($n = 530$), Granada ($n = 668$), Valencia ($n = 855$), Sabadell ($n = 657$), Asturias ($n = 494$) and Gipuzkoa ($n = 638$) cohorts. The period of recruitment varied across the cohorts and spanned from 1997 to 2006. Clinical, cognitive and behavioural measures were made at the different follow-ups, and the levels of several contaminants were analysed prenatally and postnatally. The PBDEs analysed were BDE-12-13, -17, -**28**-33, -32, -**47**, -66, -71, -85, -**99**, -**100**, -116, -119, -126, -**138**, -**153**, -**154**, -155, -183, -190).

Gascon et al. (2011) assessed the following domains at 4 years of age: motor and cognitive function (McCarthy Scales of Children's Abilities), attention-deficit, hyperactivity and impulsivity (ADHD-DSM-IV) and social competence (California Preschool Social Competence Scale) using PBDE concentrations in cord blood ($n = 88$) and in serum of 4 year-old children ($n = 244$). Only exposure to **BDE-47** was analysed further. Postnatal exposure to **BDE-47** was statistically significantly related to an increased risk of symptoms on the attention deficit subscale of ADHD symptoms (RR = 1.8; 95% CI: 1.0, 3.0) and to poor social competence symptoms (RR = 2.6; 95% CI: 1.2, 5.9).

In another study, Gascon et al. (2012) assessed the association between concentrations of PBDEs (**BDE-47**, -**99**, -**100**, -**153**, -**154**, -**183**, -**209**) and other POPs in colostrum samples and neurodevelopment ($n = 290$, Bayley Scales of Infant Development, 12–18 months). After adjustment for other contaminants, none of the PBDE congeners reached statistical significance in the performed analyses.

The PIN Babies Study

The Pregnancy, Infection and Nutrition (PIN) Babies Study is a birth cohort from the USA (North Carolina). The study began in 2004 to follow the infants born to women who participated in the PIN Pregnancy and Postpartum studies through 3 years of age ($n = 585$, Daniels et al., 2010). A total of 304 mothers provided human milk samples at 3 months postpartum, which were analysed for the following nine PBDEs: **BDE-28**, -**47**, -66, -85, -**99**, **100**, -**153**, -**154** and -**183**. Five of these (**BDE-28**, -**47**, -**99**, -**100** and -**153**) were detected in > 91% of the samples and were evaluated in relation to developmental outcomes.

Hoffman et al. (2012) investigated the association between the levels of the 5 PBDEs in human milk and social and emotional development in toddlers at 30 months of age ($n = 222$, Infant–Toddler Social and Emotional Assessment (ITSEA)). None of the congeners reached statistical significance in the performed analyses.

In the same study, Adgent et al. (2014) evaluated the association between the levels of the 5 PBDEs in human milk and child behaviour ($n = 192$, BASC-2) and cognitive skills ($n = 184$, Mullen Scales of Early Learning) at 36 months. Among the numerous analyses performed per congener, per scale component and per quartile, statistically significant associations were observed for certain child behaviour components, usually for the comparison between the lowest and highest quartiles and only for **BDE-28** (anxiety and withdrawal), **BDE-99** (anxiety, withdrawal, functional communication), **BDE-100** (anxiety) and **BDE-153** (somatisation, withdrawal, activities of daily living). For cognitive skills, statistically significant associations were observed usually for the comparison between the lowest and highest quartiles and only for **BDE-28** (expressive language), **BDE-99** (receptive language) and **BDE-153** (fine motor).

The DACE Study.

The Development at Adolescence and Chemical Exposure (DACE) Study, is a follow-up of two Dutch birth cohorts: the Risk of Endocrine Contaminants on human health (RENCO) study ($n = 104$ mother-infant pairs included between 1998 and 2000) and the Groningen-Infant-COMPARE (GIC) study ($n = 90$ mother-infant pairs included between 2001 and 2002). Children of both cohorts were invited for participation in the DACE-study during adolescence (13 and 15 years old). Besides PCBs, OH-PCBs and TEQs via CALUX assay, the following five PBDEs were analysed in maternal serum samples from the GIC study: **BDE-47**, -**99**, -**100**, -**153** and -**154**.

Berghuis et al. (2018) studied whether prenatal exposure to PBDEs and other POPs was associated with cognitive and motor development in 13- to 15-year-old adolescents ($n = 101$, WISC-III-NL). **BDE-47**, -**99**, -**100**, -**153** and -**154** were measured. **BDE-154** was associated with Verbal memory-Delayed recognition ($\beta = -0.348$; 95% CI: −1.617, −0.037).

In the same study, Ruel et al. (2019) investigated the PBDE exposure effect on mental and motor development in children at the age of 18 months ($n = 60$, Bayley Scales of Infant Development II (BSID-II)). A statistically significant correlation was observed for **BDE-100** (rho, 0.273).

The MIREC Study

The Maternal–Infant Research on Environmental Chemicals (MIREC) Study is a prospective pregnancy cohort from women recruited during the first trimester of pregnancy ($n = 2001$) across 10 Canadian cities (11 sites). The period of recruitment was between 2008 and 2011. Blood samples were collected during the first trimester of pregnancy to measure the prenatal levels of nine PBDEs: BDE-15, -17, -25, -**28**, -33, -**47**, -**99**, -**100** and -**153**. Of these, four were detected in at least 10% of the plasma samples and were further included in the analysis (**BDE-47**, -**99**, -**100** and -**153**).

The MIREC participants from seven sites were invited to participate in the MIREC-Infant Development (MIREC-ID) follow-up ($n = 525$ women from the original MIREC cohort), conducted at birth and around 6 months of age.

Oulhote et al. (2018) examined the relation between prenatal PBDE concentrations and predisposition to frustration (arm restraint task, ART, $n = 333$) in the MIREC-ID follow-up. Of the four PBDEs retained for the analysis, **BDE-47** levels were statistically significantly associated with negative vocalisations using the ART (adjusted RR = 1.04; 95% CI: 1.00, 1.09). Moreover, infants whose mothers had detectable levels of **BDE-100** showed an increase of 24.1 s (95% CI: 4.1, 44.1) in the 75th quantile of the distribution of proportion of time in negative vocalisations compared with infants of mothers with undetectable levels.

In an additional follow-up study of the original MIREC cohort, Azar et al. (2021) examined the association between prenatal PBDE exposure and cognitive ability (WPPSI-III) in children at age 3 years ($n = 592$). After adjusting for covariates, there was a statistically significant association for Sum 4 PBDEs (sum of **BDE-47**, -**99**, -**100**, -**153**) and performance IQ (–2.4 points; 95% CI: −4.8, −0.1). In the sex-stratified analysis, the associations for **BDE-47** were significant in boys (verbal IQ, −3.7 points, 95% CI: −7.1, −0.3; performance IQ, −4.0 points, 95% CI: −7.8, −0.3; FSIQ, −4.4 points, 95% CI: −7.9, −0.9) but not in girls. A tenfold increase in maternal blood Sum 4 PBDEs levels was associated with lower Full Scale scores in boys (−3.4 points; 95% CI: −7.0, 0.1), after adjusting for confounders. **BDE-47** was the congener with the highest concentrations in maternal blood and a 10-fold increase in exposure was associated with significantly lower Full Scale IQ scores in boys (−4.4 points; 95% CI: −7.9, −0.9), after adjusting for confounders. Verbal and Performance IQ scores were similarly associated with PBDE exposure. Maternal blood PBDE concentrations were not associated with IQ scores in girls. A tenfold increase in maternal blood Sum 4 PBDEs levels was associated with lower Full Scale scores in boys (−3.4 points; 95% CI: −7.0, 0.1), after adjusting for confounders.

The GESTE Study

The GEStation and the Environment (GESTE) cohort enrolled recruited pregnant women from Quebec (Canada) between 2007 and 2008. A total of 800 women were recruited, half of them during pregnancy (12 weeks of gestation) and the other half at the time of delivery. Maternal blood was collected at early pregnancy and delivery and levels of several POPs measured in plasma, including PCBs and the following four PBDEs: **BDE-47**, -**99**, -**100** and -**153**. Children were followed up until 9–11 years old.

Solazzo et al. (2021) examined the association between PBDE concentration at two different prenatal times and cognitive function in children 6–8 years of age. At that age, 355 children completed a series of subtests spanning multiple neuropsychologic domains: verbal and memory skills were measured using the WISC-IV; visuospatial processing using both WISC-IV and NEPSY-II; attention was assessed through the Test of Everyday Attention for Children (TEA-Ch); child motor control was assessed through parent-completed subtests from the Developmental Coordination Disorder Questionnaire (DCD-Q). No significant associations were detected between Sum 4 PBDEs and any of the child psychologic scores. In single exposure models, **BDE-99** levels at delivery were associated with higher scores on short-term and working memory (higher digit span scores from WISC-IV; $\beta = 0.14$; 95% CI: 0.03, 0.26), while higher **BDE-100** levels at delivery were associated with a decrease in spatial perception and reasoning (Block Design score from WISC-IV; $\beta = 0.14$; 95% CI: 0.03, 0.26).

Sussman et al. (2022) ($n = 46$) investigated the association between PBDEs (**BDE-47**, -**99**, -**100**, -**153** and their sum) and inhibitory control performance (Simon spatial incompatibility task), neural correlates of inhibitory control (task-based fMRI assessment) and ADHD-related symptoms (BASC-PRS). All four PBDEs as well as their sum (per-SD increase) were statistically significantly associated with decreased accuracy on congruent trials (Sum 4 PBDEs rate ratio = 0.94; 95% CI: 0.90, 0.99). In the assessment of the accuracy on incongruent trials, no statistically significant associations were observed. In the fMRI studies, increased **BDE-153** exposure was associated with decreased activity in the rAI (per-SD increase, $\beta = -0.41$; 95% CI: −0.75, −0.07). Across the BASC-PRS assessment, only the prenatal **BDE-153** levels were associated with lower executive functioning scores (per-SD increase, $\beta = -2.34$; 95% CI: −4.24, −0.43).

The Endocrine Disruption in Pregnant Women: Thyroid Disruption and Infant Development Study

The 'Endocrine Disruption in Pregnant Women: Thyroid Disruption and Infant Development Study' is a birth cohort in New York (USA) consisting of 316 mother–child pairs. Pregnant women were enrolled between 2009 and 2010. Maternal blood collected during the first half of pregnancy was analysed for the following PBDEs: BDE-17, -**28**, -**47**, -66, -85, -**99**, -**100**, -**153**, -**154**, -**183** and -**209**.

de Water et al. (2019) longitudinally assessed the association between prenatal PBDE serum concentrations and executive functioning at the age 5 years (BRIEF-*P*, $n = 106$) coupled with functional MRI data. Only congeners with concentrations > LOD at > 50% of the participants were further analysed (i.e. **BDE-28**, **-47**, **-99**, **-100**, **-153**). Weighted quantile sum (WQS) regression analyses were performed, and the Global Executive Composite (GEC) and Inhibitory Self-Control Index (ISCI) subscales were statistically significantly associated with the weighted PBDE Index.

Margolis et al. (2020) implemented a resting-state functional magnetic resonance imaging (rs-fMRI) assessment to examine associations between prenatal PBDE concentrations, reading ability (Woodcock Reading Mastery Test, WRMT-2) and functional connectivity of a reading-related network in 5-year-old children ($n = 33$). Weighted quantile sum regression analyses evaluated the contributions of specific PBDE congeners to observed associations. Children with higher Sum 4 PBDE levels (Sum of **BDE-47**, **-99**, **-100** and **-153**) showed reduced global efficiency of the reading-related network but not with altered WRMT-2 scores.

Other Cohort studies

Chao et al. (2011) reported on the results of a small birth cohort ($n_{analyzed} = 70$, Taiwan) assessing the association between 14 PBDEs in human milk (**BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**, **-183**, -196, -197, -203, -206, -207, -208, **-209**; 1 month postpartum) and neurodevelopment in infancy (8–12 months, Bayley Scales of Infants and Toddlers Development, third edition (Bayley-III)). The median of Sum 14 PBDEs was 2.92 ng/g lipid and the predominant congeners were **BDE-47**, **-153** and **-209** that accounted for 61.7% of the total. The Sum 14 PBDEs concentrations were not correlated with Bayley-III scores on cognitive, language, motor, social–emotional or adaptive behaviour scales. A significantly inverse association between **BDE-209** and the cognitive scale was found after multivariate stepwise linear regression analyses ($\beta = 0.007$, adjusted $R = 0.224$, $p < 0.032$). In contrast, the language scale was positively correlated with BDE-196 ($\beta = 0.096$, adjusted $R = 0.315$, $p < 0.002$).

Shy et al. (2011) examined the association between prenatal exposure to 11 PBDEs on infant neurodevelopment ($n = 36$, BDE-15, **-28**, **-47**, **-49**, **-99**, **-100**, **-153**, **-154**, **-183**, -196, -197, Bayley Scales of Infant and Toddler Development, III). The mean (median) levels for the sum of 11 PBDEs were 6.63 (4.63) ng/g lipid. As compared to the lower PBDEs group (Sum 11 PBDEs < 4.63 ng/g lipid), the higher PBDEs group (Sum 11 PBDEs > 4.63 ng/g lipid) had a significantly higher actual OR of the cognition score (OR = 1.13, $p < 0.05$) as well as a lower OR of the adaptive behaviour score (OR = 0.904, $p < 0.01$).

Gump et al. (2014) in a cross-sectional analysis assessed the association between cardiovascular stress responses and psychological states in children (including hostility, depression) and levels of four PBDEs (**BDE-28**, **-47**, **-99**, **-100**; $n = 43$). **BDE-28** was associated with significantly greater heart rate, lower pre-ejection period[41] and lower total peripheral resistance. **BDE-47** was associated with significantly lower diastolic blood pressure and **BDE-100** was associated with significantly lower diastolic blood pressure and shorter pre-ejection periods during acute stress. No associations for task performance were observed. Parental reports of conduct problems in their children were significantly associated with greater **BDE-28**, **-47** and **-99**. Depressive symptoms (based on child reports) were not significantly associated with PBDE congener levels in blood.

Ding et al. (2015) reported on the results of a birth cohort in China ($n = 232$) assessing the associations between cord blood PBDE concentrations and children's developmental quotients at 12 ($n = 192$) and 24 ($n = 149$) months of age based on the Gesell Developmental Schedules (motor, adaptive, language and social domains). Median cord blood levels of **BDE-47**, **-99**, **-100** and **-153** were 3.71, 6.70, 2.63 and 2.19 ng/g lipid, respectively. At 24 months of age, a 10-fold increase in **BDE-99** levels was associated with a statistically significant decrease (2.16 points; 95% CI: 4.52, 0.20) in the language domain and a 10-fold increase in **BDE-47** levels was associated with a statistically significant decrease (1.89; 95% CI: 3.75, 0.03) in the social domain.

Bruckner-Davis et al. (2015) prospectively assessed the association between human milk PBDE concentrations (**BDE-47**, **-99**, **-100**, **-153**) and neurodevelopment at age 2 years ($n = 44$, Bayley test). None of the PBDE congeners reached statistical significance in the performed analyses.

Cowell et al. (2015) investigated the association between prenatal PBDE levels in cord blood and attention (Child Behaviour Checklist, attention problems syndrome subscale) measured annually from 3 to 7 years in 210 mother–child pairs. Four PBDE congeners (**BDE-47**, **-99**, **-100**, **-153**) were detected in more than 50% of the samples, with concentrations highest for **BDE-47** (median (IQR): 11.2 (19.6) ng/g). Various comparisons were tested and marginal statistically significant associations were observed for **BDE-47** (incidence rate ratio: 1.21; 95% CI: 1.00, 1.47), and **BDE-153** (incidence rate ratio: 1.18; 95% CI: 1.00, 1.39) in cord plasma and increased attention problems among children at age 4 ($n = 109$) but not 6 ($n = 107$) years.

Chevrier et al. (2016) investigated the association between prenatal and childhood exposure to PBDEs and neurodevelopment at the age of 6 years in the PELAGIE Study (France, $n = 246$). PBDEs levels were measured in cord blood ($n = 159$; **BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**, **-183**, **-209**, although only **BDE-209** was analysed further) and in dust from vacuum cleaner bags collected from the children's homes ($n = 246$; BDE-85, **-99**, **-100**, -119, **-209**, although only **BDE-99** and **-209** concentrations were analysed further). The neurodevelopment endpoints pertained to cognition (Wechsler Intelligence Scale for Children-IV; WISC-VCI and WISC-WMI subscores).[42] No association was observed between cord blood **BDE-209** concentrations and WISC indices. For **BDE-99**, the WISC-VCI score was lower in the children with the highest concentrations (≥ 54 ng/g) in house dust

[41]The pre-ejection period is an index of myocardial contractility and beta-adrenergic sympathetic control of the heart. It is defined as the time between electrical systole to the initial opening of the aortic valve (Forouzanfar et al., 2019).

[42]For WISC-IV, six subtests were administered (similarities, vocabulary, comprehension, digit span, letter-number sequencing and block design) which allow the calculation of two index scores: (1) the Verbal Comprehension Index (WISC-VCI; subtests similarities, vocabulary, comprehension) and (2) the Working Memory Index (WISC-WMI; subtests digit span, letter-number sequencing).

(p trend 0.02), higher dust concentrations were associated with lower scores for two subtests: similarities (p trend 0.005) and vocabulary (p trend 0.02). Although dust **BDE-99** concentrations were not statistically significantly related to the overall WISC-WMI score, higher **BDE-99** concentrations in dust were associated with a lower score for Digit Span (overall p trend = 0.02). For **BDE-209**, higher concentrations in house dust were associated with lower WISC-VCI scores in boys (p trend = 0.04), the association with concentrations in dust was statistically significant for the 14 comprehension subtest score (overall p trend = 0.007) and dust concentrations were not statistically significantly related to the WISC-WMI score.

Kim, Eom, et al. (2018) in the CHECK birth cohort (China) assessed early neurodevelopment and prenatal levels of a number of contaminants, including 19 PBDEs (BDE-17, -**28**, -**47**, -**49**, -66, -71, -77, -85, -**99**, -**100**, -119, -126, -**138**, -**153**, -**154**, -156, -**183**, -184, -191) measured in maternal serum. Neurodevelopment was assessed using the Bayley Scales of Infant Development-II (BSID-II), the Social Maturity Scale (SMS) and the Child Behaviour Checklist (CBCL). **BDE-47** showed a statistically significant association with externalising problems (CBCL).

Ji et al. (2019) reporting on the Shanghai-Minhang Birth Cohort Study (China) examined the associations of prenatal PBDE levels (**BDE-28**, -**47**, -66, -85, -**99**, -**100**, -**153**, -**154** and -**183**) with thyroid hormones in cord plasma and neurobehavior of children (Child Behaviour Checklist, CBCL/1.5–5) at 2 (n = 199) and 4 (n = 307) years. The association analysis included the exposure to **BDE-47** (detection rate, 84%, median, 0.19 ng/g lipid) and to the Sum 5 PBDEs (sum of **BDE-47**, -**28**, -**99**, -**100** and -**153**). Among the numerous associations tested across the nine CBCL scales, statistically significant associations were observed for somatic complaints, being withdrawn, sleep problems and internalising problems in girls, and somatic complaints and attention problems in boys.

Lenters et al. (2019) using the framework of the HUMIS birth cohort (Norway, n controls = 1144; n ADHD cases = 55) assessed the association between 27 early-life chemical levels including 10 PBDEs (**BDE-28**, -**47**, -66, -85, -**99**, -**100**, -**153**, -**154**, -**183**, -**209**) and ADHD. Levels were measured in human milk and postnatal exposures in the first 2 years of life were estimated using a pharmacokinetic model. **BDE-47** showed one of the highest human milk concentrations along with PFOS, PCB-153 and p,p'-DDE. The values < LOD were 10% for **BDE-28** and 28% for **BDE-154**. None of the PBDE congeners reached statistical significance in the performed analyses. Forns et al. (2016) reporting on the same study assessed child behavioural problems at 12 and 24 months using the Infant Toddler Symptom Checklist (ITSC) in 548 children. None of the PBDE congeners reached statistical significance in the performed analyses.

Tsai et al. (2021) assessed associations between PBDEs in human milk and infant neurodevelopment at 8–12 months of age using a lipidomic analysis (n = 100). Human milk samples were analysed for 30 PBDEs (BDE-7, -15, -17, -**28**, -**47**, -**49**, -66, -71, -77, -85, -**99**, -**100**, -119, -126, -**138**, -139, -140, -**153**, -**154**, -156, -**183**, -184, -191, -196, -197, -203, -206, -207, -208, -**209**). Infants were examined at 8 to 12 months of age by using the Bayley-III to assess neurodevelopment in 5 scales: cognitive, language, motor, social–emotional and adaptive behaviour scales. Unadjusted correlation coefficients showed BDE-206 (r = −0.189, p = 0.06) and **BDE-209** (r = −0.218, p = 0.03) to be negatively associated with the cognitive domain, and BDE-140 (r = 0.175, p = 0.081) and BDE-203 (r = 0.216, p = 0.031) to be positively associated with the social–emotional domain. RDA map analyses showed seven out of the 30 PBDEs (i.e. BDE-17, -**49**, -66, -71, -**99**, -126, -206) to have a strong negative correlation with the five domains of Bayley-III scores, indicating a highly negative impact. In final multivariate models, **BDE-209** was associated with a decrease in the cognitive scale (β = −0.0068, 95% CI: −0.0125, −0.0011).

Case Control Studies

Cheslack-Postava et al. (2013) in the Finnish Prenatal Study of Autism (FiPS-A) performed a nested case–control (n = 150) and investigated the association between prenatal exposure to various contaminants including **BDE-47** and autism. No statistically significant association was observed for **BDE-47**.

Lyall et al. (2017) reporting on the Early Markers for Autism (EMA) study performed a nested case control study in order to assess the association between prenatal exposure to 9 PBDEs (BDE-17, -**28**, -**47**, -66, -85, -**99**, -**100**, -**153**, -**154**) and PBB-153 and autism spectrum disorder (n = 545) or intellectual disability without autism (n = 181). Five congeners were detected in ≥ 55% of samples above the limit of detection (**BDE-28**, -**47**, -**99**, -**100**, -**153**). Of these, a statistically significant lower geometric mean were observed in the case group for Sum PBDEs (**BDE-47**, -**99**, -**100**, -**153**) and ASD and for **BDE-153** and Sum PBDE and intellectual disability. In the fully adjusted model, **statistically significant inverse associations** were observed for autism spectrum disorder and **BDE-100** [quartiles 2 (OR, 95% CI; 0.66, 0.45 to 0.95) and 3 (OR, 95% CI; 0.68, 0.47 to 0.98)], the highest quartiles of **BDE-153** (OR, 95% CI; Q2, 0.62, 0.43 to 0.90; Q4, 0.56, 0.38 to 0.84) as well as the highest quartile of the Sum BFRs[43] (OR, 95% CI; 0.64, 0.44 to 0.93). In the fully adjusted model, no statistically significant associations were observed for intellectual disability. For the same study and using a Bayesian approach, Hamra et al. (2019) evaluated the associations between five PBDEs (**BDE-28**, -**47**, -**99**, -**100**, -**153**) in maternal serum with autism spectrum disorder (ASD) (n = 491) and intellectual disability (n = 155), compared with 373 general population controls. No statistically significant associations were reported.

In a USA case–control study, Hertz-Picciotto et al. (2011) evaluated associations between child serum concentrations of PBDEs and autism and developmental delay diagnosis. Eleven PBDE congeners (**BDE-28**, -**47**, -66, -85, -**99**, -**100**, -**153**, -**183**, -197, -207, -**209**) were measured in serum samples collected after children were assessed for autism (cross-sectional). Cases of autism (n = 49) were confirmed using the Autism Diagnostic Observation Schedules (ADOS) and interview the primary caregiver using the Autism Diagnostic Interview-revised (ADI-R). Cases of developmental delay were identified using the

[43]Including PBB-153.

Mullen's Scales of Early Learning and the Vineland Adaptive Behaviour Scales ($n = 24$). Typically developing controls ($n = 21$) were those with no evidence of delay, autism or autism spectrum disorder. Children with autism/autism spectrum disorder and developmental delay were similar to typically developing controls for all PBDE congeners.

In a case–control study, Mitchell et al. (2012) analysed a total of 107 human frozen post-mortem brain samples for PCBs and 7 PBDEs (**BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183**). Human brain samples were grouped as neurotypical controls ($n = 43$), neurodevelopmental disorders with known genetic basis ($n = 32$, including Down, Rett, Prader-Willi, Angelman and 15q11-q13 duplication syndromes), and autism of unknown aetiology ($n = 32$). **BDE-153** detection (yes/no) was significantly negatively associated with idiopathic autism spectrum disorder (OR = 0.8, 95% CI: 0.1, 0.7) but the continuous variable was not (OR = 0.9, 95% CI: 0.8, 1.04).

Cross-sectional studies

In a cross-sectional study, Kiciński et al. (2012) evaluated associations between brominated flame retardants and neurobehavioral function in 13–17 year old adolescents ($n = 515$). **BDE-47**, -**99**, -**100**, -**153**, -**209**, and HBCDDs and TBBPA were measured in serum samples. Four tests from the Neurobehavioral Evaluation System (NES) Version 3 were used to assess neurobehaviour: the Continuous Performance test assessed sustained attention, the Digit-Symbol test assessed visual scanning and information processing, the Digit Span test assessed working memory and the Finger tapping test assessed motor function. A two-fold increase of the sum of serum PBDEs was associated with a reduced motor function (decrease of the number of taps with the preferred-hand in the Finger Tapping test by 5.31 (95% CI: 0.56, 10.05). No associations were observed between PBDEs and neurobehavioral domains other than motor function.

Finally, Przybyla et al. (2016) reporting on the NHANES cross-sectional study evaluated the association between PBDE serum concentrations (**BDE-28**, -**47**, -**99**, -**100**, -**153**) and self-reported ADHD in 12-15-year-olds ($n = 292$). No statistically significant associations were observed with the exception of the serum PBDE concentrations in the second tertile (OR = 6.16, 95% CI: 1.19, 31.90).

3.1.3.2.2 | *Neurotoxicity in adults*

Five publications (4 study populations) all conducted in the USA assessed the associations between PBDE levels in adults and endpoints pertaining to neurotoxicity including amyotrophic lateral sclerosis (ALS) ($n = 1$) and prognosis thereof ($n = 1$), antenatal or postnatal depressive symptoms ($n = 2$), and parameters related to cognitive and motor function, affective state and olfactory function ($n = 1$). Two studies were longitudinal with a short follow-up and assessed ALS prognosis and antenatal or antenatal depressive symptoms.

In the following paragraphs, the evidence stemming from all studies is discussed. Further details of these studies can be found in Annex D (Table D.2).

Su, Goutman, et al. (2016) in a cross-sectional fashion evaluated the association of 122 environmental contaminants (including **BDE-28**, -**47**, -66, -85, -**99**, -**100**, -**154**) and ALS (USA, $n_{ALS} = 156$, $n_{non\text{-}ALS} = 128$). No statistically significant associations were reported for PBDEs in the multi-chemical model while, in the adjusted single-chemical analyses, **BDE-28** and -66 surpassed the Bonferroni-corrected *p*-value threshold yielding identical effect estimates (OR = 3.68, 95% CI: 1.89, 7.18). Using the same study population and assessing survival longitudinally, Goutman et al. (2019) investigated the association between composite exposure to POPs including PBDEs (**BDE-28**, -**47**, -85, -**99**, -**100**, -**153**, -**154**) and survival in patients with ALS ($n = 167$). **BDE-154** was one of the most frequently detected POP (28% < LOD) and one of the largest contributors to the environmental risk score. However, no statistically significant association was found for any PBDE congener.

Regarding postnatal depressive symptoms, Vuong, Yolton, et al. (2020) examined the associations between serum PBDE concentrations (**BDE-28**, -**47**, -**99**, -**100**, -**153** and Sum PBDEs) during pregnancy and repeated measures of depressive symptoms (Beck Depression Inventory-II) in women assessed from pregnancy to 8 years postpartum within the HOME study framework ($n = 377$). A 10-fold increase in prenatal **BDE-28** was associated with significantly increased BDI-II scores ($\beta = 2.5$, 95% CI 0.8, 4.2) from pregnancy to 8 years postpartum. Significant positive associations were also observed with **BDE-47**, -**100**, -**153** and Sum PBDEs. A 10-fold increase in Sum PBDEs was associated with a 4.6-fold increased risk (95% CI: 1.8, 11.8) of a high trajectory for BDI-II compared to a low trajectory. Mutic et al. (2021) in a cross-sectional assessment (USA, $n = 193$) examined whether PBDE levels (**BDE-47**, -85, -**99**, -**100**, -**153** and -**154**) in pregnant women were associated with antenatal depressive symptomatology (Edinburgh Depression Scale). **BDE-47** and -**99** exposures were statistically significantly associated with the risk of being mild to moderately depressed (adjusted OR, 95% CI; **BDE-47**, 4.43, 1.47–13.40; **BDE-99**, 1.58, 1.08–3.00). The weighted body burden estimate of the PBDE mixture (driven by **BDE-47**) was also associated with a higher risk of mild to moderate depression (OR = 2.93; CI 1.18, 7.82).

Finally, Fitzgerald et al. (2012) in a cross-sectional study design fashion evaluated the association between PBDE levels (**BDE-28**, -**47**, -66, -85, -**99**, -**100**, -**138**, -**153**, -**154**) and neuropsychological function among older adults using an extensive battery of 34 tests (USA, $n = 144$). After adjustment for relevant confounders and across a very large number of comparisons, no overall associations were observed between the PBDE congener concentrations and scores on the neuropsychological tests.

Given the very small number of small studies per relevant endpoint, the implemented study design methodology and the lack of replicated findings, the currently available evidence coming from human studies on neurotoxicity in adults cannot be used for hazard characterisation.

3.1.3.2.3 | *Summary*

From the previous sub-sections and Table 21 it is clear that epidemiological studies on neurodevelopmental toxicity of PBDE show great diversity in the endpoints evaluated and tools used, making it hard to summarise evidence for all neurodevelopmental domains. For many endpoints evidence is scattered over few studies using non-comparable tools. Therefore, three main domains were selected as a focus for the summary sections below: cognitive function, autism and ADHD. These present the highest level of comparability between studies.

Cognitive function

Overall, eight cohort studies (13 publications) assessed the association between levels of PBDEs and cognitive function, including intelligence, using any of the Wechsler scales. All the studies addressed populations of European ancestral descent with the exception of the CHAMACOS study (Latino) and the CCCEH study (African American and Dominican). The sample size ranged from 101 to 592 analysed participants and the assessed timepoints at follow up were 2 years ($n = 2$), 3 years ($n = 3$), 5 years ($n = 2$), 6 years ($n = 1$), 6–8 years ($n = 1$), 7–9 years ($n = 1$) and 13–15 years ($n = 1$). The tools that were used were the WPPSI-III, WISC-III and WISC-IV, along with their subscales.

BDE-28 was analysed in six cohort studies and one showed a positive signal for the full-scale IQ at 8 years (per 10-fold increase; −7.9 points; 95% CI: −13.6, −2.3) (Adgent et al., 2014; Chen, Yolton, et al., 2014; Eskenazi et al., 2013; Kalloo et al., 2021; Kim, Eom, et al., 2018; Liang, Vuong, et al., 2019; Margolis et al., 2020; Sagiv et al., 2015; Tsai et al., 2021; Vuong, Yolton, Xie, et al., 2017; Vuong, Yolton, et al., 2018; Vuong, Xie, et al., 2020; Zhang, Yolton, et al., 2017).

BDE-47 was assessed in all studies and showed a positive signal for the full-scale IQ in two different studies but at different timepoints (10-fold BDE increase; at 2 years (Herbstman et al., 2010); at 5 years, −4.5, 95% CI: −8.8, −0.1; Chen, Yolton, et al., 2014). **BDE-47** also gave a positive signal at 2 years follow-up for the verbal IQ subscale (REF). Moreover, a 10-fold **BDE-47** increase in exposure was associated with significantly lower Full Scale IQ scores in boys (−4.4 points; 95% CI: −7.9, −0.9), after adjusting for confounders (Oulhote et al., 2018; Azar et al., 2021). Finally, childhood **BDE-47** levels were associated with visual spatial abilities (Virtual Morris Water Maze time, visual space memory retention) at 8 years (Vuong, Braun, Yolton, et al., 2017).

BDE-99 was assessed in all studies and two statistically significant associations were observed for the IQ components at two different timepoints (2 years and 6–8 years) but with opposite effects (Herbstman et al., 2010; Solazzo et al., 2021).

BDE-100 was also assessed in all studies and gave four positive signals arising from two studies at three different timepoints; **BDE-100** levels were statistically significantly associated with full-scale, performance and verbal IQ at 2 years, with performance IQ at 3 years, and with spatial perception and reasoning at 6–8 years (Vuong, Xie, et al., 2020; Herbstman et al., 2010).

BDE-153 was assessed in seven studies and two statistically significant associations were identified in two different studies at different timepoints [full-scale IQ at 2–8 years (Vuong, Yolton, Xie, et al., 2017); verbal memory at 13–15 years (Berghuis et al., 2018). No statistically significant associations were observed for **BDE-154** and **-183** in the subgroup of studies that assessed them. For the Sum PBDEs, there were five statistically significant associations across three different studies for full-scale IQ ($n = 2$), verbal IQ ($n = 1$), performance IQ ($n = 1$) and processing speed ($n = 1$). Overviewing the evidence base using the endpoints as a reference point, full-scale IQ has been statistically significantly associated with **BDE-28**, **-47**, **-99**, **-100**, **-153** or the sum, in three studies.

In summary, there is a growing evidence base stemming from longitudinal studies on the associations between PBDE levels and intelligence indices that is characterised by a harmonised endpoint assessment through the Weschler scales. However, statistically significant associations that were replicated in other studies are scarce, thus limiting the use of the data on IQ for hazard characterisation.

Autism

Five studies (six publications; Boggess et al., 2016; Braun et al., 2014; Cheslack-Postava et al., 2013; Hamra et al., 2019; Hertz-Picciotto et al., 2011; Lyall et al., 2017) investigated autism (either as a binary endpoint or through the Social Responsiveness Scale) using different reported study designs (cohort, $n = 1$; case–control, $n = 1$; nested case–control, $n = 2$; cross-sectional, $n = 1$). The case–control study assessed the associations between PBDE levels and autism in a cross-sectional fashion where exposure and disease status were assessed simultaneously. Moreover, in the cross-sectional study no PBDE-specific estimates were available as the concentrations of all xenobiotics per individual were pooled into one variable, termed 'mean xenobiotic body-burden'. In the three studies which evaluated autism as a binary endpoint and provided PBDE-specific data, the case sample size ranged from 45 to 545. Among these studies, statistically significant – yet inverse – associations were only reported in one study for **BDE-100** (Q2, Q3), **BDE-153** (Q4), and Sum BFRs[44] (Q4); these findings were not corroborated

[44]Including PBB-153.

by a Bayesian analysis within the same study. In the cohort study (Braun et al., 2014) that assessed autistic behaviours at 4 and 5 year using the Social Responsiveness Scale, fewer autistic behaviours were observed among children born to women with detectable vs. non-detectable concentrations of BDE-85 ($\beta = -3.2$; 95% CI: −5.9, −0.5).

In summary, the evidence base related to the association between PBDE levels and autism is characterised by small sample sizes, small total number of studies and lack of replication of the few postulated associations. Based on the above, the potential of using of epidemiological data on autism for hazard characterisation is limited.

ADHD, hyperactivity, attention

The association between PBDE concentrations and ADHD or ADHD subscales is evaluated in 15 publications. Six of these assess ADHD as a distinct outcome or as a continuous score, and in 12 publications continuous ADHD subscores relating to hyperactivity and/or inattention are assessed.

Of the six publications that assess ADHD as a dichotomous diagnosis/symptoms or continuous score, five are based on longitudinal cohort studies and the other is a cross-sectional analysis based on NHANES data with self-reported ADHD (Przybyla et al., 2016). Of the five longitudinal publications, two are based on the CHAMACOS cohort (at 5–7 and 9–12 years old) (Eskenazi et al., 2013, Sagiv et al., 2015), and one each on the HUMIS, HELIX and INMA cohorts (Gascon et al., 2011; Lenters et al., 2019; Maitre et al., 2021, respectively).

Tools used to assess ADHD include parent or teacher completed Conners DSM-IV-ADHD scales (CHAMACOS, HELIX, INMA), clinical ADHD registration (HUMIS), parent-reported CBCL-ADHD problems scale (CHAMACOS) and the Continuous Performance Test (CPT)-ADHD index (CHAMACOS).

Statistically significant associations between prenatal maternal PBDE concentrations and ADHD scales were reported in CHAMACOS at 5 years (Sum PBDEs with CBCL and CPT) and at 7 years (Sum PBDEs with DSM-IV) (Eskenazi et al., 2013), but the other studies reported null associations between prenatal or human milk PBDEs levels and ADHD scores (Maitre et al., 2021; Sagiv et al., 2015), clinical ADHD diagnosis (Lenters et al., 2019) or dichotomous ADHD symptoms (Gascon et al., 2011).

Childhood Sum PBDE levels were associated with the DSM-IV ADHD scores in CHAMACOS at 7 years (Eskenazi et al., 2013), but the other studies reported null associations (Sagiv et al., 2015; Gascon et al., 2011; Maitre et al., 2021). The cross-sectional NHANES study also reported null associations (Przybyla et al., 2016).

Twelve publications assessed inattention or hyperactivity subscales through a range of tools, including the CBCL, Conners DSM-IV, CPT, BASC, SDQ and TEA-Ch (Gascon et al., 2011; Kiciński et al., 2012; Eskenazi et al., 2013; Adgent et al., 2014; Chen, Yolton, et al., 2014; Gump et al., 2014; Cowell et al., 2015; Julvez et al., 2021; Ji et al., 2019; Sagiv et al., 2015; Solazzo et al., 2021; Vuong, Yolton, Xie, et al., 2017). Four of these studies observed statistically significant associations related to prenatal PBDE levels:

- the CHAMACOS cohort reported an association between Sum PBDEs and increased CBCL-attention problems and DSM-IV-inattention problems at 5 and 7 years (Eskenazi et al., 2013);
- The HOME cohort reported an association between **BDE-47** and increased BASC-hyperactivity problems (Chen, Yolton, et al., 2014);
- Ji et al. (2019) reported an association between **BDE-47** and increased CBCL-attention problems in boys; and
- Cowell et al. (2015) reported an association between **BDE-47** and **-153** and increased CBCL-attention problems.

In the five other studies that studied association between prenatal maternal levels of PBDEs and attention or hyperactivity scores, null associations were reported (Adgent et al., 2014; Gascon et al., 2011; Julvez et al., 2021; Sagiv et al., 2015; Solazzo et al., 2021).

Regarding childhood exposures, three studies reported statistically significant associations: Eskenazi et al. (2013) for Sum PBDEs and teacher reported DSM-IV-inattention, BASC hyperactivity and BASC-attention problem scores, Vuong, Yolton, Xie, et al. (2017) for **BDE-28** and **-153** with BASC-hyperactivity scores, and Gascon et al. (2011) for **BDE-47** levels and dichotomous DSM-IV attention deficit symptoms. Four other studies did not find associations between childhood PBDE levels and hyperactivity or attention problems (Gump et al., 2014; Julvez et al., 2021; Kiciński et al., 2012; Sagiv et al., 2015).

In conclusion, although 15 studies assessed ADHD or its separate inattention or hyperactivity subscales, results are heterogeneous with both positive and null associations reported in relation to prenatal and childhood PBDE levels. Some statistically significant associations were replicated between studies, in particular those for Sum PBDE or **BDE-47** exposure with attention deficit subscales, but such replication was still scarce. Inconsistencies in the evidence limit at present the use of epidemiological data on ADHD for hazard characterisation.

3.1.3.3 | *Lipid and sugar metabolism*

3.1.3.3.1 | *Diabetes*

In the previous EFSA Opinion on PBDEs (EFSA CONTAM Panel, 2011b), two cross-sectional studies on type 2 diabetes (T2D) (NHANES, Great Lakes Sport Fish Consumers Cohort) were included bearing inconclusive results. Since then, 17 study publications were identified assessing the association between levels of PBDEs and any outcome related to diabetes (see Table 22).

The evidence-base included in the current Opinion consists of six cohort studies (7 publications), two nested case–controls studies, one case-cohort study and seven cross-sectional studies where the PBDE levels were assessed simultaneously or even later than the outcome ascertainment. The sample size of the included observational studies ranged from 30 to 71,415 participants. Four of the evaluated populations came from EU countries (France, The Netherlands, Sweden), two from Canada, four from the USA, one from Saudi Arabia, one from Iran, two from China, one from Taiwan and one from Qatar.

The populations under study were diverse. One study recruited adolescents, while the remaining 15 studies assessed adult female ($n = 6$) or mixed ($n = 11$) populations. Female populations mostly represented women in pregnancy ($n = 5$).

PBDE levels were assessed via biomarkers in serum or plasma ($n = 14$), or adipose tissue ($n = 1$), while one study performed an estimation of PBDE dietary exposure. The congeners analysed in the eight longitudinal studies (6 cohort studies, 2 nested case–control studies) were **BDE**, **-28**, -**47**, -85, -**99**, -**100**, -**153**, -**154,** -**183** and -**209**.

The endpoints assessed were also diverse. T2D was assessed in eight studies (three cohorts, two case–control studies, three cross-sectional studies) and four studies investigated gestational diabetes. The remaining studies investigated a broad group of biomarkers including some that are directly linked to diabetes (fasting glucose, insulin, HbA1c, leptin, glucose: insulin, BMI:leptin) as well as biomarkers related to diabetes pathogenesis (BMI, high-density lipoprotein cholesterol (HDLC), triglycerides (TG), interleukin 6 (IL6), ALP).

In the following paragraphs, the evidence stemming from cohort and nested case–control studies is discussed. Further details of these studies can be found in Annex D (Table D.3), as well as for the remaining case–control and cross-sectional studies identified.

TABLE 22 Overview of the epidemiological studies identified on the association between levels of PBDEs and diabetes.

Reference	Study design	Population studied Matrix analysed	Endpoint
Lee et al. (2011). Polychlorinated biphenyls and organochlorine pesticides in plasma predict development of type 2 diabetes in the elderly: the prospective investigation of the vasculature in Uppsala Seniors (PIVUS) study	Cohort	Adults Serum	Incident T2D
Pal et al. (2013). The association of type 2 diabetes and insulin resistance/secretion with persistent organic pollutants in two First Nations communities in northern Ontario	Cross-sectional	Adults Plasma	T2D, glucose, HOMA-IR
Turyk et al. (2015). Persistent organic pollutants and biomarkers of diabetes risk in a cohort of Great Lakes sport caught fish consumers	Cohort	Adults Serum	Incident T2D, C-reactive protein, GGT, Adiponectin, HbA1c
Suarez-Lopez et al. (2015). Persistent organic pollutants in young adults and changes in glucose related metabolism over a 23-year follow-up[b]	Nested case–control	Adults Serum	T2D, fasting plasma glucose concentrations, fasting insulin concentrations, HbA1c
Zhang, Li, Liu, et al. (2016). Environmental exposure to BDE47 is associated with increased diabetes prevalence: Evidence from community-based case–control studies and an animal experiment	Cross-sectional	Adults Serum	T2D
Ali et al. (2016). Organohalogenated contaminants in type 2 diabetic serum from Jeddah, Saudi Arabia	Cross-sectional	Adults Serum	T2D
Eslami, Naddafi, et al. (2016). Association between serum concentrations of persistent organic pollutants and gestational diabetes mellitus in primiparous women	Cross-sectional	Adults Serum	Gestational Diabetes
Smarr et al. (2016). Persistent organic pollutants and pregnancy complications	Cohort	Adults Serum	Gestational Diabetes
Leijs et al. (2017). Alterations in the programming of energy metabolism in adolescents with background exposure to dioxins, dl-PCBs and PBDEs	Cohort	Adolescents Serum	Fasting glucose, Insulin, HbA1c, Leptin
Liu et al. (2018). A nested case–control study of the association between exposure to polybrominated diphenyl ethers and the risk of gestational diabetes mellitus[a]	Nested case–control	Adults Serum	Gestational diabetes
Helaleh et al. (2018). Association of polybrominated diphenyl ethers in two fat compartments with increased risk of insulin resistance in obese individuals	Cross-sectional	Adults Subcutaneous and omental adipose tissue	Insulin Resistance, Fasting plasma glucose, Insulin, HOMA-IR
Ongono et al. (2019). Dietary exposure to brominated flame retardants and risk of type 2 diabetes in the French E3N cohort	Cohort	Adults Dietary intake	T2D
Rahman et al. (2019). Persistent organic pollutants and gestational diabetes: A multi-center prospective cohort study of healthy US women	Cohort	Adults Plasma	Gestational diabetes

TABLE 22 (Continued)

Reference	Study design	Population studied Matrix analysed	Endpoint
Cordier et al. (2020). Association between exposure to persistent organic pollutants and mercury, and glucose metabolism in two Canadian Indigenous populations	Cross-sectional	Adults Blood	Fasting Plasma Glucose, Insulin, HOMA-IR, HOMA-B
Mehta et al. (2021). Persistent organic pollutants and maternal glycemic outcomes in a diverse pregnancy cohort of overweight women	Cross-sectional	Adults (pregnancy) Serum	Fasting plasma glucose, insulin, insulin resistance)
Magliano et al. (2021). Exposure to persistent organic pollutants and the risk of type 2 diabetes: a case-cohort study[b]	Case-cohort	Adults Blood	T2D
Vuong et al. (2021). Exposure to endocrine disrupting chemicals (EDCs) and cardiometabolic indices during pregnancy: The HOME Study	Cohort	Adults Serum	Plasma glucose

Abbreviations: T2D, type 2 diabetes; IGF-1, Insulin-like growth factor 1; HbA1c, haemoglobin A1c; HDLC, high-density lipoprotein cholesterol; TG, triglycerides; IL6, interleukin 6; GGT, gamma-glutamyltransferase.

[a]Primary publication of Liu et al. (2021). *Identification and prioritisation of the potent components for combined exposure of multiple persistent organic pollutants associated with gestational diabetes mellitus* is described in the text.

[b]The authors reported that the concentrations of PBDEs were < LOD and no further statistical analysis was presented. Thus the study is not further considered in the Opinion.

Lee et al. (2011) assessed 19 plasma POPs including **BDE-47** at baseline followed by prospective analyses for incident type 2 diabetes after 5 years in the PIVUS cohort ($n = 725$). No statistical associations were found for **BDE-47**.

Turyk et al. (2015) continued the reporting of the Great Lakes Sport Fish Consumers Cohort – already assessed in the previous Opinion – in a larger study group. Despite the non-statistically significant findings in the overall sample and for incident T2D ($n = 287$, $n_{cases} = 16$), the authors mention results from subgroup analyses on specific biomarkers; Sum 10 PBDEs and **BDE-47** were associated with GGT in persons of above median age ($p = 0.02$ and 0.008, respectively), Sum PBDEs was associated with adiponectin in persons with above median BMI ($p = 0.05$) and above median age ($p = 0.003$), and **BDE-47** was associated with adiponectin in persons with above median age ($p = 0.009$).

Suarez-Lopez et al. (2015) assessed, nested within the Coronary Artery Risk Development in Young Adults study (CARDIA, USA) with a 23-year follow up, the association between PBDEs in serum and T2D in a case–control fashion ($n = 180$). None of the PBDEs measured were detectable in > 75% of participants and no further information on the study results was reported.

Ongono et al. (2019) reported on a cohort study conducted on the association between PBDEs and T2D; 71,415 middle-aged women were followed for 19 years in France (3667 incident T2D cases, 3% attrition). The dietary exposure to PBDEs was calculated by merging the usual food consumption over the previous year estimated through a validated 208-item semi-quantitative dietary questionnaire sent in 1993 and food contamination data available from the 2nd French Total Diet Study (TDS2) published by Anses in 2011. The mean dietary exposure to PBDEs was 1.21 ng/kg bw per day; **BDE-209** and **-47** represented 44% and 29% of the overall exposure to PBDEs, respectively. There was a statistically significant non-linear association between exposure to PBDEs and T2D (hazard ratio (HR) 2nd vs. 1st quintile: 1.12, 95% CI: 1.02, 1.24; HR 4th vs. 1st quintile: 1.20, 95% CI: 1.08, 1.34).

Liu et al. (2018) conducted a nested case–control study in 439 pregnant women in China to investigate the association between levels of PBDEs (**BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**, **-183**) and gestational diabetes. The median (IQR) level of Sum PBDEs was 87.37 (62.01, 122.29) and 71.69 (53.52, 96.71) pg/g ww in cases and controls, respectively. Statistically significant associations were observed for continuous **BDE-153** (4.04, 95% CI: 1.92, 8.52), **BDE-154** (1.88, 95% CI: 1.15, 3.09) and **BDE-183** (1.91, 95% CI: 1.31, 2.08). In the quartile analyses, a significant increase in the OR of gestational diabetes was associated with the highest levels of **BDE-153** (OR = 3.42, 95% CI: 1.49, 7.89) and **BDE-183** (OR = 3.70, 95% CI: 1.58, 8.65). In addition, **BDE-153** and **-154** were significantly positively associated with fasting glucose, and both 1 h and 2 h glucose level ($p < 0.05$). At a later publication on the same study population, Liu et al. (2021) attempted an assessment of the contribution of the combined exposure to multiple POPs components including seven PBDEs to the risk of gestational diabetes. They proposed a significant mixture effect with a prioritisation rank as follows: Dioxin-like compounds[45] > PBDEs > PFAAs > PCBs. For glucose homeostasis, **BDE-153** was the chemical of top-ranked priority of concern.

Rahman et al. (2019) prospectively investigated the association between early-pregnancy PBDEs levels (**BDE-28**, **-47**, -85, **-99**, **-100**, **-153**, **-154**, **-183**, **-209**) and gestational diabetes in 2334 healthy non-obese women (NICHD Fetal Growth Study, USA). The mean (95% CI) total PBDE concentration was 19.91 (18.97–20.9) ng/g lipid; **BDE-47** was detected in over 93% of the participants followed by **BDE-100** (72%) and **-99** (62%). Among women without a family history of T2D, **BDE-47** (risk ratio (RR) = 1.18, 95% CI: 1.08, 1.29 per 1-SD PBDE increment) and **BDE-154** (RR = 1.23, 95% CI: 1.12, 1.34 per 1-SD PBDE increment) showed statistically significant associations. The remaining associations did not reach statistical significance.

[45]7 PCDDs, 10 PCDFs and 12 dioxin-like PCBs.

Smarr et al. (2016) used the LIFE study ($n = 258$ pregnancies) to assess gestational diabetes and gestational hypertension. **BDE-153** was positively associated with an increased odds of gestational diabetes (OR = 1.79, 95% CI: 1.18, 2.74; adjusted for serum lipids, age, body mass index, race, smoking and the sum of the remaining POPs in each chemical class).

The HOME study is a birth cohort conducted in the USA ($n = 389$) and prenatal levels of PBDEs were assessed at around 16 weeks of gestation. All analysed subjects had detectable **BDE-47** levels and 279 subjects were tested for the remaining PBDEs. Vuong et al. (2021) focused on blood pressure, glucose, and lipids in the pregnant women. Non-fasting glucose levels were measured at 1-h after drinking 50 g glucose load ($n = 234$), with the average assessment completed at ~ 27.6 ± 1.4 weeks gestation. Mean maternal serum concentrations of **BDE-28** and -**47** were 1.1 and 20.7 ng/g lipid, respectively. **BDE-28** concentrations (per 10-fold increase) were statistically significantly associated with a 13.1 mg/dL increase in glucose (95% CI: 2.9, 23.2).

Leijs et al. (2017) reported on a Dutch birth cohort study investigating the association between metabolic parameters (FPG, insulin, leptin, HbA1c) and prenatal levels of PBDEs (**BDE-28**, -**47**, -85, -**99**, -**100**, -**153**, -**154**, -**183**) in 30 adolescents. The mean (range) level of Sum PBDEs was 14 (4.9–73.6) ng/g lipid. No statistically significant association was observed.

Across all longitudinal studies and as regards the individual congeners, no statistically significant associations were reported for **BDE-28**, -85, -**99**, -**100** and -**209** whereas **BDE-47** and -**183** were statistically significantly associated with gestational diabetes in one study without further replication. As for **BDE-153** and -**154**, statistically significant results were reported in two studies related to gestational diabetes. The evidence coming from the cross-sectional studies were characterised by mainly small studies and few were relevant to European populations. When assessed at the level of the individual congeners and even after taking into consideration diabetes-related biomarkers, this body of evidence was not able to further support any of the associations postulated by the longitudinal data.

Regarding studies on PBDE metabolites, one cross-sectional study was identified that investigated the potential effect of OH-PBDEs and endpoints related to diabetes. Mehta et al. (2021), including a group of overweight and obese pregnant women ($n = 95$, USA), assessed the association between PBDEs and OH-PBDEs (5-OH-BDE-47, 6-OH-BDE-47) among other contaminants and fasting plasma glucose, fasting plasma insulin, and HOMA-IR. In the model assessing fasting plasma glucose in association with the doubling of 5-OH-BDE-47 adjusting for other pollutants in mixture, a statistically significant inverse association was observed (% change = −0.78, 95% CI: −1.48, −0.08).

In summary, the evidence on the association between diabetes-related endpoints and PBDEs has grown since the publication of the previous Opinion. Longitudinal studies are now available although the number of studies per specific endpoint is limited. Moreover, the currently available body of evidence is characterised by relatively small sample sizes, considerable heterogeneity in the assessed populations, exposures and outcomes, varying methodological quality and effect inconsistency.

Based on the above, the currently available evidence on diabetes coming from human studies cannot be used for hazard characterisation.

3.1.3.3.2 | *Obesity*

In the previous EFSA Opinion on PBDEs (EFSA, 2011a), no epidemiological data on obesity were assessed. Since then, 13 publications corresponding to 10 individual studies were identified assessing the association between levels of PBDEs and any outcome related to obesity (see Table 23).

The evidence-base included in the current Opinion consists of six cohort studies (nine publications) and four cross-sectional studies where the PBDE levels were assessed simultaneously or even later than the outcome ascertainment. The sample size of the included observational studies ranged from 50 to 1116 participants. Four of the evaluated populations came from EU countries (Belgium, Finland, Spain, Sweden, multi-centre), three from the USA, one from Canada, one from China and one from South Korea.

The populations under study were diverse. PBDE concentrations were assessed via biomarkers in serum in most of the studies. Adipose tissue was also used in a number of cross-sectional studies. Most studies reported data on **BDE-47**. A variety of endpoints were assessed either binary or continuous. Binary outcomes assessed in more than one study included obesity and being overweight. Continuous endpoints investigated in more than one study consisted of BMI and waist circumference.

In the following paragraphs, the evidence stemming from cohort studies is discussed. Moreover, we describe the results from the baseline assessment of the Prospective Investigation of the Vasculature in Uppsala Senior (PIVUS) study which, despite its cross-sectional design, provides useful information on the largest population of predominantly European ancestral origin within the cross-sectional study design group and completes the report on the PIVUS study (three publications with longitudinal data). Further details on these studies can be found in Annex D (Table D.4), as well as for the remaining cross-sectional studies identified.

TABLE 23 Overview of the epidemiological studies identified on the association between levels of PBDEs and obesity.

Reference[a]	Study design	Population studied Matrix analysed	Endpoint
Rönn et al. (2011). Circulating levels of persistent organic pollutants associate in divergent ways to fat mass measured by DXA in humans	Cohort	Adults Plasma	Fat mass
Lee et al. (2012a). Associations of persistent organic pollutants with abdominal obesity in the elderly: The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study	Cohort	Adults Serum	Waist circumference
Roos et al. (2013). Circulating levels of persistent organic pollutants in relation to visceral and subcutaneous adipose tissue by abdominal MRI	Cross-sectional	Adults Blood	Obesity/overweight, Visceral and subcutaneous adipose tissue
Gauthier et al. (2014). The metabolically healthy but obese phenotype is associated with lower plasma levels of persistent organic pollutants as compared to the metabolically abnormal obese phenotype.	Cross-sectional	Adults Plasma	Metabolically abnormal obesity
Pereira-Fernandes et al. (2014). Expression of obesity markers and persistent organic pollutants levels in adipose tissue of obese patients: reinforcing the obesogen hypothesis?	Cross-sectional	Adults Adipose tissue	Adiponectin, leptin, TNFa, PPARy
Erkin-Cakmak et al. (2015). In utero and childhood polybrominated diphenyl ether exposures and body mass at age 7 years: the CHAMACOS study	Cohort	Children Serum	Obesity, Overweight, BMI, Waist circumference
Kim, Park, Kim, Lee, Choi, Choi, Kim, Kim, Lee, et al. (2015). Association between Several Persistent Organic Pollutants in Serum and Adipokine Levels in Breast Milk among Lactating Women of Korea	Cross-sectional	Adults Maternal serum	Leptin, adiponectin (human milk)
Agay-Shay et al. (2015). Exposure to Endocrine-Disrupting Chemicals during Pregnancy and Weight at 7 Years of Age: A Multi-pollutant Approach	Cohort	Children Human milk (colostrum)	BMI
Vuong, Braun, et al. (2016). Prenatal polybrominated diphenyl ether exposure and body mass index in children up to 8 years of age	Cohort	Children Serum	BMI, waist circumference, body fat
Lind et al. (2017). Mixture effects of 30 environmental contaminants on incident metabolic syndrome-A prospective study	Cohort	Adults Plasma	Metabolic syndrome
Vuong et al. (2019). Exposure to polybrominated diphenyl ethers (PBDEs) during childhood and adiposity measures at age 8 years	Cohort	Children Maternal blood	BMI, waist circumference, body fat percentage
Guo et al. (2020). Umbilical cord serum PBDE concentrations and child adiposity measures at 7 years	Cohort	Children Cord serum	Waist circumference, BMI, obesity
Vrijheid et al. (2020). Early-Life environmental exposures and childhood obesity: an exposome-wide approach	Cohort	Children Maternal blood	BMI, overweight/ obesity

Abbreviations: HDLC, High-density lipoprotein cholesterol; NAFLD, non-Alcoholic fatty liver disease; LFLC, Low-density lipoprotein cholesterol; TG, triglycerides.
[a]The study by Pan et al. (2020) entitled 'Polybrominated diphenyl ethers exposure in late pregnancy and child growth at 8 years of age' was also identified. However, only an English abstract is available and the study is not further considered in the Opinion.

Erkin-Cakmak et al. (2015) reporting in the CHAMACOS study (birth cohort, USA) evaluated the association between in utero and child PBDE levels and BMI, waist circumference and being overweight at 7 years. Overall, no statistically significant associations were observed with **BDE-47**, **-99**, **-100** and **-153** or their sum.

The HOME study is a birth cohort conducted in the USA ($n = 389$) and prenatal assessment of PBDE levels was done at around 16 weeks of gestation. All analysed subjects had detectable **BDE-47** levels and 279 subjects were tested for the remaining PBDEs. Median maternal serum concentrations of **BDE-28** and **-47** were 1.0 and 19.1 ng/g lipid, respectively. In the Vuong, Braun, et al. (2016) publication, BMI, weight, waist circumference and body fat was assessed up to 8 years ($n = 318$). A 10-fold increase in maternal serum **BDE-153** was associated with lower BMI z-score at 2–8 years ($\beta = -0.36$, 95% CI: −0.60, −0.13), smaller waist circumference at 4–8 years ($\beta = -1.81$ cm, 95% CI: −3.13, −0.50), and lower % body fat at 8 years ($\beta = -2.37$%, 95% CI: −4.21, −0.53). A decrease in waist circumference at 4–8 years was observed with a 10-fold increase in **BDE-100** ($\beta = -1.50$ cm, 95% CI: −2.93, −0.08) and Sum PBDEs ($\beta = -1.57$ cm, 95% CI: −3.11, −0.02). Vuong et al. (2019) for the same study corroborated these findings by using levels of PBDEs at ages 1, 2, 3, 5 and 8 years and endpoints related to obesity at 8 years. Significant inverse associations were observed between **BDE-153** with all adiposity measures that became increasingly stronger with later childhood measurements. A 10-fold increase in **BDE-153** at ages 1 and 8 years was associated with 2% (95% CI: −3.9, −0.1) and 7% (95% CI: −9.1, −4.7) lower body fat, respectively. No statistically significant associations were found with **BDE-28**, **-47**, **-99** or **-100**.

Vrijheid et al. (2020) using the European Human Early-Life Exposome (HELIX) multi-cohort performed an exposome-wide association study that also assessed the associations between prenatal levels of **BDE-47** and **-153** and obesity ($n = 1301$) in children aged 6–11 years. **BDE-47** was excluded from the final childhood multi-exposure analysis due to collinearity with

BDE-153. **BDE-153** levels in pregnancy were statistically significantly associated with reduced zBMI in children (β = -0:23; 95% CI, −0.34, −0.13) and decreased odds for overweight and obesity (OR = 0.63, 95% CI: 0.47, 0.85).

Agay-Shay et al. (2015) in a Spanish birth cohort (n = 470) evaluated the associations between pre- and perinatal levels of 27 contaminants, including **BDE-47**, -**99**, -**100**, -**153**, -**154**, -**209** and child weight status at 7 years of age. In single-pollutant models, no statistically significant associations were identified for PBDEs.

The PIVUS study (n = 970) included a random sample of subjects aged 70 living in the community of Uppsala, Sweden. Twenty-one plasma POPs including **BDE-47** were measured at baseline with prospective analyses after 5 years. Rönn et al. (2011) assessed fat mass parameters (DXA) at 2 years and no statistically significant associations were identified for **BDE-47**. Lee et al. (2012a) assessed abdominal obesity as defined by an increased waist circumference (5-year follow up) and no statistically significant association was identified for **BDE-47**. Lind et al. (2017) assessed the incidence of metabolic syndrome (10-year follow up) and no statistically significant association was identified for **BDE-47**. In the baseline assessment of the study, Roos et al. (2013) investigated whether the contaminants under study were more closely related to visceral adipose tissue than to subcutaneous adipose tissue. No statistically significant association was observed for **BDE-47** and either obesity/overweight or visceral and subcutaneous adipose tissue.

Guo et al. (2020) for the Sheyang Mini Birth Cohort Study (SMBCS) in China assessed the associations between PBDEs concentrations (**BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183**, -207, -**209**) in cord serum and childhood adiposity measures at 7 years (BMI, waist circumference; n = 318). **BDE-153** and **BDE-154** concentrations were associated with lower childhood BMI z score ($\beta_{\mathbf{BDE\text{-}153}}$ = −0.15, 95% CI: −0.29, −0.02; $\beta_{\mathbf{BDE\text{-}154}}$ = −0.23, 95% CI: −0.43, −0.03) and lower waist circumference ($\beta_{\mathbf{BDE\text{-}153}}$ = −0.75, 95%CI: −1.43, −0.06; $\beta_{\mathbf{BDE\text{-}154}}$ = −1.22, 95% CI: −2.23, −0.21). Moreover, **BDE-154** was statistically significantly associated with a decreased obesity risk (OR = 0.46, 95% CI: 0.22, 0.94).

The remaining cross-sectional studies were small, in diverse populations (children, lactating women, morbidly obese participants) and they provide no further support to the associations discussed in the longitudinal studies.

No studies were identified that investigated the potential effect of OH-PBDEs and endpoints related to obesity.

In summary, there is a growing body of epidemiological research related to PBDEs levels and endpoints relevant to obesity. However, the currently available evidence-base is characterised by a relatively small number of studies overall and a small number of prospective studies assessing diverse populations (children, adolescents, elderly). Of these, the few statistically significant findings related to prenatal PBDEs levels and obesity attributes (BMI, waist circumference, % body fat) point to an inverse association that is difficult to put in context and integrate with the respective data on T2D or on cardiometabolic risk factors.

Based on the above, the currently available evidence coming from human studies on obesity cannot be used for hazard characterisation.

3.1.3.4 | *Cardiovascular*

In the previous EFSA Opinion on PBDEs (EFSA CONTAM Panel, 2011b), no studies were included directly related to cardiovascular disease endpoints or risk factors thereof other than diabetes and obesity. Since then, seven publications corresponding to four individual studies were identified assessing the association between levels of PBDEs and any outcome related to cardiovascular endpoints (see Table 24).

The evidence-base included in the current Opinion consists of three cohort studies (of which one is supplemented by three associated cross-sectional assessments) and one cross-sectional study where the PBDE concentrations were assessed simultaneously with the outcome ascertainment. The sample size of the included observational studies ranged from 43 to 970 participants. The evaluated populations came from Sweden (n = 1), Canada (n = 1) and the USA (n = 1).

The populations under study were diverse included the elderly, pregnant women or children. Studies in the elderly assessed indices of cardiovascular disease (e.g. diastolic function) or clinical entities (e.g. stroke). PBDE concentrations were assessed via biomarkers in serum in all studies.

In the following paragraphs, the evidence stemming from all studies is discussed. Further details of these studies can be found in Annex D (Table D.5).

TABLE 24 Overview of the epidemiological studies identified on the association between levels of PBDEs and cardiovascular effects.

Reference	Study design	Population studied Matrix analysed	Endpoint
Lee et al. (2012b). Background exposure to persistent organic pollutants predicts stroke in the elderly	Cohort	Adults Plasma	Stroke (incidence)
Lind et al. (2012). Circulating levels of persistent organic pollutants (POPs) and carotid atherosclerosis in the elderly	Cross-sectional	Adults Serum	Atherosclerosis indices[a]
Sjöberg Lind et al. (2013a). Persistent organic pollutants and abnormal geometry of the left ventricle in the elderly	Cross-sectional	Adults Serum	Left ventricular hypertrophy
Sjöberg Lind et al. (2013b). Circulating levels of persistent organic pollutants (POPs) are associated with left ventricular systolic and diastolic dysfunction in the elderly	Cross-sectional	Adults Serum	Left Ventricular systolic and diastolic function
Penell et al. (2014). Persistent organic pollutants are related to the change in circulating lipid levels during a 5 year follow-up	Cohort	Adults Serum	Lipid profile: total cholesterol, triglycerides, HDL-, LDL-cholesterol
Vuong et al. (2021). Exposure to endocrine disrupting chemicals (EDCs) and cardiometabolic indices during pregnancy: The HOME Study	Cohort	Adults Serum	Cardiometabolic indices
Boutot et al. (2021). In utero exposure to persistent organic pollutants and childhood lipid levels	Cohort	Children Maternal blood	Blood pressure, lipid profile

[a]Overt carotid plaques, intima-media thickness, carotid artery intima-media complex.

The PIVUS study ($n = 970$) included a random sample of subjects aged 70 living in the community of Uppsala, Sweden. Twenty-one plasma POPs, including **BDE-47**, were measured at baseline with prospective analyses after 5 years. The median **BDE-47** concentration at baseline was 1.9 ng/g lipid (IQR: 1.5, 2.9). After adjusting for known stroke risk factors, no statistically significant association was observed for **BDE-47** and stroke ($n_{cases} = 35$) (Lee et al., 2012b). Lind et al. (2012) in a cross-sectional analysis of the baseline data focused on atherosclerosis assessed through the prevalence of carotid artery plaques (ultrasound), the intima-media thickness and grey scale median of the intima-media complex. No statistically significant association was observed for **BDE-47**. Sjöberg Lind et al. (2013a) focused on left ventricular hypertrophy assessed via the left ventricular mass index, the relative wall thickness, and the geometric groups of left ventricular hypertrophy. No statistically significant association was observed for **BDE-47**. Sjöberg Lind et al. (2013b) focused on left ventricular systolic and diastolic dysfunction assessed via left ventricular ejection fraction, E and A waves ratio and isovolumic relaxation time. No statistically significant associations were observed for **BDE-47**. Finally, Penell et al. (2014) investigated the change in lipids levels at 5 years follow up ($n = 598$). No statistically significant associations were observed for **BDE-47.**

The HOME study is a birth cohort conducted in the USA ($n = 389$) and prenatal levels of PBDEs were assessed at around 16 weeks of gestation. All analysed subjects had detectable **BDE-47** levels and 279 subjects were tested for the remaining PBDEs. As also discussed above, Vuong et al. (2021) focused on blood pressure, glucose, and lipids in the pregnant women. Mean maternal serum concentrations of **BDE-28** and **-47** were 1.1 and 20.7 ng/g lipid, respectively. **BDE-28**, **-47** and **-99** were positively associated with total cholesterol in both single- and multi-pollutant models, whereas a suggestive inverse association was noted with **BDE-153**.

Boutot et al. (2021) using the GESTation and Environment (GESTE) birth cohort in Canada investigated the association between levels of a large number of compounds including PBDEs (**BDE-47**, **-99**, **-100**, **-153**) at delivery and total cholesterol, triglycerides, low- and high-density lipoproteins, and total lipids at ages 6–7 ($n = 147$). Among the numerous analyses performed, a statistically significant inverse association was reported for **BDE-99** and triglycerides ($\beta = -0.043$; SE: 0.014; p-value, 0.003).

No studies were identified that investigated the potential effect of OH-PBDEs and cardiovascular endpoints.

In summary, the evidence base pertaining to PBDE levels and endpoints relevant to cardiovascular disease or risk factors thereof remains small (both in terms of the accumulated number of studies and sample size) and diverse with regards to the endpoints under study. The only single statistically significant associations are related to cholesterol and triglycerides, they come from small studies and they have not been replicated.

Based on the above, the currently available evidence coming from human studies on cardiovascular endpoints cannot be used for hazard characterisation.

3.1.3.5 | *Effects on male reproduction*

In the previous EFSA Opinion on PBDEs (EFSA CONTAM Panel, 2011b), three epidemiological studies on male reproductive toxicity were included bearing inconclusive results. Since then, 18 publications corresponding to 17 individual studies were identified assessing the association between levels of PBDEs and any outcome related to male reproductive endpoints (see Table 25).

The evidence base included in the current Opinion consists of three cohort studies and 14 cross-sectional studies where the PBDE levels were assessed simultaneously or even later than the outcome ascertainment. The sample size of the included observational studies ranged from 27 to 501 participants. Five of the evaluated populations came from EU countries (Belgium, Denmark-Finland, The Netherlands), four from Canada, five from the USA, three from China.

The populations under study were diverse. Studies in children mainly assessed congenital defects of the reproductive system. PBDE concentrations were assessed via biomarkers in serum in most of the studies. Sperm was also used in a number of cross-sectional studies. A variety of endpoints were assessed either binary or continuous. Binary endpoints assessed in more than one study included hypospadias ($n = 2$) and cryptorchidism ($n = 4$). Binary endpoints in adults (e.g. subfertility) were not investigated in any prospective study; subfertility was assessed in one cross-sectional study. Continuous endpoints investigated in more than one study consisted of semen parameters ($n = 6$) and sex hormones ($n = 7$). For the latter, some studies have measured changes in sex hormone concentrations in serum in addition to other endpoints or alone. As changes in serum sex hormones can contribute to mechanistic explanations for adverse reproductive endpoints, they are reported in conjunction with the studies. However, in this Opinion, changes in serum sex hormone levels in adults or children can be considered key events in the Adverse Outcome Pathway, but were not considered by the CONTAM Panel to be apical outcomes by themselves, although these studies are reported for completeness.

In the following paragraphs, the evidence stemming from cohort and nested case–control studies is discussed. Moreover, we describe the only study investigating subfertility albeit a cross-sectional one. Further details of these studies can be found in Annex D (Table D.6), as well as for the remaining case–control and cross-sectional studies identified.

TABLE 25 Overview of the epidemiological studies identified on the association between PBDE levels and effects in the male reproductive system.

Reference	Study design	Population studied Matrix analysed	Endpoint
Carmichael et al. (2010). Hypospadias and halogenated organic pollutant levels in maternal mid-pregnancy serum samples	Nested case–control	Neonates Maternal serum	Hypospadias
Abdelouahab et al. (2011). Polybrominated diphenyl ethers and sperm quality	Cross-sectional	Adults Serum	Sperm quality
Meijer et al. (2012). Influence of prenatal organohalogen levels on infant male sexual development: sex hormone levels, testes volume and penile length	Cohort	Infants Maternal serum	Testes volume, Penile length, Sex hormones
Krysiak-Baltyn et al. (2012). Association between chemical pattern in breast milk and congenital cryptorchidism: modelling of complex human exposures	Cross-sectional	Infants Human milk	Cryptorchidism
Johnson et al. (2013). Associations between brominated flame retardants in house dust and hormone levels in men	Cross-sectional	Adults Dust	Sex hormones
Toft et al. (2014). Exposure to polybrominated diphenyl ethers and male reproductive function in Greenland, Poland and Ukraine	Cross-sectional	Adults Serum	Semen quality, Sex hormones
Mumford et al. (2015). Persistent organic pollutants and semen quality: The LIFE Study	Cohort	Adults Serum	Semen quality
Den Hond et al. (2015). Human exposure to endocrine disrupting chemicals and fertility: A case–control study in male subfertility patients	Cross-sectional	Adults Serum	Subfertility, Sex hormones
Koskenniemi et al. (2015). Association between levels of persistent organic pollutants in adipose tissue and cryptorchidism in early childhood: a case–control study	Cross-sectional	Children Adipose tissue	Cryptorchidism
Makey, McClean, Braverman, Pearce, Sjödin, et al. (2016). Polybrominated diphenyl ether exposure and reproductive hormones in North American men	Cross-sectional	Adults Serum	Sex hormones
Eskenazi et al. (2017). In utero and childhood DDT, DDE, PBDE and PCBs exposure and sex hormones in adolescent boys: The CHAMACOS study	Cohort	Children Maternal serum	Sex hormones
Goodyer et al. (2017). A case–control study of maternal polybrominated diphenyl ether (PBDE) exposure and cryptorchidism in Canadian populations	Cross-sectional	Infants Maternal hair	Cryptorchidism
Yu et al. (2018). Associations between PBDEs exposure from house dust and human semen quality at an e-waste areas in South China-A pilot study	Cross-sectional	Adults Semen, dust	Semen quality
Poon et al. (2018). Association of in utero exposure to polybrominated diphenyl ethers with the risk of hypospadias[a]	Cross-sectional	Infants Maternal hair	Hypospadias
Albert et al. (2018). Exposure to polybrominated diphenyl ethers and phthalates in healthy men living in the greater Montreal area: A study of hormonal balance and semen quality	Cross-sectional	Adults Serum	Semen quality, Sex hormones
Yu et al. (2019). Polybrominated diphenyl ethers in human serum, semen and indoor dust: Effects on hormones balance and semen quality	Cross-sectional	Adults Serum, semen, dust	Semen quality, Sex hormones
Desalegn et al. (2021). A case-cohort study of perinatal exposure to potential endocrine disrupters and the risk of cryptorchidism in the Norwegian HUMIS study	Cohort	Infants Human milk	Cryptorchidism

[a]Koren et al. (2019) provides congener-specific estimates (secondary analysis).

Desalegn et al. (2021) reporting on the Norwegian Human Milk Study ($n = 641$) investigated the correlation between 27 contaminants measured in human milk (including **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**) and cryptorchidism assessed at 1, 6, 12 and 24 months of age. The human milk concentrations for **BDE-47** were 73.6 ng/g lipid. No statistically significant results were reported for PBDEs.

The Groningen Infant COMPARE (GIC) birth cohort was founded in 2001 in The Netherlands and consisted of 90 healthy pregnant women, who delivered a single, full term, healthy infant. **BDE-47**, -**99**, -**100**, -**153**, -**154** were measured in maternal serum at the 35th week of pregnancy. Several additional neutral organohalogen compounds were also assessed (4,4′-DDE, PCB-153, HBCDDs) as well as four phenolic organohalogen compounds (4-OH-CB-107, 4-OH-CB-146, 4-OH-CB-187, PCP). Exposure to these compounds was assessed independently without being included in an adjusted analysis. Meijer et al. (2012) addressed the association between prenatal PBDE levels and testosterone, free testosterone, sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), free E2 and inhibin B (InhB), at the age of 3 months, and testes volume and penile length at the age of 3 and 18 months. **BDE-154** was significantly bivariately correlated with free E2, E2 and InhB ($\rho = 0.49$, 0.54 and 0.34, respectively) as well as with testes volume at 18 months of age ($\rho = 0.34$).

Eskenazi et al. (2017) reporting in the CHAMACOS Study (birth cohort, USA) evaluated the association between PBDEs (BDE-17, -**28**, -**47**, -66, -85, -**99**, -**100**, -**153**, -**154**, -**183**) in utero (maternal serum) and at 9 years (serum) and reproductive hormones in adolescent boys. **BDE-47**, -**99**, -**100**, -**153** and their sum were used as the primary exposure measure. In adjusted models, a 10-fold increase in maternal prenatal serum concentrations of **BDE-153** was associated with a 22.2% increase (95% CI: 1.0, 47.9) in FSH, a 96.6% increase (95% CI: 35.7, 184.7) in LH, and a 92.4% increase (95% CI: 20.9, 206.2) increase in testosterone at age 12 years. Similarly, **BDE-100** concentrations were associated with increases in LH levels at age 12 years. Moreover, **BDE-153** concentration measured at age 9 years also showed associations for LH (59.0%, 95% CI: 8.6, 132.6) and testosterone (149.1%, 95% CI: 42.7, 334.6) although this effect appeared to be mediated by BMI.

Den Hond et al. (2015) in a Dutch cross-sectional study measured biomarkers of exposure in 163 men, recruited through four fertility clinics, and using a cut-off levels for the total motility count of 20 million to define subfertility ($n = 40$ cases). Men with serum levels of **BDE-209** above the LOQ had an OR of 7.22 (95% CI: 1.03, 50.6) of being subfertile, a result that is hindered by the study limitations (cross-sectional design, 'controls' not selected from the general 'healthy' population, lack of intermediate endpoints, e.g. DNA fragmentation in sperm).

In many of the cross-sectional studies, PBDE levels were assessed in correlation with a large number of attributes of semen quality ($n = 6$, sample size range = 32–468). Besides the limitations related to their design, these studies are also prone to errors related to multiple testing (multiple congeners, multiple semen quality characteristics). Of these, the largest one pertained to the baseline assessment of the LIFE study in the USA ($n = 501$); Mumford et al. (2015) measured 35 semen quality endpoints and BDE-17, -**28**, -**47**, -66, -85, -**99**, -**100**, -**153**, -**154** and -**183** in serum among other contaminants. Although most of the multiple correlations assessed were null, BDE-17 was correlated with sperm morphometry (coiled tail (%), β: −4.05, SE: 1.53; immature sperm, β: 6.47, SE: 2.42) while **BDE-28** was correlated with sperm morphology (bicephalic (%), β: 0.69, SE: 0.26). In another two of the cross-sectional studies sex hormones were assessed (Johnson et al., 2013; Makey, McClean, Braverman, Pearce, Sjödin, et al., 2016). Johnson et al. (2013) investigated an indirect measure of BFR exposure (house dust) grouped by commercial mixtures (i.e. Penta-, Octa- and DecaBDE) and sex hormones ($n = 38$); significant positive associations were found between concentration of PentaBDE and serum levels of FT4, TT3, E2 and SHBG, along with an inverse association with FSH. There were also positive associations of OctaBDE with serum FT4, TSH, LH and testosterone, and an inverse association of DecaBDE with testosterone. Makey, McClean, Braverman, Pearce, Sjödin, et al. (2016) assessed the association between PBDE levels in serum and sex hormones in a North American male adult group ($n = 27$). PBDEs were inversely associated with Inhibin B and, in older men, **BDE-47** and -**100** were significantly associated with a decrease in Inhibin B and an increase in FSH. Besides their cross-sectional nature, the small sample size of these studies does not allow for valid conclusions to be made on the postulated effect of PBDE exposure on sex hormones.

No studies were identified that investigated the potential effect of OH-PBDEs and endpoints related to male reproduction.

In summary, there is a growing body of epidemiological research in the field of adverse events related to PBDEs exposure and endpoints related to the male reproductive system. However, the currently available body of evidence is characterised by only a small number of prospective studies, variable follow-up periods, relatively small sample sizes, considerable heterogeneity in the assessed populations, exposures and outcomes, varying methodological quality and effect inconsistency. Based on the currently available epidemiological evidence, the association between PBDE exposure and 'hard' clinical endpoints cannot be considered likely due to lack of data and the same applies for semen quality and sex hormones which are assessed in a larger number of studies but with a high risk of bias and no replication efforts.

Based on the above, the currently available evidence coming from human studies on male reproduction cannot be used for hazard characterisation.

3.1.3.6 | *Effects on female reproduction*

In the previous EFSA Opinion on PBDEs (EFSA CONTAM Panel, 2011b), three epidemiological studies on female reproduction were included bearing inconclusive results. Since then, 27 publications corresponding to 23 individual studies were identified assessing the association between levels of PBDEs and any outcome related to female reproductive endpoints (see Table 26).

The evidence base included in the current Opinion consists of 10 cohort studies and 17 cross-sectional studies where the PBDE levels were assessed simultaneously or even later than the outcome ascertainment. The sample size of the included

observational studies ranged from 30 to 3421 participants. Six of the evaluated populations came from EU countries (Belgium, Italy, France), one from Canada, one from Iran, seven from the USA, two from China, one from Taiwan.

The populations under study were diverse. Four studies (17%) recruited younger children or adolescents, while the remaining 19 studies assessed adult female populations. PBDE levels were assessed via biomarkers in serum in most of the studies. Adipose tissue was also used in a number of cross-sectional studies. A variety of endpoints were assessed either binary or continuous. Binary outcomes assessed in more than one study included fecundability/time to pregnancy ($n = 4$), pregnancy loss ($n = 4$), gestational hypertension ($n = 2$), endometriosis ($n = 4$) and fibroids/leiomyoma ($n = 3$). Age at menarche/thelarche and sex hormones were the only continuous endpoints investigated in more than one study.

In the following paragraphs, the evidence stemming from cohort studies is discussed starting from the larger studies. The single publication on the NHANES study is also described in detail. Further details of these studies can be found in Annex D (Table D.7), as well as for the remaining case–control and cross-sectional studies identified.

TABLE 26 Overview of the epidemiological studies identified on the association between PBDEs and effects in the female reproductive system.

Reference	Study design	Population studied Matrix analysed	Endpoint
Qin et al. (2010). Persistent organic pollutants and heavy metals in adipose tissues of patients with uterine leiomyomas and the association of these pollutants with seafood diet, BMI, and age	Cross-sectional	Adults Adipose tissue	Uterine leiomyomas
Harley et al. (2010). PBDE Concentrations in women's serum and fecundability	Cross-sectional	Adults Serum	Time to pregnancy, menstrual cycle characteristics
Chen et al. (2011). Serum PBDEs and age at menarche in adolescent girls: Analysis of the National Health and Nutrition Examination Survey 2003–2004	Cross-sectional	Adolescents Serum	Age at menarche
Johnson et al. (2012). Serum and follicular fluid concentrations of polybrominated diphenyl ethers and *in vitro* fertilisation outcome	Cross-sectional	Adults Serum, follicular fluid	Assisted reproduction technique endpoints; failed implantation
Buck Louis et al. (2012). Persistent Lipophilic Environmental Chemicals and Endometriosis: The ENDO Study	Cross-sectional	Adults Serum, omental fat	Endometriosis
Petro et al. (2012). Endocrine-disrupting chemicals in human follicular fluid impair *in vitro* oocyte developmental competence	Cohort	Adults Serum, follicular fluid	Assisted reproduction technique endpoints; Fertilisation rate, high quality embryos
Chevrier et al. (2013). Organochlorine pesticides, polychlorinated biphenyls, seafood consumption, and time-to-pregnancy	Cross-sectional	Adults Cord blood	Time to pregnancy
Buck Louis et al. (2013). Persistent environmental pollutants and couple fecundity: the LIFE study	Cohort	Adults Serum	Time to pregnancy
Vagi et al. (2014). Exploring the potential association between brominated diphenyl ethers, polychlorinated biphenyls, organochlorine pesticides, perfluorinated compounds, phthalates, and bisphenol A in polycystic ovary syndrome: a case–control study	Cross-sectional	Adults Serum	Polycystic Ovary Syndrome
Trabert et al. (2015). Persistent organic pollutants (POPs) and fibroids: results from the ENDO study	Cross-sectional	Adults Serum, adipose tissue	Fibroids
Windham et al. (2015). Brominated flame retardants and other persistent organohalogenated compounds in relation to timing of puberty in a longitudinal study of girls	Cohort	Children Serum	Pubertal onset (breast, pubic hair)
Deodati et al. (2016). Serum levels of polybrominated diphenyl ethers in girls with premature thelarche	Cross-sectional	Adolescents Serum, Dietary	Idiopathic central precocious puberty, Premature thelarche, Sex hormones
Smarr et al. (2016). Persistent organic pollutants and pregnancy complications	Cohort	Adults Serum	Gestational hypertension
Warembourg et al. (2016). Exposure of pregnant women to persistent organic pollutants and cord sex hormone levels	Cross-sectional	Newborns Cord blood	Sex hormones
Gao et al. (2016). Exposure to polybrominated diphenyl ethers and female reproductive function: A study in the production area of Shandong, China	Cross-sectional	Adults Serum	Time to pregnancy, pregnancy loss, premature birth, Sex hormones
Wainman et al. (2016). Menstrual cycle perturbation by organohalogens and elements in the Cree of James Bay, Canada	Cross-sectional	Adults Plasma	Menstrual cycle

TABLE 26 (Continued)

Reference	Study design	Population studied Matrix analysed	Endpoint
Eslami, Malekafzali, et al. (2016). Association of serum concentrations of persistent organic pollutants (POPs) and risk of pre-eclampsia: a case–control study	Cross-sectional	Adults Serum	Gestational hypertension
Ploteau et al. (2017). Associations between internal exposure levels of persistent organic pollutants in adipose tissue and deep infiltrating endometriosis with or without concurrent ovarian endometrioma	Cross-sectional	Adults Adipose tissue	Endometriosis
Choi et al. (2019). Polybrominated diphenyl ethers and incident pregnancy loss: The LIFE Study	Cohort	Adults Serum	Pregnancy loss
Matta et al. (2020). Associations between persistent organic pollutants and endometriosis: A multipollutant assessment using machine learning algorithms	Cross sectional	Adults Adipose tissue	Endometriosis[a]
Ingle, Mínguez-Alarcón, Carignan, Stapleton, Williams, Ford, Moravek, Hauser, and Meeker (2020). Exploring reproductive associations of serum polybrominated diphenyl ether and hydroxylated brominated diphenyl ether concentrations among women undergoing *in vitro* fertilisation	Longitudinal prospective pre-conception cohort	Adults Serum	Assisted reproduction technique endpoint outcomes[b]
Ingle, Mínguez-Alarcón, Carignan, Stapleton, Williams, Ford, Moravek, O'Neill, et al. (2020). Reproductive outcomes associated with flame retardants among couples seeking fertility treatment: a paternal perspective	Longitudinal prospective pre-conception cohort	Adults Serum	Assisted reproduction technique endpoints[b]
Pollack et al. (2021). Adipose to serum ratio and mixtures of persistent organic pollutants in relation to endometriosis: findings from the ENDO Study	Cross sectional	Adults Serum, omental fat	Endometriosis
Björvang, Hassan, et al. (2021). Persistent organic pollutants and the size of ovarian reserve in reproductive-aged women	Cross sectional	Adults Serum	Ovarian reserve
Björvang, Hallberg, et al. (2021). Follicular fluid and blood levels of persistent organic pollutants and reproductive outcomes among women undergoing assisted reproductive technologies	Cohort	Adults Serum	Assisted reproduction technique endpoints
Orta et al. (2021). Brominated flame retardants and organochlorine pesticides and incidence of uterine leiomyomata: A prospective ultrasound study	Cohort	Adults Plasma	Uterine leiomyomata
Smarr et al. (2021). A multi-pollutant assessment of preconception persistent endocrine disrupting chemicals and incident pregnancy loss	Cohort	Adults Serum	Pregnancy loss

[a]Auxiliary analysis of Ploteau et al. (2017).

[b]Including: Total oocyte yield, M2 oocyte yield, endometrial wall thickness and fertilisation rate, implantation, clinical pregnancy and live birth.

Pubertal Development

Windham et al. (2015) reported on the BCERP study ($n = 645$) which included a cohort study of girls, recruited at ages 6–8 years in 2004–2007, and followed annually to measure onset and progression of pubertal maturation (time ratios for age at Tanner stages 2 or higher, for breast development (B) and pubic hair (PH)). The study included 10 PBDEs (congeners in the final analysis: **BDE-28**, **-49**, **-99**, **-100**, **-153**, **-154**), PCBs, OCPs and lipids. As regards the endpoints under study, the time ratios compare the median age at onset among girls in the specific exposure group to girls in the reference category. With typical median ages of B2+ and PH2+ between 9 and 10 years old, small time ratios can reflect a relatively large difference in age (e.g. 10.5 years/10 years = 1.05, representing 5% later onset or a 6-month lag). The statistically significant associations with pubertal onset were fairly consistent across the individual PBDE congeners in the adjusted models with some patterns of monotonic increase. **BDE-154** was the only congener not associated with either endpoint in adjusted (without BMI) models, whereas **BDE-153** was most strongly associated with both endpoints (adjusted time ratios for Q4 vs. Q1; Breast hair: 1.04, 95% CI: 1.01, 1.08; Pubic hair: 1.05, 95% CI: 1.02, 1.09).

Chen et al. (2011) reporting on NHANES assessed the association between individual and total serum PBDEs (**BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**) and the age at menarche in adolescent girls in a cross-sectional fashion ($n = 271$). The median total serum PBDE concentration was 44.7 ng/g lipid. Each natural log unit of total PBDEs was statistically significantly associated with an increased relative risk for experiencing menarche before 12 years of age, after adjustment for potential confounders (RR = 1.60; 95% CI: 1.12, 2.28).

Fertility

Buck Louis et al. (2013) for the LIFE cohort (*n* = 501, follow up 12 months) investigated the association between levels of a large number of contaminants including 10 PBDEs (BDE-17, -**28**, -**47**, -66, -85, -**99**, -**100**, -**153**, -**154**, -**183**) and couple fecundity as measured by time to pregnancy. The adjusted analysis showed no statistically significant results. Choi et al. (2019) for the same study assessed incident pregnancy loss as the endpoint of interest. Statistically significant HRs for incident pregnancy loss were observed for BDE-17 (1.23, 95% CI: 1.07, 1.42), **BDE-28** (1.25, 95% CI: 1.03, 1.52), BDE-66 (1.23, 95% CI: 1.07, 1.42) and homologue triBDE (1.25, 95% CI: 1.05, 1.49). In couple-based models, four additional associations were observed: **BDE-47** (1.31, 95% CI: 1.00, 1.71), BDE-85 (1.26, 95% CI: 1.04, 1.53), **BDE-99** (1.28, 95% CI: 1.02, 1.61) and **BDE-154** (1.22, 95% CI: 1.03, 1.45). Finally, Smarr et al. (2021) embarked into a multi-pollutant assessment on the same study and incident pregnancy loss. In the final multivariable multi-pollutant Cox proportional hazard models, **BDE-28** (HR: 1.16, 95% CI: 1.02, 1.31) remained associated with human gonadrophin chorionic (hCG) pregnancy loss.

Ingle, Mínguez-Alarcón, Carignan, Stapleton, Williams, Ford, Moravek, Hauser, and Meeker (2020) reporting on the Environmental and Reproductive Health (EARTH) Study in the USA (*n* = 215 women, 330 *in vitro* fertilisation (IVF) cycles) investigated the association between PBDE levels preconceptionally in women. Five PBDE congeners were analysed (**BDE-47**, -**99**, -**100**, -**153**, -**154**) and 4 OH-PBDEs (3-OH-BDE-47, 5-OH-BDE-47, 6-OH-BDE-47, 4-OH-BDE-49) and IVF-related endpoints (total oocyte yield, M2 oocyte yield, endometrial wall thickness and fertilisation rate, implantation, clinical pregnancy and live birth). An IQR increase of **BDE-153** was associated with an increase in the probability of implantation (RR = 1.26, 95% CI: 1.16, 1.36), clinical pregnancy (RR = 1.32, 95% CI: 1.19, 1.46) and live birth (RR = 1.34; 95% CI: 1.15, 1.54). In the same study, Ingle, Mínguez-Alarcón, Carignan, Stapleton, Williams, Ford, Moravek, O'Neill, et al. (2020) investigated the same endpoints but in association with PBDE levels in both women and men (*n* = 189 couples, 285 IVF cycles). PBDEs and OH-PBDEs levels were higher in females than in male partners. No overall statistically significant associations were observed for PBDEs and OH-PBDEs; some statistically significant results were reported for isolated quartiles occasionally with opposite effect direction.

Björvang, Hallberg, et al. (2021) studied a cohort of 185 women in Sweden who were seeking assisted reproductive technology treatment and assessed the association between multiple contaminants including 3 PBDEs (**BDE-47**, -**99**, -**153**) and 10 assisted reproductive technology endpoints were investigated. No statistically significant results were reported for PBDEs.

Petro et al. (2012) assessed the association between different compounds including PBDEs (**BDE-28**, -**47**, -**49**, -**99**, -**100**, -**153**, -**154**, -**183**) in serum and follicular fluid and assisted reproductive technique results such as fertilisation rate, proportion of high-quality eggs and assisted reproductive technology- or pregnancy outcomes (*n* = 40). Only **BDE-47** was analysed further due to non- or low detection of the remaining congeners. No statistically significant results were reported for **BDE-47**.

Other endpoints

As discussed before, Smarr et al. (2016) used the LIFE study (*n* = 258 pregnancies) to assess the association between pre-conception PBDE levels (BDE-17, -**28**, -**47**, -66, -85, -**99**, -**100**, -**153**, -**154**, -**183**) and gestational diabetes and gestational hypertension. No statistically significant associations were observed for gestational hypertension.

Orta et al. (2021) for the SELF study investigated the association between PBDEs (BDE-17, -**28**, -**47**, -66, -85, -**99**, -**100**, -**153**, -**154**, -**183**, -**209**) and uterine leiomyoma in the USA (*n* = 1693). No statistically significant associations were observed.

Regarding OH-PBDEs, as discussed above, Ingle, Mínguez-Alarcón, Carignan, Stapleton, Williams, Ford, Moravek, Hauser, and Meeker (2020) for the EARTH study focused on IVF-related endpoints. Due to coelution occurrence, 3-OH-BDE-47 and 5-OH-BDE-47 were presented individually and combined. Per IQR increase of 4-OH-BDE-49, a statistically significant association was reported for total oocyte yield (39%, 95% CI: 0.5%, 94%) and M2 oocyte yield (48%, 95% CI: 5%, 109%). A statistically significant association was also observed per IQR increase for the combined 3-OH-BDE-47 and 5-OH-BDE-47 levels and implantation (RR = 1.52; 95% CI: 1.11, 2.09), clinical pregnancy (RR = 1.66; 95% CI: 1.17, 2.36), and live birth (RR = 1.61; 95% CI: 1.07, 2.40). Moreover, an IQR increase in 6-OH-BDE-47 was associated with implantation (RR = 1.56, 95% CI: 1.14, 2.14), clinical pregnancy (RR = 1.56; 95% CI: 1.12, 2.18) and live birth (RR = 1.84, 95% CI: 1.26, 2.68). Ingle, Mínguez-Alarcón, Carignan, Stapleton, Williams, Ford, Moravek, O'Neill, et al. (2020) for the same study but assessing PBDE levels in the male partners, reported no overall statistically significant results for OH-PBDEs. Among the numerous analyses performed, the Sum OH-PBDE levels in Q2 and Q4 (vs. Q1) were statistically significantly associated with live birth (RR = 2.17; 95% CI: 1.34, 3.53; RR = 2.12; 95% CI: 1.29, 3.49).

In summary, there is a growing body of epidemiological research in the field of adverse events related to PBDEs exposure and endpoints related to the female reproductive system. Two domains were characterised by the presence of longitudinal data, statistically significant associations and more than one available study. Pubertal development in girls was assessed in three studies (one cohort, two cross sectional studies) with all of them reporting some statistically significant results but indicating an opposite effect direction; the proposed delayed pubertal development described in the longitudinal study is not supported by the statistically significant associations with premature pubertal development reported in the two cross sectional studies. The second domain included endpoints related to fertility and/or assisted reproduction techniques investigated in nine studies. Of these, four studies included participants undergoing assisted reproduction techniques (two cohorts, two cross-sectional studies); among the numerous endpoints assessed, two statistically significant associations

were reported for failed implantation with opposite effect direction and single statistically significant inverse associations were reported for pregnancy and live birth. Five studies assessed endpoints related to fertility in couples not attending a fertility clinic (three cohorts, two cross-sectional studies); two cross sectional studies reported the single statistically significant adverse associations observed on time to pregnancy, pregnancy loss, and prematurity. Overall, the currently available body of evidence is characterised by a small number of prospective studies, short follow up periods, relatively small sample sizes, multiple comparisons and effect inconsistency.

Based on the above, the currently available evidence coming from human studies on female reproduction cannot be used for hazard characterisation.

3.1.3.7 | *Birth outcomes*

In the previous EFSA Opinion on PBDEs (EFSA CONTAM Panel, 2011b), three studies on birth outcomes were included bearing inconclusive results. Since then, 30 publications were identified assessing the association between levels of PBDEs and any outcome related to offspring health outcomes during pregnancy (fetal growth), at birth (weight, length, head circumference, Apgar score, placental size, sex ratio, gestational age, neural tube defects) or in the early years after birth (infant growth, anogenital distance, Second-to-fourth digit ratio) (see Table 27). The evidence from all studies is discussed in under two subheadings: (i) Outcomes measured before or at birth and (ii) Outcomes measured postnatally.

TABLE 27 Overview of the epidemiological studies identified on the association between levels of PBDEs and birth outcomes.

Reference	Study design	Matrix	Endpoint
Wu et al. (2010). Polybrominated diphenyl ethers in umbilical cord blood and relevant factors in neonates from Guiyu, China	Case–control	Cord blood	Cases with adverse birth outcome (premature delivery, low birth weight or stillbirth)
Harley et al. (2011). Association of prenatal exposure to polybrominated diphenyl ethers and infant birth weight	Cohort	Maternal blood	Birth weight, Length, Head Circumference, Gestational Age
Ren et al. (2011). Association of selected persistent organic pollutants in the placenta with the risk of neural tube defects	Case–control	Placenta	Neural tube defects
Ma et al. (2012). Using placenta to evaluate the polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) exposure of fetus in a region with high prevalence of neural tube defects	Case–control	Placenta	Neural tube defects
Lignell, Aune, Darnerud, et al. (2013). Prenatal exposure to polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) may influence birth weight among infants in a Swedish cohort with background exposure: a cross-sectional study	Cross-sectional	Human milk	Birth weight
Vafeiadi et al. (2014). Persistent organic pollutants exposure during pregnancy, maternal gestational weight gain, and birth outcomes in the mother–child cohort in Crete, Greece (RHEA study)[a]	Cohort	Maternal serum	Birth weight, Birth length, Head circumference
Xu, Huo, et al. (2015). Polybrominated diphenyl ethers in human placenta associated with neonatal physiological development at a typical e-waste recycling area in China	Cross-sectional	Placenta	Birth weight, Birth length, Birth BMI, Head circumference, Apgar score, Gestational age
Peltier et al. (2015). Does exposure to flame retardants increase the risk for preterm birth?	Case–control	Maternal plasma (delivery)	Preterm birth
Chen et al. (2015). Prenatal exposure to polybrominated diphenyl ethers and birth outcomes	Cross-sectional	Maternal serum (delivery)	Birth weight, Birth length, Head Circumference, Gestational Age
Lopez-Espinosa et al. (2015). Prenatal Exposure to Polybrominated Flame Retardants and Fetal Growth in the INMA Cohort (Spain)	Cohort	Maternal serum (pregnancy), cord blood	Birth Weight, Birth length, Head circumference, Fetal growth parameters
Miranda et al. (2015). Associations of birth outcomes with maternal polybrominated diphenyl ethers and thyroid hormones during pregnancy	Cohort	Maternal serum (pregnancy), cord blood	Birth Weight, Birth length, Head Circumference, Fetal growth parameters
Robledo et al. (2015). Preconception Maternal and Paternal Exposure to Persistent Organic Pollutants and Birth Size: The LIFE Study	Cohort	Maternal and paternal serum (preconception)	Birth weight, Birth length, Head circumference, Ponderal index
Hoffman et al. (2016). Lactational Exposure to Polybrominated Diphenyl Ethers and Its Relation to Early Childhood Anthropometric Measurements	Cohort	Human milk	Weight-for-height *Z*-score, Height-for-age *Z*-score

(Continues)

TABLE 27 (Continued)

Reference	Study design	Matrix	Endpoint
Serme-Gbedo et al. (2016). Maternal levels of endocrine disruptors, polybrominated diphenyl ethers, in early pregnancy are not associated with lower birth weight in the Canadian birth cohort GESTE	Cohort	Maternal plasma (pregnancy)	Birth weight
Gao et al. (2016). Exposure to polybrominated diphenyl ethers and female reproductive function: a study in the production area of Shandong, China	Cross-sectional	Maternal serum (delivery)	Premature birth (further outcomes described in the section on female reproductive outcomes)
Müller et al. (2016). Brominated flame retardants (BFRs) in breastmilk and associated health risks to nursing infants in Northern Tanzania	Cross-sectional	Human milk	Birth weight, Birth length
Woods et al. (2017). Gestational exposure to endocrine disrupting chemicals in relation to infant birth weight: a Bayesian analysis of the HOME Study	Cohort	Maternal serum (pregnancy)	Birth weight
Zhao et al. (2018). Umbilical cord blood PBDEs concentrations in relation to placental size at birth	Nested case–control	Cord blood	Placental size (length, breadth, surface area)
García-Villarino et al. (2018). Prenatal exposure to persistent organic pollutants and anogenital distance in children at 18 months	Mother–child cohort	Maternal blood (collected during the 1st trimester of gestation)	Anogenital distance in boys and girls at 18 months of age
Bae et al. (2018). Maternal and paternal serum concentrations of persistent organic pollutants and the secondary sex ratio: A population-based preconception cohort study	Cohort	Maternal and paternal serum (preconception)	Secondary sex ratio
Chen, Wang, et al. (2018). Polybrominated diphenyl ethers in cord blood and perinatal outcomes from Laizhou Wan Birth Cohort, China	Cross-sectional	Cord blood	Birth weight, Birth length, Head circumference, Gestational age
Cabrera-Rodríguez et al. (2019). Association between prenatal exposure to multiple persistent organic pollutants (POPs) and growth indicators in newborns	Cross-sectional	Cord blood	Birth weight, Small for gestational age
Zhao et al. (2019). Associations between in utero exposure to polybrominated diphenyl ethers, pathophysiological state of fetal growth and placental DNA methylation changes	Nested case–control	Cord blood	Fetal growth restriction
Luan et al. (2019). Prenatal polybrominated diphenyl ethers exposure and anogenital distance in boys from a Shanghai birth cohort	Cohort	Cord plasma	Anogenital distance at birth, at 6 months, at 12 and 48 months
Bell et al. (2019). Exposure to persistent organic pollutants and birth characteristics: the upstate KIDS study	Cross-sectional	Dried blood spots	Birth weight, Low birth weight, Large for gestational age, Small for gestational age, Ponderal index, Gestational age, Preterm birth
García-Villarino et al. (2020). Association between pre/perinatal exposure to POPs and children's anogenital distance at age 4 years: A study from the INMA-Asturias cohort	Cohort	Maternal serum and cord blood	Anogenital index at 4 years
Eick et al. (2020). Associations between prenatal maternal exposure to per- and polyfluoroalkyl substances (PFAS) and polybrominated diphenyl ethers (PBDEs) and birth outcomes among pregnant women in San Francisco	Cohort	Maternal serum (pregnancy)	Birth weight, Gestational age
Gross et al. (2020). Persistent organic pollutants exposure in newborn dried blood spots and infant weight status: A case–control study of low-income Hispanic mother-infant pairs	Case–control	Newborn blood spots	Birth weight, Child weight status at 18 months
Jin, Deng, et al. (2020). Concentrations of polybrominated diphenyl ethers in maternal blood, placental size, and risk for fetal growth restriction: a nested case–control study	Nested case–control	Maternal serum (pregnancy)	Fetal growth restriction, Birth length, Quetelet index, Gestational age, Placental size (length, breadth, surface area)
Jin, Li, et al. (2020). Association between fetal growth restriction and maternal exposure to polybrominated diphenyl ethers	Nested case–control	Maternal serum (pregnancy) and colostrum	Fetal growth restriction, Birth weight
Peltier et al. (2020). Women with high plasma levels of PBDE-47 are at increased risk of preterm birth	Nested case-cohort	Maternal plasma (pregnancy)	Preterm birth

TABLE 27 (Continued)

Reference	Study design	Matrix	Endpoint
Agier et al. (2020). Association between the pregnancy exposome and fetal growth	Cohort	Maternal blood (pregnancy)	Birth weight
Pearce et al. (2021). Exploring associations between prenatal exposure to multiple endocrine disruptors and birth weight with exposure continuum mapping	Cohort	Maternal plasma (pregnancy)	Birth weight
Luan et al. (2021). Association between prenatal exposure to polybrominated diphenyl ethers and anogenital distance in girls at ages 0–4 years	Cohort	Cord plasma	Anogenital distance
Chen et al. (2021). Effects of prenatal exposure to polybrominated diphenyl ethers (PBDEs) on the second to fourth digit ratio in children aged 4 years	Cohort	Cord plasma	Second-to-fourth digit ratio
Li, Ma, et al. (2020). Lactational exposure to polybrominated diphenyl ethers and its association with infant developmental measurements	Cohort	Human milk	Postnatal growth: Head circumference-for-age, Length-for-age, Weight-for-age, Weight-for-length
Hjermitslev et al. (2020). Persistent organic pollutants in Greenlandic pregnant women and indices of foetal growth: The ACCEPT study	Cohort	Maternal serum (pregnancy)	Birth weight, Birth length, Head circumference, Gestational age
Lazarevic et al. (2022). Prenatal exposure to mixtures of persistent environmental chemicals and fetal growth outcomes in Western Australia	Cohort	Maternal blood 2 weeks before delivery	Birth weight, Birth length, Head circumference

[a]The authors reported that the concentrations of PBDEs were < LOD and no further statistical analysis was presented. Thus the study is not further considered in the Opinion.

3.1.3.7.1 | *Outcomes measured before or at birth*

Thirty publications from 22 separate studies evaluated birth weight and/or growth restriction ($n = 21$), birth length ($n = 11$), weight-for-length (ponderal index, BMI, Quetelet index) ($n = 4$), head circumference ($n = 9$), placental parameters ($n = 3$), neural tube defects ($n = 2$), Apgar score ($n = 1$), sex ratio ($n = 1$) and gestational age and/or prematurity ($n = 11$), at birth, following maternal or fetal exposure to PBDEs. One study also assessed fetal growth parameters from ultrasound measures. One other study analysed cases of adverse outcomes combined (low birth weight, preterm birth and stillbirth).

Out of the 30 publications, 10 were cohort studies where PBDE levels were assessed in maternal serum or plasma samples collected during the pregnancy. Two further cohort studies assessed PBDE levels in maternal and paternal blood preconceptionally. Eight studies had a cross-sectional assessment of PBDEs in samples collected at or after delivery, including cord blood ($n = 2$), maternal blood ($n = 3$), placenta ($n = 1$), dried newborn blood spots ($n = 1$), and human milk ($n = 2$). Ten studies used a case–control design, where PBDE levels were assessed either during pregnancy ($n = 3$) or at birth in cord blood ($n = 3$), maternal blood ($n = 1$), placenta ($n = 2$) or dried newborn blood spots ($n = 1$). All studies are discussed in this Section, and further details of the studies can be found in Annex D (Table D.8).

The sample size of the included studies ranged from 95 to 1287 participants, with the majority of studies having sample sizes of between 100 and 500 participants ($n = 18$), 3 studies having between 500 and 1000 participants, and one study having > 1000 participants. Four of the studies were based on populations from European countries, including one from Sweden (Lignell, Aune, Darnerud, et al., 2013), two from Spain (Lopez-Espinosa et al., 2015) and one multi-country study (France, Greece, Lithuania, Norway, Spain, UK; Agier et al., 2020). The majority of the other studies were based in the USA or China.

In the CHAMACOS Study, Harley et al. (2011) assessed the association between PBDEs measured in maternal serum collected in week 26 of pregnancy with birth weight, birth length, head circumference and gestational age ($n = 286$). Of the 10 PBDE congeners measured (BDE-17, -**28**, -**47**, -66, -85, -**99**, -**100**, -**153**, -**154**, -**183**), four of them (**BDE-47**, -**99**, -**100**, -**153**) were detected in ≥ 75% of samples and were considered in the analysis. In adjusted models, **BDE-47**, **-99** and -**100** were associated with reductions in birth weight of between 114 and 122 grams per 10-fold increase in concentration (**BDE-47**: -115 (-229, -2), **BDE-99**: -114 (-225, -4), **BDE-100**: -122 (-235, -9)). After including maternal gestational weight gain in the models in sensitivity analyses as a suspected mediator or confounder, these estimates were no longer statistically significant. PBDE congeners were not associated with birth length, head circumference and gestational age.

Two publications, by Ren et al. (2011) and Ma et al. (2012), report results from the same case–control study in Shanxi province, China. In this study, placental concentrations of PBDEs and several other persistent organic pollutants were compared in 80 cases of neural tube defects and 50 healthy control births. The sum of six PBDE congeners (**BDE-47**, -66, -**99**, -**100**, -**153**, -**154**) was analysed. The concentration of PBDEs was not associated with risk of neural tube defects in either of the publications.

In the Swedish POPUP cohort, Lignell, Aune, Darnerud, et al. (2013) measured 4 congeners (**BDE-47**, -**99**, -**100**, -**153**, and their sum) in human milk collected 3 weeks after birth ($n = 413$). In adjusted models, the Sum 4 PBDEs was not significantly associated with birth weight in the full study population, but when analyses were restricted to subjects with data on length

of gestation ($n = 295$), the Sum 4 PBDEs was statistically significantly associated with a reduction in birth weight (-117 grams per ln unit increase in concentration, $p = 0.05$) and this reduction was also seen when adjusting for gestational length (-106 grams per ln unit, $p = 0.04$). This association was stronger and statistically significant in male infants (-139 grams, $p = 0.03$), compared to female infants.

In the USA LIFE study cohort (Robledo et al., 2015), 10 PBDEs congeners (as well as many other POPs) were measured in serum of mothers and fathers collected preconceptionally (BDE-17, -**28**, -**47**, -66, -85, -**99**, -**100**, -**153**, -**154**, -**183**). Associations with birth weight, birth length, head circumference and ponderal index were evaluated ($n = 234$, 117 F, 113 M). Effect estimates were not provided for the overall study population. In girls, statistically significant reductions in birth weight were observed for maternal concentrations of **BDE-28** (–151.3 grams per 1 SD increase in ln concentration) and **BDE-183** (-84 grams), and paternal concentrations of **BDE-183**. In boys, maternal BDE-66 and -**99** were associated with an increase in birth weight. Maternal concentrations of **BDE-28** were associated with a decrease in birth length in girls, and maternal concentrations of **BDE-99** were associated with an increase in birth length in boys. Maternal **BDE-28** concentrations were also associated with a reduction in head circumference in girls, and maternal BDE-66, -85 and -**99** concentrations with an increase in head circumference in boys. There were no associations with the ponderal index. The LIFE study cohort was also used to assess associations between maternal and paternal preconceptional PBDE concentrations and offspring sex ratio (Bae et al., 2018, $n = 235$). Excess male births were observed in adjusted model for maternal concentrations of **BDE-99** and -**154**, and for paternal concentrations of **BDE-47**. These associations were no longer statistically significant in couple-based models where maternal and paternal concentrations were added at the same time.

In the North Carolina based HPHB cohort study, Miranda et al. (2015) measured eight PBDE congeners and two OH-PBDEs in maternal serum samples collected during the third trimester of pregnancy, and studied their association with infant birth weight, birth length, head circumference and birthweight percentile for gestational age ($n = 136$). Four PBDE (**BDE-47**, -**99**, -**100**, -**153**) and 4′-OH-BDE-49 and 6′-OH-BDE-47 were detected in > 50% of samples and included in analyses, as well as the sum of the PBDEs and the sum of the OH-PBDEs. Associations generally showed reductions in the birth outcomes, especially for head circumference, but none reached statistical significance in adjusted or unadjusted models. Thyroid hormone concentrations did not appear to mediate the associations.[46]

In a USA study, Peltier et al. (2015) measured **BDE-47** in maternal plasma samples collected at delivery in 82 cases with preterm birth (< 37 weeks gestation) and 197 control term births. **BDE-47** concentrations were categorised in five groups ('very low', 'low', 'moderate', 'high', 'very high') and those in the 'high' and 'very high' categories were found to have a higher odds of preterm birth compared to the 'very low' category in unadjusted (high: OR: 3.8, 95% CI: 1.6, 9.7, very high: 5.6, 95% CI: 2.2, 15.2) and adjusted (OR not given, only shown in figure) models.

In the Spanish INMA cohort study, 14 PBDEs were assessed in maternal serum collected at 12 weeks of gestation and in cord blood serum (Lopez-Espinosa et al., 2015) in 670 and 534 subjects, respectively. Five congeners (**BDE-47**, -**99**, -**153**, -**154**, -**209**) were detected in > 50% of samples and included in analyses, as well as their sum. Fetal growth parameters were assessed from ultrasound measures at 12, 20 and 34 weeks of gestation. Growth models estimated abdominal circumference, biparietal diameter, fetal weight, femur length between 12–20 and 20–34 weeks. Birth weight, length and head circumference were measured at birth. The Sum 5 PBDEs in cord serum was associated ($p < 0.05$) with reductions in abdominal circumference and fetal weight at 20–34 weeks, and Sum 5 PBDEs in maternal serum with reductions in biparietal diameter at weeks 20–34 and in head circumference at birth. **BDE-99** in cord serum was associated with reductions in abdominal circumference and fetal weight at 20–34 weeks, and **BDE-99** in maternal serum with reductions in biparietal diameter at 20–34 weeks, and in head circumference and birth weight (–1.4% [–2.7, –0.2], corresponding to a mean difference of ~ 46.8 g per doubling of concentration).

In the Laizhou Wan study in China (Chen et al., 2015), eight PBDEs were measured in maternal serum collected at the day of delivery, and cross-sectional associations with birth weight, birth length, head circumference and gestational age were evaluated in 215 mother–child pairs. Five PBDEs (**BDE-28**, -**47**, -**99**, -**100**, -**153**) were detected in > 90% of samples and were included in analyses, as was their sum. After adjusting for potential confounders, **BDE-28** and **-100** concentrations were associated with a reduction in birth length (**BDE-28**: −0.92 cm per log10 increase in concentration, 95% CI: –1.82, –0.02, **BDE-100**: –0.972, 95% CI: –1.83, –0.08). **BDE-99** and -**153** were non-significantly associated with a reduction in birth length. The association between **BDE-99** and length was significant in girls and the association between **BDE-100** and length was significant in boys. All congeners apart from **BDE-153** were associated with non-statistically significant reductions in birth weight, with an association of marginal significance noted for **BDE-28** (–126.31 grams, 95% CI: –253.69, 1.08), which was significant in boys (–253.76, 95% CI: –438.16, –69.36). **BDE-153** was positively associated with birth weight among female infants (212.36, 95% CI: 31.41, 393.31). There were no associations with head circumference or gestational age. In the same Laizhou Wan study, Chen, Wang, et al. (2018) also measured PBDEs in cord serum samples in 222 mother–child pairs and evaluated the same birth outcomes (birth weight, birth length, head circumference and gestational age). Eight congeners were measured and detection rates of four congeners (**BDE-28**, -**47**, -**99**, -**100**) were > 80%. **BDE-47**, -**100** and the sum of the four PBDEs were associated with an increase in gestation age (0.70 weeks, 95% CI: 0.25, 1.15; 0.48 weeks, 95% CI: 0.03, 0.94; and 0.73 weeks, 95% CI: 0.12, 1.34, per log unit increase in concentration, respectively). Cord serum **BDE-47** was also positively associated with infant head circumference (0.42 cm, 95% CI: 0.00, 0.84). Associations were generally stronger in boys, and statistically significant in boys for associations between Sum PBDEs and **BDE-47** with gestational age and head

[46]The authors reported that in separate modelling with TT4, FT4, FT3 and TSH, thyroid hormones did not appear associated with PBDEs (data not shown) (Miranda et al., 2015).

circumference. There were no associations for birth weight or birth length. In the same Laizhou Wan study, Gao et al. (2016), analysed associations between PBDEs levels in maternal serum (collected at delivery) and a range of female reproductive outcomes, as described in the section on female reproduction. Preterm birth was included as an outcome in the study and is thus discussed here. This study included eight congeners (**BDE-28**, -**47**, -85, -**99**, -**100**, -**153**, -**154** and -184). A statistically significant association was reported between **BDE-153** and preterm birth (OR = 1.05, 95% CI: 1.01–1.09).

A study in an e-waste area in Guiyu and a reference area in Haojiang (China), measured eight PBDE congeners (**BDE-28**, -**47**, -**99**, -**100**, -**154**, -**153**, -**183**, -**209**) in placenta samples from 155 mothers (69 in the e-waste area, 86 in the reference area) (Xu, Huo, et al., 2015). PBDE concentrations were significantly higher in the e-waste area compared to the reference area. Adjusted partial correlation analyses were used to test correlations between PBDE concentrations and birth weight, birth length, head circumference, neonatal BMI, Apgar 1 score and gestational age. Statistically significant negative correlations were observed between the sum of PBDEs and head circumference, neonatal BMI and Apgar 1 score. **BDE-47** was negatively correlated with head circumference, neonatal BMI and Apgar 1 score, and positively with body length. **BDE-99** was negatively associated with neonatal BMI. **BDE-28** and **-153** were negatively correlated with Apgar1 score and **BDE-183** correlated negatively with Apgar1 score and neonatal BMI. No significant correlation was observed for birth weight or gestational age. In a previous publication of the same e-waste area (Wu et al., 2010) birth outcomes (height, weight, gestational age, delivery mode, sex, premature delivery rate) did not differ between the exposed ($n = 102$) and reference area ($n = 51$), except for Apgar score. Wu et al. (2010) also measured cord blood levels of the same 8 congeners, and **BDE-28**, -**47**, -**99**, -**153**, -**183** and Sum PBDEs were found to be higher in cases with adverse birth outcomes (defined as low birth weight, prematurity or still birth); none of these analyses were adjusted for confounders.

A study in Tanzania (Müller et al., 2016) analysed PBDE congeners in human milk (colostrum) samples collected from 95 mothers in the days after delivery (within 24–28 h) and reported correlations with birth weight and birth length for the four congeners (**BDE-47**, -**99**, -**100**, -**153**) that were detected in more than 80% of samples. Statistically significant positive correlations (higher birthweight or length with higher concentrations) are reported for all four congeners and their sum, but no adjustments were made for potential confounding variables.

In the Canadian GEStation Thyroid and Environment (GESTE) birth cohort study (Serme-Gbedo et al., 2016), concentrations of four PBDE congeners (**BDE-47**, -**99**, -**100**, -**153**) were analysed in maternal plasma samples collected before week 20 of gestation in 349 pregnant women. Multivariate adjusted models showed no associations between any of the congeners or their sum and birth weight corrected for gestational age.

In the HOME birth cohort study of 272 mother–child pairs (Woods et al., 2017), 53 endocrine disrupting chemicals were measured in maternal blood and urine samples collected at 16 and 26 weeks of gestation. Nine PBDE congeners were included in analyses (**BDE-17**, -**28**, -**47**, -66, -85, -**99**, -**100**, -**153**, -**183**). Bayesian Hierarchical Linear Models showed no evidence for an association between the PBDEs (together or individually) and birth weight.

Four publications were based on the same nested case–control study in Wenzhou, China (Zhao et al., 2018, 2019; Jin et al., 2020,b). Zhao et al. (2018) analysed PBDEs in umbilical cord blood of 54 cases with fetal growth restriction (FGR) and 67 healthy controls. FGR was defined as birth weight below the 10th percentile for the same gestational age. In FGR cases, concentrations of BDE-206, -207, -208, -**209** and the sum of 19 PBDEs were associated with reductions in placental length, breadth and surface area. **BDE-47** was associated with a reduction in placental length only. In controls, these associations were not observed. Zhao et al. (2019) included 124 FGR cases and 125 controls with PBDE measurements in cord blood. Placental DNA methylation changes of one repetitive element (LINE1) and two candidate genes (HSD11B2, IGF2) were characterised. Concentrations of BDE-206, Sum BDE-17-190, Sum BDE 196–209 and Sum 19 PBDEs were associated with an increased risk of FGR in newborns. The Sum BDE-17-190 also showed significant associations with DNA methylation of HSD11B2 and IGF2, indicating that placental DNA methylation changes of HSD11B2 and IGF2 were related to both lower PBDE congeners levels and fetal growth. Further mediation analyses showed that IGF2 methylation mediated about 40% of the association between Sum BDE-17-190 on neonatal FGR. Jin, Deng, et al. (2020) included 101 FGR cases and 101 controls. 19 PBDEs were measured in third trimester maternal serum samples. Associations were assessed between PBDE levels and FGR status, as well as placental growth indicators (length, breadth and surface area) and birth outcomes (birth weight, birth length, gestational age and Quetelet index [weight/length]). In adjusted models, BDE-207 and the Sum 19 PBDEs were associated with an increased odds of FGR (1.10, 95% CI: 1.02, 1.19; 1.01, 95% CI: 1.00, 1.02, respectively). Overall, BDE-17, -**153**, -207, -208, -**209** and Sum 19 PBDEs were associated with a decrease in placental length, breadth and surface area. Birthweight and Quetelet index reductions were observed in association with all congeners; the associations were statistically significant for all congeners except BDE-17. Statistically significant reductions in birth length and gestational age were observed in association with BDE-207, -208, **-209** and Sum 19 PBDEs. Jin, Li, et al. (2020) reported another nested case–control analysis, including 98 FGR cases and 195 controls. This analysis added colostrum PBDE measurements and reports associations with FGR status and birth weight. Adjusted OR for FGR were significantly increased in relation to maternal serum concentrations of BDE-207, -**209**, Sum BDE-196-209 and Sum all PBDEs, as well as in relation to colostrum concentrations of **BDE-99**, -**153**, Sum BDE-17-154 and Sum all PBDEs. PBDEs were also associated with reductions in birth weight both for maternal serum concentrations (BDE-17, -**47**, -**49**, -**99**, -**100**, -**153**, -203, -206, -207, -208, -**209**, Sum BDE-17-154, Sum BDE-196-209 and Sum all PBDEs) and for colostrum concentrations (**BDE-99**, -**153**, -**154**, Sum BDE-17-154 and Sum all PBDEs). The overlapping study populations in these four publications make it hard to treat the results of the studies independently, especially where identical outcomes (FGR, birth weight) are assessed. Further, the study was designed as a case–control study (with FGR cases and controls) which makes it hard to interpret the analyses done in all participants combined.

Bell et al. (2019) measured PBDEs and other persistent organic pollutants in dried blood spots collected from 2065 newborns in the Upstate KIDS study (New York State, USA). The birth outcomes analysed were: birth weight, large for gestational age, small for gestational age, low birth weight, ponderal index, gestational age and preterm birth. **BDE-47** was determined in pooled dried blood samples (pools of five samples) and imputations were used to estimate individual levels. There were no statistically significant associations between **BDE-47** and any of the outcomes.

Cabrera-Rodríguez et al. (2019) measured eight PBDE congeners (**BDE-28**, **-47**, -85, **-99**, **-100**, **-153**, **-154**, **-183**) in cord blood of 447 newborns in the Canary Islands, Spain, as well as several other POPs. For the PBDEs analysed, only **BDE-47** was detected in about 10% of the samples. Birth weight measures were used to create the main outcome variable in three categories: small for gestational age, appropriate for gestational age (birth weight between the 10th and 90th percentiles) and large for gestational age. Among girls, a significant negative association was observed between the cord blood concentration of **BDE-47** and birth weight (Spearman r = −0.643, $P = 0.001$), and when comparing **BDE-47** levels between large for gestational age and non-large for gestational age infants. No adjustments for confounding variables were made.

In the Chemicals in our Bodies (CIOB) cohort study in San Francisco (Eick et al., 2020), 19 PBDEs were measured in maternal serum collected in the 2nd trimester of pregnancy and associations with gestational age and birth-weight-for-gestational-age z-scores were evaluated ($n = 506$). Only **BDE-47** and **-99** were detected in > 80% of samples and included in analyses. The highest compared to lowest tertile of **BDE-47** was associated with shorter gestational age (−0.49 weeks, 95% CI: −0.95, −0.02). Levels of **BDE-47**, **-99** and the sum of these two PBDEs in the middle tertile was also associated with a reduction in birth weight z-scores (−0.26, 95% CI: −0.48, −0.04; −0.25, 95% CI: −0.47, −0.04; −0.26, 95% CI: −0.48, −0.04, respectively) compared to those in the lowest tertile of concentrations.

In a Californian case–control study of 184 preterm births and 184 term control births, Peltier et al. (2020) measured **BDE-47** in maternal plasma samples collected during the pregnancy (trimester not specified). Adjusted ORs for the highest quartile of **BDE-47** concentrations were statistically significant for all preterm births (1.97, 95% CI: 1.24, 3.14), indicated preterm births (2.28, 95% CI: 2.19, 4.05), and spontaneous preterm birth (1.75, 95% CI: 1.02, 2.99).

Gross et al. (2020) measured three PBDE congeners (**BDE-28**, **-47**, **-99**) in dried blood spots collected from newborns participating in a case–control study in the USA comparing diet and POPs levels in cases of overweight at 18 months ($n = 52$) and healthy weight controls ($n = 46$). PBDEs were not associated with birth weight z-scores or with weight status at 18 months in adjusted models.

In the HELIX cohort (Agier et al., 2020), including data from 6 European cohorts (France, Greece, Lithuania, Norway, Spain, UK), 131 prenatal environmental exposure variables were assessed in 1287 mother–child pairs, including maternal blood levels of **BDE-47** and **-153**. Exposome-wide analyses showed no association between **BDE-47** and **-153** with birth weight.

In the ACCEPT cohort study in Greenland (Hjermitslev et al., 2020), serum levels of persistent organic pollutants were analysed in 504 pregnant women and associations with birth weight, birth length, head circumference and gestational age were evaluated. The sum of nine PBDEs (BDE-15, -17, -25, **-28**, -33, **-47**, **-99**, **-100**, **-153**) plus PBB-153 was analysed, among a large number of other persistent organic pollutants. The sum of PBDEs was not associated with any of the birth outcomes analysed in this study.

In the ECHO-FGS cohort in the USA, maternal plasma samples collected at 8–12 weeks of gestation were analysed for 16 endocrine disrupting chemicals in 604 subjects (Pearce et al., 2021). Four BDE congeners were included: **BDE-47**, **-99**, **-100** and **-153**. A two-stage exposure continuum mapping approach was used to investigate the combined association of the EDCs with birth weight. Single chemical analysis models found no significant *p*-values for associations between EDCs and birth weight after correction for false discovery rate. However, beta estimates (95% CIs) suggested lower birth weights were associated with increasing maternal levels to both **BDE-47** and **-100** at the 0.05 *p*-value level (exact beta estimates not given). Further, the mapping approach showed that exposure combinations with higher levels of PBDEs were associated with lower birth weight.

The AMETS study in Australia (Lazarevic et al., 2022) measured PBDEs, organochlorine pesticides, metals and perfluorinated alkyl substances in blood and urine samples collected ~ 2 weeks prior to delivery in 166 non-smoking pregnant women. Outcomes analysed were birth weight, birth length and head circumference. Two PBDE congeners (**BDE-47** and **-153**) had detectable concentrations in over 88% of samples and were included in analyses. No associations were found between single chemicals or mixtures with any of the birth outcomes.

In summary, the evidence on the association between PBDE levels during pregnancy and birth outcomes has grown since the publication of the previous Opinion. More studies are now available, especially studying birth weight (21 studies), but also birth length, head circumference, and gestational age (≥ 8 studies each). For other specific endpoints, the number of studies is limited (≤ 4 studies). This available body of evidence is characterised by relatively small sample sizes (< 500) for the majority of studies, and considerable heterogeneity in the assessed outcomes, exposures, and time points and biological matrices used for PBDE measurement. Further, the studies were of varying methodological quality (e.g. small cross-sectional case–control studies, no adjustment of effect estimates) and most did not address the issue of multiple testing even though many statistical tests were conducted on often small sample sizes.

For birth weight, good quality longitudinal cohort studies (PBDEs measured during or before pregnancy) show inconsistent results, with 5 studies showing reductions in birth weight (Eick et al., 2020; Harley et al., 2011; Lopez-Espinosa et al., 2015; Pearce et al., 2021; Robledo et al., 2015), and 6 studies showing no association (Agier et al., 2020; Hjermitslev et al., 2020; Lazarevic et al., 2022; Miranda et al., 2015; Serme-Gbedo et al., 2016; Woods et al., 2017). In the five longitudinal studies showing associations, **BDE-47** was most often associated with birth weight reductions (three studies), followed by **BDE-99** and **-100** (two studies). The cross-sectional studies mostly reported null associations, with the exception of the

Swedish cohort that measured PBDEs in human milk 3 weeks after birth (Lignell, Aune, Darnerud, et al., 2013). The overlapping Chinese nested case–control studies (Jin et al., 2020a, 2020b; Zhao et al., 2019) also reported reductions in birth weight and increased risk of fetal growth restriction. In conclusion, evidence for birth weight reductions associated with maternal PBDE levels can be classified as inconsistent at this moment.

For birth length, the majority of longitudinal cohort studies did not show an association, with the exception of Robledo et al. (2015) who reported a reduction in birth length associated with maternal preconceptional **BDE-28** exposure. Two case–control studies also reported birth length reductions: Chen et al. (2015, **BDE-28**, -**100**) and Jin et al. (2020, BDE-207, -208, -**209**, Sum 19 PBDEs). Associations between PBDE exposure and reductions in head circumference were reported in 3 studies: two longitudinal cohorts (Lopez-Espinosa et al., 2015; Robledo et al., 2015), and one cross-sectional study (Xu, Huo, et al., 2015). PBDE exposure was negatively associated with gestational age in the longitudinal cohort study by Eick et al. (2020) and the Jin, Deng, et al. (2020) case–control study. In summary, for these outcomes, the number of studies is small and the findings are heterogeneous across studies. Evidence can therefore be classified as insufficient. Similarly, for the other outcomes reported in this section (weight-for-length, Apgar score, placental size, sex ratio, neural tube defects) there are too few studies to draw conclusions.

OH-PBDEs were measured in only one study, as described above. Miranda et al. (2015) did not observe statistically significant associations between maternal serum levels of 4′-OH-BDE-49, 6′-OH-BDE-47 or their sum, and birth outcomes.

3.1.3.7.2 | *Outcomes measured postnatally (infancy, early childhood*

In this section, eight publications that assessed associations between pre- or perinatal levels of PBDEs and offspring health outcomes in the first years of life are discussed. These include: four publications from two separate longitudinal cohort studies on anogenital distance (one in Spain, one in China), one cohort study on the second-to-fourth digit ratio (China), and two cohort studies (one in USA, one in China) and one case–control study (USA) on postnatal growth outcomes.

García-Villarino et al. (2018) assessed the association between **BDE-28**, -**99** and -**153**, as well as other POPs, and anogenital distance in 43 mother–child pairs from the INMA-Asturias birth cohort. PBDEs were measured in maternal blood samples collected in the first trimester of pregnancy. At age 18 months, anoscrotal distance (anus to scrotum) was measured in boys ($n = 27$) and anofourchetal distance (anus to fourchette) in girls ($n = 16$). **BDE-99 and -153** were statistically significantly associated with a reduction in anoscrotal distance in boys after adjustment for height (β **BDE-99** = −0.28, 95% CI: −0.51, −0.04 and β **BDE-153** = −0.61, 95% CI: −1.11, −0.11). Associations for **BDE-28** in boys were not statistically significant and no associations were observed in girls.

In the same birth cohort, a larger study population was included to assess associations between POPs and anogenital distance at 4 years of age (García-Villarino et al., 2020). In this study, POPs (including **BDE-28**, -**47**, -**99**, -**153**, -**154**, -**209**) were measured in blood samples of 155 mothers and in cord blood samples of 229 infants. PBDEs were analysed by tertiles if more than 50% of samples were > LOD and dichotomised to ≤ LOD and > LOD if less than 50% of samples were > LOD. In males, **BDE-209 in** maternal blood ($n = 74$) was associated with a decreased anoscrotal distance (> LOD vs. < =LOD: $\beta = -0.031$, 95% CI: −0.058, −0.006) and **BDE-153** in cord blood ($n = 116$) was associated with an increase in anoscrotal distance (> LOD vs. ≤ LOD: $\beta = 0.023$, 95% CI: 0.001, 0.045). **BDE-153** in cord blood was also associated with a decrease in anofourchetal distance in girls ($n = 113$) of borderline statistical significance (> LOD vs. ≤ LOD: $\beta = -0.021$, 95% CI: −0.043, −0.000).

Luan et al. (2019) in the Shanghai-Minhang Birth Cohort Study (S-MBCS, $n = 192$) assessed the association between the levels of nine PBDEs (cord blood) and anopenile distance and anoscrotal distance in boys at birth, and at 6, 12 and 48 months of age. **BDE-47** had the highest detection rate (83.68%) and the highest median concentration (0.18 ng/g lipid). Significant reductions in anoscrotal distance were observed at 12 months ($\beta = -5.57$, 95% CI: −9.89, −1.25) and at 48 months of age ($\beta = -4.32$, 95% CI: −8.18, −0.46) in the fourth compared to first quartile of **BDE-47** levels. Reductions in anoscrostal distance were also observed at 12 months of age for comparison between the fourth and first quartile of Sum 4 PBDEs levels ($\beta = -5.13$, 95% CI: −9.89, −1.25).

In the same S-MBCS birth cohort Luan et al. (2021) also assessed associations between prenatal PBDE levels and anogenital distance in girls at ages 0–4 years. The same nine PBDEs were measured in cord plasma collected from 148 girls at birth, and 5 PBDEs and their sum were included in the analyses (**BDE-28**, -**47**, -**99**, -**100**, -**153**). Two anogenital distance metrics were measured (AGD_{AC}: from the anterior surface of the clitoral hood to the centre of the anus, and AGD_{AF}: from the posterior end of the fourchette to the centre of the anus) in 142, 114, 104 and 120 girls at birth, and at 6, 12 and 48 months of age, respectively. In categorical analyses, comparing PBDE concentrations ≥ 75th with < 75th percentile, associations for AGD_{AF} were statistically significant for **BDE-47**, **-99** and -**100** at 6 months of age ($\beta = 2.34$, 95% CI: 0.21, 4.48 for **BDE-47**; $\beta = 2.21$, 95% CI: 0.05, 4.36 for **BDE-99**; $\beta = 2.12$, 95% CI: 0.01, 4.23 for **BDE-100**), and for **BDE-99** and **-100** at 48 months of age ($\beta = 4.49$, 95% CI: 1.27, 7.71 for **BDE-99**; $\beta = 5.04$, 95% CI: 1.87, 8.22 for **BDE-100**). A statistically significant continuous association was observed for Sum 5 PBDEs and AGD_{AF} at 6 months of age ($\beta = 2.48$, 95% CI: 0.61, 4.34) and between **BDE-47** and AGD_{AF} at 12 months of age ($\beta = 1.93$, 95% CI: 0.13, 3.72). Statistically significant categorical (≥ 75th vs. < 75th percentile) associations with AGD_{AC} were observed for **BDE-99, -100, -153** and Sum 5 PBDEs at 48 months of age ($\beta = 7.62$, 95% CI: 2.59, 12.64 for **BDE-99**; $\beta = 7.04$, 95% CI: 2.01, 12.07 for **BDE-100**; $\beta = 5.41$, 95% CI: 0.45, 10.38 for **BDE-153**; $\beta = 5.05$ mm, 95% CI: 0.09, 10.01 for Sum 5 PBDEs). A consistent pattern of positive associations (increased AGD with increasing PBDE concentration) was also observed between prenatal concentrations of PBDEs and anogenital distance across the ages in linear mixed models; these were statistically significant for categorical **BDE-47**, **-99**, **-100**, **-153** and Sum 5 PBDEs with AGD_{AF}, for continuous **BDE-47** and Sum 5 PBDEs with AGD_{AF}, and for categorical **BDE-99**, **-100**, Sum 5 PBDEs with AGD_{AC}.

The S-MBCS birth cohort was further used to study the association between cord blood levels of PBDEs and the second to fourth digit ratio at 4 years of age (2D:4D), which is assumed to be a biomarker of prenatal sex steroid exposure, correlating negatively with prenatal testosterone and positively with prenatal oestrogen ($n = 281$) (Chen et al., 2021). Five PBDEs and their sum were included in analyses (**BDE-28**, -**47**, -**99**, -**100**, -**153**) and analysed in three categories (< LOD, LOD-median, > median). In girls ($n = 121$), statistically significant associations were observed between PBDEs and left-handed 2D:4D increases (feminisation) for: **BDE-47** (β high vs. low level = 0.0247, 95% CI: 0.0017, 0.0477), **BDE-100** ($\beta = 0.0264$, 95% CI: 0.0087, 0.0441) and Sum 5 PBDEs ($\beta = 0.0201$, 95% CI: 0.0027, 0.0374). Also, the average 2D:4D for both hands was associated with the Sum 5 PBDEs ($\beta = 0.0201$, 95% CI: 0.0027, 0.0374). No associations were observed for the right hand in girls. For boys ($n = 180$), PBDE levels were statistically significantly associated with higher (feminised) 2D:4D for both hands, and for the average of the two hands, for **BDE-100** ($\beta = 0.0147$, 95% CI: 0.0005, 0.0289 for the left hand; $\beta = 0.0182$, 95% CI: 0.0046, 0.0318 for the right hand) and **BDE-153** (β high vs. low level = 0.0162, 95% CI: 0.0017, 0.0307 for the left hand; $\beta = 0.0152$, 95% CI: 0.0011, 0.0294 for the right hand).

In the Pregnancy Infection and Nutrition (PIN) Babies cohort in North Carolina (Hoffman et al., 2016), PBDE concentrations in human milk collected at 3 months of age were associated with child's height and weight measures through to age 36 months of age in 246 mother–child pairs. Five PBDE congeners were measured: **BDE-28**, -**47**, -**99**, -**100** and -**153**. Outcomes were child's weight-for-age, height-for-age and weight-for-height z-scores. Overall, PBDE levels in via human milk were not associated with early-life anthropometric measures. When stratified by sex, associations did not follow a consistent pattern and did not reach statistical significance.

The study by Gross et al. (2020) described above, in a case–control study of 52 cases with overweight at 18 months and 46 control infants, did not find an association between levels of **BDE-28**, -**47** and -**99** measured in dried blood spots collected at birth and overweight at 18 months.

Li, Ma, et al. (2020) assessed associations between PBDEs measured in human milk samples (within 2 months after delivery) and child growth measures at 42 weeks, 6 months and 12 months of age, in 77 cases with fetal growth restriction and 159 health control births. 18 PBDEs were measured. Outcomes were z-scores of the child's head circumference-for-age, length-for-age, weight-for-age and weight-for-length. The sum of BDE-28-153 and the sum of BDE-28-209 were associated with reduced head circumference-for-age in boys with fetal growth restriction (mean difference - 0.71, 95% CI: −1.22, −0.22; and −0.88, 95% CI: −1.31, −0.33). **BDE-153** and **BDE-196** concentrations were associated with a reduction in body length in boys with fetal growth restriction (mean difference - 0.28, 95% CI: −0.48, −0.07; and −0.52, 95% CI: −0.91, −0.14). **BDE-154** was associated with greater weight and weight-for-length in boys in the healthy group, with each 10 ng/g lipid increase in the concentration of **BDE-154** correlated with a 0.16 increase in weight-for-age and weight-for-length ($p < 0.05$; no 95% CI given). No significant association between PBDE levels and body length, weight or head circumferences in either healthy or fetal growth restricted girls.

To summarise, for the outcomes measured in the early years after birth (anogenital distance, 2nd to 4th digit ratio, infant growth), the number of studies for each outcome is small, the population size in each study is small ($n < 300$), and results are generally not consistent between studies, so that conclusions cannot be drawn at this stage. It is noted that reductions in anogenital distance in boys are reported in the two main studies on this topic (García-Villarino et al., 2018, 2020; Luan et al., 2019), even though the PBDE congeners for which statistically significant associations were found do not coincide.

3.1.3.8 | *Immune system*

In the previous EFSA Opinion on PBDEs (EFSA CONTAM Panel, 2011b), no epidemiological data on endpoints related to immunity were assessed. Since then, 6 studies were identified assessing the association between exposure to PBDEs and clinical endpoints such as atopy and/or asthma in childhood (see Table 28).

The evidence base included in the current Opinion and pertaining to asthma and/or atopy consists of two cohort studies, one nested case control study and three cross-sectional studies where the PBDE exposure was assessed simultaneously or even later than the outcome ascertainment. The sample size of the included observational studies ranged from 81 to 2040 participants. The evaluated populations came from EU countries (Finland, Sweden, multi-centre (UK, France, Spain, Lithuania, Norway, Greece)), two from China and one from Japan.

The populations under study were diverse. PBDE exposure was assessed via biomarkers in serum in four studies while another two studies used house dust. A variety of binary endpoints were assessed including asthma and atopy.

In the following section, the evidence stemming from cohort and nested case control studies on atopy and asthma is reported in detail. The detailed information on cross-sectional studies is provided in Annex D (Table D.9).

TABLE 28 Overview of epidemiological studies identified on the association between exposure to PBDEs and effects in the immune system.

Reference	Study design	Matrix	Endpoint
Ochiai et al. (2014). A pilot study for foetal exposure to multiple persistent organic pollutants and the development of infant atopic dermatitis in modern Japanese society	Cohort	Umbilical cord	Atopic dermatitis
Canbaz et al. (2016). Exposure to organophosphate and polybrominated diphenyl ether flame retardants via indoor dust and childhood asthma	Nested case control	House dust	Childhood asthma
Meng, Feng, et al. (2016). Internal exposure levels of typical POPs and their associations with childhood asthma in Shanghai, China	Cross-sectional	Serum	Childhood Asthma
Meng, Nie, et al. (2016). Typical halogenated persistent organic pollutants in indoor dust and the associations with childhood asthma in Shanghai, China	Cross-sectional	House dust	Childhood Asthma
Koskinen et al. (2016). Common environmental chemicals do not explain atopy contrast in the Finnish and Russian Karelia	Cross-sectional	Serum	Atopy
Granum et al. (2020). Multiple environmental exposures in early-life and allergy-related outcomes in childhood	Cohort	Maternal serum	Allergy related outcomes (rhinitis, itchy rash, eczema, food allergy)

Canbaz et al. (2016) in a case control study nested within the Swedish BAMSE (Barn, Allergy, Milieu Stockholm Epidemiology; $n = 220$) birth cohort investigated whether the concentrations of 21 PBDEs (**BDE-28**, -**47**, -**49**, -66, -71, -77, -85, -**99**, -**100**, -119, -126, -**138**, -**153**, -**154**, -156, -**183**, 184, -191, -196, -197, -**209**) in indoor dust are associated with the development of childhood asthma at 4 or at 8 years. No statistically significant associations were observed for PBDEs.

Ochiai et al. (2014) in a subgroup of a birth cohort in Japan ($n = 81$) investigated whether the concentrations of 27 PBDEs (BDE-3, -7, -15, -17, -**28**, -**47**, -**49**, -66, -71, -77, -85, -**99**, -**100**, -119, -126, -**138**, -**153**, -**154**, -156, -**183**, -184, -191, -196, -197, -206, -207, -**209**) in umbilical cord blood were associated with total IgE and the development of childhood atopic dermatitis at 7 months of age. No statistically significant associations were observed for PBDEs and IgE levels. There was a statistically significant association between the Sum 27 PBDEs (per tertile) and childhood atopic dermatitis at 7 months (OR: 0.263, 95% CI: 0.084, 0.821 for the middle tertile; 0.136, 95% CI: 0.037, 0.501 for the high tertile).

Granum et al. (2020) using the European Human Early-Life Exposome (HELIX) multi-cohort performed an exposome-wide association study that also assessed the associations between exposure to **BDE-47** and -**153** and allergy-related outcomes (rhinitis, itchy rash, eczema, food allergy; $n = 1270$) in children aged 6–11 years. No statistically significant associations were identified for the two PBDEs under study.

The three cross-sectional studies assessed the association between atopy and asthma in childhood do not support any of the associations under study.

In summary, there is a limited but growing body of epidemiological research in the field of adverse events related to PBDEs exposure and endpoints related to immunity. The evidence based on asthma and atopy in childhood did not exhibit consistent statistically significant associations. Thus, the currently available body of evidence is characterised by only a small number of prospective studies, short follow up periods, relatively small sample sizes, considerable heterogeneity in the assessed populations, exposures and outcomes, varying methodological quality and effect inconsistency.

Based on the above, the currently available evidence coming from human studies on immunity cannot be used for hazard characterisation.

3.1.3.9 | *Cancer*

In the previous EFSA Opinion on PBDEs (EFSA CONTAM Panel, 2011b), limited epidemiological data on any association between exposure to PBDEs and the risk of cancer were identified. Since then, 13 studies were identified assessing the association between exposure to PBDEs and any outcome related to cancer (see Table 29).

The evidence base included in the current Opinion consists of one cohort study, one nested case control and eight cross-sectional studies where the PBDE exposure was assessed simultaneously or even later than the outcome ascertainment. The sample size of the included observational studies ranged from 91 to 1838 participants. One of the evaluated populations came from EU countries (Greenland), one from Singapore, two from China, five from the USA.

The populations under study were diverse. PBDE exposure was assessed in serum in most of the studies. The outcomes assessed included thyroid cancer, prostate cancer, breast cancer, leukaemia and NHL.

In the following paragraphs, the evidence related to thyroid cancer ($n = 5$) and breast cancer ($n = 6$) is reported in detail. The detailed information on the remaining cross-sectional studies on childhood leukaemia ($n = 1$) and prostate cancer ($n = 1$) is provided in Annex D (Table D.10).

TABLE 29 Overview of epidemiological studies identified on the association between PBDEs exposure and cancer risk.

Reference	Study design	Population studied Matrix analysed	Endpoint
Hurley et al. (2011). Adipose levels of polybrominated diphenyl ethers and risk of breast cancer	Cross-sectional	Adipose tissue	Breast Cancer
Holmes et al. (2014). Case–control study of breast cancer and exposure to synthetic environmental chemicals among Alaska Native women	Cross-sectional	Serum	Breast cancer
Ward et al. (2014). Residential levels of polybrominated diphenyl ethers and risk of childhood acute lymphoblastic leukaemia in California	Cross-sectional	House dust	Acute lymphoblastic leukaemia
Aschebrook-Kilfoy et al. (2015). Polybrominated diphenyl ethers and thyroid cancer risk in the prostate, colorectal, lung, and ovarian cancer screening trial cohort	Case control	Serum	Thyroid cancer All thyroid cancers Papillary cancer
Pi et al. (2016). Associations of serum organohalogen levels and prostate cancer risk: Results from a case–control study in Singapore	Cross-sectional	Serum	Prostate cancer
Wielsoe et al. (2017). Serum levels of environmental pollutants is a risk factor for breast cancer in Inuit: a case control study[a]	Cross-sectional	Serum	Breast cancer
Hoffman et al. (2017). Exposure to flame retardant chemicals and occurrence and severity of papillary thyroid cancer: A case–control study	Cross-sectional	House dust	Papillary thyroid cancer
He et al. (2018). Adipose tissue levels of polybrominated diphenyl ethers and breast cancer risk in Chinese women: A case–control study	Cross-sectional	Adipose tissue	Breast cancer
Hurley et al. (2019). A breast cancer case–control study of polybrominated diphenyl ether (PBDE) serum levels among California women	Cross-sectional	Serum	Breast cancer
Deziel et al. (2019). Exposure to Polybrominated Diphenyl Ethers and a Polybrominated Biphenyl and Risk of Thyroid Cancer in Women: Single and Multi-Pollutant Approaches	Cross-sectional	Serum	Thyroid cancer
Huang et al. (2020). polybrominated diphenyl ethers, polybrominated biphenyls, and risk of papillary thyroid cancer: a nested case–control study	Case control	Serum	Thyroid cancer
Mancini et al. (2020). Plasma concentration of brominated flame retardants and postmenopausal breast cancer risk: a nested case–control study in the French E3N cohort	Case control	Plasma	Breast cancer
Zhang, Hu, et al. (2021). Plasma polybrominated diphenyl ethers, urinary heavy metals and the risk of thyroid cancer: A case–control study in China	Cross-sectional	Plasma	Thyroid cancer

[a]The authors reported that the concentrations of PBDEs were < LOD and no further statistical analysis was presented. Thus the study is not further considered in the Opinion.

Thyroid cancer

Huang et al. (2020) in a nested case control study in USA ($n = 1484$) assessed the association between serum concentrations of 11 PBDEs (BDE-17, -**28**, -**47**, -66, -85, -**99**, -**100**, -**153**, -**154**, -**183**, -**209**) and thyroid cancer. **BDE-28** was associated with significantly increased risk of classical papillary thyroid cancer (for the third tertile vs. < LOD, OR = 2.09, 95% CI: 1.05, 4.15; *P* for trend = 0.02), adjusting for other congeners, BMI and branch of military service. This association was observed mainly for larger classical papillary thyroid cancer (tumour size > 10 mm), with a significantly stronger association among women than men (*P* for interaction = 0.004). No consistent associations were observed for other congeners, including those at higher concentrations.

Aschebrook-Kilfoy et al. (2015) investigated whether serum concentrations of PBDEs (BDE-17, -**28**, -**47**, -66, -85, -**99**, -**100**, -**153**, -**154**, -**183**, and their sum) were associated with thyroid cancer using a nested case–control study within the prostate, lung, colorectal and ovarian cancer screening trial ($n_{cases} = 104$, $n_{controls} = 208$). No statistically significant associations were identified.

Hoffman et al. (2017) in a cross-sectional study on the USA ($n = 140$) investigated the association between PBDE levels (**BDE-47**, -**99**, -**100**, -**153**, -**154**, -**209**) in house dust and thyroid cancer. In this small study, higher levels of **BDE-209** in house dust were associated with increased odds of thyroid cancer (OR = 2.29, 95% CI: 1.03, 5.08, adjusted for participant age and house-hold income).

Deziel et al. (2019) in a cross-sectional study in the USA ($n = 500$) investigated the relationship between PBDE exposure (BDE-17, -**28**, -**47**, -85, -**99**, -**100**, -**153**, -**154**, -**183**, -**209**) and papillary thyroid cancer. Seven congeners (**BDE-28**, **47**, **99**, **100**, **153**, **209**) plus PBB-153 were measured in > 80% of samples. **BDE-47** was present at the highest concentrations, with a median (IQR) concentration among controls of 7.28 ng/g lipid (4.04–15.33). Two statistically significant associations were observed of opposite direction. In single-pollutant models, a decreased risk was observed at the highest category of **BDE-209** exposure (> 90th percentile) compared with the reference (≤ median; OR = 0.47; 95% CI: 0.23, 0.98). No other statistically significant associations were observed. In the multi-pollutant models, an interquartile range increase in **BDE-100** concentrations was associated with increased thyroid cancer risk (OR = 1.18; 95% CI, 1.01, 1.38).

Zhang, Hu, et al. (2021) in a cross-sectional study from China ($n = 616$) assessed the levels of eight PBDEs in human serum (**BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183**, -**209**) and the odds of thyroid cancer. **BDE-209** accounted for 80% of the total concentration. A joint-effect interaction term was inserted into the logistic regression models to assess the multiplicative interaction effects of PBDEs-heavy metals (Cd, Pb, As and Hg) on thyroid cancer risk. PBDEs levels were classified into 'high', 'moderate' and 'low' exposure groups according to the tertiles among the controls. A number of statistically significant associations were reported. After adjustment for potential confounders, the dose–response relationships between the PBDE congeners and thyroid cancer risk were still significant (p trend < 0.05). Both the 'moderate' and 'high' exposure levels of **BDE-47**, -**99**, -**183** and Sum 8 PBDEs could increase the risk of thyroid cancer ('moderate' exposure vs. 'low' exposure: OR = 2.30, 95% CI: 1.21, 4.35; OR = 4.07, 95% CI: 1.89, 8.74; OR = 2.30, 95% CI: 1.16, 4.57; OR = 1.78, 95% CI: 1.02, 3.13, respectively; 'high' exposure vs. 'low' exposure: OR = 2.48, 95% CI: 1.30, 4.72; OR = 4.43, 95% CI: 2.10, 9.32; OR = 4.53, 95% CI: 2.37, 8.64; OR = 2.47, 95% CI: 1.43, 4.24, respectively). For **BDE-28**, -**209**, and Sum 7 PBDEs (without **BDE-209**), only 'high' exposure levels (< 2.90, > 131.39 and > 22.63 ng/g lipid, respectively) were associated with increased thyroid cancer risk.

Breast cancer

Mancini et al. (2020) conducted a nested case control study in France ($n = 394$) to assess the association between plasma levels of PBDE congeners (**BDE-28**, -**47**, -**99**, -**100**, **153**, -**154**) and breast cancer. No evidence of an association was reported.

Hurley et al. (2011) conducted a cross-sectional study in the USA evaluating the adipose PBDE concentrations (**BDE-47**, -**99**, -**100**, -**153**, -**154**) and breast cancer ($n = 134$). Adjusted ORs for the highest compared with lowest levels of PBDE exposure yielded no statistically significant results. Holmes et al. (2014) conducted a cross-sectional study in the USA (Alaska Native population) evaluating the serum **PBDE-47** concentrations and breast cancer ($n = 170$). Adjusted analyses yielded no statistically significant results.

Hurley et al. (2019) in a cross-sectional study in the USA ($n = 1838$) investigated the association between serum levels of **BDE-47**, -**100** and -**153** and breast cancer. Adjusted analyses yielded no statistically significant results.

He et al. (2018) conducted a cross-sectional study in China evaluating the concentrations of 14 PBDEs in adipose tissue (BDE-17, **-28, -47**, -66, -71, -85, -**99**, -**100**, -138, -**153**, -**154**, -**183**, -190, -**209**) and breast cancer ($n = 374$). In the adjusted univariate models, breast cancer risk was increased with both 2nd and 3rd tertiles vs. the 1st tertile of **BDE-47** level (OR, 95% CI) (2.05 (1.08, 3.92); 5.47 (2.96–10.11), respectively) and **BDE-209** level (2.48 (1.30, 4.73; 4.72 (2.52, 8.83), respectively), and with the 3rd tertile of **BDE-28** level (2.83 (1.63, 4.92)), **BDE-99** (3.22 (1.85, 5.60)), **BDE-100** (5.45 (2.90, 10.23)), **BDE-138** (2.40 (1.37, 4.20)), **BDE-153** (1.74 (1.02, 2.97)), **BDE-154** (1.84 (1.05, 3.22)), and Sum 14 PBDE levels (1.83 (1.07, 3.14)) but decreased with the 3rd tertile of BDE-71 level (0.38 (0.22, 0.65)). After stratifying by ER-positive or -negative status, the adjusted results were similar for ER-positive patients except for **BDE-153** and -**154**, with no statistical significance. In the multivariate model for all cases, age, menarche age, **BDE-47**, -71, -**99**, -**100**, -**183** and -**209** were independent factors associated with breast-cancer risk.

In summary, there is a growing body of epidemiological research in the field of adverse events related to PBDEs exposure and endpoints related to cancer. For thyroid cancer, five studies were identified of which two were longitudinal. A statistically significant association between **BDE-28** and thyroid cancer was reported in one of the nested case–control studies in the USA that was further replicated in one cross-sectional study in China and only for the comparison between 'high' vs. 'low' levels. No consistent association were observed in the remaining studies. For breast cancer, one nested case control and 5 cross-sectional studies were identified mostly from the USA. Statistically significant results were seen only in one cross-sectional study from China without further replication. Thus, the currently available body of evidence is characterised by only a very small number of prospective studies, short follow up periods, relatively small sample sizes, considerable heterogeneity in the assessed populations, exposures and outcomes, varying methodological quality and effect inconsistency.

Based on the above, the currently available evidence coming from human studies on cancer cannot be used for hazard characterisation.

3.1.3.10 | *Other endpoints*

This section provides a brief summary of epidemiological studies on other endpoints that could not be classified in the above sections on human evidence. These endpoints include mortality (2 studies), lung function (3 studies), hyperuricemia (1 study), celiac disease (1 study), microbiome (3 studies), and inflammatory and oxidative stress related biomarkers (8 studies) and epigenetics related biomarkers (15 studies). The studies are listed in Table 30 and detailed information on these studies related to other endpoints is provided in Annex D (Table D.11).

Mortality was studied in the NHANES dataset including 483 adults over 60 years of age (Fry & Power, 2017). There were no statistically significant associations between PBDE serum levels and all-cause or cause-specific mortality, although an association of borderline significance ($p = 0.06$) was noted between **BDE-153** and all-cause mortality (HR = 1.07 per 1 SD unit increase in **BDE-153**, 95% CI: 1.00, 1.14). In a Swedish cohort of 992 adults over 70 years, there was no association between **BDE-47** and all-cause mortality (Lind et al., 2019).

Lung function was studied in the HELIX cohort including 1033 mother–child pairs (Agier et al., 2019). Prenatal and postnatal **BDE-47** and -**153** levels were not associated with lung function in 6–11 year old children, measured as the forced expiratory volume in 1 s. Further, in a cross-sectional study of 596 children, school dust levels of Sum 20 PBDEs showed a statistically significant correlation with some lung function parameters (Wallner et al., 2012). Another cross-sectional study

in a small sample of 33 adolescents found statistically significant correlations between Sum 7 PBDE levels and some measures of impaired lung function such as forced expiratory volume in 1 s (Leijs et al., 2018).

The association between serum PBDE levels (**BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183**) and hyperuricemia (high urinary uric acid levels) was studied in a cross-sectional analysis of 365 adults in Spain (Arrebola et al., 2019). **BDE-153** was inversely associated with risk of hyperuricemia.

Celiac disease was studied as an endpoint in a small case–control study of 28 children with celiac disease compared to 53 controls, in which PBDEs (**BDE-28**, -**47**, -**99**, -**100**, -**153**, -**183**, -**209**) were analysed in blood serum (Gaylord et al., 2020). In male children, serum **BDE-153** levels were associated with an increased risk of celiac disease.

The gut microbiome has recently become of interest in epidemiological studies of chemical exposures because of its potential role in human health. Related to this, gut microbiome composition has been investigated in two studies in relation to exposure to PBDEs. One cross-sectional study analysed infant gut microbiota and human milk concentrations of 28 chemicals, including 6 PBDE congeners (**BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**), at 1-month post-partum in 267 mother–child pairs (Iszatt et al., 2019). **BDE-28** was associated with less microbiome diversity. The other study was a pilot study that examined the association between PBDEs (**BDE-47**, -**99**, -**100**, -**153**) measured in maternal plasma during pregnancy and at delivery, and the child gut microbiome at 6–8 years in 43 mother–child pairs (Laue et al., 2019). Prenatal PBDE levels were associated with changes in microbiome profiles. Additionally, one study analysed cross-sectional NHANES data on one component of the nasal microbiome: *Staphylococcus aureus* (Eggers et al., 2020). Eleven PBDEs (including **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154** and -**183**) were evaluated in a mixture analysis in 1756 subjects and were not associated with the nasal colonisation by *S. aureus*. Large prospective studies will be needed to further explore these associations. Also, it is still unclear what the clinical implications of changes in microbial structure are.

Another eight studies assessed a wide range of inflammatory biomarkers investigating potential pathways involved in PBDE toxicity. The studies on biomarkers of inflammation were mostly cross-sectional. Endpoints consisted of a long list of biomarkers related to oxidative stress (Kumar, Lind, Salihovic, van Bavel, Ingelsson, & Lind, 2014; Yuan et al., 2017), inflammation (Kumar, Lind, Salihovic, van Bavel, Ekdahl, et al., 2014; Schaebel et al., 2017; Yuan et al., 2017; Zota, Geller, et al., 2018), immune system (Kumar, Lind, Salihovic, van Bavel, Ekdahl, et al., 2014) and non-alcoholic fatty liver disease (Rantakokko et al., 2015, Midya et al., 2022), as full listed in Table 30 and **Appendix D**. The large variation in biomarkers between studies and mostly cross-sectional study designs preclude an integrative assessment of the evidence at this stage. In the only prospective study in this group, liver injury and hepatocellular apoptosis was assessed in relation to prenatal **BDE-47** and -**153** levels by Midya et al. (2022) using a collaborative network of six ongoing, population-based prospective birth cohort studies from six European countries (France, Greece, Lithuania, Norway, Spain and the UK; HELIX study, $n = 1108$). Child serum levels of ALT, AST, γ-glutamyltransferase (GGT) and CK-18 were measured at 6 to 11 years of age and risk for liver injury was defined as having ALT, AST and/or GGT levels above the 90th percentile. No association was identified for liver injury. A statistically significant association was observed for **BDE-153** and CK-18 ($\beta = 5.88$; 95% CI, 3.03, 8.74).

Finally, 15 studies on epigenetics assessed DNA methylation, gene expression and telomere length and their involvement in PBDE toxicity. These studies were mostly cross-sectional (see Table 30) and included the following markers: global DNA methylation (Lind et al., 2013, Kappil et al., 2016), gene-specific DNA methylation (Kim et al., 2010; Kim, Cho, et al., 2018; Huen et al., 2014; Dao et al., 2015; Zhao et al., 2016), gene expression (Karmaus et al., 2011; Xu et al., 2013; Li et al., 2015; He et al., 2015; Kappil et al., 2016) and cellular aging markers such as telomere length and mitochondrial DNA content (Shin et al., 2010; Guzzardi et al., 2016; Zota, Geller, et al., 2018; Vriens et al., 2019). The studies are listed in Table 30 and details provided in **Appendix D**. The large variation in epigenetic and gene expression markers between studies and mostly cross-sectional study designs preclude an integrative assessment of the evidence at this stage.

TABLE 30 Overview of epidemiological studies identified on the association between PBDEs levels and effects not covered in previous sections.

Reference[a]	Study design	Matrix	Endpoint
Clinical endpoints			
Wallner et al. (2012). Indoor air in schools and lung function of Austrian school children	Cross-sectional	School dust Children	Lung function
Fry and Power (2017). Persistent organic pollutants and mortality in the United States, NHANES 1999–2011	Cohort	Serum	Mortality
Leijs et al. (2018). Exposure to environmental contaminants and lung function in adolescents-is there a link?	Cross-sectional	Serum	Lung function
Lind et al. (2019). Association of exposure to persistent organic pollutants with mortality risk: an analysis of data from the Prospective Investigation of Vasculature in Uppsala Seniors (PIVUS) Study	Cohort	Plasma	Cardiovascular mortality
Agier et al. (2019). Early-life exposome and lung function in children in Europe: an analysis of data from the longitudinal, population-based HELIX cohort	Cohort	Serum (maternal and child)	Lung function
Arrebola et al. (2019). Associations of multiple exposures to persistent toxic substances with the risk of hyperuricemia and subclinical uric acid levels in BIOAMBIENT.ES study	Cross-sectional	Serum	Prevalence of hyperuricemia
Gaylord et al. (2020). Persistent organic pollutant exposure and celiac disease: A pilot study	Case–control	Serum	Celiac disease
Inflammatory biomarkers			
Midya et al. (2022). Association of prenatal exposure to endocrine-disrupting chemicals with liver injury in children	Cohort	Serum	ALT, AST, γGT, CK-18
Kumar, Lind, Salihovic, van Bavel, Ingelsson, and Lind (2014). Influence of persistent organic pollutants on oxidative stress in population-based samples	Cross-sectional	Serum Adults	Oxidative stress markers: GSH: reduced glutathione; oxidised glutathione; total glutathione; oxidised LDL; Oxidised-LDL antibodies; conjugated dienes; baseline conjugated diene of LDL; homocysteine; total anti-oxidative capacity
Kumar, Lind, Salihovic, van Bavel, Ekdahl, et al. (2014). Persistent organic pollutants and inflammatory markers in a cross-sectional study of elderly swedish people: The PIVUS Cohort	Cross-sectional	Serum Adults	Inflammatory markers: vascular cell adhesion molecule 1 (VCAM1), intercellular adhesion molecule 1 (ICAM1), E-selectin, C-reactive protein (CRP), total leucocyte count, TNFα, MCP1, IL6
Kumar, Lind, Salihovic, van Bavel, Ekdahl, et al. (2014). Influence of persistent organic pollutants on the complement system in a population-based human sample	Cross-sectional	Serum Adults	Complement system markers: protein complement 3 (C3), 3a (C3a), 4 (C4) and C3a/C3 ratio
Rantakokko et al. (2015). Persistent organic pollutants and non-alcoholic fatty liver disease in morbidly obese patients: a cohort study	Cohort	Adults Serum	Liver histology, alanine transaminase (ALT)
Schaebel et al. (2017). The influence of persistent organic pollutants in the traditional Inuit diet on markers of inflammation	Cross-sectional	Serum	Inflammation markers: YKL-40, hsCRP levels
Yuan et al. (2017). Serum polybrominated diphenyl ether (PBDE) concentrations in relation to biomarkers of oxidative stress and inflammation: The National Health and Nutrition Examination Survey 2003–2004	Cross-sectional	Serum	Oxidative stress markers: γ-glutamyltransferase (GGT), bilirubin. Inflammation markers: absolute neutrophil count (ANC), alkaline phosphatase (ALP) and C-reactive protein (CRP)
Zota, Geller, et al. (2018). Association between persistent endocrine-disrupting chemicals (PBDEs, OH-PBDEs, PCBs, and PFASs) and biomarkers of inflammation and cellular aging during pregnancy and postpartum[b]	Cohort	Maternal serum	Inflammation markers: interleukin 6 (IL-6), interleukin 10 (IL-10), and tumour necrosis factor (TNF-α)
Gut microbiome			
Iszatt et al. (2019). Environmental toxicants in breast milk of Norwegian mothers and gut bacteria composition and metabolites in their infants at 1 month	Cohort	Human milk	Gut microbial composition

(Continues)

TABLE 30 (Continued)

Reference[a]	Study design	Matrix	Endpoint
Laue et al. (2019). Associations of prenatal exposure to polybrominated diphenyl ethers and polychlorinated biphenyls with long-term gut microbiome structure: a pilot study	Cohort	Plasma (maternal)	Changes in childhood microbiome in faeces
Eggers et al. (2020). Exposure to environmental chemical mixtures is associated with nasal colonisation by Staphylococcus aureus: NHANES 2001–2004	Cross-sectional	Serum	*Staphylococcus aureus* nasal colonisation
DNA methylation and gene expression			
Kim et al. (2010). Association of low-dose exposure to persistent organic pollutants with global DNA hypomethylation in healthy Koreans	Cross-sectional (adults)	Serum	Alu and LINE-1 methylation
Karmaus et al. (2011). Prenatal and concurrent exposure to halogenated organic compounds and gene expression of CYP17A1, CYP19A1, and oestrogen receptor a and b genes	Cross-sectional	Blood	CYP19A1, CYP17A1, ESR 1, ESR2 gene expression
Lind et al. (2013). Global DNA hypermethylation is associated with high serum levels of persistent organic pollutants in an elderly population	Cross-sectional (adults)	Serum	Global DNA methylation
Xu et al. (2013). Placental IGF-1 and IGFBP-3 expression correlate with umbilical cord blood PAH and PBDE levels from prenatal exposure to electronic waste	Cross-sectional	Cord blood / Placenta	IGF-1, IGFBP-3 gene expression
Huen et al. (2014). Effects of age, sex, and persistent organic pollutants on DNA methylation in children	Cohort	Maternal serum	Alu and LINE-1 methylation in newborns and children
Li et al. (2015). Exploring the associations between microRNA expression profiles and environmental pollutants in human placenta from the National Children's Study (NCS)	Cross-sectional	Placenta	654 miRNAs (112 miRNAs consistently expressed in >70% of the samples)
He et al. (2015). Significant accumulation of persistent organic pollutants and dysregulation in multiple DNA damage repair pathways in the electronic-waste-exposed populations	Cross-sectional (adults)	Plasma	ROS activity, micronucleus test, RNAseq profile assay
Dao et al. (2015). Aberrant 5 '-CpG methylation of cord blood TNF alpha associated with maternal exposure to polybrominated diphenyl ethers	Cross-sectional (delivery)	Maternal serum	Promoter methylation of TNFα in cord blood
Kappil et al. (2016). In utero exposures to environmental organic pollutants disrupt epigenetic marks linked to fetoplacental development	Cross-sectional	Placenta	IGF2 / H19 imprint control region methylation, IGF2 and H19 expression, IGF2 loss of imprinting (LOI), global DNA methylation levels
Zhao et al. (2016). Umbilical cord blood PBDEs concentrations are associated with placental DNA methylation	Cross-sectional (delivery)	Cord blood	Placental DNA methylation of LINE1, NR3C1 and IGF2
Kim, Cho, et al. (2018). Prenatal exposure to persistent organic pollutants and methylation of LINE-1 and imprinted genes in placenta: A CHECK cohort study	Cross-sectional (delivery)	Maternal serum	Placental DNA methylation of LINE1, IGF2 and H19
Telomere length			
Shin et al. (2010). Low-dose persistent organic pollutants increased telomere length in peripheral leukocytes of healthy Koreans.	Cross-sectional (adults)	Serum	Leukocyte telomere length
Guzzardi et al. (2016). Exposure to persistent organic pollutants predicts telomere length in older age: results from the Helsinki Birth Cohort Study	Cohort (adults)	Serum	Leukocyte telomere length
Zota, Geller, et al. (2018). Association between persistent endocrine-disrupting chemicals (PBDEs, OH-PBDEs, PCBs, and PFASs) and biomarkers of inflammation and cellular aging during pregnancy and postpartum[b]	Cohort	Maternal serum	Leukocyte telomere length.
Vriens et al. (2019). Exposure to environmental pollutants and their association with biomarkers of aging: a multipollutant approach	Cross-sectional (adults)	Serum	Leukocyte telomere length and mtDNA content

[a]The study by Zhou et al. (2020) entitled 'Effects of Polybrominated Diphenyl Ethers on the Human Body Exposure in E-Waste Dismantling Region' was also identified. However, only an English abstract is available and the study is not further considered in the Opinion.

[b]Listed under inflammatory biomarkers and under telomere length.

3.1.4 | Mode of action

In its previous Opinion, the CONTAM Panel summarised the modes of action potentially underlying the toxicity of PBDEs, focussing on aryl hydrocarbon receptor (AHR)-dependent activity, activation of the constitutive androstane (CAR) and pregnane-X (PXR) receptors, neurotoxicity, changes in thyroid hormone signalling and oestrogenic pathways (EFSA CONTAM Panel, 2011b).

Since then, numerous new studies have been published relating to possible modes of action of PBDEs. Possible effects of PBDEs on the immune system are not well characterised. Effects on the liver are well-established, but tend to be observed at higher doses than other effects, and therefore are not critical for the risk assessment. Reports of effects on lipid and sugar metabolism are inconsistent and do not provide a robust basis for hazard characterisation. Individual PBDE congeners have not been tested for carcinogenicity, but there is evidence of carcinogenicity for the technical products DecaBDE (at high doses) and DE-71. Therefore, the mechanistic data in relation to genotoxicity are of particular importance.

The CONTAM Panel decided to focus its current evaluation of modes of action on the endpoints of most relevance for the hazard characterisation. Therefore, the current mode of action evaluation focuses on activation of biotransformation enzymes regulated via AHR, CAR and PXR, neurotoxicity, thyroid hormone signalling, reproductive and other endocrine related effects, and secondary genotoxicity via oxidative stress.

3.1.4.1 | *AHR mediated effects*

The possible potential of PBDEs to act via the AHR was discussed in the previous CONTAM Opinion on this group of chemicals following reports of both agonistic and antagonistic effects *in vitro* (EFSA CONTAM Panel, 2011b). The Panel concluded that effects of PBDEs occurring through AHR- and anti-AHR activities would only be of minor importance because effects were reported only at micromolar concentrations. It was further concluded that some of the effects reported with technical PBDE products could be due to dioxin-like contaminants (EFSA CONTAM Panel, 2011b). Key to that conclusion was a study investigating the ability of a range of PBDE congeners (**BDE-47**, -77, -**99**, -**100**, -**153**, -**154**, -**183**, -**209**) to induce expression and activity of cytochrome P4501A1 (CYP1A1; measured as ethoxyresorufin-O-deethylase (EROD) activity) after purification with activated charcoal and Celite to remove any contamination with dioxin-like compounds (Peters et al., 2004). None of the PBDE congeners tested induced CYP1A1 activity up to the highest concentration tested (10 μM). However, all PBDEs tested inhibited TCDD-induced (1 nM) EROD activity at concentrations of 1 μM or 10 μM.

Since the previous Opinion, studies addressing AHR-mediated effects of PBDEs and their metabolites include use of reporter-gene assays, animal studies in some cases with genetically modified animals and QSAR models of predicted binding of PBDEs to the AHR.

Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Rescio, et al. (2018) investigated the correlation between *Ahr* genotype and the occurrence of DE-71 induced liver tumours in female Wistar Han rats and found no evidence for such a relationship as treatment related tumours occurred in animals with wildtype, mutant or heterozygous *Ahr* for the single nucleotide polymorphism that renders these Han/Wistar (H/W) (Kuopio) rats resistant to dioxins.

Exposure of MCF-7aroERE cells, which is an oestrogen-dependent cell line, to 20 μM of **BDE-100** resulted in strong upregulation of mRNA for *CYP1A1* (15-fold) and *CYP1B1* as measured by qPCR (Kanaya, Bernal, et al., 2019). Exposure to 20 μM of **BDE-153** caused a smaller (~two-fold) but statistically significant upregulation of the same genes, while 20 μM of **BDE-47** had no effect. Exposure of cells to 20 μM **BDE-100** also resulted in increased CYP1A1 enzymatic activity. Potential contamination of the PBDE solutions with brominated dioxin/furan impurities was assessed by GC–HRMS and concentrations were below the LOD (not specified). Exposure of HepG2 cells to **BDE-209** induced expression of CYP1A1 (Yuan, Sun, et al., 2021). However, induction was relatively weak (maximum 4-fold) and occurred only at concentrations causing cytotoxicity (> 1 μM).

Su et al. (2012) investigated AHR activation by PBDE analogues in the H4IIE-luc rat hepatoma transactivation bioassay at concentrations ranging from 0 to 10,000 μg/L. The authors claimed that the methods of synthesis of the PBDE analogues did not generate any brominated dioxins and/or furans based on analysis by Nuclear Magnetic Resonance and electrospray mass spectrometry, but LOD was not reported (He, Murphy, Yu, Lam, Hecker, Giesy, et al., 2008; Su et al., 2012). It was found that several of these PBDEs activated the AHR in H4IIE-luc cells with some analogues having a maximum efficacy exceeding 50% of the response elicited by TCDD, albeit at high concentrations (2500 μg/L; >4 μM). OH-PBDEs with strong efficacy included 2′-OH-BDE-28, 2′-OH-BDE-68, 6-OH-BDE-47, 6-OH-BDE-85, 6-OH-BDE-90, 2-OH-BDE-123, 4-OH-BDE-90, 6-OH-BDE-137, 3-OH-BDE-100, 2′-OH-BDE-66 and 2′-OH-BDE-25. MeO-PBDEs showed lower AHR activation than did the corresponding OH-PBDEs. In a later investigation with the same lead author, it was observed that sunlight irradiation of the highly brominated **BDE-209** formed degradation products that elicited dioxin-like gene expression profiles in chicken embryonic hepatocytes (Su, Letcher, et al., 2016).

AHR antagonistic activities of **BDE-47** and **-99** were assessed using the DR-H4IIE reporter cell line derived from rat hepatoma cells (Doan et al., 2019). The experiments were performed by co-exposing DR-H4IIE cells to different concentrations of the tested compounds together with a constant saturating TCDD concentration (20 nM). **BDE-47** and **-99** exhibited antagonistic effects, both with a lowest observed effect concentration (LOEC) of 0.25 μM. Using much higher concentrations of **BDE-47**, Tang et al. (2021) found that the lowest concentration tested (10 μM) reduced expression of *Cyp1a1* and *Cyp1b1* mRNA in a murine cell line derived from the organ of Corti (HEI-OC1) with no effect observed on *Cyp2b* gene expression.

Several in silico computational workflows have been generated to predict binding of PBDEs to the AHR. Molecular docking simulations suggested that hydrogen-bond and hydrophobic interactions are the major driving forces for the binding of ligands to AHR, and several key amino acid residues were also identified (Li, Wang, Shi, et al., 2013; Xiao et al., 2021). The

position of Br substitutions was predicted to influence interactions between PBDEs and AHR, including halogen interaction, π-S interaction, π-π stacking interaction and hydrophobic effect. Predicted relative binding affinities were highest for BDE-17, -**153**, and -**154**. The preferential bromination at *para*- and *meta* (particularly 3,3′-)-sites of PBDEs was indicated to be a key molecular determinant to improve the AHR binding affinity of PBDEs (Gu et al., 2012). Including calculated energies of AHR binding interaction, molecular docking scores and experimentally derived AHR binding affinities for PBDEs, strongest binding was predicted for **BDE-49**, **-100**, -**153** and -**154** (Gu et al., 2020). Similarly, Li, Wang, Shi, et al. (2013) predicted that of PBDE congeners commonly occurring in the environment, **BDE-100**, -**153** and -**154** had the highest predicted binding affinities with 60 to 67% of that for BDE-173, which was predicted to be the most potent AHR ligand.

3.1.4.1.1 | *Summary on the MOA for AHR mediated effects*

In summary, there is some evidence that PBDEs and their metabolites can act as ligands of the AHR and have both agonistic and antagonistic effects, generally at micromolar concentrations. New data reporting effects on AHR-activity come mostly from reporter gene assays and in silico simulations, which are interesting but inconclusive in terms of dosimetry *in vivo*. It is also difficult to assess if experimental results were influenced by any contamination with dioxins, which is important in light of evidence that PBDEs purified to remove any contamination with brominated dioxin/furan impurities were unable to activate AHR activity (Peters et al., 2004). Of the different PBDE congeners prevalent in the environment, **BDE-47**, -**49**, -**100**, -**153** and -**154**, including some of their metabolites, appear to be the ones most likely to influence AHR activity. Notably, the PentaBDE technical product DE-71 did not induce AHR dependent liver tumours in rats. It does appear that several PBDEs can inhibit TCDD-induced AHR activity.

3.1.4.2 | *Activation of CAR and PXR*

In its previous Opinion, the CONTAM Panel suggested that many of the changes in liver following exposure of rodents to PBDEs are consistent with CAR and PXR mediated induction of biotransformation enzymes (EFSA CONTAM Panel, 2011b). This conclusion was based on observations *in vivo* (Sanders et al., 2005; Fery et al., 2009; Szabo et al., 2009) and *in vitro* (Pacyniak et al., 2007; Wahl et al., 2008; Fery et al., 2009) that isolated PBDE congeners (**BDE-47**, -**99**, -**153**, -**209**) as well as technical products (DE-71) induce CAR/PXR-dependent gene expression. It was further proposed that hepatic CAR/PXR mediated expression of biotransformation enzymes was responsible for the decreased levels of circulating oestradiol, testosterone and T4 reported in *in vivo* studies with PBDEs.

Since the previous Opinion, a few new studies were identified on PBDE effects on CAR and PXR.

$CAR^{-/-}$ and $PXR^{-/-}$ mice as well as primary human hepatocytes and a human liver cell line (Huh-7) transfected with reporter genes for CAR or PXR activation along with expression constructs for mouse or human CAR or PXR genes (aka steroid X receptor, SXR) were used to investigate the response to **BDE-47** (Sueyoshi et al., 2014). Oral doses of **BDE-47** of 30 mg/kg bw and above in a single administration to wild-type C3H/HeNCrlBR mice induced expression of *Cyp2b10* mRNA. Use of $CAR^{-/-}$ and $PXR^{-/-}$ mice compared with wild type mice on the same genetic background revealed that CAR was responsible for *Cyp2b10* induction with no contribution from PXR. In human primary hepatocytes, 10 and 50 μM **BDE-47** stimulated translocation of CAR from the cytoplasm to the nucleus. Expression of *CYP2B6* and *CYP3A4* were induced in human primary hepatocytes at the lowest concentration of **BDE-47** tested (5 μM). CAR and PXR from human and mouse were activated by **BDE-47** in reporter gene assays. **BDE-47** activated mouse CAR at 50 and 100 μM concentrations while human CAR, human PXR and mouse PXR were activated at 10 μM, which was the lowest concentration tested. These results support earlier observations (Pacyniak et al., 2007) and the conclusion of the previous EFSA Opinion (EFSA CONTAM Panel, 2011b) that CAR and PXR are activated by **BDE-47**.

Binding of PBDEs to the ligand binding domain of CAR from mouse and harbour seal was assessed by surface plasmon resonance and in silico docking experiments (Dau et al., 2022). PBDEs had more interactions than and higher binding affinities with CARs than did PCBs which were included as a comparison. K_D for binding ranged from 0.9 μM for **BDE-153** to > 10 μM for **BDE-47**. It was concluded that di- or tri-*ortho*-, mono-*meta*- and di-*para*-bromine substitutions were requirements for PBDE binding to CAR.

Upregulation of expression of the nuclear receptors, CAR and PXR, and of the biotransformation enzymes CYP1A2, CYP2B1 and CYP3A1 was observed in male rats exposed to **BDE-209** (100, 300 or 600 mg/kg bw per day) by gavage for 30 days (Lee et al., 2010[47])[28]. Sakamoto et al. (2013) used $CAR^{-/-}$ (C3H/HeNCrl background) and wild-type (C3H/HeNCrlCrlj) mice to investigate the involvement of CAR in hypertrophy and carcinogenesis of the liver in response to oral **BDE-209** exposure (50,000 mg/kg diet for 4 weeks) following diethylnitrosamine initiation. The number of basophilic altered foci/adenomas was increased both in wild-type and $CAR^{-/-}$ mice, leading the authors to suggest that **BDE-209** may act via CAR-independent pathways during hepatocarcinogenesis.

3.1.4.2.1 | *Summary on the MOA for CAR/PXR activation*

In summary, combined evidence from new reports and studies reviewed in the previous EFSA Opinion suggest that several PBDEs are capable of activating CAR/PXR-dependent gene expression, at least at relatively high exposure levels

[47]This study was cited in the previous EFSA assessment on PBDEs (EFSA CONTAM Panel, 2011b) and it is included in the current assessment to provide insight into additional observations by the study authors not reported in the previous Opinion.

(micromolar in cell culture), but that PXR has higher sensitivity than CAR to PBDEs. CAR/PXR-dependent expression of biotransformation enzymes would be expected to accelerate metabolism of steroid and thyroid hormones and provides a possible explanation of decreased concentrations of circulating oestradiol, testosterone and T4 as reported in several studies below (see **Section 3.1.4.4**).

3.1.4.3 | *Neurotoxicity*

In its previous Opinion, the CONTAM Panel concluded that '*the majority of PBDE congeners, with the exception of BDE-209, share mechanisms of neurotoxicity, including (i) induction of oxidative stress, reduction of antioxidant activity, mitochondrial alterations and apoptosis; (ii) interference with calcium homeostasis, and (iii) effects on neurotransmitter systems'. There was also evidence that PBDEs 'can interfere with neural migration, differentiation and cytoskeleton organisation in neural precursor cells in culture*' (EFSA CONTAM Panel, 2011b). For **BDE-209** there was also evidence at that time that neurotoxicity involved effects on calcium homeostasis, apoptosis, and differentiation of neural stem cells. However, for **BDE-209** (and **BDE-100** and -**153**) there was evidence that interaction with the thyroid hormone system could contribute to neurotoxicity.

Since then, new mechanistic studies have been published related to potential neurotoxicity of **BDE-28**, -**47**, -**49**, -66, -88, -**99**, -**153**, -**154**, -175, -**183**, -**209** and various OH-PBDEs.

BDE-47

Newer studies have provided additional evidence for the involvement of oxidative stress, mitochondrial dysfunction and apoptosis in the neurotoxicity of **BDE-47**, and for the molecular changes leading to them. These effects are likely to be interlinked and are not specific to neurotoxicity. However neuronal cells are particularly vulnerable to oxidative stress because relatively high levels of ROS are generated during normal metabolism and neuronal activity (Dingemans et al., 2011). Studies have been conducted in a variety of model systems, including primary neuronal cultures, neuronal cell lines and *in vivo* in mice and rats.

Possible mechanisms leading to **BDE-47** induced ROS production, mitochondrial dysfunction and apoptosis include:

- Activation of the unfolded protein response by increasing the expression of proteins related to the inositol-requiring enzyme (IRE1) pathway in human neuroblastoma SH-SY5Y cells treated at 1–10 μM (Jiang et al., 2012).
- Mitochondrial impairment, up-regulation of p53 and Bax, down-regulation of Bcl-2 and Bcl-2/Bax ratio, enhancement of cytochrome c release and activation of caspase-3 in SH-SY5Y cells treated at 1–10 μM (Zhang, Kuang, et al., 2013).
- Changes in neural gene and protein expression profiles related to calcium homeostasis and excitotoxicity in juvenile mice exposed to **BDE-47** at 0.45 mg/kg bw per day via a fish diet (Rasinger et al., 2014).
- Increased extracellular glutamate, which activated ionotropic glutamate receptors, leading to increased intracellular calcium levels, oxidative stress and cell death in cultured cerebellar neurons (treated at 5 μM) prepared from 7-day old mice (Costa et al., 2016).
- Altered calcium homeostasis mainly due to extracellular Ca^{2+} influx resulting in collapse of the mitochondrial membrane potential, cytochrome c release, caspase-3 activation and apoptosis in SH-SY5Y cells treated at 5–10 μM. Similar effects were seen in the hippocampus of mice dosed at 5 and 10 mg/kg bw on PND10 (Zhang, Chen, Wu, et al., 2016).
- Overproduction of ROS in a mitochondria-mediated pathway in Neuro-2a cells treated at 10–20 μM (Chen, Tang, Zhou, Xu, et al., 2017).
- Upregulation of nuclear TAR-DNA binding protein-43 (TDP-43), in the hippocampus of adult mice dosed with **BDE-47** by gavage for 8 weeks at 20 mg/kg bw per day, which was associated with impaired cognition (Zhuang et al., 2017).
- Autophagosome accumulation mediated by oxidative stress in SH-SY5Y cells treated at 5 μM (Zhang, Li, et al., 2017) and by blockage of autophagosome degradation at 10–20 μM in PC12 cells (a neuronal-like cell line), which preceded induction of apoptosis (Li, Ma, et al., 2019).
- Autophagy impairment in hippocampal neurons of adult offspring of rats orally administered 0.1, 1.0 or 10.0 mg/kg bw per day, 10 days before mating until PND21, which was associated with reduction in spatial learning and memory performances (Li, Ma, et al., 2019).
- Increased ROS, malondialdehyde, and protein carbonyl levels in the hippocampus of adult mice dosed with **BDE-47** by gavage for 8 weeks at 20 mg/kg bw per day, related to overexpression of the neuroprotective protein DJ-1 in the hippocampus (Zhuang et al., 2018).

Mechanistic studies related to neurotransmitters have identified:

- Changes in global gene expression in the cerebral cortex of mice indicated disturbance of the glutamate signalling system at a dose level not resulting in over neurobehavioral effects when **BDE-47** was orally administered to their dams during gestation and lactation at 0.227–0.421 mg/kg bw per day in a casein-based diet, but not in a fish-based diet (Haave et al., 2011).
- Altered expression of genes related to nerve impulse transmission, and to nervous system development and function in brains of rat pups following oral dosing of dams at 0.002 and 0.2 mg/kg bw per day during gestation and lactation (Suvorov & Takser, 2011).

– Down-regulation of NMDA receptors, especially NR_1 and NR_2B, in association with impaired learning and memory, in adult male rats orally dosed at 0.1, 0.5 and 1 mg/kg bw per day for 30 days (Yan et al., 2012).

Studies on cell differentiation and migration have included:

– Dishaw et al. (2011) reported that 10–50 μM **BDE-47** had no effect on cell number, cell growth or neurite growth in undifferentiated and differentiating PC12 cells. In contrast, Behl et al. (2015) reported decreased human neurite outgrowth and spontaneous activity of rat neural networks at around 10 μM.
– Increased *in vitro* migration and invasion of SH-SY5Y cells treated at 0.1 and 10 μM, associated with down-regulation of expression of E-cadherin and zona occluding-1, and upregulation of expression of matrix metalloproteinase-9 (Tian et al., 2016).
– Inhibition of the proliferation of Neuro-2a cells (a mouse neural crest-derived cell line) at 10 and 20 μM via up-regulation of expression of p53 and p21, which down-regulated expression of cyclin D1 and CDK2, and inhibited retinoblastoma protein phosphorylation, resulting in arrest at the cell cycle G1 phase (Chen, Tang, Zhou, Zhou, et al., 2017).
– Differentiation of PC-12 cells promoted by 25 and 50 μM **BDE-47**, mediated by enhancing the expression of the tyrosine kinase receptor and the phosphorylation levels of ERK and Akt. Transcriptomic analysis of adult mice orally dosed with **BDE-47** at 1, 10 or 100 mg/kg bw per day for 56 days (effective dose level(s) unclear) suggested that many pathways related to neuron death and neurological functions were altered by either up- or down-regulation (Liu et al., 2022).

In addition, a study has investigated epigenetic effects of **BDE-47** in a mouse model with social behavioural defects due to truncation of the methyl-CpG binding protein ($Mecp2^{308}$). Global hypomethylation of female offspring of dams orally dosed during gestation and lactation at 0.03 mg/kg bw per day coincided with reduced sociability in a genotype-independent manner. However, performance in short-term memory, learning and long-term memory were dependent on the genotype, indicating a gene–environment interaction in the outcome (Woods et al., 2012).

BDE-49

One study on **BDE-49** has been identified. Napoli et al. (2013) reported that **BDE-49** acted as an uncoupler of electron transport at concentrations < 1 nM and inhibited electron transport at concentrations > 1nM in isolated brain mitochondria and neuronal progenitor striatal cells.

BDE-99

Studies described in the previous Opinion, reported that **BDE-99** induced ROS production and apoptosis, and interfered with mitochondrial function. A few new studies are available.

Viberg and Eriksson (2011) reported that oral administration of **BDE-99** at 12 mg/kg bw to mouse pups on PND10 resulted in changes in the levels of calcium/calmodulin-dependent protein kinase II, growth-associated protein-43 (GAP-43) and synaptophysin in the brains. One study reported a small statistically significant increase in lipid peroxidation in the brain of offspring of rats dosed with **BDE-99** at 0.2 mg/kg bw per day from GD1 to PND21 (at a dose that did not result in neurobehavioral effects), but no effects on other measures of oxidative stress (Zhao, Cheng, et al., 2014).

In relation to neurotransmitters, Hallgren et al. (2015) reported changes in transcription of several cholinergic genes in the hippocampus and cortex of mice orally dosed on PND10 with **BDE-99** at 12 mg/kg bw. Changes in the hippocampus were already seen 24 h after dosing, whereas the changes in cortex were seen when the mice were age 2 months, at which time changes in spontaneous behaviour were also reported. Hallgren and Viberg (2016) observed no significant changes in dopaminergic gene transcription in brains of mice orally dosed on PND10 with 12 mg/kg bw **BDE-99**.

New studies have also been published relating to cell differentiation and migration. Slotkin et al. (2013) reported that non-cytotoxic concentrations (10–50 μM) of **BDE-99** inhibited differentiation of PC12 cells into both the dopamine and acetylcholine neurotransmitter phenotypes. The authors noted that these effects had not been found with **BDE-47** in other studies, and suggested that **BDE-99** acts as a developmental neurotoxicant by targeting neurodifferention directly in neuronal cells, independent of its other actions. Zimmer et al. (2014) found that **BDE-99** reduced migration of neural crest cells derived from human embryonic stem cells (hES) at non-cytotoxic concentrations (from 10 μM). Pallocca et al. (2016) investigated transcriptome changes triggered by **BDE-99** in hES-derived human neural crest cells and found a distinct gene expression profile associated with inhibition of migration at the non-cytotoxic concentration of 15 μM. Dach et al. (2017) found that differentiation of cultured human and mouse neural progenitor cells was impaired by **BDE-99** at 2–10 μM, independent of changes in thyroid hormone signalling.

BDE-153

Limited data are available for **BDE-153**, mainly relating to apoptosis. Zhang, Li, et al. (2013) reported hippocampus neuron apoptosis in the brain and impaired learning and memory and hypoactivity in adult rats following i.p. administration of **BDE-153** at 1, 5 or 10 mg/kg bw on PND10. In subsequent studies, Zhang, Chang, et al. (2017) reported that the calpain/35-p25/Cdk5 pathway is involved in **BDE-153**-induced neuronal apoptosis in the hippocampus of rats dosed as in

their 2013 study, based on upregulation of calpain-2 but not calpain-1. Similar results were obtained with primary neurons at 10–40 μM, however these concentrations were cytotoxic. The authors also reported that neuronal apoptosis was dependent on p53 and calpain-2 down-regulated neurotrophins and cholinergic enzymes *in vivo* and in primary neurons (Zhang et al., 2018). From related studies in the same laboratory, Li, Yang, et al. (2019) reported that **BDE-153**-induced apoptosis in rat cerebral cortex was dependent on p53 and mediated more by endoplasmic reticulum than by mitochondria, based on ultrastructural changes and altered gene expression in the cortex of rat pups dosed intraperitoneally and cultured primary neurons from neonatal rats.

BDE-209

Effects of **BDE-209** on ROS production, calcium homeostasis, mitochondrial dysfunction and apoptosis appear similar to those of **BDE-47**, including:

- Induction by 10–50 μM **BDE-209** of apoptosis, expression of p38 MAPK, calcium ion concentration, ROS level and cytotoxicity in primary rat hippocampal neurons, all of which were reduced by *N*-acetylcysteine indicating a role of oxidative stress (Zhang, Liu, et al., 2010).
- Decreased voltage-gated sodium channel currents in primary cultured rat hippocampal neurons at 0.1–2 μM, which was ameliorated by ascorbic acid or vitamin E, indicating a mechanism involving oxidative stress (Xing et al., 2010).
- Induction of cell death, at least in part by apoptosis through activation of caspases, and increased intracellular Ca^{2+} and ROS leading to mitochondrial dysfunction in SH-SY5Y cells at 10–50 μM. Release of β-amyloid peptide (Aβ-42) was also observed, leading the authors to conclude that **BDE-209** is both neurotoxic and amyloidogenic *in vitro* (Al-Mousa & Michelangeli, 2012).
- Concentration-related increase in malonaldehyde in freshly isolated mouse brain cells *in vitro* at 4–8 μg/mL (4.2–8.4 μM) (Zhu et al., 2012).
- Apoptosis together with ROS and increased expression of Fas and the Fas-associated death domain-containing protein (FADD) in Neuro-2a cells at 20–40 μM. In addition, the cellular mitochondrial membrane potential was increased, leading to cytochrome c release into the cytoplasm (Chen, Tang, et al., 2016).
- Decreased proliferation of neural stem cells, NF-κB activation and increased apoptosis and protein levels of cleaved caspase 3 at 0.01–1.0 μM. Expression levels of phosphorylated JnK1/2(*p*-JnK1/2) and phosphorylated erK1/2(*p*-erK1/2) were not altered and the NF-κB inhibitor pyrrolidine dithiocarbamate (PDTC) attenuated **BDE-209**-induced apoptosis. The authors concluded that **BDE-209**-induced apoptosis may be associated with the activation of NF-κB pathways (Zhang, Chen, Liu, & Du, 2016).
- Decreased neurite outgrowth, oxidative stress and apoptotic cell death in association with a decrease in expression of GAP-43 and calcitonin gene-related peptide at 40 μM in cultured bilateral dorsal root ganglia cells isolated from newborn rats. These effects were ameliorated by concomitant treatment with IGF-1, via a mechanism that involved the extracellular signal-related protein kinase (ERK 1/2) phosphatidylinositol 3-kinase (PI3K) signalling pathways (Bai et al., 2017).
- Deficits in learning and memory in rat offspring on PND21, following oral dosing of dams at 10 and 20 mg/kg bw per day from GD1–21, were associated with increased autophagy, decreased neuron viability and apoptosis in the hippocampus of fetal rats. Inhibition of autophagy reduced apoptotic cell death induced in freshly isolated neonatal rat hippocampal cells *in vitro* at 5–20 μM **BDE-209** (Sun et al., 2017).
- In the hippocampus of male mice dosed with **BDE-209** at 50 and 100 mg/kg bw per day for 28 days, there was a dose-related increase in ROS and decrease in GSH levels, a significant increase in the expression of the pro-apoptotic genes at 100 mg/kg bw per day, and significant reductions in the memory-related proteins BDNF and PSD-95 (Wang and Dai, 2022). Such effects were also associated with significant impairment in the metabolism of acetylcholine in the same brain region and concomitant spatial memory disturbances.

Mechanistic studies related to neurotransmitters have identified:

- Effects on habituation, learning and memory induced by oral dosing of mouse pups on PND2 with **BDE-209** at 1.4, 6 or 14 μmol/kg bw (1.3, 3.8 or 13.4 mg/kg bw per day) were modified by the cholinergic agents paraoxon and nicotine, indicating involvement of the cholinergic system, and the levels of the neuroprotein tau were increased in mice exhibiting neurobehavioral effects (Buratovic et al., 2014).
- Increased expression of the *N*-methyl-D-aspartate receptor NR1 subunit in the frontal cortex and hippocampus of neonatal and young male mice orally dosed with 20 mg/kg bw per day **BDE-209** during PND3-10, which was attributed to increased ROS levels (Verma et al., 2015).
- Altered levels of the second messengers nitric oxide and cGMP in rodent neurons treated with 0.1–0.4 μM **BDE-209** *in vitro*, which could be blocked by the NMDA receptor antagonist MK-801 (Chen, Chen, et al., 2018).
- Decreased expression of glutamate receptor subunits NR1, NR2B and GluR1 and their phosphorylation in the hippocampi of adult rats orally dosed at 250, 500 or 1000 mg/kg bw per day for 30 days, in association with spatial learning and memory impairment at the two higher doses (Xiong et al., 2018).
- In the hippocampus of male mice dosed with **BDE-209** at 50 and 100 mg/kg bw per day for 28 days, there was a dose-related decrease in the activity of acetylcholine transferase (Wang and Dai, 2022). The higher dose was also associated

with an increase in the activity of AChE. Such results are correlated with a significant reduction in spatial memory performances at both doses.

Studies on cell differentiation and migration have included:

- Changes in brain morphometry (decreased corpus callosum area and density of the CNPase-positive oligodendrocytes) in male offspring of rats fed 100 or 1000 mg/kg **BDE-209** from GD10 to PND20 (equal to doses of 7–224 mg/kg bw per day depending on the stage of gestation/lactation). The authors considered the findings to be related to developmental hypothyroidism (Fujimoto et al., 2011). However, changes in T4 (but not T3) were only seen at the highest dose, and effects on the liver and kidney were reported at lower doses.
- An increase in reelin-expressing interneurons was observed in the dentate hilus of the male rat pups on PND20 in the study of Fujimoto et al. (2011). This increase was no longer present on PND77, at which time an increase in neuron-specific nuclear protein (NeuN) was observed in mature neurons (Saegusa et al., 2012). Based on comparison with doses leading to changes in thyroid hormones, the authors suggested that **BDE-209** may exert a direct effect on neuronal development in the brain and that the effect of hypothyroidism may also operate at higher doses.
- Suppression by 10^{-10} M **BDE-209** of the T4-promoted differentiation of Purkinje cells in a time-dependent manner, with a greater effect after 2 days of culture than after a longer period (Ibhazehiebo & Koibuchi, 2012).
- A study of global gene expression profiles in the white matter of the male rat pups in the study of Fujimoto et al. (2011) revealed increased expression of vimentin and Ret which the authors suggested to be a direct effect on glial cell development, with a minor contribution of hypothyroidism at higher doses (Fujimoto et al., 2013).
- Decreased cell viability and differentiation, and increased apoptosis in rat embryonic hippocampal neural stem cells isolated from pregnant rats orally dosed with **BDE-209** at 10, 30 or 50 mg/kg bw per day, and impaired learning in 30 and 50 mg/kg bw per day male offspring on PND25 (Chen, Li, et al., 2014).
- Decreased dendritic branches and synaptic proteins in cultured neurons from fetal mouse hippocampus and cerebellum treated with 0.42 and 420 nM DE-83R (a technical product containing 96.9 ± 1.3% **BDE-209**). Impaired fetal CNS development was reported in 13-day embryos of mice dosed with 0.075–7.5 mg/kg bw per day from GD9-9 (Mariani et al., 2015).

Expression of synaptobrevin2, Synaptosome Associated Protein25 (SNAP-25), syntaxin 1A and synaptophysin was decreased in the hippocampi of adult rats following oral dosing with **BDE-209** at 1, 10 or 20 mg/kg bw per day on PND5–10, associated with impaired learning and memory (Li, Wang, et al., 2017).

- Impaired neurogenesis, neuronal migration and dendritic development in the hippocampus of offspring of mice orally dosed with **BDE-209** at 20 or 100 mg/kg bw per day from GD6 to PND16 (Xu, Huang, et al., 2018).
- Decreased neural differentiation efficiency in human embryonic stem cells treated with 10 nM **BDE-209** and induction of neuronal progenitor cells was associated with increased copy number variants in the neuronal progenitor cells, attributed to DNA hypo-methylation (Du et al., 2018).

In addition, Reverte et al. (2013) investigated the effects of **BDE-209** in transgenic mice with genotypes for apolipoprotein E (apoE), a genetic factor that is associated with varied vulnerability for the development of neurodegenerative diseases. Oral exposure to **BDE-209** at 10 or 30 mg/kg bw on PND10 induced long-term effects in spatial learning, which were dependent upon age, sex and genotype; these effects were more evident in apoE3 mice. Levels of brain-derived neurotrophic factor (BDNF) were increased in the hippocampus, independent of the genotype. Mice carrying apoE4 and exposed to **BDE-209** showed a reduction in BDNF levels in the frontal cortex. A subsequent study (Reverte et al., 2014), investigated the physical and neuromotor maturation of transgenic mice carrying different apoE polymorphisms (ε2, ε3 and ε4), following oral dosing at 10 or 30 mg/kg bw on PND10 with observations conducted up to PND36. A subtle delay in eye opening was observed in mice carrying the apoE4 genotype, but there were few other effects of **BDE-209** during development. The authors concluded that the vulnerability conferred by the apoE genotype may vary depending on age.

Chen et al. (2019) administered **BDE-209** to pregnant mice during gestation and lactation by osmotic minipump at 0.12 ng per day and reported increased production of IL-10, TNFα and IL-17A in the serum of male offspring, in association with impaired spatial learning).

Other individual PBDE congeners

One study was available relating to BDE-85. Vagula et al. (2011) injected BDE-85 at 0.25 mg/kg bw per day i.*p*. into adult mice for 4 days and found that markers of oxidative stress were elevated in the liver and brain. Isolated sciatic nerves treated with BDE-85 *in vitro* showed reduced nerve conduction velocity.

Comparative studies of different PBDE congeners and metabolites

Dingemans et al. (2011) reviewed studies of the neurotoxicity of PBDEs on the developing nervous system, and concluded that the OH-PBDEs are more potent than their parent congeners, and that modes of action based on direct neurotoxicity and on changes in thyroid hormones could be postulated. A number of studies, either not included in the 2011

Opinion (EFSA CONTAM Panel, 2011b) or published since then, compare the effects, and in some instances also the potency, of different PBDEs and their metabolites and are reviewed below. These all include **BDE-47**, which can therefore be used as a benchmark.

Li, Wang, Pan, et al. (2013) reported that 6-OH-BDE-47, but not **BDE-47**, was cytotoxic in primary adult neural stem/progenitor cells. At increasing concentrations, it reduced differentiation (≤ 1 μM), inhibited proliferation (2.5–5 μM) and induced apoptosis (7.5 μM), possibly acting through interference with ERK5 MAP kinase signalling and the function of neurotrophin 3 (NT3). Gassmann et al. (2014) investigated the effects of **BDE-47** and 6-OH-BDE-47 on intracellular Ca^{2+} levels in human neural progenitor cells. **BDE-47** (2 μM) and 6-OH-BDE-47 (0.2 μM) increased intracellular Ca^{2+} due mainly to extracellular Ca^{2+} influx and ryanodine receptor independent Ca^{2+} release from the endoplasmic reticulum. Poston et al. (2018) found that 6-OH-BDE-47 had a greater effect than **BDE-47**, 3-OH- or 5-OH-BDE-47 on several aspects of maturation and function of dissociated rat cortical neurons treated with each of the chemicals at the concentration of 1 μM. These effects were, at least in part, mediated by interference with BAF chromatin remodelling complexes via dysregulation of BAF170 expression.

Kim et al. (2011) compared ryanodine receptor binding and Ca^{2+} homeostasis of 1–10 μM BDE-4, -15, -17, -42, **-47**, **-49**, 6-OH-BDE-47 and 4′-OH-BDE-49 with cytotoxicity in primary cultures of mouse and rat cortical neurons. They found that PBDEs with two *ortho*-bromine substituents (e.g. **BDE-49**) were more potent than the corresponding congeners with two *para*-bromine substitutions (e.g. **BDE-47**). The OH-metabolites exhibited biphasic effects on receptor binding with either receptor activation and Ca^{2+} release from intracellular stores or attenuation of Ca^{2+} release, depending on concentration and duration of treatment. The authors proposed that the *in vivo* neurotoxicity of **BDE-47** might be mediated via a ryanodine receptor independent mechanism, or might be due to the 6-OH metabolite.

Ibhazehiebo et al. (2011) investigated the effects of 10^{-14}–10^{-9} M **BDE-28**, **-47**, -66, -85, **-99**, **-100**, **153**, **-154**, -175, **-183**, **-209** and the OH-metabolites 2′-OH-BDE-68, 4′-OH-BDE-49, 6-OH-BDE-47 and the technical product DE-71 on thyroid hormone receptor mediated transcription and on thyroid hormone induced differentiation of cerebellar Purkinje cells. The greatest suppression of transcription was seen with **BDE-209** and **-100**, and this suppression may, at least partly, inhibit differentiation.

Fan et al. (2010) reported that **BDE-47** and **-153** are more cytotoxic than BDE-77 and **-99** in cerebellar granule cell cultures. These four congeners all stimulated phosphorylated extracellular signal-regulated kinase (*p*-ERK1/2) at sub-cytotoxic concentrations, and the authors speculated that *p*-ERK1/2 might be involved in the neurobehavioral effects. **BDE-47** and **-153** were most potent (lowest concentration with significant effect was 1 μM) followed by BDE-77 (3 μM) and **BDE-99** (10 μM).

Dingemans et al. (2010,b) compared the effects of **BDE-47**, **-49**, **-99**, **-100**, **-153**, and several metabolites of **BDE-47**, i.e. 6-OH-BDE-47 (and its methoxylated analogue 6-MeO-BDE-47), 6´-OH-BDE-49, 5-OH-BDE-47, 3-OH-BDE-47 and 4´-OH-BDE-49, on Ca^{2+} homeostasis in neuroendocrine pheochromocytoma (PC12) cells. The lowest observed effect concentrations were for fluctuations in intracellular Ca^{2+}, in the order 6-OH-BDE-47 (0.2 μM) > 5-OH-BDE-47 (1 μM) > **BDE-47** = 4′-OH-BDE-49 (2 μM) > 6-OH-BDE-97 = 3-OH-BDE-97 (20 μM). The authors also concluded that shielding of the OH-group on both sides with bromine atoms and/or the ether bond to the other phenyl ring lowers the potency of OH-PBDE metabolites.

Chen, Karin, Singh, Yang, et al. (2017) reported that both **BDE-47** and **-49** at 0.2 μM had an effect on axonal but not dendritic growth in neuronal-glial co-cultures from neonatal rat hippocampus. Both congeners delayed neuronal polarisation, resulting in inhibition of axonal outgrowth, independent of cytotoxicity and at similar concentrations. The effects were blocked by antagonism or knockdown of ryanodine receptors.

Dusza et al. (2018) compared the effects of a large number of suspected neurotoxicants, including **BDE-47**, **-49** and 6-OH-BDE-47 (each at 10 μM) on Ca^{2+} homeostasis in rat cortical microsomes. The decreasing order of potency was **BDE-49** > 6-OH-BDE-47 > **BDE-47**.

Fournier et al. (2017) compared the relative potency of a large number of semi-volatile organic compounds based on published *in vitro* data in systems of relevance to the nervous system. The potencies of **BDE-47**, **-99** and **-209** were found to be similar, with benchmark concentrations for a 10% fall in neuronal viability of 5–10 μM.

Song et al. (2014) found that **BDE-47** (3.2 μg/mL) and **-209** (6 μg/mL) induced changes in proteins involved in metabolism, signal transduction, translation, transcription, transport and cell structures in hippocampal neural stem/progenitor cell cultures, but did not provide data on relative potency. Chen, Tang, Zhou, Xu, et al. (2017) reported that **BDE-209** had little effect on proliferation or cell cycle of Neuro-2a cells in contrast to **BDE-47** when tested at the same concentrations (5–40 μM). Wang, Wu, et al. (2018) reported that 10–50 μM **BDE-47** and **-209** can interact with AChE, resulting in altered confirmation. Based on the binding energies, the authors predicted that **BDE-47** is more likely to bind with AChE than **BDE-209**.

Liang, Liang, et al. (2019) performed a toxicogenomic study in human embryonic stem cells with a number of BFRs including **BDE-47** and **-209**, both at 1 μM, and identified dysregulation of transcription factors crucial for neurodevelopment. They concluded that **BDE-47** and **-209** had similar toxicity.

In addition, a small number of studies have reported that synthetic di- and tri-brominated PBDE-quinones[48] resulted in apoptosis and activation of autophagy in microglial BV2 cells (Zhu et al., 2021; Liu et al., 2021; Xu, Wang, et al., 2021). The CONTAM Panel noted that these studies do not allow comparison of potency with PBDEs, and formation of PBDE-quinones has not been demonstrated either *in vitro* or *in vivo*.

Overall, the data do not provide a clear picture of the relative potency of the neurotoxicity of different PBDE congeners. **BDE-47** was tested in all of these studies, with fewer studies including **BDE-99**. Some studies indicated that **BDE-47** is

[48] 2-(2′,4′-Bromophenoxyl)-benzoquinone and 2-(2′,4′-Bromophenoxyl)-5-benzoquinone.

more toxic while others indicated a similar toxicity in those congeners that were tested, including **BDE-99**. The available data indicate that the OH-metabolites are more potent than their parent congeners.

Technical products

A number of mechanistic studies have involved technical products, particularly DE-71 (Bradner et al., 2013,b; Dreiem et al., 2010; Gill et al., 2016; Kingsley & Noriyuki, 2012; Kodavanti et al., 2010, 2015; Kozlova et al., 2021). Whilst these studies support the evidence that PBDEs affect neurotransmitters, mitochondrial metabolism, oxidative stress, calcium homeostasis and apoptosis, they are not informative for effects of specific PBDE congeners.

3.1.4.3.1 | *Summary on the MOA of neurotoxicity*

Overall, there is a growing body of evidence that PBDEs interfere with mitochondrial calcium homeostasis, leading to oxidative stress and apoptosis, both *in vitro* at low μM concentrations in cellular systems of relevance to the nervous system, and *in vivo* at dose levels relevant for neurobehavioral effects. Changes in neurotransmitters (or in expression of related genes) and cell migration and differentiation are also observed. These direct effects seem to be common to all congeners, and the OH-metabolites are more active than the parent congeners. However, the data do not provide a clear picture of the relative potency of the neurotoxicity of different PBDE congeners.

There is a separate and additional line of evidence relating to involvement of the thyroid hormones in neurotoxicity of **BDE-209**. There is a lack of data on whether thyroid hormones are similarly involved for other PBDE congeners.

3.1.4.4 | *Thyroid hormone signalling*

The CONTAM Panel considered in its previous Opinion on PBDEs that alteration of thyroid hormone signalling is a principal mode of action of PBDEs that is related to their effects on developmental processes (EFSA CONTAM Panel, 2011b). It was proposed that PBDEs may affect thyroid hormone signalling *'(1) by binding to thyroid hormone transport proteins, (2) by activation of thyroid hormone metabolising enzymes which results in alterations in thyroid hormone concentrations; (3) by affecting transcription activation of thyroid hormone receptors'*. It was further noted that OH- metabolites of PBDEs, may be more potent than the parent compounds in perturbing thyroid hormone functions.

Studies since the previous Opinion have provided additional evidence primarily regarding these mechanisms. The ability of PBDEs to induce expression of thyroid hormone metabolising biotransformation enzymes through CAR and PXR activation is also discussed in separately in **Section 3.1.4.2**.

BDE-47

Binding to thyroid hormone transport proteins:

- In silico docking simulations indicating that affinities of **BDE-47**, 6-OH-BDE-47 and 6-MeO-BDE-47 to thyroxine-binding globulin (TBG) are lower than that for T4 (Sheikh & Beg, 2020). This can be regarded as evidence that **BDE-47** and its metabolites bind relatively weakly to TBR.

Altered expression of biotransformation enzymes:

- Human PXR activation was observed in HepG2 cells transfected with a human PXR reporter gene construct in response to **BDE-47** at concentrations of 1 μM and above (Hu et al., 2014). Exposure to 1–100 μM **BDE-47** in HepG2 cells overexpressing human PXR led to dose-dependent reduction in expression of mRNA for thyroid hormone receptor (THR) isoforms THRA1 and THRB1, and upregulation of CYP3A4, UGT1A3 and SULT2A1. In contrast, in HepG2 cells expressing only the endogenous PXR none of these responses were observed at concentrations below 100 μM, which was highly cytotoxic.
- Several OH-PBDE metabolites were found to be potent inhibitors of thyroid hormone sulfotransferase (SULT) activity but **BDE-47** itself had no effect (Butt & Stapleton, 2013). IC_{50} concentrations for OH-PBDEs were generally in the nM range. 3-OH-BDE-47 was the most potent **BDE-47** metabolite with an IC_{50} of 60 nM, and 4-OH-BDE-90 was the overall most potent PBDE metabolite with an IC_{50} of 24 nM. 4-OH-BDE-90 was found to act by a non-competitive mechanism, but it was not investigated if this applies to other OH-BDEs.
- **BDE-47** had no effect on 3,3′-T2 SULT activity in a choriocarcinoma placenta cell line (BeWo). In contrast, 3-OH-BDE-47 and 6-OH-BDE-47 decreased 3,3′-T2 SULT activity by 23%–42% at concentrations of 0.5 μM and 1.0 μM following 24 h exposures. Expression of SULT1A1, THRA and THRB were unaffected by PBDE exposure (Leonetti et al., 2018).

Effects on deiodinases:

- **BDE-47** accelerated conversion of T4 to T3 in rats which was associated with increased expression of type 1 deiodinase (DIO1) and type 3 deiodinase (DIO3) (Wang, Zhu, et al., 2020). Evidence in rats and in H4-II-E rat hepatoma cells suggested

that this was mediated by downregulation of miRNA rno-miR-224-5p, which targets *Dio1* mRNA and for *Dio3* mRNA indirectly via downregulation of the MAPK/ERK pathway.
- The **BDE-47** metabolite, 5-OH-BDE-47 had no effect on deiodinase activity in human liver microsomes at the highest concentration tested (0.1 μM) (Butt et al., 2011).
- Astrocytes are responsible for providing more than half of the T3 present in the brain (Roberts et al., 2015). Whilst 500 nM **BDE-47** or 6-OH-BDE-47 had no effect on DIO2 activity in microsomes from H4 glioma cells, the same concentration of 3-OH-BDE-47 caused a rapid inhibition of the enzyme and the IC_{50} was determined to 3.74 μM.

Effects on thyroid hormone receptors:

- Argument against a direct role of **BDE-47** in acting as THR agonist were obtained in *Xenopus laevis* tadpole assays showing that **BDE-47** concentrations causing toxicity did not activate THR reporter *in vivo* and did not exhibit developmental effects associated with thyroid hormone stimulation (Mengeling et al., 2017).
- Using receptor binding studies and reporter gene assays with human THRB1, it was found that **BDE-47** up to a high concentration of 10 μM does not compete with ^{125}I-T3 for THRB1-binding and does not stimulate transactivation by THRB1 in HEK293 QB1 cells (Suvorov et al., 2011). A mixture '*imitating proportions of major congeners, of BDE-47, -99, -100 and -153, found in US donor blood*' competed with ^{125}I-T3 for THRB1-binding at a concentration of 10 μM but not significantly at 10 nM. The mixture had no effect on T3-stimulated THRB1 transactivation at a concentration of 10 μM.

Direct effects on the thyroid:

- **BDE-47** was a non-competitive inhibitor of iodide uptake in rat thyroid follicular cells with a relatively high K_i of 77.8 μM, which was a cytotoxic concentration. At a lower concentration of 30 μM, expression of thyroid peroxidase (TPO) mRNA was reduced, but with no effect on TPO activity (Wu et al., 2016).
- Female rats orally exposed to **BDE-47** showed increased apoptosis in the thyroid as indicated by increased PARP (1 and 10 mg/kg bw per day) and caspase-3 activation (10 mg/kg bw per day) (Li, Liu, et al., 2018; Ma et al., 2021). This was associated with endoplasmic reticulum ER stress, unfolded protein response, and autophagy in apoptotic cells at doses of 0.1 mg/kg bw per day and above.

BDE-49

Binding to thyroid hormone transport proteins:

- Experiments on competitive binding of 4-OH-BDE-49 with ^{125}I-TH for thyroid hormone transport proteins resulted in *K*i values of 12.2 nM for TTR and 1.1 nM for ALB (Hill et al., 2018). The competition was 7.5 and 4.2 times stronger than that with unlabelled T4 for TTR and ALB, respectively.

BDE-99

Binding to thyroid hormone transport proteins:

- In silico docking simulations indicated that **BDE-99** and its metabolites (5-OH-BDE-99, 6-OH-BDE-99, 5-MeO-BDE-99, 6-Me-OH-BDE-99) have stronger binding to thyroxine-binding globulin (TBG) than **BDE-47** with the metabolite 5-MeO-BDE-99 showing equal binding affinity to that of T4 (Sheikh & Beg, 2020).

Altered expression of biotransformation enzymes:

- **BDE-99** inhibited 3,3′-T2 SULT activity dose-dependently at 0.5 and 1 μM in a choriocarcinoma placenta cell line (BeWo) (Leonetti et al., 2018). Expression of SULT1A1, THRA, and THRB were unaffected by **BDE-99** exposure.

Effects on deiodinases:

- **BDE-99** decreased DIO2 activity by 50% in primary astrocyte cells and by up to 80% in the H4 cells at doses of 0.5 and 2.5 μM (Roberts et al., 2015). The IC_{50} in H4 cells was determined to 77.6 μM. 5′-OH-BDE-99 was less potent than **BDE-99**, but inhibited DIO2 activity in H4 cells at 1 and 5 μM. In addition, expression of Dio2 mRNA was also suppressed by **BDE-99** and 5′-OH-BDE-99.

Mechanisms associated with effects of **BDE-99** on brain function through the thyroid hormone system might include:

- Reduced expression of BDNF as observed in hippocampus of rat pups at weaning exposed during gestation and lactation via dams exposed orally to 2 mg/kg bw per day (Blanco et al., 2013) and in primary culture of rat cerebellar granule neurons exposed to 25 μM **BDE-99** (Blanco, Mulero, et al., 2011).

- Reduced expression of BCL-2 protein in primary culture of rat cerebellar granule neurons exposed to 25 μM **BDE-99**, indicating activation of apoptotic pathways (Blanco, Mulero, et al., 2011).
- 5′-OH-BDE-99 appeared to be the most potent inhibitor of deiodinase activity among 14 different halogenated phenolic compounds, including **BDE-99**, 5′-OH-BDE-47, 6′-BDE-99 and 4′-OH-BDE-101 (Butt et al., 2011).

BDE-100

Binding to thyroid hormone transport proteins:

- Fluorescence spectroscopy techniques and molecular dynamics simulations were used to study the interactions of **BDE-100**, 3-OH-BDE-100 and 3-MeO-BDE-100 with TTR (Xu, Yi, et al., 2017). The results obtained suggest that binding of **BDE-100** or its metabolites can induce conformational changes in TTR and that hydrogen and van der Waals forces are dominating binding of **BDE-100** to TTR while hydrophobic interactions govern binding of the OH- and MeO- metabolites. Docking simulations further highlighted the importance of Lys15, Leu110 and Thr119 for the interaction of **BDE-100** and its metabolites with TTR.

BDE-209

The mechanisms leading to reduced serum thyroid hormone levels may be explained by:

- Dose-dependent reduction in expression of the genes for proteins involved in thyroid hormone biosynthesis in rats orally exposed to **BDE-209** (50 or 500 mg/kg bw per day) for 28 days as well in the gene for Pax8, which regulates their expression (Wang et al., 2019).

Effects on thyroid hormone receptors:

- Decreased expression of *Thra* and its splice variant *Thra1* as observed in Sertoli cells from juvenile mice administered **BDE-209** *s.c.* at a dose of 0.025 mg/kg bw per day on PND1 to 5 and then killed at 12 weeks of age (Miyaso et al., 2014). Notably, no effect was observed at much higher doses of 0.25 and 2.5 mg/kg bw per day.
- Dose-dependent attenuation of thyroid hormone-stimulated transcription via the TRHB1 receptor, using a reporter-gene assay in African Green Monkey Kidney Fibroblast (CV-1) cells with a significant two-fold reduction observed at an exposure concentration of 0.01 nM (Xiong et al., 2012). However, **BDE-209** concentrations ranging from 0.5 to 50 nM had no effect on thyroid hormone activation of THRA1 and RXR/THRA1 reporter genes in HEK293 cells (Guyot et al., 2014).

Direct effects on neurons:

- A study showing that 10 nM of **BDE-209** inhibits thyroid hormone-stimulated dendritic arborisation of Purkinje cells in a primary culture from newborn rats (Xiong et al., 2012).

Technical mixtures

Primary human thyroid cells were exposed to 10, 100, 1000, 5000, 10,000 and 50,000 μg DE-71/L, respectively (Kronborg et al., 2017). Exposure to DE-71 reduced cAMP levels in primary human thyrocytes dose-dependently with a significant reduction at concentrations higher than 1000 μg/L. DE-71 also inhibited thyroglobulin-release from TSH-stimulated thyrocytes, but only at the highest concentration tested. Levels of mRNA for thyroglobulin, thyroid peroxidase and thyroid stimulated hormone receptor were decreased in response to DE-71 treatment with the most sensitive effect being on thyroglobulin, which was significantly depressed at concentrations of 1000 μg/L and above.

Comparative studies with multiple PBDEs and/or their metabolites

Interactions with thyroid hormone transport proteins:

- Molecular docking and 3D-QSAR predictions of PBDE binding to TTR indicated that hydrogen bonding with amino acid residues Asp74, Ala29, and Asn27 may be an important determinant for OH-PBDEs binding to TTR (Yang, Shen, et al., 2011).
- Spectroscopic methods, molecular simulations and quantum chemistry were used to find that **BDE-49**, -108 and -155 binding to TTR is mainly hydrophobic and that the cation–π formed by the C atom of the benzene ring and the polar residue Lys15 (NH_3^+) of TTR are important for the binding (Xu, Wei, et al., 2018).
- Binding affinities of 14 OH-PBDEs for TTR and TBG were measured by competitive fluorescence displacement assay and affinity (*K*) ranged from 0.14 to 6.9×10^8 M^{-1} for TTR and 0.065 to 2.2×10^8 M^{-1} for TBG (Cao et al., 2010). Of the metabolites investigated 3-OH-BDE-47 had the highest binding constant for TTR while 3-OH-BDE-154 had the highest binding constant for TBG. In general, binding affinities increased with bromination substitutions up to 4 bromines. Molecular

docking simulations indicated that binding of OH-PBDEs to TTR was mostly by hydrophobic interactions but that positively charged Lys15 was important for the coordination.

- Fourier transform infrared spectroscopy and dynamics simulation combined with thermodynamic analysis suggested that 4′-OH-BDE-49, 4-OH-BDE-187 and 4-OH-BDE-188 induce changes in TTR secondary structure by altering the internal microenvironment of TTR. OH-PBDEs bind to TTR mainly by hydrophobic interaction, inducing changes in TTR secondary structure (Wei et al., 2019). Molecular docking simulations indicated that 4′-OH-BDE-49 and 4-OH-BDE-188 have non-covalent cationic–π interactions with TTR, whereas 4-OH-BDE-187 was bonded to TTR by hydrogen bonds and van der Waals force.
- Spectroscopic analysis indicated that OH-PBDEs bind to the T4 binding site of TTR (Ren & Guo, 2012). Competitive binding assays for TBG and TTR with fluorescently labelled T4 and 11 OH-PBDEs indicate that the binding affinity generally increases with bromine number, but that the position of the OH also matters. The K_d ranged from 101 to 828 nM for binding to TTR and 19 to 4278 for binding to TBG. 3-OH-BDE-47 and 3′-OH-BDE-154 were found to bind to TTR and TBG stronger, respectively, than T4.
- Molecular docking indicated that 6-OH-BDE-85 associated with the binding cavity of TTR by interactions with hydrophobic residues and formed hydrogen bonds with Lys15 (Huang et al., 2021a). 6-OH-BDE-85 was suggested to bind TBG mainly through cation-π interaction and hydrophobic interaction. Molecular dynamics simulations supported by infrared spectroscopy suggested that binding of 6-OH-BDE-85 to either protein induced a change in protein structure increasing the hydrophobic area of interaction.
- The relative potencies (compared with T4) of different PBDE sulfates of BDE-7 and **BDE-28** for binding to TBG were similar to those of the respective OH-PBDEs and ranged from 0.1% (3′-OH-BDE-7) to 1.4% (2′-BDE-28 sulfate) (Qin et al., 2019). In contrast, three of the four sulfated PBDE metabolites tested bound stronger to the TTR than their respective OH-PBDEs with relative potencies (compared with T4) of 3.9% (2′-BDE-7 sulfate) to 49.1% (3′-BDE-7 sulfate). 2′-OH-BDE-3 and 2′-BDE-3 sulfate had low affinity for both thyroid hormone transport proteins and relative potencies could not be calculated.
- Molecular docking and molecular dynamics simulations were used to investigate the interactions of hydroxylated and sulfated PBDEs with TTR (Cao et al., 2017). Docking scores suggested that sulfated PBDEs have stronger affinity for TTR than the corresponding OH-PBDEs. Free energy calculations indicated that van der Waals forces dominate the binding and residues Ser117 and Lys15 have important roles in determining the binding orientations of the -OSO_3^- group of sulfated PBDEs.
- Molecular docking suggested that 2′-MeO-BDE-3, 5-MeO-BDE-47 and 3-MeO-BDE-100 bind to the thyroid hormone binding site of TBG (Huang et al., 2021b). Analysis with spectroscopic techniques together with free energy calculations indicated that the MeO-PBDE combined with TBG primarily by hydrogen bonding and hydrophobic interactions and that van der Waals force is important. Circular dichroism analysis combined with molecular dynamics simulations showed that binding induced changes in secondary structure of the protein.

Inhibition of deiodinases:

- Density functional theory calculations indicated that PBDEs and OH-BDEs may competitively bind to the active site of deiodinases to prevent THs from being deiodinated (Marsan & Bayse, 2017). Halogen binding interactions were more favourable at the *ortho* and *meta* positions relative to the ether group, and weaker at the *para* position.
- The potential of PBDEs and OH- and MeO-metabolites to inhibit deiodinase was tested in HEK-293 T cells expressing recombinant human deiodinase using 0.6 M 3-iodo-L-tyrosine as substrate (Shimizu et al., 2013). No inhibition was of deiodinase activity was observed after exposure to **BDE-47**, **-99**, -85 or **- 100** at concentrations up to 100 μM. Likewise, none of the MeO- metabolites tested (2-MeO-BDE-15, 4′-MeO-BDE-17, 4-MeO-BDE-42, 4′-Me-BDE-49, 4-MeO-BDE-90) affected deiodinase activity. OH-metabolites did, however, inhibit deiodinase activity with IC_{20} values ranging from 16 μM (4′-OH-BDE-17) to 26 μM (2′-OH-BDE-28).

Effects on thyroid hormone receptors:

- Using thyroid hormone dependent cell proliferation of the GH3 rat pituitary tumour cell line, it was found that 13 out of 16 tested OH-PBDEs were thyroid hormone antagonists (Chen, Wang, et al., 2016). Although inhibition of thyroid hormone-stimulated proliferation occurred at the low nM level the magnitude of the effect was generally small. Molecular dynamics simulations indicated that modulation of co-regulator binding sites favouring binding of co-repressors over co-activators contributes to the antagonistic activities of OH-PBDEs.
- Fluorescence competitive binding assays with THRA and THRB showed that binding potency of 10 OH-PBDEs depended on their degree of bromination with increasing level of bromination promoting binding (Ren, 2013). Whereas the mono-, di- and tri-BDEs bound only very weakly, penta-, hexa- and heptaBDEs had relative potencies compared with T3 between 0.2 and 0.5 for THRA and 0.1 to 0.8 for THRB. 2′-OH-BDE-28, 3′-OH-BDE-28, 5-OH-BDE-47 and 6-OH-BDE-47 were TR agonists at μM concentrations, recruiting a coactivator peptide and enhanced GH3 cell proliferation. In contrast, μM concentrations of 3-OH-BDE-100, 3′-OH-BDE-154 and 4-OH-BDE-188 acted antagonistically to T3 (0.2 nM) on GH3 cell proliferation assays. Molecular docking simulations indicated that PBDEs with low level of bromination bind differently to the THR binding pocket than PBDEs with higher level of bromination, possibly explaining their different effects on receptor activity.

- A recombinant two-hybrid yeast assay to measure activity of THRβ in response to 18 OH-PBDEs and two PBDEs (BDE-30, -116) (Li, Xie, et al., 2010). All compounds tested activated THRβ in this system with the two parent PBDEs having lowest activity. 6-OH-BDE-157, 6-OH-BDE-140, 3´-OH-BDE-154, 6-OH-BDE-82 and 6-OH-BDE-47 were the strongest THRβ agonists in this system. A molecular docking model indicated that hydrogen bonding and electrostatic interactions are key for OH-PBDE binding and activation of THRβ. Partial least squares regression was performed on the experimental dataset to develop a QSAR to predict OH-PBDE activation of THRβ.
- Quantum chemical calculations were used to build a multilinear regression model to predict binding of OH-PBDEs to THRB (Yu et al., 2015). The analysis indicated that the ability of the hydroxyl oxygen and hydrogen atom of OH-PBDE to donate or accept additional electron charges is important in determining the ability to bind to THRβ.
- A combination of 3D-QSAR, molecular docking and molecular dynamics simulations were used to predict binding of OH-PBDEs to THRB (Li et al., 2012). Molecular docking indicated that Asn331 and His435 in the ligand binding pocket of THRB are important for OH-PBDE binding.
- Rat pituitary tumour GH3 cells constitutively expressing a TRE-driven luciferase reporter gene construct was used to test agonistic activity of BDE-69, 4-OH-BDE-69, BDE-121 and 4-OH-BDE-121 (Freitas et al., 2011). Whereas the parent compounds showed no THR activation, both OH- metabolites were weak THR agonists with a maximum response of 7% for 4-OH-BDE-121 and 22% for 4-OH-BDE-69 of that elicited by 10 nM of T3. However, stimulation did occur at relatively low concentrations with EC_{10} of 61 nM for 4-OH-BDE-69 and 460 nM for 4-OH-BDE-121.
- Ability of 2′-OH-BDE-3, 2′-OH-BDE-7, 2′-OH-BDE-28 and their respective sulfated metabolite were tested for binding to THRA and THRB (Qin et al., 2019). Of the six OH- and sulfate PBDE metabolites tested, only 2′-OH-BDE-28 and 2′-BDE-28 sulfate showed binding and only to THRA with 2′-BDE-28 sulfate having higher apparent affinity than 2′-OH-BDE-28. However, when tested in the for TR-like activity in the G3 proliferation assay, the sulfated PBDE metabolites showed similar or lower activity than their corresponding OH-metabolites.

Changes in gene expression:

- Changes in gene expression of thyroid hormone-response genes in liver in rat neonates was investigated 24 h after i.p injection of either 4-OH-BDE-42, 4′-OH-BDE-49 or 4-OH-BDE-90 (Fujimoto et al., 2018; Matsubara et al., 2017). Out of the eight genes tested across these two studies, three (*Ethr1*, *Hac*, *Slc25a25*) showed changes in expression to one or several of the three OH-PBDEs. Although far from conclusive, these results indicated that the three OH-PBDEs tested possibly could have acted on the thyroid hormone system to alter expression of these genes.

3.1.4.4.1 | *Summary on the MOA of thyroid hormone signalling*

In summary, new studies published since the previous Opinion on PBDEs have primarily been carried out in silico and *in vitro* on human and mouse cell lines. These studies support the conclusions made in the previous EFSA Opinion that many PBDEs have the potential to interfere with thyroid hormone signalling at different levels (EFSA CONTAM Panel, 2011b). Also, as previously proposed, new studies provide evidence that PBDEs are more potent in causing changes in thyroid hormone function following metabolism through hydroxylation, methoxylation and sulfation.

Several OH-PBDEs, MeO-PBDEs and PBDE sulfates bind strongly to thyroid hormone transport proteins, including TTR, with K_d typically in the nanomolar range. Binding affinities tend to increase with bromination substitutions up to 4 bromine atoms. Several studies have provided evidence, primarily from in silico models, that binding of these metabolites of PBDEs to TTR are mostly by hydrophobic interactions but that positively charged Lys15 is important for the coordination.

There is substantial evidence for a role of PBDE-induced changes in metabolism of thyroid hormones as mechanistic explanation for altered levels of thyroid hormones and thyroid hormone-dependent functions observed *in vivo*. Increased expression of the nuclear receptors CAR and PXR plays a role as discussed in **Section 3.1.4.2**, but other regulatory pathways may also be involved. This may include inhibition of SULT which occurs at nanomolar concentrations, and reduced expression of enzymes involved in biosynthesis of thyroid hormones. OH-PBDEs appear to be particularly potent inhibitors of SULT. Numerous studies have addressed the potential of PBDEs and their metabolites to influence the conversion of T4 to T3, but the reports are more variable with some suggesting increased expression of deiodinases and other showing inhibited activity or no effects. Transport of T4 into the liver might also be accelerated following exposure to PBDEs because the gene for OATP2, which transports T4 into the liver, is a CAR target (Gong et al., 2018).

The possible potential of PBDEs and their metabolites to modify function of THRs has also been abundantly addressed but without a clear conclusion. It appears that some PBDEs can bind to THRs but the outcome in terms of changes in THR activities is less clear. This could perhaps be related to different activities dependent to the level of bromination. For example, molecular docking results have suggested that PBDEs with low level of bromination bind differently to the THR binding pocket than PBDEs with a high level of bromination, which might explain reported agonistic effects of PBDEs with a low level of bromination and antagonistic effects of PBDEs with a high level of bromination. Regardless, most studies addressing the influence of PBDEs on THR transcriptional activity have reported modest amplitude of the effects. Perhaps remarkable in terms of sensitivity are the effects reported after apparently low doses of **BDE-209** *in vivo* on expression of THRs (*s.c.* 0.025 mg/kg bw per day on PND1 to 5; Miyaso et al., 2014) and *in vitro* on TRE reporter genes (0.01 nM; Xiong et al., 2012), but the lack of monotonic dose–response and inconsistency between studies complicate conclusions.

Overall, there is good mechanistic evidence that PBDEs and in particular their OH-metabolites affect the thyroid hormone system by: (1) competing with T4 for thyroid binding proteins, with binding affinities increasing with bromination substitutions up to 4 bromines and (2) by altering expression and activities of enzymes that metabolise thyroid hormone. This could explain or contribute to the observed effects of PBDEs on thyroid hormone homeostasis and possibly on neurodevelopment.

3.1.4.5 | *Reproductive effects*

There is evidence of the involvement of endocrine effects, oxidative stress, mitochondrial dysfunction, apoptosis, DNA damage and epigenetic mechanisms in the generation of adverse effects on reproduction.

3.1.4.5.1 | *Endocrine related effects*

Studies in rodents with several PBDE congeners have identified effects on sex hormones which may result in adverse outcomes in reproduction. In the previous Opinion, estrogenic effects of some PBDE congeners were reported based on the oestrogen receptor (ER)-dependent luciferase reporter gene expression assay. Other mechanisms also affect the endocrine system, including modulations of steroidogenesis and induction of drug-metabolising enzymes (CYP17, CYP19, …) leading to changes in steroid hormones. PBDEs could also modulate metabolism (inactivation) of steroid as well as thyroid hormones via induction of CAR/PXR-mediated gene expression of biotransformation enzymes including CYP and transferase enzymes (EFSA CONTAM Panel, 2011b).

Since the publication of the previous Opinion, several new studies have been identified:

BDE-47

- A significant increase in serum testosterone level was noted as well as a decrease in LH level in 21-day-old male rats exposed by gavage to 0.4 mg **BDE-47**/kg bw per day for 14 days (Li, Gao, et al., 2021, see **Appendix E**, Table E.1). There was no effect on oestradiol or FSH levels. **BDE-47** induced Leydig cell hyperplasia and up-regulated the expression of Leydig cell genes in the testis. Exposure of male rats to **BDE-47** during prepuberty significantly stimulated the proliferation and differentiation of Leydig cell precursors. Proliferation may be due to the increased phosphorylation of AKT1, AKT2, ERK1/2 and to the decrease of p53 and p21, thereby increasing the expression of CCND1 (encodes the cyclin D1 protein), leading to cell cycle progression. Differentiation may be due to increased phosphorylation of CREB (transcription factor that regulates diverse cellular responses) leading to increases in expression of Star (steroidogenic acute regulatory protein) and then increases in testosterone synthesis. Androgen production was stimulated in immature Leydig cells from rats exposed *in vitro* for 24 h to 100 nM **BDE-47** under basal, LH, and 8Br-cAMP stimulated conditions (Li, Gao, et al., 2021).
- Pregnant ICR mice were exposed by gavage to 0, 0.36, 3.6, 36 mg **BDE-47**/kg bw per day for 4 days (from GD13.5 to GD16.5) (Zhu et al., 2017, see **Appendix E**, Table E.1). Increased rates of stillborn (at the two highest doses) and low birth weight (at the highest dose) were observed in treated mice. At 36 mg/kg bw per day, plasma testosterone and progesterone levels were reduced in the dams. Plasma prostaglandin E2 (PEG2) was lower at the two highest doses, whereas the corticotrophin-releasing hormone was higher at 3.6 mg/kg bw per day. In addition, the group treated with 36 mg/kg bw per day displayed decreased growth hormone peptide expression in the placental tissue extracted at GD17.5. As this peptide stimulates growth, the expression pattern might suggest compromised fetal development. Moreover, the mitogen-activated protein kinases (MAPK) were activated in the placental tissue of the treated groups. The authors concluded that the activation of these signalling molecules might affect the hormonal and other physiological functions in the tissue (Zhu et al., 2017).
- Pregnant Wistar rats were exposed to 0.2 mg **BDE-47**/kg bw per day from GD8 until PND21 and male reproductive outcomes were analysed in offspring on PND120 (Khalil, Parker, Brown, et al., 2017, see **Appendix E**, Table E.1). No changes in serum testosterone were found in male rats on PND120. Perinatal **BDE-47** exposure led to significant changes in testis transcriptome, including the suppression of genes essential for spermatogenesis and activation of immune response genes. No changes in GJA1 (most ubiquitous connexin in the seminiferous epithelium) expression and localisation were found in rat testes on PND120. A decrease in expression of protamine and transition protein genes in testes was observed. According to the authors, this suggested that histone-protamine exchange may be dysregulated during spermatogenesis, resulting in an aberrant sperm epigenome.
- **BDE-47** (0.5, 25 and 50 ng/mL (1.0, 52 and 103 nM) for 24 h) increased testosterone secretion in follicles from morphologically normal pig ovaries from sexually mature animals (Karpeta et al., 2011). It significantly increased androstenedione secretion but there was no effect on progesterone and oestradiol secretion. There was also a statistically significant decrease in testosterone-stimulated oestradiol secretion due to reduced CYP19 activity. Due to activation of 17β-HSD, a corresponding failure to activate CYP19 expression and inhibition of CYP19 activity was seen.
- Granulosa cells and theca interna cells from medium sized follicles obtained from the ovaries of pigs on days 10–12 of the oestrous cycle were exposed to **BDE-47** (25 ng/mL (52 nM) for 48 h, Rak et al., 2017). **BDE-47** increased adiponectin secretion and AdipoR1 and AdipoR2 receptors expression. In addition, **BDE-47** significantly increased oestradiol secretion and CYP19 protein expression. **BDE-47** was without effect on basal testosterone secretion, but had no effect on 17β-HSD protein expression.
- **BDE-47** significantly increased basal testosterone production and steroidogenic acute regulatory protein (StAR) level of adult rat Leydig cells *in vitro* (at 10^{-4} M, Zhao et al., 2011). Compared to non-LH control group (basal), luteinizing hormone (LH) stimulated testosterone production in adult rat Leydig cells by six folds, however, LH did not increase testosterone

production in **BDE-47**-treated cells when compared to untreated ones. Both 8-Br-cAMP and 22R-hydroxycholesterol significantly increased testosterone production in cells treated with **BDE-47**.

BDE-99

- **BDE-99** (0.25, 10 and 17.5 ng/mL (0.4, 17.7 and 30.9 nM) for 24h) increased testosterone secretion in follicles from morphologically normal pig ovaries from sexually mature animals (Karpeta et al., 2011). It increased progesterone, androstenedione and testosterone secretion, but had no effect on oestradiol secretion. The lack of an effect of **BDE-99** on the expression and activity of all of the investigated enzymes indicates action on enzymes before progesterone secretion, i.e. STAR or 3β-HSD activity.
- Exposure of pregnant mice during gestation (GD1–21) to 0.2, 2 and 20 mg **BDE-99**/kg bw per day induced effects on male reproductive system in male offspring (Zhao, Tang, et al., 2021, see **Appendix E**, Table E.2). Prenatal exposure significantly inhibited the testosterone synthesis signalling pathway: the testosterone levels and expressions of testosterone regulators were significantly decreased. The number of CYP11A1-positive and 11β-HSD1-positive Leydig cells were also significantly decreased indicating that prenatal exposure to **BDE-99** induces testicular steroidogenesis disorders of immature testes by damaging Leydig cells.

BDE-100

- Three reporter gene assays were used to investigate the potency of **BDE-100** to modulate oestrogen receptor (ER)-, thyroid hormone receptor (THR)- and androgen receptor (AR)-mediated responses (Zhang, Hu, et al., 2011). The (anti) oestrogen and thyroid effects of **BDE-100** (at 10 or 50 μM) were investigated in the African green monkey kidney CV-1 cell transiently transfected with the constructed reporter gene plasmid ERE-TATA-Luc and pUAS-tk-Luc with luciferase (Luc) under control of the oestrogen response or thyroid hormone response elements. The (anti)androgenic potency was also evaluated in MDA-kb2 cells stably transfected with MMTV luciferase. **BDE-100**, can modulate the endocrine system in multiple ways by interfering with several hormonal signalling pathways simultaneously. Exposure to 10 or 50 μM **BDE-100** significantly up-regulated expression of Luc (estrogenic effects) and antagonised oestrogen-induced Luc expression (antioestogenic effect). Co-exposure to 50 μM **BDE-100** significantly enhanced Luc expression caused by 5.0 nM T3. **BDE-100** was also antiandrogenic at 10 and 50 μM.
- **BDE-100** (0.1, 4 and 12.5 ng/mL (0.2, 7.1 and 22.1 nM for 24 h) increased testosterone secretion in follicles from morphologically normal pig ovaries from sexually mature animals (Karpeta et al., 2011). It increased androstenedione and testosterone secretion at all doses, and progesterone secretion at the two lowest doses; it had no effect on oestradiol secretion. There was also a statistically significant decrease in testosterone-stimulated oestradiol secretion due to reduced CYP19 activity. Due to activation of CYP17, a corresponding failure to activate CYP19 expression and inhibition of CYP19 activity was seen.

BDE-209

- Significant reductions in both testicular mRNA and protein levels of steroidogenic factor 1 (SF-1), steroidogenic acute regulatory (StAR) protein, CYP11A1, 3β-hydroxysteroid dehydrogenase (3β-HSD) and 17β-hydroxysteroid dehydrogenase (17β-HSD) were noted in male mice exposed to 950 mg/kg bw per day for 35 days (Sarkar et al., 2016). There was also a marked decrease in proliferating cell nuclear antigen (PCNA) positive cells in testis at this dose. Exposure of adult mice to **BDE-209** caused reduction in serum levels of thyroid hormones and alteration in thyroid homeostasis may partly result into impairment of testicular steroidogenesis and cause suppression of spermatogenesis (Sarkar et al., 2016, see also **Appendix E**, Table E.3).
- Lactating mice were exposed by gavage to 0, 500 and 700 mg **BDE-209**/kg bw per from PND1 to PND28. Male pups of lactating dams were sacrificed at PND42 (Sarkar & Singh, 2018, see **Appendix E**, Table E.3). Maternal exposure markedly affected testicular histopathology, germ cell proliferation and steroidogenesis with down-regulated expression of PCNA and of various steroidogenic markers in peripubertal mice offspring. There was no adverse effect on the expression of CYP19. Decreased expressions of maturational markers of Sertoli cells (SCs) (Cx43, AR and p27Kip1) with a decline in serum TT3 and TT4 levels were also evident in these offspring. The authors concluded that maternal **BDE-209** exposure during lactation impairs germ cell proliferation via inhibition of steroidogenic pathway and differentiation of SCs in peripubertal mice offspring.
- Maternal exposure to 500 or 700 mg **BDE-209**/kg bw per day (PND1–28) markedly affected testicular histopathology, steroidogenesis and germ cell dynamics with downregulated expressions of various steroidogenic markers in mice offspring (Sarkar et al., 2018, see **Appendix E**, Table E.3). Serum TT3 and TT4 levels were markedly reduced in both pups and lactating mothers. Expression of proliferating cell nuclear antigen (PCNA) and the thyroid hormone receptor alpha 1 (THRα1) deceased in testes of BDE-209-exposed mice offspring. The authors concluded that low level of testosterone in pups of lactating dams after **BDE-209** exposure may partly be associated with decreased expression of testicular steroidogenic factor-1 (SF-1), steroidogenic acute regulatory protein (StA)R and T biosynthetic enzymes due to a decline in thyroid status.
- A significantly altered metabolic profile associated with embryotoxicity was observed in serum of pregnant C57 mice exposed by gavage to 2500 mg **BDE-209**/kg bw per day on GD7/9 to GD16 (Chi et al., 2011, see **Appendix E**, Table E.3). At this dose level, **BDE-209** induced significant alteration of thyroid hormone metabolism, the TCA cycle and lipid metabolism in maternal mice, which subsequently led to a significant inhibition of fetal growth and development.
- Postnatal exposure of mice to **BDE-209** at 0.025 mg/kg bw per day by s.c injection on PND1–5 resulted in reductions in

testicular size and number of Sertoli cells and sperm, while exposure to 2.5 mg/kg bw per day had no significant effect (Miyaso et al., 2014). Levels of serum testosterone decreased significantly at 0.25 and 0.025 mg/kg bw per day. Transcripts encoding the androgen receptor declined significantly in Sertoli cells of mice exposed to 0.025 mg/kg bw per day.

Comparative studies of different PBDE congeners and metabolites

- Granulosa cells and theca interna cells from the same follicles of morphologically normal pig ovaries from sexually mature animals were exposed to **BDE-47**, 5-OH- or 6-OH-BDE-47 (50 ng/mL (103 nM) for 3, 6 or 24 h, Karpeta et al., 2014). CAR and PXR mRNAs were not expressed in porcine ovarian follicular cells. **BDE-47** and its OH-metabolites had no effect on the expression of androgen receptor mRNA and protein. **BDE-47** inhibited ERβ mRNA and protein expression with no effect on ERα, while the OH-metabolites enhanced ERα and ERβ_mRNA and protein expression. The authors concluded that **BDE-47**, by altering the ratio of ERα to ERβ toward ERα, and the OH-metabolites of **BDE-47**, by increasing oestrogen receptors expression, may result in excessive ovarian exposure to oestrogens (Karpeta et al., 2014).
- The binding potencies of 12 PBDEs and 18 OH-PBDEs, including **BDE-47** and -**99** and their OH-metabolites with oestrogen-related receptor γ (ERRγ) were determined by using the competitive binding assay (Cao, Zheng, et al., 2018). All of the tested OH-PBDEs and some PBDEs bound to ERRγ (dissociation constant: Kd values ranging from 0.13–13.61 μM). The OH-PBDEs showed much higher binding potency than their parent PBDEs. A QSAR model indicated that the molecular size, relative ratios of aromatic atoms and hydrogen bond donors and acceptors were crucial factors for PBDEs/OH-PBDEs binding. It was reported that most of the low-brominated PBDEs/OH-PBDEs exerted agonistic activity toward ERRγ, while high-brominated PBDEs/OH-PBDEs had no effect on the basal ERRγ activity. All of the 'low-brominated OH-PBDEs' studied showed higher agonistic activity than their parent PBDEs. In addition, all of the 'high-brominated OH-PBDEs' studied showed a higher inhibitory effect on the antagonistic effects of 4-OHT than their parent PBDEs. Results from molecular docking simulations indicated that the low-brominated PBDEs/OH-PBDEs (BDE-3, -7, -**28**, -**47**, -**49**, -85, -**99**) take an agonistic binding conformation while the high-brominated (**BDE-100**, -**154**, -180, -187 and -201) take an antagonistic binding mode (Cao, Zheng, et al., 2018).
- In another study by the same authors, the binding affinities of the same 12 PBDEs and 18 OH-PBDEs with G protein-coupled oestrogen receptor (GPER) pathways were determined in a human breast cancer cell line (SKBR3) (Cao, Ren, et al., 2018). Molecular docking was performed to simulate the interactions. Eleven of the OH-PBDEs but none of the PBDEs bound to GPER directly. Relative binding affinities ranged from 1.3% to 20.0% compared to 17β-estradiol. The hydroxyl group played an essential role in the binding of OH-PBDEs to GPER by forming hydrogen bond interactions. Most of the OH-PBDEs activated subsequent GPER signalling pathways. 4'-OH-BDE-49, 5'-OH-BDE-99, and 3'-OH-BDE-154 displayed the highest activity with lowest effective concentrations. They also promoted SKBR3 cell migration via GPER pathways (Cao, Ren, et al., 2018).
- In MCF-7 cells exposed to **BDE-47, -99, -100** or **-209** alone (at 0.1, 0.5 or 1 μM for 72h) or in combination with oestradiol, no effects on basal cell proliferation were observed, with the exception of an inhibitory effect with the highest doses of **BDE-99** and -**100** (Kwiecińska et al., 2011). All congeners significantly decreased basal caspase-9 activity. An additive anti-apoptotic activity and ability to induce cell proliferation was noted in the presence of oestradiol.
- **BDE-47, -100** and -**153** regulated distinct nuclear receptor signalling pathways in MCF-7 aroERE exposed *in vitro* (5 nM–100 μM, Kanaya, Chang, et al., 2019). **BDE-47** acted as a weak agonist of both oestrogen receptor α (ERα) and oestrogen-related receptor α (ERRα). It could stimulate proliferation of MCF-7 aroERE and induce expression of ER-regulated genes (including cell cycle genes). **BDE-153** acted as a weak antagonist of ERα. **BDE-100** could act as a weak agonist/antagonist of ERα.
- Intracellular levels of glucocorticoids (cortisol in humans or corticosterone in rats) are controlled by the glucocorticoid-metabolising enzyme 11β-hydroxysteroid dehydrogenase (HSD11B). By using liver microsomes, inhibition of rat and human HSD11B1 and HSD11B2 activities was tested for 4 different PBDEs (BDE-3, -**47**, -**100** and -**153**, at 100 μM) and compared to inhibition by 4-bromobiphenyl (BBP), a structurally similar compound (Chen, Dong, et al., 2016). None of the compounds tested inhibited rat and human HSD11B1. BDE-3 and **-47** potently inhibited rat HSD11B2, and **BDE-47** and -**153** potently inhibited human HSD11B2. All PBDEs non-competitively inhibited HSD11B2 when a steroid substrate was used. However, PBDEs exerted uncompetitive inhibition when the cofactor NAD^+ was used. The authors concluded that some PBDEs are selective inhibitors of HSD11B2, possibly causing excessive glucocorticoid action in local tissues.
- The androgenic activity of **BDE-100** and **-155** was investigated in MDA-kb2 cells treated for 24 h (Christen et al., 2010). None of the congeners showed notable androgenic activity, but there was an enhancement of the androgenic action of dihydrotestosterone.
- Sheikh and Beg (2021) investigated the potential induction of functional changes of **BDE-47** and -**99** and their OH-metabolites (5-OH-BDE-47, 6-OH-BDE-47, 5-OH-BDE-99, 6-OH-BDE-99) and MeO-metabolites (5-MeO-BDE-47, 6-MeO-BDE-47, 5-MeO-BDE-99, 6-MeO-BDE-99) structural analogues on androgen receptor (AR). Following the induced fit docking and binding energy estimations, it was shown that the compounds are packed tightly in the AR ligand-binding pocket, displaying similar binding pattern to the native-ligand testosterone. The estimated binding energy values suggested higher binding affinity of **BDE-99** and its structural analogues than **BDE-47** and its structural analogues. Moreover, for both congeners, the MeO-structural analogues showed higher binding affinity compared to the OH- counterparts. The estimated binding energy values of 6-MeO-BDE-99 and 5-MeO-BDE-99 were the highest and their AR-binding affinities were comparable to testosterone. The authors suggested potential induction of functional changes of **BDE-47** and **-99** and their analogues particularly for 6-MeO-BDE-99 on AR signalling pathway, which may adversely impact the male reproductive growth and function.

Other individual PBDE congeners

- Chen, Dong, et al. (2018) reported decreased serum testosterone levels at 200 mg/kg bw per day in male rats exposed by gavage to BDE-3 for 21 days (see also **Appendix E**, Table E.4). At this dose level, BDE-3 also decreased Leydig cell size and cytoplasmic size, and down-regulated both Leydig and Sertoli cell gene expression. It also decreased the phosphorylation of AKT1, AKT2, ERK1/2, and AMPK at 100 or 200 mg/kg bw per day. *In vitro*, BDE-3 induced ROS generation, inhibited androgen production, down-regulated expression of genes associated with masculinisation in immature Leydig cells after 24-h treatment.

Technical products

- In Leydig cells from adult male rats incubated for 1 h with different concentrations of DE-71 (0.5, 1.5, 5 or 15 ng/mL (1, 3, 9 and 27 nM)), the two highest doses increased basal testosterone secretion and cAMP production by three- and two-fold, respectively (Wang, Hsia, et al., 2011). The stimulatory effect was abolished by adenylyl cyclase inhibitor. Enzyme activity of CYP11A1 was stimulated by DE-71 treatment. Furthermore, nuclear translocation of PKAa was increased by 20% and StAR gene expression was elevated by 4-fold.

Studies with PBDE metabolites alone

- 6-OH-BDE-47 showed much greater inhibition of oestradiol-3G and oestradiol-17G formation compared to 6-MeO-BDE-47 (Mercado-Feliciano & Bigsby, 2008). Although the glucuronidation efficiency of OH-PBDEs depends on many variables, the number of substituted bromine at phenolic ring was the most influential factor. While 6-OH-BDE-47 was a good substrate for glucuronidation, addition of one and two more bromine atoms at the phenolic ring (for 6-OH-BDE-85 and 6-OH-BDE-137, respectively), resulted in considerable increase of half-lives. OH-PBDEs were more potent inducers of hormonal effects compared to their parent PBDEs. The mild oestrogenic effects of PBDEs may result from OH-PBDEs that act as ligands for the oestrogen receptor (Mercado-Feliciano & Bigsby, 2008).
- Moreover, OH-PBDEs exhibited potent inhibitory activity of oestradiol-sulfotransferases (Hamers et al., 2008; Kester et al., 2002) and placental aromatases (CYP17 and CYP 19) (Cantón et al., 2008). This study indicated that substitution patterns of bromine and OH- group played an important role in the glucuronidation of OH-PBDEs and their modulation of oestradiol-UGTs activity. The structure–activity relationship of OH-PBDEs glucuronidation could help to explain why some congeners exhibit long-term accumulation and oestrogenic potency in biological system. Oestrogenic effects of PBDEs may be partly mediated via modulation of oestradiol-UGTs by OH-PBDEs, which provided an alternative mechanism for induction of endocrine effects of PBDEs (Lai et al., 2012). Regarding the modulation of oestradiol-UGTs activity, the phenolic hydroxyl group in OH-PBDEs played an essential role. Depending on the substitution patterns of bromine and hydroxyl group, OH-PBDEs inhibited or stimulated oestradiol-UGTs activity. By inhibiting the formation of oestradiol glucuronidation, OH-PBDEs may increase oestradiol bioavailability in target tissue, thereby exerting an indirect oestrogenic effect.
- In rat liver microsomes, inhibition of oestradiol metabolism by 11 OH-PBDEs[49] was significantly greater than by parent PBDEs and MeO-metabolites, providing evidence that PBDEs exerted oestrogenic activity in part by their OH-metabolites (Lai & Cai, 2012). The most potent OH-PBDE inhibitor was found to be 3′-OH-BDE-100.
- Lai et al. (2012) investigated the glucuronidation of 11 OH-PBDEs[50] and their potential in modulating UDP-glucuronosyltransferases (UGTs) activity of 17β-oestradiol (E2) in rat liver microsomes. The number of bromine atoms at phenolic ring was the most influential factor of OH-PBDEs glucuronidation. The phenolic hydroxyl group in OH-PBDEs played an essential role in the modulation of oestradiol-UGTs activity. Depending on the substitution patterns of bromine and hydroxyl group, OH-PBDEs inhibited or stimulated oestradiol-UGTs activity. OH-PBDEs with the hydroxyl group *ortho* to the ether bond appeared to be the more potent inhibitors. The number of bromine atoms at the phenolic ring also seemed to be important for the inhibition of oestradiol-UGTs (4′-OH-BDE-17 with one bromine atom at the phenolic ring was much less potent than 4′-OH-BDE-49 that had one more bromine atom adjacent to OH group). In addition, the authors reported lower inhibition by 6-OH-BDE-137 than by 6-OH-BDE-85, and suggested that increased substitution at the phenolic ring could reduce inhibitory potency due to the steric effects of bromine (Lai et al., 2012).

The authors also showed that OH-PBDEs exhibited large interindividual differences in glucuronidation and modulation of oestradiol-UGTs activity. By inhibiting the formation of oestradiol glucuronidation, OH-PBDEs may increase oestradiol bioavailability in target tissue, thereby exerting an indirect oestrogenic effect.

- Granulosa cells and theca interna cells from the same follicles of morphologically normal pig ovaries from sexually mature animals were exposed for 24 h to 5-OH-BDE-47 or 6-OH-BDE-47 (2.5, 5, 10, 25 and 50 ng/mL (5, 10, 20, 50 and 100 nM), Karpeta et al., 2013). Both metabolites failed to affect the production of androstenedione and testosterone but increased

[49]3′-OH-BDE-7, 6′-OH-BDE-17, 4′-OH-BDE-17, 2′-OH-BDE-28, 4′-OH-BDE-49, 6-OH-BDE-47, 2′-OH-BDE-66, 2′-OH-BDE-68, 6-OH-BDE-85, 6-OH-BDE-100, 6-OH-BDE-137 and 6-MeO-BDE-47.

[50]3′-OH-BDE-7, 6′-OH-BDE-17, 4′-OH-BDE-17, 2′-OH-BDE-28, 4′-OH-BDE-49, 6-OH-BDE-47, 2′-OH-BDE-66, 2′-OH-BDE-68, 6-OH-BDE-85, 6-OH-BDE-100, 6-OH-BDE-137, 6-MeO-BDE-47.

the secretion of oestradiol at all concentrations tested. The increased secretion of oestradiol was due to the stimulation of aromatase (CYP19A1) gene and protein expression. Direct assessment of aromatase activity and indirect assessment by measurement of the conversion of testosterone to oestradiol confirmed that 5-OH-BDE-47 and 6-OH-BDE-47 stimulate aromatase activity. The aromatase inhibitor CGS 16949A abolished this stimulatory activity and reduced oestradiol levels in the control and treated groups (Karpeta et al., 2013).

- The binding affinity of 22 OH-PBDEs with different degrees of bromination to oestrogen receptor (ER) was assessed quantitatively (Li, Gao, Guo, & Jiang, 2013). Seven OH-PBDEs (including 3-OH-BDE-47, 6-OH-BDE-47, 6-OH-BDE-99 and 5-OH-BDE-99) were found to bind directly with ER. There was a good correlation between oestrogenic activity and ER binding affinity of the 'low-brominated' OH-PBDEs[51] which strongly suggest that these compounds induce ER transcriptional activity by binding directly with ER. The other 12 'high brominated' OH-PBDEs[52] (including 6-OH-BDE-47, 6-OH-BDE-99 and 5-OH-BDE-99) inhibited oestradiol induced gene expression as shown in a reporter gene assay, demonstrating their antagonistic activity. Molecular docking analysis of the ER/OH-PBDE complexes revealed two distinctive binding modes between 'low- and 'high-brominated' OH-PBDEs which provided rationale for the difference in their ER activity.
- Gosavi et al. (2013) obtained crystal structures of SULT1E1 (steroid-metabolising enzyme) in complex with 3-OH-BDE-47. These structures reveal how BFRs can mimic oestradiol binding to the active site of the enzyme. The hydroxyl moiety on the BFRs enhances the binding affinity to SULT1E1.

3.1.4.5.2 | *Oxidative stress and mitochondrial damage*

BDE-47 and its metabolites

- In male rats exposed by gavage to 0, 0.001, 0.03 and 1 mg **BDE-47**/kg bw per day for 8 weeks (6 days per week), **BDE-47** significantly increased the expression and activity of CYP3A1 in liver, and 3-OH-BDE-47 dose-dependently increased in liver, serum and testis, which was aggravated by dexamethasone, an inducer of CYP3A1 (Zhang, Zhang, et al., 2013). Additionally, testicular 3-OH-BDE-47 and ROS in seminiferous tubules increased especially when **BDE-47** was administered in combination with dexamethasone, which was confirmed in GC-1 and GC-2 cells that 3-OH-BDE-47 induced more ROS production and cell apoptosis via the upregulation of FAS/FASL, *p*-p53 and caspase 3. As a result, daily sperm production dose-dependently decreased, consistent with histological observations in giant cells and vacuolar spaces and increase in TUNEL-positive apoptotic germ cells.
- In adult male rats exposed by gavage to 0.001, 0.03, 1 or 20 mg **BDE-47**/kg bw per day for 8 weeks, dose-related decreases in tubular seminiferous epithelial thickness, impaired mitochondrial function and induced apoptosis in early leptotene spermatocytes were observed (Huang, Cui, et al., 2015, see **Appendix E**, Table E.1). Proteomics analysis based on 2D gel electrophoresis detected 64 differentially regulated proteins participating in many cell processes, including apoptosis (31.3%), proliferation (17.2%), oxidative stress (17.2%) and mitochondrial damage, cell respiration and the generation of ROS. Fifteen differentially expressed proteins (23.4%) were located in the mitochondria, 13 (20.3%) in the cytoskeleton, and 6 (9.4%) were in the endoplasmic reticulum.
- In female C57BL/six mice exposed by gavage to 0, 10, 50 or 100 mg **BDE-47**/kg bw per day for 5 weeks, ovarian lipid deposition (increased lipid droplets and free fatty acid levels) and ovarian hormone changes accompanied by oxidative stress (increase in ROS and MDA concentrations) were observed, as well as downregulation of hormone biosynthesis-related proteins (Shaoyong et al., 2022). **BDE-47** exposure reduced the serum levels of oestradiol and progesterone and thereby damaged the oestrus cycle and female fertility. Using mice ovarian granulosa cells (GCs) as a cellular model, it was shown that **BDE-47** (10, 40 or 80 μM) inhibited two ovarian hormone secretion-associated pathways: (i) **BDE-47** exposure induced oxidative stress via the Nrf2/HO-1 signalling pathway and further inhibited the expressions of ovarian hormone biosynthesis-related proteins, such as StAR, 3-βHSD, CYP11A1 and CYP17A1; ii) **BDE-47** induced endoplasmic reticulum (ER) stress, mitochondrial abnormalities and lipotoxicity, which in turn disrupted the hormone biosynthesis process and inhibited ovarian hormone secretion. **BDE-47** exposure upregulated the expression of autophagy-related genes and downregulated the autophagy-degradation gene in GCs. In addition, **BDE-47** exposure also partly induced autophagy via the oxidative stress pathway. Autophagy has a positive effect in inhibiting lipotoxicity by degrading the overproduced lipid droplets and regulating the expressions of lipid metabolism-related genes, which in return promote ovarian hormone secretion. In addition it was shown that two individual pathways mediated apoptosis in GCs: the ER stress-mediated signalling pathway and the ROS-mediated mitochondrial signalling pathway (Shaoyong et al., 2022).
- In the study by Sun, Li, Xu, et al. (2020) in which female mice were exposed by gavage to 0.1 or 0.5 mg **BDE-47**/kg bw per day for 21 days, ovaries and uterus were smaller at the highest dose and showed decreased weight. At that dose, the number of mature follicles (Graafian follicle) and oocytes in the ovary was reduced. **BDE-47** had an effect on the maturation competence of mouse oocytes, and lead to the failure of the polar body extrusion in the oocytes. Exposure to **BDE-47** modified actin filaments distribution, changed the level of histone methylation and altered multiple gene expression in mouse oocytes. The authors concluded that **BDE-47** exposure affected the maturation of mouse oocyte via its effects on mitochondria function, ROS level and its related apoptosis.

[51] 2′-OH-BDE-3, 3′-OH-BDE-7, 2′-OH-BDE-7, 4′-OH-BDE-17, 3′-OH-BDE-28, 2′-OH-BDE-28, 4-OH-BDE-42, 4′-OH-BDE-49, 3-OH-BDE-47, 3′-OH-BDE-154.

[52] 6-OH-BDE-47, 2′-OH-BDE-68, 6-OH-BDE-82, 6-OH-BDE-85, 4-OH-BDE-90, 6′-OH-BDE-99, 5′-OH-BDE-99, 3-OH-BDE-100, 6-OH-BDE-140, 6-OH-BDE-157, 4-OH-BDE-188.

- Prostaglandins regulate trophoblast functions necessary for placentation and pregnancy. Park and Loch-Caruso (2015) investigated **BDE-47** induction of prostaglandin synthesis in a human extravillous trophoblast cell line, HTR-8/SVneo. Treatment with 20 μM **BDE-47** significantly increased mRNA expression of prostaglandin-endoperoxide synthase 2 at 4, 12 and 24 h. 24-h exposure significantly increased cyclooxygenase (COX)-2 cellular protein expression and PGE2 concentration in culture medium. The **BDE-47**-stimulated PGE2 release was inhibited by the COX inhibitors indomethacin and NS398, implicating COX activity. Exposure to 20 μM **BDE-47** significantly increased ROS generation and this response was blocked by cotreatment with the peroxyl radical scavenger (±)-a-tocopherol. (±)-a-Tocopherol cotreatment suppressed **BDE-47**-stimulated increases of PGE2 release without significant effects on COX-2 mRNA and protein expression, implicating a role for ROS in post-translational regulation of COX activity.
- Mouse spermatogonial cells (GC1-spg cells) treated with **BDE-47** (0.1, 1, 10 or 100 μM for 50 h) showed induced apoptosis, impaired mitochondria and decreased Bcl-2 (an important anti-apoptotic factor of the mitochondrial pathway) in cells (Huang, Cui, et al., 2015). Proliferation in GC1-spg cells was not sensitive to **BDE-47** at concentrations lower than 100 μM.
- In MA-10 mouse Leydig tumour cells exposed to **BDE-47**, cytotoxicity was observed at ≥ 50 μM (Schang et al., 2016). There were significantly reduced mitochondrial activity (≥ 50 μM) and cell number (≥ 10 μM), however, **BDE-47** had no significant effect on superoxide production or on basal or stimulated progesterone production.
- Mitochondrial dysfunction may result in failure of spermatogenesis. In immortalised mouse spermatocyte cells (GC2) exposed to 0.1, 1, 10 or 100 μM **BDE-47** for 48 h, a decrease in cell viability and cell cycle arrest at S and G2/M phase was observed (Huang et al., 2016). **BDE-47** caused damage to the ultrastructure of GC2 cells characteristic of apoptosis: condensation of nuclear and vacuolated mitochondria. Decreases in mitochondrial membrane potential and ATP, induction of ROS and reductions of mitochondrial proteins were observed. The authors suggested that **BDE-47** reduced cell viability, injured mitochondria in spermatocytes probably by decreasing mitochondrial protein Atp5b and Uqcrc1.
- In human placental choriocarcinoma BeWo cells, exposure to **BDE-47** decreased progesterone production but had no effect on key enzymes (Cyp11a1 and 3β-HSD) (Shan et al., 2019). It depolarised the mitochondrial membrane potential and downregulated ATP levels. The expression levels of genes involved in mitochondrial dynamics and cholesterol transport were disturbed. The demethylation of some CpG loci of mitochondrial biomarkers (*Drp1*, *Opa1*, *Vdac2* and *Atad3*) was induced in the 1 μM **BDE-47** exposure group, but no methylation change was observed with 50 μM treatment. The authors concluded that the reduction of progesterone synthesis induced by **BDE-47** might be associated with cholesterol transportation, mitochondrial dynamics and mitochondrial functions.

In fertilised chicken eggs dosed via *in ovo* administration of 6-OH-BDE-47 (at 0.474, 0.158, 0.053, 0.018 and 0.006 nmol/g egg) followed by 18 days of incubation, a significant embryo lethality and increased relative liver weight were observed (Peng et al., 2016). It was shown that the functional enrichment of differentially expressed genes was associated with oxidative phosphorylation, generation of precursor metabolites and energy, and electron transport chains.

BDE-99

- In the Blanco et al. (2012) study (see Section **3.1.2.3** and **Appendix E**, Table E.2), a dose-dependent increase in the level of all evaluated oxidative stress markers (SOD, CAT, GPx, and GR and the total level of TBARS in the fetal rat liver) was found indicating that the production of ROS in fetal rat liver was proportional to the level of **BDE-99** exposure in pregnant dams (0.5, 1 and 2 mg/kg bw per day GD6–19). The transplacental effect was demonstrated by the activation of nuclear hormones receptors AHR, PXR and primarily CAR, that induce the upregulation of CYP1A1, CYP1A2, CYP2B1 and CYP3A2 isoforms in fetal liver. These isoforms were correlated with the activity level of the enzyme catalase and the levels of thiobarbituric acid reactive substances. The authors concluded that clear signs of embryo/fetal toxicity, due to possible hormonal changes or effects, were evidenced by a large increase in the CYP system and the production of ROS in fetal liver (Blanco et al., 2012).
- In TM3 Leydig cells (from testes of immature mice) exposed to **BDE-99** (0.01, 0.1, 1, 10 and 100 μM for 12, 24 and 48 h, respectively), a significant time- and dose-dependent inhibition of cell viabilities was observed (Zhao, Tang, et al., 2021). **BDE-99** upregulated reactive oxygen species, activated the ERK1/2 pathway, inhibited the ubiquitination degradation pathway and finally induced apoptotic mitochondrial changes in Leydig cells.

BDE-209

- In the study by Sarkar and Singh (2017), lactating female Parkes mice were orally gavaged with 500 and 700 mg **BDE-209**/kg bw per day from PND0 to PND28, and male pups euthanised at PND21 and 28, see **Section 3.1.2.2.3** and **Appendix E**, Table E.3), on both dates, the level of lipid peroxidation was markedly high in testes of exposed mice, whereas the activities of antioxidant enzymes (SOD and CAT) decreased significantly. Cell apoptosis was noted with altered expressions of various cell survival and apoptotic markers along There was significant reduction in expression levels of Cx43, p27Kip1, GLUT8 and Bcl-2 protein in exposed mice at both PND21 and PND28. However, **BDE-209** treatment did not affect the expression of GLUT3 at PND21, while a significant reduction in expression level of GLUT3 was noted at PND28. A significant increase in expression levels of CYP19, Bax and CASP-3 protein in exposed mice at both days. Testicular glucose and lactate dehydrogenase (LDH) as well as lactate concentrations were markedly reduced in these pups with down-regulation in GLUT3 and GLUT8 expressions. There was an increase in oxidative stress in testes and increased oestrogen level in these pups. The authors concluded that

maternal exposure to **BDE-209** during lactation affects germ cell survival with altered testicular glucose homeostasis and oxidative status through down-regulation of Cx43 and p27Kip1 in prepubertal mice offspring (Sarkar & Singh, 2017).

- In the study by Sarkar et al. (2019), see **Appendix E**, Table E.3), exposure during lactation of female mice to 500 or 700 mg **BDE-209**/kg bw from PND1-28, increased apoptosis and oxidative status with altered expressions of various cell survival (Bcl-2), apoptotic (Bax and caspase-3) and oxidative stress (Nrf2 and HO-1) markers in testes and epididymis of peripubertal mice offspring (on PND42). A significant reduction was noted in the level of sialic acid in the epididymis in offspring and in the activities of SOD and catalase in the testes and epididymis. The level of lipid peroxidation was markedly high in testes and epididymis. Testicular glucose and lactate concentrations were markedly reduced in these pups with down-regulation in GLUT3 and GLUT8 expressions and decreased LDH activity. Maternal **BDE-209** exposure markedly affected fertility potential, epididymal histology, sialic acid concentration and sperm quality with decreased expression of epididymal Cx43 and AR in these mice offspring (Sarkar et al., 2019).
- In male rats exposed by gavage to **BDE-209** at 0, 5, 50 and 500 mg/kg bw per day for 28 days, decreased sperm quality and quantity, correlated with glycolipid metabolism dysbiosis of testis, was shown (Zhang, Li, et al., 2021, see **Appendix E**, Table E.3). **BDE-209** exposure activated the glycolipid metabolism pathways (PPARγ/RXRα/SCAP/SREBP-1) and mitochondrial apoptotic pathway, thereby inducing the apoptosis of spermatogenic cells.
- In male ICR mice s.c. injected with **BDE-209** from PND1 to 5 at doses of 0.025, 0.25 and 2.5 mg/kg bw per day, decreased epididymal weight was noted at 12 weeks of age (Nakamoto et al., 2014). However, no histological change was observed on epididymal tissues, unlike the effect of diethylstilbestrol. **BDE-209** exposure did not induce alterations in gene expression observed with diethylstilbestrol exposure. Instead, alterations in gene expression of certain oxidative stress-related genes (i.e. PTEN-induced putative kinase 1 (Pink1)) were observed, and the expression of ubiquitin C increased in **BDE-209** exposed mouse epididymides. The authors concluded that increased oxidative stress may play a role in the harmful effects observed in mouse epididymides (decreased sperm quality and/or immature sperm formation) after **BDE-209** exposure (Nakamoto et al., 2014). The relative importance of different potential mechanisms of induction of oxidative stress upon **BDE-209** exposure remains unclear. However, other investigations have reported the relationship between thyroid hormone and oxidative stress (D'adamo et al., 2012).
- Zhang, Li, et al. (2021) exposed the spermatogenic cell line GC-2spd to **BDE-209** (32 μg/mL (33 μM)) in presence or absence of fatostatin (lipid metabolism pathways inhibitor) and observed triglyceride and total cholesterol disorder and apoptosis of GC-2spd cells. Fatostain down-regulated the elevation of triglyceride and total cholesterol concentrations, and suppressed apoptosis and the activation of the mitochondrial apoptotic pathway in GC-2spd cells caused by **BDE-209**.

3.1.4.5.3 | *Oxidative DNA damage*

BDE-209

- In the Tseng et al. (2013) study (see **Section 3.1.2.3** and **Appendix E**, Table E.3), effects on male reproduction were observed on PND71 in offspring exposed in utero (GD0–17) to 1500 mg **BDE-209**/kg bw per day. The sperm chromatin structure assay (SCSA) has been widely used as an indicator of sperm DNA fragmentation. Statistically significant increases in two indicators of sperm chromatin DNA damage: the mean of αT distribution (reflecting the level of sperm with DNA damage) and the DNA fragmentation index (DFI, representing spermatozoa with abnormal structure or DNA damage), were observed in offspring exposed to 10, 500 and 1500 mg **BDE-209**/kg bw per day. These markers are usually associated with increase male infertility. To investigate sperm oxidation stress, hydrogen peroxide (H_2O_2) and O_2 levels were measured in epididymal sperm. The authors found significant increases of sperm H_2O_2 generation in the 10 and 1500 mg/kg bw per day groups. However, there were no dose-dependent effects in sperm DNA damage and H_2O_2 generation among **BDE-209**-treated groups and controls (Tseng et al., 2013). The Panel considered that some methodological aspects (use of only the cauda of the epididymis, some manipulations, no pre-analysis for the assessment of the sperm membrane potential) may alter these conclusions.
- In mature male Balb/c mice were exposed by i.*p*. to 0 (DMSO), 8, 40 or 80 mg **BDE-209**/kg bw per day for 2 weeks (6 days/week), negative effects on male reproduction were shown: mean testis and seminal vesicle weights were significantly decreased at 80 mg/kg bw per day, and decreases in sperm count in epididymis and cauda epididymis and abnormal spermatozoa (head abnormalities and coiled tail) were found at the highest dose (Zhai et al., 2021). The diameter and the height of the epithelium of the seminiferous tubules were decreased a 40 and 80 mg/kg bw per day. GSH-Px activity decreased in testes at 80 mg/kg bw per day, whereas MDA level increased at 40 and 80 mg/kg bw per day indicating oxidative stress. Cytological and flow cytometry analysis of the seminiferous epithelium revealed a relative accumulation of pachytene spermatocytes compared to the other cell types. At the same time a marker of meiotic activity, as Stra8, along with a marker of progression from pachytene spermatocytes to round spermatids, as the testicular H1 histone (H1t) were analysed. There was a statistically significant decrease in the expression of mRNAs and proteins of Stra8 at 80 mg/ kg bw and of H1t at at 40 and 80 mg/ kg bw. On the other hand, elements of meiotic activity, such as Sycp3 (protein of the synaptonemal complex of homologous chromosomes) and γH2AX (role in the DNA damage response including meiotic recombination) were also significantly deregulated at 80 mg/ kg bw; decrease of Sycp3 and increase of γH2AX. In addition, proteins involved in meiotic recombination: RAD51, DMC1 and MLH1 showed lower expression at this high dose. All together, the results indicated an abnormal arrest in meiosis I of spermatogenesis at the level of pachytene spermatocytes. with logical consequences at the spermatogenic level (decreasing sperm quality and quantity) in the male reproductive system and impairment of male fertility (Zhai et al., 2021).

In GC-2 spd cells treated *in vitro* with 0, 12.5, 25, 50, 100 µM and 200 µM **BDE-209**, ROS and MDA testis levels increased, whereas GSH-Px activity decreased (Zhai et al., 2021).

3.1.4.5.4 | *Molecular changes – gene expression*

BDE-47

- Newborn female rats were exposed by gavage to **BDE-47** at 0, 1, 5 or 10 mg/kg bw on PND10, and an additional 10 mg/kg bw **BDE-47** group was given the endoplasmic reticulum stress (ERS) inhibitor 4-PBA i.*p.* for 3 weeks beginning on PND8 (Wang et al., 2016, see **Appendix E**, Table E.1). At 2 months of age, **BDE-47** exposure significantly reduced the ovarian coefficients (body weight/ovarian weight), increased the expression of ERS and autophagy markers, including GRP78, IRE1, Caspase-12, Beclin1, LC3 and P62. In the 10 mg/kg bw dose group, PARP and Caspase-3 were markedly activated, indicating apoptosis. These were accompanied by histopathological damage: a thinning of the ovarian granular cell layer and corpus luteum was observed at the two lowest doses and the ovarian granular cell layer, graafian follicles and oocytes were reduced, and the corpus luteum was increased at the highest dose. 4-PBA attenuated all these effects. The authors concluded that ERS plays a vital role in **BDE-47**-induced ovarian injury by regulating autophagy and apoptosis (Wang et al., 2016).
- In C57BL/6J mice administered 10 mg **BDE-47**/kg bw per day by i.*p.* injection once daily from PND22 for 3 weeks, **BDE-47** induced testicular toxicity (Zhang, Xia, et al., 2022). ScRNA-seq were performed to characterise the underlying mechanism of how prepubertal **BDE-47** exposure may contribute to testicular toxicity in mice. Single-cell suspensions from mice testes were obtained (spermatogonia, meiotic spermatocytes, pachytene, acrosomal, post-meiotic haploid round, spermatids, elongating spermatids, innate lymph, telocytes, Leydig and Sertoli cells). A variety of genes that play a major role in regulating spermatogenesis were shown to be significantly upregulated or downregulated upon **BDE-47** treatment in at least one cell type of testis. Spermatogenesis is a complex process and transcriptomic changes in different cell types and even in individual cells within the same cell type vary greatly. Several pathways such as hormone homeostasis, inflammation response and ER stress were enriched in response to **BDE-47**. Multiple shared or cell-type-specific enrichment of pathways such as double-strand break repair, cytokinesis, and histone modification in different cell types were shown. The increase of innate lymph cells may reflect the increased inflammatory response in testicular tissue possibly through increased permeability of the blood–testis barrier. In addition, **BDE-47** inhibited gene sets associated with the steroid metabolic process indicating that **BDE-47** may inhibit spermatogenesis via inhibition of testosterone production (Zhang, Xia, et al., 2022).
- Impaired trophoblast migration and invasion during early pregnancy have been implicated as potential mechanisms of pregnancy disorders. Park et al. (2020) investigated the effect of **BDE-47** on cell migration, invasion and matrix metalloproteinase expression. Human first trimester extravillous trophoblast cell line (HTR-8/SVneo) were exposed to 5, 10, 15 and 20 mM **BDE-47**. **BDE-47** stimulated cell migration in HTRSV/neo cells while decreasing invasion of cells into Matrigel. In addition, **BDE-47** led to differential expression of matrix metalloproteinase-1, -2, -3 and -9 at protein and mRNA levels.
- To study the potential consequences of PBDEs exposure on human placental development, Robinson et al. (2019) used an *in vitro* model in which primary human villous cytotrophoblasts, isolated from second trimester placentas, were exposed to **BDE-47**. **BDE-47** significantly reduced cell viability (from 10 µM) and increased death in a concentration-dependent manner. After exposure to sub-cytotoxic concentrations (5 µM), **BDE-47** accumulation was observed in cytotrophoblasts with limited evidence of hydroxylated metabolism. Significant inhibition of migration/aggregation (after 5 h exposure) and invasion (after 40 h exposure) were observed with **BDE-47** (5 µM). Transcriptomic analyses of **BDE-47** effects showed changes in gene expression, involving stress pathways (e.g. inflammation and lipid/cholesterol metabolism) as well as processes underlying trophoblast fate (e.g. differentiation, migration and vascular morphogenesis). In addition, **BDE-47** induced low-level global increases in methylation of CpG islands, including a subset that were proximal to genes with roles in cell adhesion/migration.

BDE-209

- In pregnant female rats exposed by gavage to 0, 1, 5 and 10 mg **BDE-209**/kg bw per day from GD0–GD21, the mRNA expression of ET-1 and iNOS in the placenta was gradually and significantly increased after exposure to increasing doses of **BDE-209**, while the mRNA level of eNOS in the placenta was gradually and significantly reduced (Du et al., 2015, see **Appendix E**, Table E.1). The production of total NO was significantly increased after exposure to 5 and 10 mg//kg bw per day. It was also shown that the birth weight of the offspring rats was significantly reduced after maternal exposure to this compound.
- Pregnant mice were exposed by gavage to 0, 100, 300 or 500 mg **BDE-209**/kg bw per day from GD7 to PND21. F1 male pups were observed on PND35 and 105 (Zhai et al., 2019, see **Appendix E**, Table E.3). In addition, SerW3 cells (rats Sertoli cells immortalised with SV40 large-T antigen) were treated with methylpiperidino pyrazole (MPP) for 30 min before being treated with **BDE-209** at 50 µg/mL. **BDE-209** increased ERα in time- and dose-dependent manners and decreases formin 1 and the blood-testis barrier (BTB)-associated protein in F1 male mice. Furthermore, it impaired the structure and function of the blood-testis barrier. The highest protein level of ERα occurred in SerW3 cells treated with 50 µg/mL of **BDE-209** for 24 h. The role of ERα in BTB perturbation during spermatogenesis was identified and suggested that BTB perturbation occurs because of exposure to **BDE-209**, which could potentially affect spermatogenesis. **BDE-209** mainly im-paired the expression of TJ mRNA and decreased the expression of BTB protein in F1 mice at PND35. Regulation of formin 1 and F-actin occurred differently *in vivo* (downregulation of formin 1 and F-actin) and *in vitro* (downregulation of

formin 1 and upregulation of F-actin). The authors concluded that Sertoli cells seem to be the primary target of **BDE-209** in the perinatal period, and this period constitutes a critical window of susceptibility to **BDE-209** (Zhai et al., 2019).

- Pregnant mice were exposed by gavage to 0, 2, 20 or 200 mg **BDE 209**/kg bw per day from GD0-18. Effects on placenta are reported in **Appendix E** (Zhao et al., 2022, Table E.3). Impaired placental transport and endocrine function was demonstrated by markedly downregulated expression of *Glut1* (glucose transporter), *Znt1* (Zn transporter), *Pgf* (placental growth factor) and *Igf2* (insulin growth factor 2) in treated placentas. **BDE-209** induced also placental ER stress. An *in vitro* study was also performed on human JEG-3 cells and PERK silenced cells treated with or without 50 μM **BDE-209** for 48 h which shows that PERK siRNA pretreatment reversed BDE-induced cell apoptosis. The authors suggest that the activation of the ER stress-mediated PERK signalling might play a role in **BDE-209** induced cell apoptosis (Zhao et al., 2022).
- Rat vascular endothelium cells (RAOEC) and human umbilical vein endothelial cells (HUEVCs) were treated with various concentrations (1, 50 and 100 μM) of **BDE-209**. The endothelial function of RAOEC and HUEVC was impaired after treatment with 50 μM and 100 μM **BDE-209**. It was also demonstrated that 5 transcription factors (NFKB1, NR3C1, E2F5, REL, IRF4) might regulate endothelial function by affecting the expression of genes like BCL-2, CAP3, CAT, TNF, MAPK1 and MAPK3. The authors suggested that **BDE-209** might affect downstream genes by binding to transcription factors, leading to corpus cavernosum endothelial dysfunction, thus contributing to erectile dysfunction in rats (Zhou et al., 2022).

3.1.4.5.5 | *Epigenetic mechanisms*

BDE-47

- Pregnant rats were exposed from GD8 to PND21 to 0.2 mg **BDE-47**/kg bw per day and caudal epididymal sperm were collected from offspring on PND65 and PND120 (Suvorov et al., 2018). **BDE-47** exposure increased DNA methylation of epididymal sperm on PND65 in genes, promoters and intergenic regions. However, on PND120, methylation decreased in these genomic elements. 21 and 9 exposure-related differentially methylated regions were identified in sperm collected on PND65 and PND120, respectively. Two differentially methylated regions over-lapped between the two time-points.

BDE-209

- **BDE-209** induced testicular damage (reduction of sperm cells and pathological changes in seminiferous tubules), decreased sperm number and motility, and increased the sperm malformation rates in male rats after exposure for 28 days (5, 50 and 500 mg/kg bw per day, Li, Liu, et al., 2021, see **Section 3.1.2.3** and **Appendix E**, Table E.3). Cell senescence and apoptosis were demonstrated in the seminiferous tubules that could contribute to the decline of sperm quality and quantity. **BDE-209** could also damage the telomeric function by shortening telomere length and reducing telomerase activity. The signalling pathway of p53/p21/p16 was activated in testis after exposure to **BDE-209**.
- **BDE-209** (32 μg/L (33 nM)) caused genomic methylation changes in GC-2 cells (spermatocytes co-transfected cells, which have lost their differentiation potential and arrested at a premeiotic stage), including hypermethylated and hypomethylated sites. **BDE-209** might affect the functional transcription in cell growth and sperm development by differential gene methylation. p53-dependent DNA damage response was involved. The authors concluded that **BDE-209**-induced genome wide methylation changes could be interrelated with reproductive dysfunction (Li, Zhang, et al., 2021).

3.1.4.5.6 | *Summary on the MOA for reproductive effects*

There is evidence of the involvement of endocrine effects, oxidative stress, mitochondrial dysfunction, apoptosis, oxidative damage to DNA, changes in gene expression and epigenetic mechanisms in the generation of adverse effects on reproduction. PBDE can modulate the endocrine system in multiple ways by interfering with several hormonal signalling pathways simultaneously: binding to androgen receptor, disruption of oestrogenic and testosterone synthesis signalling pathways, and modulation of the thyroid hormone receptor. It is demonstrated that overall thyroid dysfunction with alteration in thyroid homeostasis induce impairment of testicular steroidogenesis and cause suppression of spermatogenesis, which may result in reduced fertility and infertility.

BDE-47 stimulated the proliferation and differentiation of progenitor Leydig cells in rats during puberty by upregulation of Leydig cell genes (*Scarb 1*, *Star*, *Hsd 11b1*, *Pcna1*, *Ccnd1*) and increasing phosphorylation of several pathway signal proteins, causing increased testosterone synthesis. **BDE-47** and its OH metabolites may result in excessive ovarian exposure to oestrogens by increasing the ratio of ERα to ERβ, or by increasing oestrogen receptor expression, respectively.

There was a good correlation between oestrogenic activity and ER binding affinity of the low brominated OH-PBDE suggesting that these compounds induce ER transcriptional activity by binding directly with ER. High-brominated OH-PBDEs inhibited oestradiol induced gene expression, demonstrating their antagonistic activity.

By inhibiting oestradiol glucuronidation, OH-PBDEs may increase oestradiol bioavailability in target tissues, thereby exerting an indirect oestrogenic effect. Inhibition of oestradiol metabolism by OH-PBDEs *in vitro* was significantly greater than for parent PBDEs and MeO-metabolites.

The potential effects of **BDE-47** and **-99** and their analogues, particularly 6-MeO-BDE-99, on AR signalling pathway may adversely impact the male reproductive growth and function.

Prenatal exposure of mice to **BDE-99** significantly inhibited the testosterone synthesis signalling pathway and induced testicular steroidogenesis disorders of immature testes by damaging Leydig cells.

Exposure of adult mice to **BDE-209** caused reduction in serum levels of thyroid hormones and alteration in thyroid homeostasis which may partly result into impairment of testicular steroidogenesis and cause suppression of spermatogenesis. Maternal exposure of mice to **BDE-209** during lactation impaired germ cell proliferation via inhibition of steroidogenic pathway and differentiation of Sertoli cells in peripubertal mice offspring. It was also shown that **BDE-209** induced significant changes of thyroid hormone metabolism, the TCA cycle and lipid metabolism in maternal mice, which subsequently led to a significant inhibition of fetal growth and development.

ROS played an important role in reduction of spermatogenesis by **BDE-47** by germ cell apoptosis. **BDE-47** may affect progesterone synthesis and induce failure in spermatogenesis through induction of mitochondrial dysfunction. 6-OH-BDE-47 exposure may alter the embryo development by altering the function of energy production in mitochondria. In female mice, it was demonstrated that **BDE-47** exposure affected the maturation of mouse oocyte via its effects on mitochondrial function, ROS level and its related apoptosis.

Exposure of rats during gestation to **BDE-99** resulted in increases in oxidative stress markers (SOD, CAT, GPx and GR) in fetal rat liver which can result in signs of embryo/fetal toxicity.

Maternal exposure to **BDE-209** during lactation increased apoptosis and oxidative stress with altered expressions of various cell survival, apoptotic and oxidative stress markers in testes and epididymis of male mice offspring. **BDE-209** induced male reproductive toxicity by causing glycolipid metabolism dysbiosis of testis resulting in activating of the mitochondrial apoptotic pathway in spermatogenic cells.

Impaired trophoblast migration and invasion during early pregnancy have been implicated as potential mechanisms of pregnancy disorders. **BDE-47** significantly inhibited migration/aggregation and invasion in relation to changes in gene expression involving stress pathways. Endoplasmic reticulum stress plays an important role in **BDE-47**-induced ovarian injury by regulating autophagy and apoptosis.

Sertoli cells seem to be the primary target of **BDE-209** in the perinatal period. The role of ERα in BTB changes during spermatogenesis was identified and suggested that BTB modifications occur because of exposure to **BDE-209**, which could potentially affect spermatogenesis.

Low concentrations of DE-71 could stimulate testosterone secretion by acting directly on Leydig cells to activate the cAMP pathway and increase expression of StAR.

A variety of genes that play a major role in regulating spermatogenesis (steroid hormone homeostasis, inflammation response, ER stress, double-strand break repair, cytokinesis, and histone modification) were shown to be significantly upregulated or downregulated upon **BDE-47** treatment in at least one cell type of mice testis.

Exposure to **BDE-47** caused ovarian lipid deposition and ovarian hormone changes accompanied by oxidative stress (OS) and downregulation of hormone biosynthesis-related proteins in mice.

3.1.4.6 | *Genotoxicity*

3.1.4.6.1 | *Oxidative stress*

PBDEs have been shown to generate oxidative stress, which may lead to DNA strand breaks and oxidative base modifications as well as to activation of apoptosis in various cellular systems.

BDE-47

- Treatment of human hepatocyte L02 cells with **BDE-47** (5 and 10 μM) resulted in a small increase (not statistically significant) of DNA strand breaks in a Comet assay, and of ROS level (An, Yin, et al., 2011).

BDE-209

- Exposure of human colon carcinoma cells (SW 480) to **BDE-209** at 5 and 10 μM caused significant decreases in cell survival, significantly increased ROS production and induced a significant increase of single strand breaks (increase in % DNA in tail) (Curčić et al., 2014, see also Table 14).
- Exposure of the human embryonic stem cell lines (hESCs) FY-hES-10 and FY-hES-26 to **BDE-209** (1, 10, 100 nM) reduced the expression of pluripotent genes via epigenetic regulation and induced apoptosis (Du et al., 2016). In addition, **BDE-209** increased the generation of intracellular ROS and decreased SOD2 expression. The ROS increase and OCT4 downregulation after **BDE-209** exposure was reversed partly by antioxidant *N*-acetylcysteine supplement.

Comparative studies of different PBDE congeners and metabolites

- Ji et al. (2011) studied the genotoxicity of **BDE-47**, -**49**, -**99**, -**138**, -**209**, and two tetra-OH-PBDEs (6-OH-BDE-47 and 4-OH-BDE-49) by using chicken DT40 cell lines including wild-type cells and a panel of mutant cell lines deficient in DNA repair pathways (see also Table 14). **BDE-47** and -**49** had greater genotoxic potential than the other PBDEs tested. The tetra-OH-metabolites were more genotoxic than parent tetraBDEs. Both chromatid- and chromosome-type breaks were

frequently observed in cells exposed to **BDE-47** and 6-OH-BDE-47. Induction of γ-H2AX was measured after exposure to these compounds confirming the occurrence of double strand breaks. Pretreatment with *N*-acetyl-L-cysteine significantly rescued the Polβ_¯/¯ and REV3 ¯/¯ mutants, which is consistent with the hypothesis that PBDEs and OH-PBDEs cause DNA damage mediated through ROS. The authors concluded that some tetra-BDEs and OH-tetra-BDEs caused base damage through ROS leading to replication blockage and subsequent chromosomal breaks.

- **BDE-47** and **-209** (5, 10 and 20 μM) induced single strand breaks in human neuroblastoma cells (SK-*N*-MC) (Pellacani et al., 2012, see Table 14). Pretreatment with the antioxidant melatonin significantly reduced the DNA damage induced by both congeners. The Comet assay carried out in the presence of FPG suggested that both congeners increased purine oxidation. In all cases, **BDE-47** was more potent than **BDE-209**.
- In the study by Montalbano et al. (2020), 16HBE cells (SV40 large T antigen-transformed cell line from normal human bronchial epithelial cells) and NHBE cells (primary normal human bronchial epithelial cells) were exposed to **BDE-47**, **-99** and **-209** (0.01, 0.1 or 1 μM). All congeners showed a significant increase of intracellular ROS formation in 16HBE cells stimulated for 24 h and exposure for 4 h to all congeners significantly increased the levels of NOX4 expression. All congeners activated the mechanism of DNA-damage and repair affecting Olive Tail length (comet assay) production and H2AX phosphorylation (ser139) after 4 h exposure of 16HBE as well as they increased γH2AX double strand breaks reparation foci in the cells stimulated for 72 h. In pNHBE, the 3 congeners significantly increased intracellular ROS production, induced mitochondrial injury and increased single strand breaks. Both **BDE-47** and **-99** significantly increased the percentage of apoptotic cells.
- BDE-7, **-47**, **-28**, 6-OH-BDE-47, 5-OH-BDE-47, 2-OH-BDE-8, 4-OH-BDE-17, 2,4-DBP and 4-BP increased ROS generation in HepG2 cells (Tang et al., 2018). Exposure to these compounds at 50 μM significantly enhanced single strand breaks, among which brominated phenols caused the greatest damage, followed by OH-PBDEs and then **BDE-47** and its debromination products. Exposure to 50 μM **BDE-47** significantly increased apoptosis. Pretreatment with lower concentrations (2 μM) had protective effects against higher concentrations of the same compounds.

Studies with PBDE metabolites alone

- 6-OH-BDE-47 and 6-MeO-BDE-47 inhibited cell proliferation, induced concentration-dependent micronuclei and single strand breaks and increased apoptosis in HepG2 cells. 6-OH-BDE-47 showed generally higher effects than 6-MeO-BDE-47 on intracellular ROS levels as indicated by GSH depletion and elevation of SOD levels (An, Li, et al., 2011).

PBDE-quinones

Two studies have reported that treatment of HeLa or LO2 cells with a synthetic tri-brominated PBDE-quinone[53] resulted in oxidative stress and associated damage (Dong et al., 2018; Wang et al., 2021). The CONTAM Panel noted that formation of PBDE-quinones has not been demonstrated either *in vitro* or *in vivo* and the relevance of these effects to the PBDEs of interest could not be assessed.

3.1.4.6.2 | *Aneugenicity*

BDE-47

Exposure for 4 h up to 80 μM **BDE-47** did not induce micronuclei in V79-Mz (parental cell line) and V79-derived cell lines expressing human CYP1A1 or 1A2 (Song et al., 2021). It was moderately positive in human CYP2B6-, 2E1-and 3A4-expressing cell lines (V79-hCYP2B6, V79-hCYP2E1-hSULT1A1 and V79-hCYP3A4-hOR, respectively). **BDE-47** exposure for 24 h increased the induction of micronuclei in the two last cell lines. **BDE-47** (48 h exposure) was inactive in HepG2 cells up to 40 μM, however, pretreatment of the cells with ethanol (inducer of CYP2E1) or rifampicin (inducer of CYP3A4) led to significant micronuclei formation by **BDE-47** (at 28 and 40 μM). Pretreatment with bisphenol AF, a potent inducer of CYPs 1A1, 1A2, 1B1, 2E1 and 3A4 in this cell line, also potentiated **BDE-47**-induced micronuclei formation. Selective formation of centromere-containing micronuclei formed by **BDE-47** in HepG2 cells pretreated with ethanol or rifampicin was demonstrated and indicated that **BDE-47** has also aneugenic properties (after metabolic activation). The increased phosphorylation of H3 histone in HepG2 cells by **BDE-47** is consistent with an aneugenic potential (Song et al., 2021).

3.1.4.6.3 | *DNA-protein crosslinks*

BDE-47

BDE-47 induced micronuclei and single strand breaks in human neuroblastoma cells (SH-SY5Y). A significant non-concentration-related increase in DNA-protein crosslinks (DCP) was also observed at the concentrations (2, 4 and 8 μM) tested (He et al., 2010). It is known that DPCs disturb DNA replication, transcription and repair (Hong & Lee, 1999).

[53] 2-(2′,4′-Bromophenoxyl)-benzoquinone.

3.1.4.6.4 | *DNA adducts*

PBDE-quinones

DNA adducts have been detected by incubation of synthetic PBDE-quinones with cell free systems (Lai et al., 2011c; Huang, Li, et al., 2015). Lai, Lu, Gao, et al. (2011) also reported the formation of adducts when metabolites of 6′-OH-BDE-17 produced via microsomal-mediated metabolism, were incubated with deoxyguanosine, horseradish peroxidase and H_2O_2. However, formation of PBDE-quinones has not been demonstrated either *in vitro* or *in vivo*. DNA adducts from PBDE metabolites have only been demonstrated using sub-cellular systems and it is not clear if these adducts are identical to DNA adducts produced by synthetic PBDE quinones. The relevance of these studies of adduct formation with synthetic PBDE-quinones or quinones produced after incubation of OH-PBDEs with rat liver microsomes to the PBDEs of interest in this Opinion therefore cannot be assessed.

3.1.4.6.5 | *Recombination*

Helleday et al. (1999) examined the effects of BDE-1 (20 μg/mL), BDE-12 (30 μg/mL) and **BDE-47** (40 μg/mL) in two *in vitro* assays for intragenic recombination at the hprt locus in mammalian cells (clones from V79 cells). In the SPD8 assay system statistically significant increases in recombination frequency were observed with BDE-1, -12 and -**47**. In the Sp5 assay system, only BDE-12 (35 μg/mL) and BDE-1 (40 μg/mL) caused statistically significant increases in recombination frequency.

3.1.4.6.6 | *Summary on the MOA for Genotoxicity*

Several *in vitro* studies on mammalian cells showed that genotoxic effects (DNA strand breaks or micronuclei) induced by **BDE-47**, -**99** and -**209** and their OH-metabolites are primarily mediated by oxidative stress. Increases in ROS level were demonstrated as well as changes in SOD level and increases in MDA content (see also **Section 3.1.2.6**). The enhancement of single strand breaks by Fpg in the Comet assay was in line with oxidatively damaged DNA.

Based on the data available PBDEs can induce DNA damage via an indirect mechanism of action.

3.1.5 | Considerations of critical effects and dose–response analysis

3.1.5.1 | *Considerations of critical effects*

The previous Opinion on PBDEs reviewed toxicological studies performed with technical products and the limited number of individual PBDE congeners that had been tested (i.e. **BDE-47**, -**99**, -**153** and -**209**). The purity of the individual congeners and technical mixtures varied considerably. At that time, the CONTAM Panel noted that technical products of PBDEs may contain polybrominated dioxins as impurities, and that '*In contrast to technical mixtures, it is unlikely that individual PBDE congeners would contain PBDDs or PBDFs, since, based on the production method used, they are not expected to be formed as byproducts during the synthesis of individual PBDE congeners*' (EFSA CONTAM Panel, 2011b). Thus, from studies on purified technical products and individual congeners, the Panel concluded that the main targets for PBDE toxicity were the liver, and the thyroid hormone, reproductive and nervous systems. The BMDLs calculated for neurodevelopmental effects of **BDE-47**, -**99**, -**153** and -**209** (the only congeners for which data were available) provided the lowest Reference Points compared to the BMDLs, NOAELs or LOAELs for other effects (for more details see **Section 1.3.5** on previous risk assessments).

The new studies published since then have provided additional data in relation to effects on the liver, thyroid hormone, the reproductive, nervous and immune systems, and on lipid and sugar metabolism. The congeners studied were predominantly **BDE-47**, **-99** and -**209**, with limited data on BDE-3, -15, -**183**, -203 and -206. New data were also available for the technical products DE-71, PentaBDE, OctaBDE and DecaBDE. The CONTAM Panel concluded that data on technical products added to the body of evidence for the effects of PBDEs but were not suitable for identifying a Reference Point for use in risk characterisation. This is because they are complex mixtures often with limited information on the congener profile, and little or no information on relevant impurities such as dioxin-like compounds. Also, they are not representative of the profile of PBDEs that humans are exposed to via food due to differing persistence of the congeners in the environment and the food chain.

As noted in **Section 3.1.4**, the effects of PBDEs on the immune system, liver, lipid and sugar metabolism were not considered critical for the hazard assessment.

Although there is evidence of genotoxicity *in vitro* for some congeners, there was no evidence for *in vivo* genotoxicity. The CONTAM Panel concluded that the 10 congeners considered in the Opinion are not genotoxic *in vivo*.

Individual PBDE congeners have not been tested for carcinogenicity. In studies with technical products, there was an increase in liver adenoma in Fischer 344/*N* rats and in liver adenoma and carcinoma in male B6C3F1 mice exposed to DecaBDE (containing 94%–97% **BDE-209**) at very high doses (> 1000 mg/kg bw per day). These tumours were not considered relevant as they were observed at very high dose levels, and because of the mode of action underlying their generation (as discussed below).

There is evidence of carcinogenic activity of the PentaBDE technical product DE-71 in Wistar Han rats (liver, thyroid and uterine tumours) and in B6C3F1/*N* mice (liver tumours). The authors of the study noted that the carcinogenic activity of DE-71 could be related to oxidative damage and changes in hormone homeostasis (Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Recio, et al. 2018). The Panel noted that liver tumours are likely due to CAR

activation (see **Section 3.1.4**), which is a well-documented key event for rodent liver tumour development. This mode of action is not plausible for humans. The key species difference is that while such compounds induce proliferation in rat and mouse hepatocytes, other species including humans are refractory to the mitogenic effects of CAR activators in rodents and thus CAR activators would not be expected to be carcinogenic in humans (Lake, 2018). The thyroid tumours observed in rodents may result from adaptive thyroid proliferation (chronic stimulation of the thyroid gland by TSH leading to thyroid follicular hyperplasia and finally subsequently to thyroid follicular adenomas and carcinomas). Furthermore, the Panel noted that it is unclear if one or more congeners present in the technical product are responsible for the effects observed. Moreover, the presence of impurities in the technical product DE-71 (e.g. PBDD/Fs) may have a possible impact on the effects including tumours observed in the thyroid as well as elsewhere. Based on the above and the lack of evidence for a direct mechanism of genotoxicity *in vivo*, carcinogenicity was not considered a critical effect.

The CONTAM Panel focused on the effects on neurodevelopment, reproduction/development and thyroid hormones. Table F.1 and F.2 in **Appendix F** summarises the available NOAELs and LOAELs for these effects. Changes in thyroid hormone levels induced by PBDEs could plausibly contribute to the neurodevelopmental and reproductive/developmental effects and were regarded as a possible key event for both of these adverse outcomes. In addition, changes in sex hormones induced by PBDEs could contribute to the reproductive effects. In both cases other modes of action are also implicated.

All individual PBDE congeners and technical products that have been tested showed evidence of neurobehavioural effects in rats and mice. These include alterations in locomotion and spontaneous activity, anxiety and learning and memory abilities. Supporting these observations are *in vitro* studies which provide evidence for PBDEs causing interference with mitochondrial calcium homeostasis, leading to oxidative stress and apoptosis, and changes in neurotransmitters and cell migration and differentiation. Changes in thyroid hormone concentrations are implicated in the neurobehavioral effects of **BDE-209**, but there is a lack of data on whether thyroid hormones are similarly involved for other PBDE congeners. Effects were seen at lower doses when tests are performed in adulthood following exposure in early life including in utero and/or postnatal (direct gavage or lactational), than with dosing at later life stages. The study protocols used in animal studies were mostly not according to OECD test guidelines, and many involved only one or two dose levels plus control, thereby providing limited information on the dose–response. Effects were reported at repeated doses as low as 0.03 mg/kg bw per day for **BDE-47** and at a single dose of 0.6 mg/kg bw per day for **BDE-99**. The lowest doses with reported effects were higher for **BDE-153** (0.9 mg/kg bw per day after single administration, as reported in EFSA CONTAM Panel, 2011b) and **BDE-209** (1 mg/kg bw per day after 5 days exposure) (see Table F.1 in **Appendix F**).

Since the previous Opinion many data have become available on the effects of **BDE-47**, **-99** and **-209** on reproduction and development. Exposure of adult rats or mice to PBDEs affected both male (e.g. changes in testis weights, degeneration of seminiferous tubules, decreased sperm production and motility, increased sperm malformations) and female (e.g. decreased ovarian weight, alteration of folliculogenesis) reproductive systems. In utero exposure and/or exposure during lactation or exposure after weaning causes developmental toxicity in offspring (increases in rates of stillbirth, incomplete or delayed ossification, increases in internal variations, decreased rates of live fetuses/litter and effects on the male reproductive system). Embryotoxicity was also reported with increased rates of post-implantation loss and resorptions. There is evidence of effects on sex hormone levels (e.g. changes in oestradiol and testosterone levels), oxidative stress, mitochondrial dysfunction, apoptosis, oxidative damage to DNA and epigenetic changes in the generation of adverse effects on reproduction. Increased expression of biotransformation enzymes would also contribute to a reduction in serum sex steroid concentrations. The doses at which the effects are observed after exposure to **BDE-47, -99** and **-209** are lower than or at the same level as those inducing neurodevelopmental effects. Histological changes in the testes were observed at repeated doses of 0.03 mg/kg bw per day for **BDE-47**. For **BDE-99** female reproductive tract changes and increased fetal resorptions were observed at 0.06 mg/kg bw per day (single dose on GD6). The female reproductive tract changes included degenerative changes in the ovary, hyperplastic vacuolar degeneration of the vaginal epithelium, serosal hyperplasia in the uterus. For **BDE-209**, the lowest dose with impaired spermatogenesis was 50 mg/kg bw per day and effects on placenta were observed at 2 mg/kg bw per day both after repeated dosing (see Table F.1 in **Appendix F**).

Studies in rodents published after the previous Opinion consistently report effects on the thyroid hormone system following exposure to **BDE-47**, **-99** or **-209**. These effects include reduced serum TT3 and/or TT4, increased serum TSH, and changes in thyroid weight and structure (see Table F.2 in **Appendix F**). Data available at the time of the previous Opinion suggested that the effects on the thyroid hormone system were a consequence of increased expression of biotransformation enzymes regulated by CAR and PXR, resulting in an accelerated metabolism of thyroid hormones (EFSA CONTAM Panel, 2011b). More recent studies still support a mode of action in which PBDEs alter expression and activities of enzymes that metabolise thyroid hormones and identify additional mechanisms by which PBDEs may interfere with the thyroid hormone system. In particular, PBDEs and their OH-metabolites may disrupt the thyroid hormone system by competing with T4 for thyroid binding proteins. There is also *in vitro* evidence that **BDE-28**, **-47**, **-49, -99, -100** and **-154** can bind to thyroid hormone transport proteins as well as for BDE-3, -7, -108, -155, -187, -188 and many metabolites.

Regarding neurodevelopment, there is a direct relationship between thyroid hormones and brain development with the ability of these hormones to impact brain cell proliferation, maturation, plasticity and metabolism (Schiera et al., 2021). Thus, deficient or excessive levels of thyroid hormones induced by exposure to chemicals such as PBDEs, can result in brain disturbances. The nature and degree of these disturbances will depend upon the specific development period and the severity of the thyroid imbalance. Reduced serum levels of thyroid hormones and alteration in thyroid hormone homeostasis can also cause impairment of testicular steroidogenesis and cause suppression of spermatogenesis in rodents (Sarkar et al., 2016, 2018). Therefore, there is a plausible mechanistic link between effects on neurodevelopment and reproduction.

Based on the available data for interactions of different PBDE congeners with the thyroid hormone system and the observed neurodevelopmental and reproductive adverse effects, the CONTAM Panel considered that **BDE-47**, **-99** and **-209** are likely to share a common mode of action that involves reduced serum levels of thyroid hormones and their downstream effects, and that it is plausible that the other PBDE congeners of interest also share this mode of action. As noted above, other modes of action are also implicated in the neurodevelopmental and reproductive effects of PBDEs.

The CONTAM Panel noted the studies showing changes in sex and thyroid hormones and considered that these changes are key events in the Adverse Outcome Pathways leading to neurodevelopmental and reproductive effects but are not apical outcomes. Therefore, changes in serum sex and thyroid hormone concentrations were not considered appropriate for the establishment of the Reference Points.

Since the previous Opinion, the number of human epidemiological studies addressing potential associations between PBDE exposure and various adverse effects has increased substantially. Study-specific limitations mainly related to the characterisation of the underlying co-exposure to multiple PBDE congeners and other chemicals (including challenges in capturing the complexity of the PBDE exposure matrix) and the relatively small sample sizes as well as domain-specific limitations related to endpoint and population heterogeneity restrict the use of this extensive evidence base for risk characterisation. However, the studies provide valuable insight for hazard identification and can corroborate the findings observed in experimental animal studies. For neurodevelopmental toxicity, the pertinent evidence base covers more subdomains and by far surpasses the volume of the evidence base on reproductive and thyroid function toxicity. More specifically, studies assessing **BDE-47**, **-99** and **-153** showed positive association signals for cognitive function, and **BDE-47** has been associated with endpoints related to ADHD, hyperactivity and attention. As far as reproductive toxicity is concerned, the number of studies is smaller and relevant clinical endpoints were scarce; thus, the proposed associations neither support nor refute the findings of the animal studies. Finally, as regards thyroid function, the volume of the assessed evidence is comparable to the one related to the reproductive system; congener-wise, statistically significant associations across the whole panel of thyroid function biomarkers were seen for **BDE-47**, and partially for **BDE-99**, but occasionally lacking consistency in effect direction.

Among the various domains assessed, neurodevelopment presented association signals both in humans and experimental animals. The CONTAM Panel concluded that the evidence from the available human data did not provide a sufficient basis for the risk assessment, and that the dose–response analysis should be performed on the neurodevelopment and reproductive/developmental data from studies in experimental animals. Given that the human data cannot be used for the derivation of the Reference Point due to methodological limitations, they can still be used as corroboration of the results of the experimental animal data taking also into consideration the relevance of the endpoints assessed in experimental animals for humans.

The following criteria were considered in the selection of the critical studies: (i) offspring examination after perinatal or neonatal exposure for neurodevelopmental studies (most sensitive periods), (ii) selection of doses (lowest doses tested) and (iii) effects observed.

Regarding the neurodevelopmental studies (see Table F.1 in **Appendix F**),

- For **BDE-47**, based on these criteria, three studies were considered: Eriksson et al. (2001), Koenig et al. (2012) and Li et al. (2019). The studies by Koenig et al. (2012) and Li et al. (2019) were selected over that of Eriksson et al. (2001) because of the higher relevance to humans of the endpoints investigated, all relating to learning and memory abilities, compared to locomotion and spontaneous activity endpoints reported in Eriksson et al. (2001). It was also noted that Eriksson et al. (2001) exposed mice via a single oral administration of **BDE-47** on PND10 (with testing at 2 or 4 months), while Koenig et al. (2012) and Li et al. (2019) exposed dams daily during gestation and lactation (starting 4 weeks or 10 days prior to mating, respectively, and until PND21, with testing on week 5–17 or on PND88-92, respectively).
  The study of Li et al. (2019) was selected over that of Koenig et al. (2012) because of the more controlled mode of administration used for **BDE-47** exposure (daily administration by gavage in Li et al. (2019) vs. daily feeding with contaminated corn flakes in Koenig et al. (2012)), and the robustness of the effects observed in the learning and memory performance reported in this study. Permanent memory impairments were observed in the Morris water maze at the two highest doses in rats exposed to **BDE-47** (Li et al., 2019) whereas a transient effect on learning and memory performances of mice was reported at the first day of testing by Koenig et al. (2012) which was the same in the three **BDE-47**-exposed groups and showed the absence of a dose–response relationship. The results of Li et al. (2019) are in concordance with those from other studies related to the assessment of the effects of **BDE-47** on learning and memory (He et al., 2011; Yan et al., 2012; Zhuang et al., 2018).
- For **BDE-99**, three studies were considered: Eriksson et al. (2001), Kuriyama et al. (2005) and Blanco et al. (2013). The increased locomotion on PND71 reported by Kuriyama et al. (2005, single dose on GD6) was statistically significant compared to control but showed no discernable dose–response and the study was not considered further.
  Both Eriksson et al. (2001) and Blanco et al. (2013) exposed the animals during the neonatal period. Eriksson et al. (2001) exposed mice to a single oral administration of **BDE-99** on PND10, reporting a significant dose-related reduction of total activity in mice measured at 2 and 4 months of age. Blanco et al. (2013) exposed rat dams during gestation and lactation from GD6 to PND21 (36 days of exposure), observing a significant reduction in the level of anxiety (with the potential to adversely affect adaptation to stressful situations) in rat offspring measured at the earlier age of 22 days. In addition, a decrease in the BDNF gene expression in the hippocampus was reported in the same animals.
  The Panel noted that the sensitive period for the brain maturation in rodents is during gestation (organogenesis), but also in the first 3-weeks of postnatal life for synaptogenesis and synaptic plasticity, with a highly critical period from brain maturation and long-term consequences between PND10 and PND14 (Rice & Barone, 2000; Semple et al., 2013). The gradients of maturation of developing regions of the nervous system in rats and humans follow the same general sequence with

a timeline of days in rodents compared to weeks to months in humans. Based on global brain indices of development, a rat pup at birth can be considered to be representative of a 25-week human fetus, a PND10 rat to a full-term infant, and a PND21 rat to a 2–3 year-old human child. As noted in EFSA CONTAM Panel (2021), PND10 marks the start of a critical period in the development of the rodent brain, which corresponds in humans to the period beginning in the third trimester of pregnancy and continues throughout the first 2 years of life, but it is unclear whether PND10 is the most critical day and if exposure at another time point produce a response at a lower dose. The Panel also noted that in Eriksson et al. (2001), mice were tested at the adult stage for spontaneous motor behaviour, but anxiety, exploration, motivation and motor ability were not assessed. Changes in these parameters could contribute to the changes in spontaneous motor behaviour.
The Panel noted that while Eriksson et al. (2001) studied a small number of animals, i.e. eight mice, male only, from three to four litters, Blanco et al. (2013) tested a higher number of animals, i.e. 20 rats, including 10 males and 10 females, from 10 litters, with no sex-related differences being observed.
Thus, the Panel identified as critical the study Blanco et al. (2013).

- For **BDE-153**, the Panel identified as critical the same study as in the previous Opinion because no new data were available, i.e. Viberg, Fredriksson, and Eriksson (2003), based on altered spontaneous behaviour and impaired learning and memory in neonatal male rats exposed on PND10 and tested up to 6 months.
- For **BDE-209**, the study of Li, Wang, et al. (2017) in which neonatal rats were dosed daily from PND5-10 and tested up to PND70 and PND75 in two spatial learning and memory tasks, was selected because of the higher relevance to humans of the endpoints investigated, all relating to learning and memory abilities and the period of exposure that encompass a critical window of the brain development. The study of Xiong et al. (2018) assessed learning and memory abilities in adult rats exposed to **BDE-209** for 30 days, while the locomotion and spontaneous activity endpoints reported in the study of Viberg et al. (2007, single dose on PND3) were considered to be less relevant to humans. The study of Buratovic et al. (2014) assessed the effects of a single dose administration at PND3 on learning and memory performances in animals at the age of 5 and 7 months. At 5 months, the animals showed a memory deficit at the two **BDE-209** dose levels on the 6th day of testing during which the relearning abilities of the animals to locate the platform moved in another quadrant of the maze were tested. At 7 months, such effect was not evaluated whereas the exposed mice showed a longer escape latency at both dose levels over the first 4 days of testing that corresponds to the learning phase of the location of the platform.
  The study by Li, Wang, et al. (2017) assessed the spatial learning and memory performances using two behavioural paradigms: the Morris water maze performed at PND70 and the eight-arm radial maze at PND75. Both paradigms showed some long-term memory impairments in **BDE-209**-exposed animals (dose-related decrease in the number of platform crossings in the Morris water maze at the 5th trial of testing (probe test), significant reductions in the number of reference memory errors at the two highest dose levels tested in the eight-arm radial maze). Both results support long-term memory impairment, but the Morris water maze provides the lowest LOAEL (1 mg/kg bw per day) whereas the LOAEL is 10-times higher for the eight-arm radial maze (10 mg/kg bw per day) with a NOAEL of 1 mg/kg bw per day.

Regarding the studies showing effects on reproduction and development (see Table F.1 in **Appendix F**),

- For **BDE-47**, a number of studies showed effects on reproduction, mainly male reproductive effects. The lowest doses at which effects were observed are from studies in which adult males have been exposed repeatedly. In three studies the LOAEL was 0.03 mg/kg bw per day: Zhang, Zhang, et al. (2013) based on changes in cell organisation of seminiferous epithelium, Zhang et al. (2017) based on changes in cell organisation of seminiferous epithelium, and Huang, Li, Lai, Qiu, and Cai (2015) based on decreased relative seminiferous epithelial thickness and increased apoptotic germ cells. Qualitatively the same type of effects had been reported to occur at higher doses in animals exposed in utero and during lactation (e.g. Khalil, Parker, Brown, et al., 2017; Li, Gao, et al., 2021).
- For **BDE-99**, two studies showed relevant effects on male and female reproduction and/or development: Kuriyama et al. (2005) based on decreased number of spermatids and sperm production, and Talsness et al. (2005) based on an increased fraction of dams with resorptions. In these two studies, dams were exposed on GD6, and male and female offspring were examined. In Talsness et al. (2005) histopathological changes were observed in ovaries in the F1 generation which were apparent at adulthood, and resorptions were also reported in female F1 mated with untreated males. In Kuriyama et al. (2005) impaired spermatogenesis (decreased sperm and spermatic counts) was recorded in male offspring on PND140. The Panel noted that the effects reported on daily sperm production were statistically significant compared to control but showed no discernible dose–response.
  Three studies showed effects on development: Talsness et al. (2005), Blanco et al. (2012) and Zhao et al. (2021). The effects were resorptions, incomplete ossification, liver and heart hypertrophy, and malformations. The effects were observed at doses as low as 0.06 mg/kg bw per day (single exposure) to 1 mg/kg bw per day (repeated exposure).
- For **BDE-153** no studies on reproductive/developmental effects were available.
- For **BDE-209**, two studies from the same research group showing reproductive effects after repeated exposure were considered: Li, Liu, et al. (2021) and Zhang, Li, et al. (2021). The effects in both studies were reduced sperm cell number and motility, and increased sperm cell malformations at 50 mg/kg bw per day.

3.1.5.2 | *Dose–response analysis*

The Panel performed benchmark dose (BMD) modelling according to the 2022 EFSA Guidance on the use of the BMD approach in risk assessment (EFSA Scientific Committee, 2022, see **Section 2.2**). More guidance is included on criteria for acceptability of the results of the modelling than in previous versions.

The results of the BMD modelling for the critical studies identified above on neurodevelopmental and reproductive/developmental effects in rodents after oral exposure to **BDE-47**, **-99**, **-153** and **-209** are summarised in Table 31. Details of the BMD analyses are reported in **Appendix G** and the individual reports of the modelling are shown in Annex E.

The EFSA guidance on BMD (2022) recommends defining the BMR as a percent change in the response relative to the control group (background response). This percentage of variation was identified in the critical studies for neurobehavioral effects to be higher than 5%. In addition, behavioural variability is relatively large (> 5% and more) because of the adaptative feature of behaviour to environmental factors. Thus, the Panel selected a BMR of 10% for the neurodevelopmental effects.

For the reproductive/developmental effects the Panel selected a BMR of 10% for daily sperm counts, based on the standard deviation of the control group of around 10% in Zhang, Zhang, et al. (2013). Similarly for other reproductive effects the Panel applied a BMR based on the standard deviation of the control groups, resulting in a BMR of 5% for sperm motility and epithelial thickness of seminiferous epithelium, of 20% for apoptotic gonadal cells and a BMR of 10% for changes in ossification.

For **BDE-47**, the lowest $BMDL_{10}$ was 0.023 mg/kg bw per day for reproductive effects based on the study by Zhang, Zhang, et al. (2013) for impaired spermatogenesis after repeated exposure, while a $BMDL_{10}$ of 0.15 mg/kg bw per day was obtained for neurodevelopmental effects (impaired spatial learning and memory after repeated exposure, Li et al., 2019).

For **BDE-99**, the lowest $BMDL_{10}$ was 0.05 mg/kg bw for developmental effects based on the study by Talsness et al. (2005) for increased resorption rates in mated female offspring following a single gavage administration to dams on GD6. The CONTAM Panel noted the non-standard design of this developmental study, with gavage administration on a single day during pregnancy (GD6), and that the resorption rate in control animals was high. However, the $BMDL_{10}$ is supported by the $BMDL_{10}$ of 0.07 mg/kg bw per day for a decreased anogenital index after repeated exposure from Zhao et al. (2021). A $BMDL_{10}$ of 0.43 mg/kg bw per day was obtained for neurodevelopmental effects (reduction in the level of anxiety, with the potential to adversely affect adaptation to stressful situations, after repeated exposure, Blanco et al., 2013).

For **BDE-153** the $BMDL_{10}$ of the selected critical study on neurodevelopment (impaired learning and memory following a single administration on PND10) was 0.11 mg/kg bw (Viberg, Fredriksson, & Eriksson, 2003). The CONTAM Panel noted uncertainty in this Reference Point (see **Section 3.5**).

For **BDE-209**, the lowest $BMDL_5$ was 0.91 mg/kg bw per day for reproductive effects based on the study by Li, Liu, et al. (2021) for decreased sperm motility after repeated exposure. A $BMDL_{10}$ of 1.59 mg/kg bw per day was obtained for neurodevelopmental effects (impaired learning and memory after repeated exposure, Li, Wang, et al., 2017).

TABLE 31 Benchmark dose (BMD) modelling for the critical neurodevelopmental and reproductive/developmental studies of **BDE-47**, **-99**, **-153** and **-209** for establishment of the critical effects (for details of the BMD analyses see **Appendix G** and Annex E).

Congener	Reference	Observed effect	BMD, BMDU (mg/kg bw per day)	BMDL (mg/kg bw per day)
BDE-47	Li et al. (2019)	Spatial learning deficiency (time spent in target quadrant)	0.77, 6.62	$BMDL_{10}$ = 0.15
	Zhang, Zhang, et al. (2013)	Impaired spermatogenesis (daily sperm count)	0.11, 0.82	$BMDL_{10}$ = 0.023
	Zhang et al. (2017)	Changes in cellular organisation of seminiferous epithelium	–	No quantitative data for histopathological observations
	Huang, Cui, et al. (2015)	Decrease in epithelial thickness of seminiferous tubules Increased apoptotic germ cells	5.61, 16.56 8.13, 18.1	$BMDL_5$ = 0.16[a] $BMDL_{20}$ = 0.04[a]
BDE-99	Blanco et al. (2013)	Reduction in the anxiety level (increased time spent in central part of the maze)	0.67, 0.91	$BMDL_{10}$ = 0.43
	Kuriyama et al. (2005)	Impaired spermatogenesis (daily sperm production)	–	Data not sufficient for estimating the BMD[b]
	Talsness et al. (2005)	Increased resorption rates in F1 females mated with (untreated) males	0.19, 0.29	$BMDL_{10}$ = 0.05 (single dose on GD6)
	Blanco et al. (2012)	Fetuses with skeletal and internal malformations and variations	0.57, 1.52	$BMDL_{10}$ = 0.18
	Zhao et al. (2021)	Decreased anogenital distance	0.18, 0.48	$BMDL_{10}$ = 0.07
BDE-153	Viberg, Fredriksson, and Eriksson (2003)	Impaired learning and memory (total activity)	0.33, 0.67	$BMDL_{10}$ = 0.11 (single dose on PND10)
BDE-209	Li, Wang, et al. (2017)	Impaired learning and memory (platform crossing in Morris water maze)	4.99, 8.44	$BMDL_{10}$ = 1.59
	Li, Liu, et al. (2021)	Decreased sperm motility	3.48, 22.55	$BMDL_5$ = 0.91
	Zhang, Li, et al. (2021)	Decreased sperm motility	5.70, 34.18	$BMDL_5$ = 1.27

[a]Criteria to judge the width of the BMD credible interval not met (EFSA Scientific Committee, 2022).

[b]The effects on daily sperm production reported in Kuriyama et al. (2005) were statistically significant compared to control but showed no discernible dose–response. Although the data could be modelled, it was considered not to contain enough information for estimating the BMD and none of the models provide an adequate fit to the data. The $BMDL_{10}$ obtained (0.002 mg/kg bw) is 30 times lower that the lowest non-zero dose tested in the study (0.06 mg/kg bw).

3.1.5.3 | *Estimation of the body burden at the BMDL*

Repeated exposure to PBDEs results in increasing concentrations of these chemicals in the body. For this reason, the accumulated concentrations in the body or body burden, rather than the daily exposure, is considered as the appropriate dose metric for the risk assessment.

Two approaches were considered by the CONTAM Panel for the calculation of the body burden at the BMDL: (i) the 1-compartment approach and (ii) the tissue level approach.

For the 1-compartment approach, the steady state body burden in rodents and humans is usually estimated by the following equation:

$$\text{body burden} = \left(F_{abs} \times \text{dose}\right) / K_{el},$$

where,

dose = daily dose applied (mg/kg bw per day), NOAEL or chronic human dietary intake.
K_{el} = elimination rate constant [ln(2)/($T_{1/2}$ in days)] (1/days).
F_{abs} = fraction of the chemical absorbed into the body.

This approach has been described and applied in the previous Opinion (EFSA, 2011b) as well as in the updated Opinion on HBCDDs (EFSA CONTAM Panel, 2021). When strain specific data are available, the absorption fraction and elimination rate were used. If no strain specific data on the absorption fraction were available, data from another strain were used. If no data were available at all, a default of 75% absorption was used (as in the previous Opinion). In the case of repeated dose studies with **BDE-47**, no elimination rate was applied due to lack of information, leading to an underestimation of the body burden.

For the tissue level approach, when strain/species specific tissue concentrations are available following an exposure close to that encountered in the critical study, this approach estimates the body burden more precisely. In this approach, all tissues with reported concentrations (e.g. adipose tissue, liver) are taken into account to calculate the overall body burden. However, this requires information on the morphometry of mice and rats, i.e. organ or tissue weights. Several publications reported mean organ weights or % organ or tissue weight/body weight in rodents (Iwata et al., 1993; Marino, 2012a, 2012b; Piao et al., 2013; Schoeffner et al., 1999). For example, following an exposure of 0.05 mg/kg of **BDE-47**, the measured concentration at 10 days was 2.33 µg/g adipose tissue and 0.31 µg/g in the skin (Sanders et al., 2006). The total amount in µg in the body is obtained by multiplying these concentrations by the weight of the organs or tissues, and then summing all the quantities (see **Appendix H**).

The CONTAM Panel considered the two approaches and selected the tissue level approach as the one resulting in the more accurate estimate of the rodent body burden at the BMDL.

For **BDE-47**, the Panel used the tissue concentrations measured by Sanders et al. (2006) in adult rats dosed with this congener for the estimation of the body burden at the BMDL:

- For the Li et al. (2019) study on neurodevelopmental effects, this resulted in a body burden of 0.806 mg/kg bw.
- For the Zhang et al. (2013) study on reproductive/developmental effects, this resulted in a body burden of 0.123 mg/kg bw.

For **BDE-99**, the Panel used the tissue concentrations measured by Chen et al. (2006) in adult rats dosed with this congener for the estimation of the body burden at the BMDL:

- For the Blanco et al. (2013) study on neurodevelopmental effects, this resulted in a body burden of 1.443 mg/kg bw.
- For the Talsness et al. (2005) study on reproductive/developmental effects, this resulted in a body burden of 0.0155 mg/kg bw.

For **BDE-153**, the Panel used the tissue concentrations measured by Sanders et al. (2006) in adult B6C3F1 mice dosed with this congener for the estimation of the body burden at the BMDL of the Viberg, Fredriksson, and Eriksson (2003) study on neurodevelopmental effects. This resulted in a body burden of 0.0125 mg/kg bw.

For **BDE-209**, the Panel used the tissue concentrations measured by Mörck et al. (2003) in adult rats dosed with this congener for the estimation of the body burden at the BMDL:

- For the Li, Wang, et al. (2017) study on neurodevelopmental effects, this resulted in a body burden of 0.0316 mg/kg bw.
- For the Li, Liu, et al. (2021) study on reproductive effects, this resulted in a body burden of 0.0181 mg/kg bw.

An overview of these results is shown in Table 32, and details of the calculations can be found in **Appendix H** as well as the results of the 1-compartment approach.

3.1.5.4 | *Chronic human dietary intake corresponding to the body burden at the BMDL*

Considering most human exposure to PBDEs occurs mainly via food, the chronic human dietary intake corresponding to the calculated body burden at the BMDL for **BDE-47**, -**99**, **-153** and -**209** in mice and/or rats was calculated.

The chronic human dietary intake can be calculated from the same equation as the body burden:

$$\text{Chronic human dietary intake} = \left(\text{body burden at the BMDL} \times K_{el}\right) / F_{abs},$$

where,

K_{el} = elimination rate constant [ln(2)/($T_{1/2}$ in days)] (1/days).
F_{abs} = fraction of the chemical absorbed into the body.

In the absence of robust information, the Panel assumed the human absorption (F_{abs}) of **BDE-47**, -**99** and -**153** to be 100%. For **BDE-209**, the Panel used a value of 30% predicted by the human PBK model by Zhang et al. (2022, see **Section 3.1.1.2** and **3.1.1.5**).

Regarding the half-life in humans, in the previous Opinion the CONTAM Panel used the worst-case longest half-life for **BDE-47**, -**99** and -**153** of 926, 1442 and 4530 days, respectively, reported by Geyer et al. (2004, extended abstract). In the current assessment, due to the lack of detail on the methodology used to estimate the half-life in that study, the Panel found it more appropriate to use the median half-life values of 510, 280, 2700 days estimated by Trudel et al. (2011), for which more detail was provided on the methodology and data (see **Section 3.1.1.2.4**).

For **BDE-209**, in the previous Opinion it was concluded that the elimination half-lives of animals and humans did not differ by orders of magnitude, and therefore the $BMDL_{10}$ calculated at that time from the study by Viberg et al. (2007) was directly used and compared with the estimated dietary exposure (EFSA CONTAM Panel, 2011b). In the current assessment, it was found more appropriate to follow the same approach as for **BDE-47**, -**99** and -**153** and to use the half-life of 15 days in humans reported by Thuresson et al. (2006) and Zhang, Hu, et al. (2022) (see **Section 3.1.1.2.4**) to estimate the chronic human dietary intake corresponding to the body burden at the BMDL.

Considering these values, the Reference Points expressed as a chronic human dietary intake corresponding to the calculated body burden at the BMDL, were calculated as follows:

- For **BDE-47**,
  For neurodevelopmental effects, based on the body burden in rats at the $BMDL_{10}$ of 0.806 mg/kg bw, and the median half-life in humans of 510 days reported by Trudel et al. (2011), the Panel concluded that the Reference Point for neurodevelopmental effects for this congener is 1096 ng/kg bw per day.
  For reproductive effects, based on the body burden in rats at the $BMDL_{10}$ of 0.123 mg/kg bw, and the median half-life in humans of 510 days reported by Trudel et al. (2011), the Panel concluded that the Reference Point for reproductive effects for this congener is 168 ng/kg bw per day.
- For **BDE-99**,
  For neurodevelopmental effects, based on the body burden in rats at the $BMDL_{10}$ in rats of 1.443 mg/kg bw, and the median half-life in humans of 280 days reported by Trudel et al. (2011), the Panel concluded that the Reference Point for neurodevelopmental effects for this congener is 3575 ng/kg bw per day.
  For developmental effects, based on the body burden in rats at the $BMDL_{10}$ in rats of 0.0155 mg/kg bw, and the median half-life in humans of 280 days reported by Trudel et al. (2011), the Panel concluded that the Reference Point for developmental effects for this congener is 38.4 ng/kg bw per day.
- For **BDE-153**, based on the body burden in mice at the $BMDL_{10}$ of 0.0125 mg/kg bw for neurodevelopmental effects, and the median half-life in humans of 2700 days reported by Trudel et al. (2011), the Panel concluded that the Reference Point for neurodevelopmental effects for this congener is 3.2 ng/kg bw per day.
- For **BDE-209**,
  For neurodevelopmental effects, based on the body burden in rats at the $BMDL_{10}$ of 0.0316 mg/kg bw, and the half-life in humans of 15 days reported by Thuresson et al. (2006) and Zhang, Hu, et al. (2022), the Panel concluded that the Reference Point for neurodevelopmental effects for this congener is about 5000 ng/kg bw per day (4861 ng/kg bw per day).
  For reproductive effects, based on the body burden in rats at the $BMDL_5$ of 0.0181 mg/kg bw, and the half-life in humans of 15 days reported by Thuresson et al. (2006) and Zhang, Hu, et al. (2022), the Panel concluded that the Reference Point for reproductive effects for this congener is about 3000 ng/kg bw per day (2782 ng/kg bw per day).

In Table 32 an overview of the values obtained is provided, and in Table 33 a comparison of the estimated chronic human dietary intakes between the previous Opinion and the current assessment is presented. Differences in how the estimates have been calculated relate to the critical studies selected, to the approach to calculate the body burden in experimental animals and the different half-lives used to estimate the chronic human dietary intake.

TABLE 32 Overview of the body burden at the BMDL (using the tissue level approach), and chronic human dietary intake corresponding to the calculated body burden at the BMDL.

Congener	Reference	BMDL (mg/kg bw per day)	Study design	Body burden at BMDL (mg/kg bw)	Chronic human dietary intake (ng/kg bw per day)
BDE-47	Li et al. (2019)	$BMDL_{10}$ = **0.15**	**Neurobehaviour** Sprague–Dawley rats Repeated exposure (10 days prior to mating to PND21) Testing on PND88-92	**0.806** Using tissue levels from Sanders et al. (2006)	**1096** F_{ABS}: 100% default $t_{1/2}$: 510 days Trudel et al. (2011)
	Zhang, Li, et al. (2013)	$BMDL_{10}$ = **0.023**	**Reproductive** Sprague–Dawley rats Repeated exposure (adults for 8 weeks)	**0.123** Using tissue levels from Sanders et al. (2006)	**168** F_{ABS}: 100% default $t_{1/2}$: 510 days Trudel et al. (2011)
BDE-99	Blanco et al. (2013)	$BMDL_{10}$ = **0.43**	**Neurobehaviour** Sprague–Dawley rats Repeated exposure (GD6-PND21) Testing on PND22/23	**1.443** Using tissue levels from Chen et al. (2006, 10 days)	**3575** F_{ABS}: 100% default $t_{1/2}$: 280 days Trudel et al. (2011)
	Talsness et al. (2005)	$BMDL_{10}$ = **0.05**	**Developmental** Wistar rats Single exposure on GD6 Testing on PND90	**0.0155** Using tissue levels from Chen et al. (2006, 1 day)	**38.4** F_{ABS}: 100% default $t_{1/2}$: 280 days Trudel et al. (2011)
BDE-153	Viberg, Fredriksson, and Eriksson (2003)	$BMDL_{10}$ = **0.11**	**Neurobehaviour** NMRI mice Single exposure on PND10 Testing on 2, 4, 6 months old	**0.0125** Using tissue levels from Sanders et al. (2006, mice, 24 h)	**3.2** F_{ABS}: 100% default $t_{1/2}$: 2700 days Trudel et al. (2011)
BDE-209	Li, Wang, et al. (2017)	$BMDL_{10}$ = **1.59**	**Neurobehaviour** Sprague–Dawley rats Repeated exposure (PND5-10) Testing up to PND74	**0.0316** Using tissue levels from Mörck et al. (2003, at day 3)	**4861** F_{ABS}: 30% $t_{1/2}$: 15 days Thuresson et al. (2006), Zhang, Hu, et al. (2022)
	Li, Liu, et al. (2021)	$BMDL_{5}$ = **0.91**	**Reproductive** Sprague–Dawley rats Repeated exposure (28 days)	**0.0181** Using tissue levels from Mörck et al. (2003, at day 3)	**2782** F_{ABS}: 30% $t_{1/2}$: 15 days Thuresson et al. (2006), Zhang, Hu, et al. (2022)

Abbreviations: bw, body weight; GD, gestational day; PND, postnatal day; $t_{1/2}$, half-life.

TABLE 33 Comparison of the Reference Points in the 2011 Opinion (EFSA, 2011b) and the current assessment.

	Previous opinion (EFSA CONTAM Panel, 2011b)			Current assessment		
	$BMDL_{10}$ (mg/kg bw)	Body Burden at the $BMDL_{10}$ (mg/kg bw)	Estimated chronic human dietary intake at the $BMDL_{10}$ body burden (ng/kg bw per day)	**BMDL**[a] (mg/kg bw per day)	Body Burden at the BMDL[b] (mg/kg bw)	Estimated chronic human dietary intake at the BMDL body burden[c] (ng/kg bw per day)
BDE-47	**0.309** Neuro Single	0.232	**172**	$BMDL_{10}$ = **0.15** Neuro Repeated	0.806	**1096**
	–	–	–	$BMDL_{10}$ = **0.023** Repro Repeated	0.123	**168**
BDE-99	**0.012** Neuro Single	0.009	**4.2**	$BMDL_{10}$ = **0.43** Neuro Repeated	1.443	**3575**
	–	–	–	$BMDL_{10}$ = **0.05** Develop Single	0.0155	**38.4**
BDE-153	**0.083** Neuro Single	0.062	**9.6**	$BMDL_{10}$ = **0.11** Neuro Single	0.0125	**3.2**
BDE-209	**1700** Neuro Single	NE	**NE**	$BMDL_{10}$ = **1.59** Neuro Repeated	0.0316	**4861**
	–	–	–	$BMDL_{5}$ = **0.91** Repro Repeated	0.0181	**2782**

Abbreviations: bw, body weight; NE, not estimated.
[a]See **Section 3.1.5.2** for details on the calculations.
[b]See **Section 3.1.5.3** for details on the calculations.
[c]See **Section 3.1.5.4** for details on the calculations.

3.1.6 | Approach to risk characterisation

The CONTAM Panel considered repeated dose toxicity studies to establish Reference Points, but in the case of **BDE-153** the only experimental animal study available involved a single administration on PND10 (same study as in the previous PBDEs Opinion, neurobehavioural effects, Viberg, Fredriksson, & Eriksson, 2003). This is not viewed as an acute effect because PBDEs are persistent in the body, and an acute high level exposure is not likely to occur during the critical period of development of the human brain. The study by Talsness et al. (2005) on the developmental effects of **BDE-99** involved a single administration on GD6. The Panel noted the non-standard study design, and there is no evidence that the effects observed/reported on development (increased fraction of resorptions in the mated female offspring, histopathological changes in ovaries in the F1 generation) are related to an acute exposure. Therefore, the CONTAM Panel decided to focus on chronic exposure in the risk characterisation.

In the previous Opinion (EFSA CONTAM Panel, 2011a, 2011b, 2011c), the Panel considered the potential for additivity of the different congeners and recognised '*that there are some similarities in the effects of the various PBDE congeners, e.g. interactions with nuclear receptors. However, the divergent responses of the different toxicological endpoints, as indicated above, and the limited information available, preclude establishment of a common mode of action. Therefore, the CONTAM Panel decided to perform the risk assessment on the basis of the individual congeners*'.

Since that Opinion, EFSA launched a new Guidance document on how to evaluate the effects of mixtures (EFSA Scientific Committee, 2019). Assignment of chemicals to an assessment group for combined risk assessment as a mixture is based on whether the chemicals have a common mode of action or a common target/system (EFSA Scientific Committee, 2019, 2021). The four PBDE congeners for which there are experimental data to derive a Reference Point all affect neurodevelopment, and for three of these data are available showing effects on reproduction, forming a scientific basis for inclusion of these four congeners in a common assessment group. The evidence that changes in the thyroid hormone system could contribute to the effects of PBDEs on both neurodevelopment and reproduction (see **Section 3.1.5**) further supports a combined risk assessment.

It was therefore concluded that **BDE-47**, **-99**, **-153** and **-209**, should be included in the same assessment group. No studies were available to identify Reference Points for **BDE-28**, **-49**, **-100**, **-138**, **-154** and **-183**, which were included as congeners of interest in the TORs. However, mechanistic studies have been conducted *in vitro* with neural cells with these six congeners of interest and also with BDE-4, -15, -17, -42, -66, -77, -85 and -175, in which effects were compared to those of **BDE-47** (and in some instances also **BDE-99** and/or **BDE-209**, see **Section 3.1.4.3**). The studies do not provide a systematic

comparison, as different congeners and endpoints were investigated in the different studies. However, they indicate that all of the tested congeners could share common modes of action with **BDE-47**, **-99**, -**153** and -**209**, and therefore a conservative approach would also include these six congeners of interest in the assessment group. It would not be feasible to include other congeners as no occurrence data were submitted to EFSA.

In the EFSA Guidance document on harmonised methodologies for risk assessment of combined exposure to multiple chemicals (EFSA Scientific Committee, 2019) different options for combined risk metrics are provided and recommendations are given, according to the amount and quality of toxicological data- available. These options include:

1. Hazard index, based on the HBGVs for each individual chemical substance in the mixture,
2. Group HBGV, which is generally established based on the Reference Point for the component that is most potent and/or for which most toxicological data are available,
3. Combined Margin of Exposure (referred to as the MOET).

Application of the Hazard Index is not possible for the PBDEs, as the available data could allow establishment of HBGVs only for **BDE-47**, **-99** and -**209**, and not for **BDE-153** or the other PBDEs of interest.

Establishment of a Group HBGV is, in principle, feasible using the Reference Point of the congener with the most complete and robust toxicological data, i.e. **BDE-47**. The HBGV for **BDE-47** would need to be converted to a group HBGV, expressed as **BDE-47** toxic equivalents. Combined exposure to the group would need to be converted to **BDE-47** toxic equivalents, by applying relative potency factors to the other PBDEs of interest, before comparison to the group HBGV. The available data could support proposal of relative potency factors for **BDE-99** and **-209**. An RPF for **BDE-153** would be subject to considerable uncertainty due to the limited data available (e.g. only one toxicity study available). It would therefore be necessary to assume that all congeners other than **BDE-99** and **-209** have equal toxicity to **BDE-47**, applying an RPF of 1 for each of them. The CONTAM Panel concluded that applying the Group HBGV approach would be conservative but would introduce excessive uncertainty into the risk characterisation. Therefore, the MOET approach was more appropriate and was used for the risk characterisation (see **Section 3.1.6.1**). Consequently, deriving an HBGV for individual congeners was considered redundant.

3.1.6.1 | *Mixture approach*

The MOET is the reciprocal sum (also known as the harmonic sum) of the reciprocals of the MOEs for the individual congeners, with the following equation:

$$\mathrm{MOET} = 1 / \left[\left(1 / \mathrm{MOE}_1\right) + \ \ldots \ + \left(1 / \mathrm{MOE}_n\right) \right].$$

Therefore, the MOET for a mixture is analogous to an MOE for a single chemical. Similar to establishment of an HBGV, interpretation of the value of the MOET takes into account inter- and intra-species differences and gaps in the database but reflects the greater uncertainty.

In accordance with the EFSA Guidance (EFSA Scientific Committee, 2019), the Panel decided to do a tiered approach in the combined risk assessment as a sensitivity analysis for the effects of PBDEs, as follows:

- **Tier 1**: As a conservative first tier in the combined risk assessment of PBDEs, the Panel used the lowest Reference Points, expressed as a chronic human dietary intake corresponding to the calculated body burden at the BMDL, for each of the four congeners with data (**BDE-47 repro**, **-99 develop**, **-153 neuro**, **-209 repro**). For the congeners for which no Reference Points were identified (**BDE-28**, -**49**, -**100**, -**138**, -**154**, -**183**), the Panel applied the Reference Point of **BDE-47**, the congener with the most complete and robust toxicological data (assuming equal potency). The Panel calculated the individual MOEs and subsequently the MOET for combined effects for all 10 congeners.
- **Tier 2**: As a second tier in the combined risk assessment, the CONTAM Panel included only the four congeners with data and used their lowest Reference Points (**BDE-47 repro**, **-99 develop**, **-153 neuro**, **-209 repro**) to calculate MOEs and subsequently the MOET for combined effects for the four congeners.
- **Tier 3:** In a third tier the CONTAM Panel included only the four congeners for which Reference Points for neurodevelopment were identified (**BDE-47 neuro**, **-99 neuro**, **-153 neuro**, **-209 neuro**). Insufficient information is available for **BDE-99 and -153** to take this approach for reproductive effects, and insufficient information is available for all congeners except **BDE-99** for developmental effects.
- **Tier 4:** In order to investigate the impact of the lack of data for **BDE-153** and the uncertainties linked to its Reference Point, a fourth tier was conducted including only the three congeners for which Reference Points for neurodevelopment were identified and for which there are sufficient/robust data, i.e. **BDE-47 neuro**, **-99 neuro**, **-209 neuro**.

3.1.6.2 | *Interpretation of the MOET*

Similar to an MOE for a single chemical, a MOET of 100 is usually considered sufficient to conclude that there is no health concern. This covers uncertainties and variability with respect to kinetic and dynamic differences between animal species and humans (factor $4 \times 2.5 = 10$) and within the human population (factor $3.2 \times 3.2 = 10$).

Since the MOET approach for PBDEs is based on a body burden comparison between animals and humans, the potential toxicokinetic differences can be considered as sufficiently covered, and consequently the default uncertainty factor of 4 for interspecies differences in toxicokinetics is not needed.

The Panel recognised that there could be interspecies differences in toxicodynamics for the critical effects observed, and thus applied the default uncertainty of factor of 2.5.

As in the previous Opinion, the Panel assumed 100% absorption in humans for **BDE-47**, **-99**, **-153**, while for **BDE-209** an absorption of 30% was now used. In the previous Opinion the Panel used the worst-case maximum half-life estimated in humans (based on Geyer et al., 2004, extended abstract). In the current assessment, the Panel decided instead to use for **BDE-47**, **-99**, **-153** the median half-lives reported by Trudel et al. (2011) for which more detail was provided on the methodology and data, and for **BDE-209** the median half-life of 15 days as reported by Thuresson et al. (2006) and Zhang, Hu, et al. (2022). The Panel considered it necessary to apply an uncertainty factor of 3.2 to cover individual differences in kinetics.

The Panel recognised that there could be differences in the individual susceptibility, and therefore concluded that the MOET should also cover individual differences in toxicodynamics by applying a factor of 3.2.

Thus, the Panel concluded that a MOET smaller than 25 ($2.5 \times 3.2 \times 3.2$) would raise a health concern.

A comparison of the previous consideration in the interpretation of the MOE and current ones is provided in Table 34.

TABLE 34 Factors used in the interpretation of the margin of exposure in the previous Opinion (MOE) and current assessment (MOET).

	Previous opinion (EFSA CONTAM Panel, 2011b)	Current assessment
Interspecies differences in kinetics	Sufficiently covered by the body burden comparison between animals and humans	Sufficiently covered by the body burden comparison between animals and humans
Interspecies differences in dynamics	Covered by a factor of 2.5	To be covered by a factor of 2.5
Intraspecies differences in kinetics	Sufficiently covered by the use of the longest worst-case human half-live values in Geyer et al. (2004, extended abstract)	To be covered by a factor of 3.2
Intraspecies differences in dynamics	Sufficiently covered by focussing on neurobehavioural effects in mice induced during a relevant period for brain development (i.e. representing the most sensitive fraction of the population)	There could be differences in the individual susceptibility in the subpopulation of infants and children. To be covered by a factor of 3.2

3.2 | Occurrence data

3.2.1 | Occurrence data on food submitted to EFSA

An initial number of 85,225 analytical results (11,002 samples) on PBDEs in food were available in the EFSA database. Data were reported by 13 European countries.[54] The analytical results were obtained between 2000 and 2019. Because the previous Opinion included data collected up to 2010, and in order to have a dataset representing current occurrence levels while retaining a sufficient high number of samples, the present assessment used data submitted to EFSA between 2010 and 2019. The raw occurrence data set on PBDEs in food as extracted from the EFSA data warehouse is available at the EFSA Knowledge Junction community in Zenodo at: https://doi.org/10.5281/zenodo.10532237

The occurrence data were carefully evaluated, and a number of validation steps were applied to each congener separately before being used to estimate the dietary exposure. The resulting dataset included a total of 84,249 analytical results (10,879 samples) on **BDE-28**, **-47**, **-49**, **-99**, **-100**, **-138**, **-153**, **-154**, **-183** and **-209** in food.

Data providers were contacted to clarify inconsistencies identified during the data check. The following modifications were made to the initial data set based on the feedback received:

- The product description of several records allowed a more accurate FoodEx2 classification. In these cases, the samples were reclassified to a more specific, lower level. In this context, infant and follow-on formula reported as solid were reclassified to their liquid form applying a dilution factor of 8 (EFSA, 2018) in alignment with the consumption data.
- Special attention was given to the analytical method reported. The majority of samples were reported being analysed by GC–MS. There were also samples which were reported being analysed by, e.g. GC-ECD, GC–HRMS, HRGC-HRMS, GC-QqQ-MS–MS. In addition, there were samples with reported analytical method 'unspecified' but containing some information in the analytical method text. These were clarified further with the data providers and the analytical methods were confirmed to be GC–MS-based methods or GC-ECD.
- Some occurrence values were expressed on a fat weight basis, but the fat content of the food item was not provided. However, the fat content was required for the calculation of the values on a whole weight basis. The data providers subsequently submitted the fat content for those samples. In addition, for 568 occurrence values provided by one country it was not clear whether the results were on a fat or whole weight basis. The data provider clarified the results were based

[54] Occurrence data included in the assessment were submitted to EFSA when the UK was a member of the EU.

on whole weight. For 847 occurrence values on mammal fat tissues expressed on a fat weight basis, the fat content was missing. The data provider indicated that this information was not available. Therefore, the CONTAM Panel decided to assign a value of 99.9% fat content as a conservative approach.

- For 3742 occurrence values on different types of muscle and kidney, from two countries, the fat percent reported was 100%. The data provider clarified that results were related to the fat tissue of the whole sample. Therefore, in order to calculate the occurrence values of the PBDEs in the whole sample (i.e. muscle and kidney), the average fat content of all foods under the specific FoodEx2 codes (i.e. muscle and kidney) was retrieved from the most recent food consumption survey submitted by these two countries.
- 23 results for tuna provided by another country were reported as 'Values above the limit of the working range' with an LOQ equal to 0.01 μg/kg, and the numerical value was missing. The data provider clarified that the upper limit of the working range used for the analysis was 0.1 μg/kg. Given that no numerical values were provided, and that other numerical and left-censored data for tuna samples from the same country were available, the Panel decided to exclude these 23 occurrence values (see Annex B, Table B.1).
- 953 occurrence values were reported as 'suspect sampling' and were excluded (see Annex B, Table B.1).
- For 117 occurrence values the sampling strategy was reported as 'Other'. After clarifying with the data provider, the sampling strategy was updated to 'Objective sampling'.
- On request for clarification to the data providers while checking for outlier values, it was confirmed that for 25 of them the unit of measurement was wrongly reported to be μg/kg though the value was expressed in mg/kg instead. The correction was implemented in the dataset.

In the final dataset (84,249 occurrence values from 10,879 samples), 61% of the data were reported as 'Objective sampling', 38% as 'Selective sampling', while the remaining 1% were reported as 'Convenient sampling'. It was decided to retain all samples regardless of the sampling strategy.

As shown in Figure 9, occurrence values from the final dataset were reported by 13 European countries, most of them by Germany (30.2%) and Norway (28.9%). The majority of the data (93%) were reported after 2012 while a substantially lower number of data was reported in 2010 and 2011 (Figure 10).

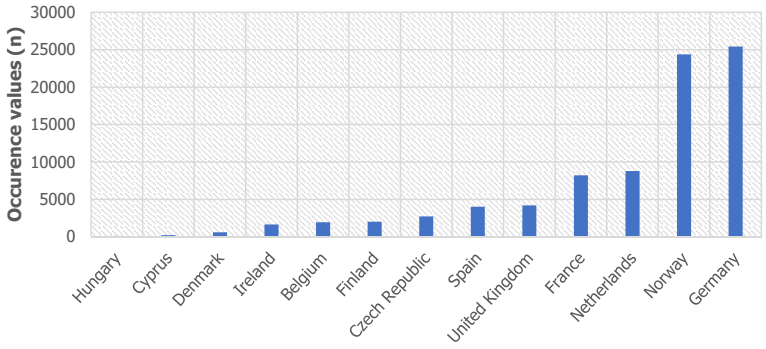

FIGURE 9 Distribution of occurrence values reported for PBDEs across different European countries.

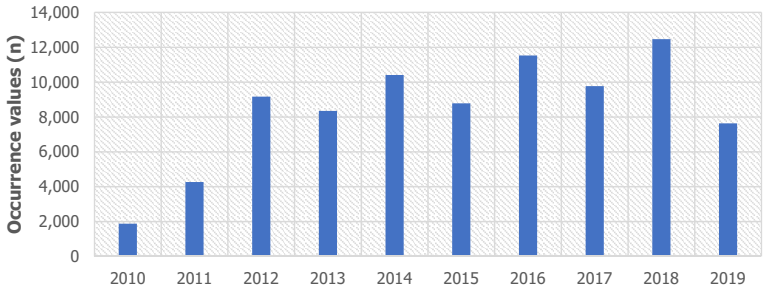

FIGURE 10 Distribution of occurrence values reported for PBDEs by year.

The left-censored data accounted for 51% of the occurrence values. Both LOQ and LOD were provided for 21% of all left-censored data, while only LOD or only LOQ were provided for 4% and 75% of the reported left-censored occurrence values, respectively. Out of the food categories in which PBDE contamination was expected, the highest percentage of quantified data was found in 'Fish, seafood, amphibians, reptiles and invertebrates'.

Based on the FoodEx2 classification, 14 food categories at FoodEx2 Level 1 were represented (Figure 11). 'Fish, seafood, amphibians, reptiles and invertebrates' was the most represented food group with 47,048 occurrence values (6185 samples) reported, followed by 'Meat and meat products' with 18,856 occurrence values (2351 samples), 'Eggs and egg products' with

6838 occurrence values (841 samples) and 'Milk and dairy products' with 6231 occurrence values (826 samples). These food categories were identified as the most important for exposure in the previous Opinion (EFSA CONTAM Panel, 2011b) and were highlighted among the most important food groups for monitoring in Commission Recommendation 2014/118/EU.

Proportions of non-detected, non-quantified and quantified analytical results by congener are presented in the Figure 12.

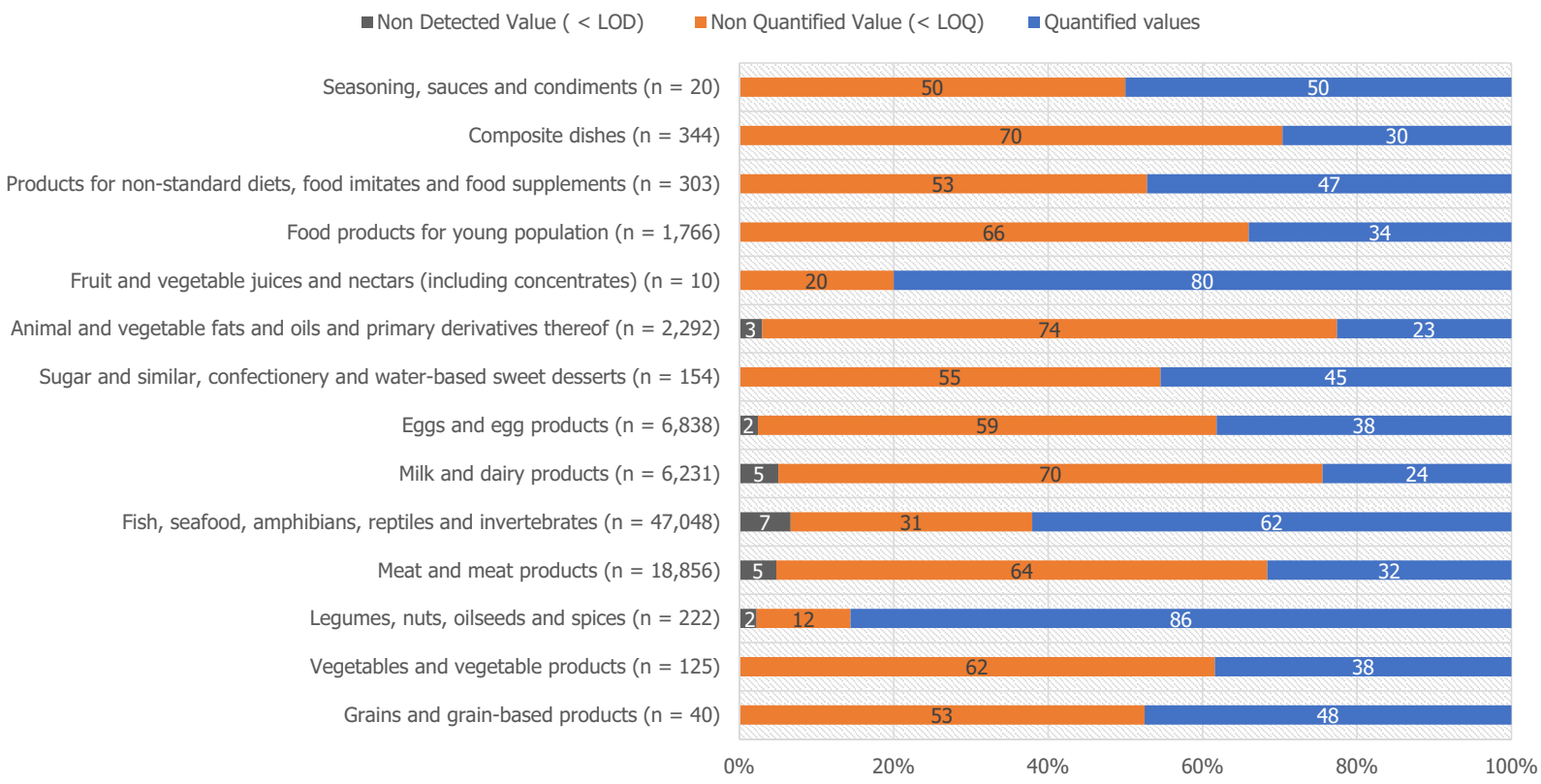

FIGURE 11 Percentage of analytical results below LOD, below LOQ and quantified values in the final dataset across the different food categories (FoodEx2 Level 1). The sum of percentages for non detected, non quantified and quantified values is not always 100% due to rounding.

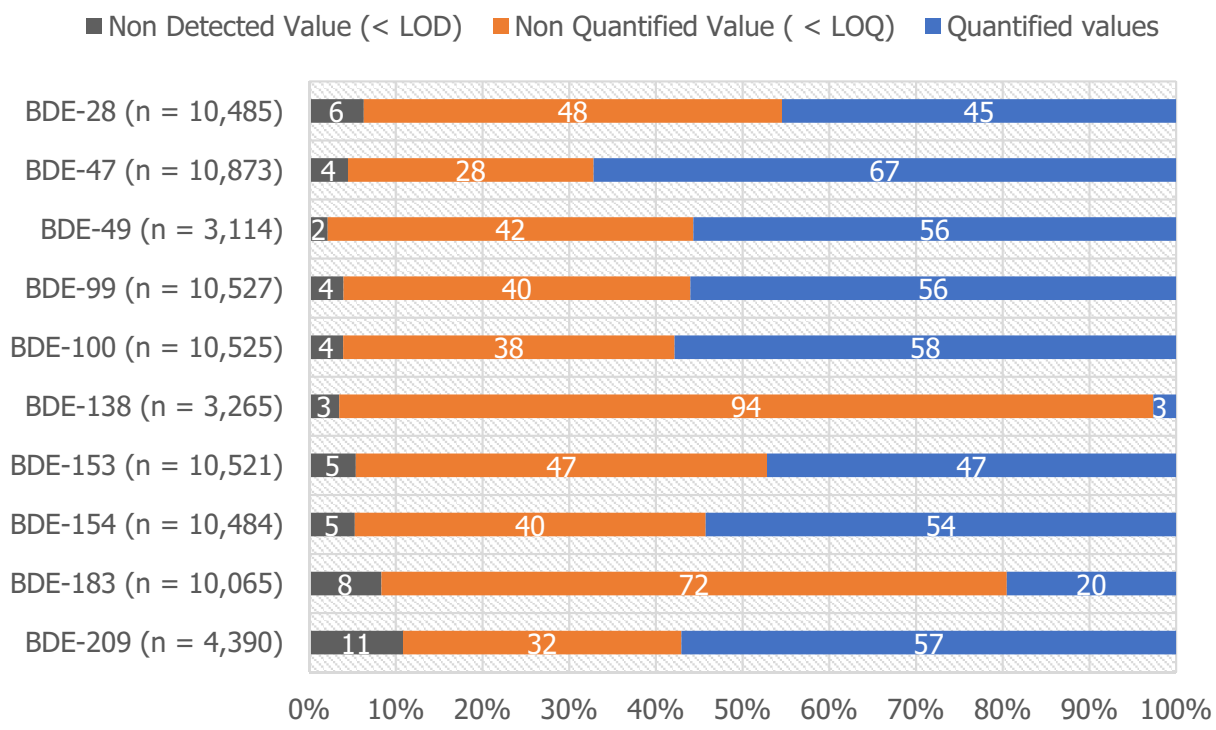

FIGURE 12 Proportion of non detected, non quantified and quantified analytical results across the 10 congeners considered (**BDE-28**, -**47**, -**49**, -**99**, -**100**, -**138**, -**153**, -**154**, -**183** and -**209**). The sum of percentages for non detected, non quantified and quantified values is not always 100% due to rounding.

At the most detailed level (FoodEx2 Level 7), the food category was retained if more than six samples with quantified values were available. If fewer than six samples were available (e.g. 'Duck fresh meat' with four samples at FoodEx2 Level 5) or data were 100% left-censored (e.g. 'Goose fresh meat' with 9 samples at FoodEx2 Level 5), the food category was taken into account at the next upper FoodEx2 level (e.g. 'Poultry fresh meat (muscle meat)' at FoodEx2 Level 4). Exceptions to this rule are detailed below:

- Food categories with more than six samples available and 100% left-censored, and in which PBDE contamination was not expected, were not taken into account for the assessment. For example, in the case of **BDE-28**, the food category 'Sugar and similar, confectionery and water-based sweet desserts' was completely excluded despite the fact that the more detailed category 'Chocolate and similar' was reported for 18 samples. Since all data were left-censored and contamination is not expected, the rule of taking the food category into account at the upper level was not applied.
- The food category 'Fish and seafood-based dishes' was the only food category from the group of 'Composite dishes' that was taken into account for the assessment but the value assigned to this category was 50% of the value calculated for the category 'Fish (meat)' at the second level of the FoodEx2 catalogue, because 'Fish and seafood-based dishes' are generally composed of less than 50% of fish, as well as other ingredients where contamination is generally expected to be lower.
- Food categories with more than six samples and not 100% left-censored at the highest FoodEx2 level were excluded only if, for the majority of their sub-categories contamination was not expected. For example, the food category 'Ready-to-eat meal for infants and young children' and its more detailed categories (except 'Ready-to-eat meat-based meal for children' and 'Ready-to-eat fish-based meal for children'), were excluded as the levels of PBDEs in fruit, vegetable and cereal ready-to-eat meals were expected to be lower.
- Samples under the food category 'Dried vegetables' were not considered in the exposure assessment despite having more than 6 samples (range from 11 for **BDE-28** to 15 samples for **BDE-100** and -**209**) and not being 100% left-censored (range from 23% for **BDE-99** to 86% for **BDE-154**). The reason for this was that they were all dried algae, not representative of the food category 'Dried vegetables', and for which the number of eating occasions and consumed amounts reported in the EFSA Comprehensive European Food Consumption Database were negligible (mean amount reported to be consumed of 4.5 g only in 71 eating occasions).
- All samples under the food categories 'Milk and dairy powders and concentrates' and 'Dairy dessert and similar' could not be included, i.e. not considered, at the upper FoodEx2 level. The reason for this was that they were all represented with less than six samples and considering them at the upper FoodEx2 level (FoodEx2 Level 1 'Milk and dairy products'), where the contamination levels were driven by samples reported for milk, cheese and yoghurt, would add to the uncertainty.
- Mean occurrence values for the food categories considered at the most detailed level of FoodEx2 were calculated as average of all samples reported within the same food category. However, for the samples reported/grouped at the upper level of the FoodEx2, mean occurrence values were calculated as an average of all samples reported at the specific level

and all associated samples reported at the more detailed level. For example, mean occurrence values for the samples reported/grouped as 'Fish (meat)' (without further specification), were calculated using all samples for which the second level was 'Fish (meat)' including those reported at more detailed levels.

After matching occurrence and consumption data via FoodEx2 classification system, the number of distinct food categories considered for the exposure assessment by congener were as follow: 172 for **BDE-28**, 217 for **BDE-47**, 208 for **BDE-99**, 204 for **BDE-100**, 208 for **BDE-153**, 202 for **BDE-154**, 193 for **BDE-183**, 154 for **BDE-209**, 118 for **BDE-49** and 59 for **BDE-138**. The detailed list of the food categories considered across all 10 congeners including LB and UB values as used for the exposure is shown in the **Annex F1** to **F10** (Tables F1.1 to F10.1).

As presented in Figure 11, the majority of the data were reported for the food category 'Fish, seafood, amphibians, reptiles and invertebrates' with 62% quantified values. The average of occurrence values reported for this category is shown at the first, second and third level of the FoodEx2 in Table 35. Occurrence values for the food category 'Fish offal' (FoodEx2 Level 2) are higher compared to the other food categories. Comparing the occurrence values across congeners, the highest were reported for **BDE-47** and the lowest for **BDE-138** for all food categories under 'Fish, seafood, amphibians, reptiles and invertebrates'. The second most reported food category was 'Meat and meat products'. The average of occurrence values reported for this category is shown at the first, second and third level of the FoodEx2 in Table 36. The highest occurrence values aggregated at FoodEx2 Level 1, were reported for **BDE-209** and the lowest were reported for **BDE-49** and **-138**. For the rest of categories where high concentrations of PBDEs were expected and that were mentioned in the Commission Recommendation 2014/118/EU[3] on the monitoring of traces of BFRs in food, the average of the occurrence values reported are shown in Table 37. The category 'Food products for young population' is not listed in this table, as the values considered for exposure estimates were only those related to 'Infant formula', 'Follow-on formula', 'Ready-to-eat meat-based meal for children' and 'Ready-to-eat fish-based meal for children' only and not the whole food category. LB and UB values for these categories as used for the exposure is shown in the **Annex F1** to **F10** (Tables F1.1 to F10.1). Among them, the occurrence values reported for the category 'Animal and vegetable fats and oils and primary derivatives thereof' are higher compared to the other three categories across all congeners except from the **BDE-209** where highest values were reported for 'Eggs and egg products'.

TABLE 35 Lower bound (LB) and upper bound (UB) mean values in μg/kg ww for 'Fish, seafood, amphibians, reptiles and invertebrates' at first three levels of FoodEx2 for all 10 congeners of interest, as used for the exposure assessment.

		BDE-28		BDE-47		BDE-49		BDE-99		BDE-100	
		LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Fish, seafood, amphibians, reptiles and invertebrates (FoodEx2 Level1)		0.087	0.137	2.072	2.144	0.100	0.164	0.116	0.167	0.496	0.542
FoodEx2 Level 2	**FoodEx2 Level 3**										
Fish (meat)		0.011	0.073	0.296	0.377	0.060	0.130	0.025	0.088	0.084	0.142
	Diadromous fish	0.012	0.120	0.462	0.584	0.114	0.125	0.051	0.152	0.184	0.279
	Marine fish	0.011	0.060	0.238	0.309	0.052	0.136	0.015	0.065	0.048	0.098
	Freshwater fish	0.008	0.033	0.277	0.323	0.008	0.038	0.026	0.063	0.057	0.081
Fish offal		0.443	0.447	11.078	11.079	0.729	0.738	0.542	0.555	2.455	2.457
	Fish roe	0.013	0.142	0.303	0.431	0.052	0.180	0.183	0.312	0.094	0.222
	Fish liver	0.446	0.449	11.151	11.151	0.765	0.768	0.544	0.557	2.471	2.472
Molluscs		0.003	0.013	0.042	0.068	0.006	0.044	0.013	0.024	0.013	0.024
	Clams, cockles, arkshells	0.003	0.004	0.005	0.006	0.002	0.005	0.004	0.005	0.001	0.003
	Scallops, pectens	< 0.001	0.001	0.004	0.004	0.006	0.044	0.002	0.003	0.001	0.002
	Oysters	0.005	0.006	0.058	0.079	0.009	0.010	0.017	0.017	0.017	0.017
	Mussels	0.003	0.010	0.055	0.084	0.009	0.010	0.018	0.024	0.018	0.025
	Squids, cuttlefishes, octopuses	0.001	0.128	0.004	0.131	0.002	0.169	0.001	0.128	0.001	0.129
Crustaceans		0.004	0.021	0.073	0.090	0.006	0.020	0.013	0.031	0.018	0.035
	Shrimps and prawns	< 0.001	0.011	0.011	0.022	0.002	0.007	0.003	0.014	0.002	0.013
	Freshwater crustaceans	< 0.001	0.258	< 0.001	0.258			< 0.001	0.258	< 0.001	0.258
	Lobsters, spiny-rock lobster	0.017	0.019	0.217	0.219	0.020	0.023	0.010	0.012	0.066	0.068
	Crabs, sea-spiders	0.010	0.011	0.195	0.196	0.019	0.020	0.039	0.041	0.048	0.049
Fish and seafood processed		0.014	0.317	0.297	0.679	0.006	0.546	0.072	0.312	0.080	0.333
	Processed or preserved fish (including processed offal)	0.015	0.338	0.310	0.704	0.004	0.604	0.081	0.332	0.089	0.354
	Processed or preserved seafood	0.001	0.149	0.039	0.184			0.003	0.151	0.008	0.156

TABLE 35 (Continued)

		BDE-138		BDE-153		BDE-154		BDE-183		BDE-209	
		LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Fish, seafood, amphibians, reptiles and invertebrates (FoodEx2 Level1)		0.002	0.015	0.033	0.082	0.302	0.342	0.001	0.072	0.051	0.135
FoodEx2 Level 2	**FoodEx2 Level 3**										
Fish (meat)		0.003	0.010	0.007	0.068	0.034	0.083	0.001	0.071	0.059	0.161
	Diadromous fish	< 0.001	0.007	0.015	0.110	0.045	0.099	0.001	0.118	0.099	0.415
	Marine fish	0.003	0.011	0.004	0.055	0.033	0.082	< 0.001	0.054	0.057	0.085
	Freshwater fish	0.005	0.006	0.010	0.047	0.025	0.057	< 0.001	0.053	0.024	0.045
Fish offal		0.002	0.076	0.151	0.159	1.560	1.562	0.003	0.088	0.027	0.103
	Fish roe	0.002	0.076	0.025	0.153	0.057	0.186	0.002	0.132	0.014	0.050
	Fish liver	0.002	0.074	0.151	0.159	1.570	1.571	0.003	0.088	0.027	0.103
Molluscs		< 0.001	0.003	0.003	0.014	0.005	0.015	< 0.001	0.014	0.022	0.025
	Clams, cockles, arkshells	< 0.001	0.003	0.001	0.002	0.001	0.002	< 0.001	0.002	0.014	0.014
	Scallops, pectens	< 0.001	0.003	0.001	0.001	0.002	0.002	< 0.001	0.001	0.016	0.016
	Oysters	< 0.001	0.003	0.004	0.004	0.009	0.009	< 0.001	0.002	0.010	0.011
	Mussels	< 0.001	0.003	0.004	0.012	0.005	0.012	< 0.001	0.010	0.038	0.043
	Squids, cuttlefishes, octopuses	< 0.001	0.003	< 0.001	0.128	0.001	0.128	< 0.001	0.128	0.019	0.023
Crustaceans		0.0001	0.006	0.007	0.024	0.014	0.031	< 0.001	0.019	0.039	0.072
	Shrimps and prawns	0.0003	0.005	0.001	0.012	0.001	0.012	< 0.001	0.011	0.046	0.081
	Freshwater crustaceans	0.0001	0.006	< 0.001	0.258	< 0.001	0.258	< 0.001	0.300	0.039	0.072
	Lobsters, spiny-rock lobster	0.0001	0.006	0.005	0.007	0.013	0.015	0.001	0.004	0.010	0.019
	Crabs, sea-spiders	< 0.001	0.002	0.020	0.021	0.046	0.046	0.001	0.006	0.066	0.136
Fish and seafood processed				0.018	0.272	0.038	0.288	0.004	0.265	0.025	0.469
	Processed or preserved fish (including processed offal)			0.020	0.288	0.042	0.305	0.005	0.280	0.026	0.507
	Processed or preserved seafood			0.001	0.149	0.005	0.153				

Notes: The values are rounded to three decimal places; Values lower than 0.001 are indicated as < 0.001; Missing values are related to food categories where fewer than six samples were available or data were 100% left-censored. For these food categories values of the next upper FoodEx2 level were used. Occurrence values presented at FoodEx2 Level 1 were used to map eating occasions of foods that could not be mapped to a more detailed FoodEx2 Level. These were calculated as average of all samples reported at this specific level and all associated samples reported at the more detailed level.

TABLE 36 Lower bound (LB) and upper bound (UB) mean values in μg/kg ww for 'Meat and meat products' at first three levels of FoodEx2 for all 10 congeners of interest, as used for the exposure assessment.

		BDE-28		BDE-47		BDE-49		BDE-99		BDE-100	
		LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Meat and meat products at FoodEx2 level 1		**< 0.001**	**0.051**	**0.013**	**0.077**	**0.000**	**0.004**	**0.014**	**0.067**	**0.002**	**0.052**
FoodEx2 level 2	**FoodEx2 level 3**										
Animal other slaughtering products				0.002	0.028			0.001	0.028	< 0.001	0.027
	Mammals other slaughtering products			0.002	0.028			0.001	0.028		
Animal edible offal, non-muscle, other than liver and kidney				0.003	0.060			0.004	0.060	0.001	0.058
	Mammals edible offal, non-muscle, other than liver and kidney			0.003	0.071			0.004	0.072	0.001	0.070
Processed whole meat products				0.001	0.066			0.001	0.066	< 0.001	0.065
	Raw cured (or seasoned) meat			0.001	0.116			0.001	0.117	< 0.001	0.115
	Cooked cured (or seasoned) meat			0.001	0.016			0.001	0.016	< 0.001	0.015
Sausages		0.006	0.055	0.067	0.118	0.004	0.018	0.078	0.126	0.001	0.050
	Preserved or partly preserved sausages	0.014	0.022	0.152	0.163	0.008	0.015	0.166	0.178	0.001	0.010
Animal kidney				0.003	0.017	< 0.001	0.001	0.001	0.016	< 0.001	0.014
	Mammals kidney			0.003	0.042	< 0.001	0.001	0.001	0.040	< 0.001	0.039
Animal liver		< 0.001	0.009	0.011	0.022	< 0.001	0.002	0.012	0.020	0.002	0.010
	Mammals liver			0.010	0.022	< 0.001	0.002	0.012	0.020	0.002	0.011
	Poultry liver	0.001	0.001	0.031	0.031			0.010	0.010	0.003	0.003
Mammals and birds meat		< 0.001	0.023	0.008	0.031	< 0.001	0.001	0.009	0.037	0.002	0.024
	Mammals meat	< 0.001	0.026	0.009	0.034	< 0.001	0.001	0.009	0.043	0.001	0.028
	Birds meat	< 0.001	0.013	0.004	0.017	< 0.001	0.001	0.005	0.017	0.001	0.014
Marinated meat		< 0.001	0.001	0.006	0.008			0.005	0.006	0.001	0.002
Animal fresh fat tissues		< 0.001	0.218	0.036	0.342	< 0.001	0.011	0.039	0.249	0.005	0.222
	Mammals fat tissue					< 0.001	0.011				

TABLE 36 (Continued)

		BDE-138		BDE-153		BDE-154		BDE-183		BDE-209	
		LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Meat and meat products at FoodEx2 level 1		**0.000**	**0.004**	**0.007**	**0.061**	**0.003**	**0.057**	**0.005**	**0.069**	**0.127**	**0.177**
FoodEx2 level 2	**FoodEx2 level 3**										
Animal other slaughtering products				0.001	0.027	< 0.001	0.026	< 0.001	0.026		
	Mammals other slaughtering products			0.001	0.027	< 0.001	0.026	< 0.001	0.026		
Animal edible offal, non-muscle, other than liver and kidney				0.002	0.059	< 0.001	0.058	< 0.001	0.058		
	Mammals edible offal, non-muscle, other than liver and kidney			0.001	0.071	0.001	0.070	< 0.001	0.070		
Processed whole meat products				< 0.001	0.065	< 0.001	0.065	< 0.001	0.103		
	Raw cured (or seasoned) meat			< 0.001	0.115	< 0.001	0.115	< 0.001	0.115		
	Cooked cured (or seasoned) meat			< 0.001	0.015	< 0.001	0.015				
Sausages		0.004	0.015	0.008	0.057	0.003	0.050	0.001	0.050	0.035	0.075
	Preserved or partly preserved sausages	0.007	0.012	0.018	0.025	0.001	0.010	0.001	0.010		
Animal kidney				< 0.001	0.014	< 0.001	0.014	< 0.001	0.014	0.025	0.039
	Mammals kidney			< 0.001	0.039	< 0.001	0.039	< 0.001	0.039	0.025	0.039
Animal liver				0.006	0.015	0.001	0.010	0.002	0.012	0.070	0.111
	Mammals liver			0.008	0.009	0.002	0.011	0.002	0.012	0.072	0.117
	Poultry liver			0.002	0.002	0.001	0.001	0.001	0.001	0.033	0.033
Mammals and birds meat		< 0.001	0.001	0.002	0.031	0.001	0.029	0.004	0.043	0.111	0.125
	Mammals meat	< 0.001	0.001	0.002	0.037	0.001	0.035	0.002	0.049	0.098	0.109
	Birds meat			0.001	0.014	< 0.001	0.012			0.111	0.134
Marinated meat				0.329	0.330	0.311	0.312	0.280	0.281	0.011	0.027
Animal fresh fat tissues		< 0.001	0.011	0.013	0.228	0.003	0.220	0.003	0.225	0.362	0.669
	Mammals fat tissue	< 0.001	0.011								

Notes: The values are rounded to three decimal places; Values lower than 0.001 are indicated as < 0.001; Missing values are related to food categories where fewer than six samples were available or data were 100% left-censored. For these food categories values of the next upper FoodEx2 level were used.

Occurrence values presented at FoodEx2 Level 1 were used to map eating occasions of foods that could not be mapped to a more detailed FoodEx2 Level. These were calculated as average of all samples reported at this specific level and all associated samples reported at the more detailed level.

TABLE 37 Lower bound (LB) and upper bound (UB) mean values in µg/kg ww in food categories other than fish and meat at the first level of FoodEx2 for all 10 congeners of interest, as used for the exposure assessment.

	BDE-28 (*n* = 10,485)		**BDE-47 (*n* = 10,873)**		**BDE-49 (*n* = 3114)**		**BDE-99 (*n* = 10,527)**		**BDE-100 (*n* = 10,527)**	
FoodEx2 level 1	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**
Eggs and egg products (*n* = 6838)	< 0.001	0.021	0.015	0.035	0.001	0.002	0.018	0.038	0.004	0.025
Animal and vegetable fats and oils and primary derivatives thereof (*n* = 2292)	0.044	0.165	0.424	0.551	0.141	0.149	0.093	0.213	0.075	0.195
Milk and dairy products (*n* = 6231)	< 0.001	0.036	0.003	0.039	< 0.001	0.005	0.002	0.038	< 0.001	0.036
	BDE-138 (*n* = 3265)		**BDE-153 (*n* = 10,521)**		**BDE-154 (*n* = 10,484)**		**BDE-183 (*n* = 10,065)**		**BDE-209 (*n* = 4390)**	
FoodEx2 level 1	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**
Eggs and egg products (*n* = 6838)	0.002	0.003	0.006	0.026	0.002	0.021	0.005	0.024	0.181	0.210
Animal and vegetable fats and oils and primary derivatives thereof (*n* = 2292)	0.108	0.115	0.038	0.159	0.127	0.244	0.011	0.113	0.093	1.016
Milk and dairy products (*n* = 6231)	< 0.001	0.004	< 0.001	0.038	< 0.001	0.037	0.001	0.038	0.013	0.137

Notes: The values are rounded to three decimal places; Values lower than 0.001 are indicated as < 0.001.

3.2.2 | Previously reported occurrence data in the open literature

The previous Opinion on PBDEs (EFSA CONTAM Panel, 2011b) summarised the available occurrence data in food submitted by European countries as well as those published in peer-reviewed journals.

The following paragraphs, which do not claim to be comprehensive, give a short overview on PBDE occurrence in food collected in European countries and published in the open literature since the previous Opinion. Only those studies were considered where the sampling was from 2010 onwards. The primary focus of the recently published studies was on fish and food of terrestrial animal origin. Most of the studies were performed to generate occurrence data in food as a basis for dietary PBDE exposure assessment. The studies comprise either congener-specific occurrence data in raw food commodities or duplicate/total diet studies on prepared meals or foods as consumed. In some cases, the studies also included data on PBDEs in dust (see **Section 3.3.3**). These data are important to estimate the contribution of dietary and non-dietary PBDE exposure to total human PBDE exposure. In **Appendix G** (Table G.1) studies that were performed in the past decade on PBDE occurrence in food are summarised. It also lists, where available, data on PBDE-metabolites, and the resulting estimates of human dietary exposure (see **Section 3.3.2**).

Some of the authors indicated that the studies were performed in response to Commission Recommendation 2014/118/EU on the monitoring of traces of PBDEs and other BFRs in food, and the resulting data might have been submitted to EFSA.

Almost all studies included at least the eight PBDEs that were considered to be of primary interest in the previous Opinion (**BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**, **-183**, **-209**), and in addition often further PBDE congeners.

Concerning the predominant PBDE congeners in the food samples, the results are generally in accordance with the occurrence data in the former EFSA Opinion on PBDEs, i.e. **BDE-47** and **-209** are not only the most frequently determined congeners, but usually showed also the highest concentration. Moreover, the concentrations of the different PBDE congeners varied widely. This is especially true for certain fish and meat samples where the minimum and maximum concentrations in several studies differed by two orders of magnitude or more depending on the food commodity and origin of sampling. For example, Aznar-Alemany et al. (2017) analysed commercial sea food samples from various European countries and found concentrations for the sum of the eight PBDEs considered to be of primary interest in the previous Opinion of < LOD–356 ng/g lipid or < LOD–41.1 ng/g ww, respectively depending on fish species, lipid content and country of sampling. The authors also looked for eight MeO-PBDEs (5-MeO-BDE-47, 6-MeO-BDE-47, 4′-MeO-BDE-49, 2′-MeO-BDE-68, 5′-MeO-BDE-99, 5′-MeO-BDE-100, 4′-MeO-BDE-101 and 4′-MeO-BDE-103), which are naturally produced by sea organisms. MeO-PBDEs were found in 90.5% of the samples with levels ranging from < LOD–305 ng/g lipid. Only 11.9% of the samples showed more than 60 ng/g lipid and half of the eight MeO-PBDEs were always < LOQ.

Trabalón et al. (2017) determined the same eight PBDE congeners and eight MeO-PBDEs (5-MeO-BDE-47, 6-MeO-BDE-47, 4-MeO-BDE-49, 2′-MeO-BDE-68, 5′-MeO-BDEE-99, 5-MeO-BDE-100, 4-MeO-BDE-101, 4-MeO-BDE-103) along with some further BFRs in 10 species of fish and shellfish widely consumed in Tarragona County (Catalonia, Spain). The sum of the eight PBDEs ranged from 0.4 to 1.3 ng/g ww, with salmon, sole, hake, cod and tuna showing the highest concentrations. MeO-PBDEs were only detected in a few samples. Mussels and tuna showed the highest concentration of total MeO-PBDEs, with mean values of 1.5 and 1.0 ng/g ww, respectively. In contrast, hake, cod and squid had for all MeO-PBDEs values < LOQ (< 0.1 for 5-MeO-BDE-100) or < LOD (< 0.01–< 0.1 for the remaining MeO-PBDEs analysed).

Menezes-Sousa et al. (2021) collected 273 biota samples from different trophic levels (macroalgae, mussel, crab, and three fish species) at four different seasons (2019–2020) in the Douro river estuary and analysed them for six PBDEs (**BDE-28**, **-47**, **-99**, **-153**, **-154** and **-183**), and eight MeO-BDEs (2-MeO-BDE-68, 6-MeO-BDE-47, 5-MeO-BDE-47, 4-MeO-BDE-49, 5-MeO-BDE-100,

4-MeO-BDE-103, 5′-MeO-BDE-99 and 4′-MeO-BDE-101. The occurrence data and corresponding exposure estimations are compiled in **Appendix G** (Table G.1). PBDEs were detected in all seafood samples analysed, with means ranging from 0.02 ng/g ww (flounder in autumn) to 3.75 ng/g ww (mussel in winter). Levels of **BDE-28**, **-47** and **-99** were significantly higher than **BDE-153**, **-154** and **-183** in all seasons ($p < 0.01$). MeO-BDEs ranged from 0.001 ng/g ww (grey mullet in summer) to 5.66 ng/g ww (green crab in spring). Crabs and mussels showed the highest means of PBDEs and MeO-BDEs. The authors report that the relationship between PBDEs and MeO-BDEs when considering all organisms vary according to the season. In summer and winter, PBDE vs. MeO-BDE concentrations were statistically different ($p < 0.05$ and $p < 0.01$, respectively), with higher mean concentrations of Sum MeO-PBDEs in summer and the opposite in winter. In spring and autumn those differences were not observed ($p > 0.05$ for both seasons). The *ortho*-substituted congeners 2′-MeO-BDE-68 and 6-MeO-BDE-47 were present in all organisms and their levels were statistically higher only in autumn ($p < 0.05$) while no differences were observed in winter (> 0.05) in comparison to meta- and *para*-substituted PBDE congeners. Otherwise, *meta*- and *para*-substituted PBDE congeners were statistically higher in spring and summer ($p < 0.01$ for both seasons).

Differences in PBDE concentrations of two orders of magnitude and more were reported by Zhihua et al. (2018) in fish from the UK and proximate marine waters, and by Nøstbakken et al. (2018) in fish from the North East Atlantic Ocean.

Substantial differences in PBDE concentrations were also reported by Pietroń et al. (2019) who analysed 199 meat samples from nine animal species and found total PBDE (sum of the 10 congeners considered in the current Opinion) concentrations between 1.5 and 666 pg/g ww. While the highest median was found for sheep (46.7 pg/g ww), the maximum value of 666 pg/g ww was determined in a pork sample.

In the duplicate diet studies (De Filippis et al., 2014; Coelho, Sousa, Isobe, Kunisue, et al., 2016; Xu, Yi, et al., 2017; Xu, Tay, et al., 2017), the concentrations of the PBDEs measured were generally low, and ranged from < 1 to 200 pg/g with **BDE-209** showing in most cases the highest concentration.

Huneau-Salaün et al. (2020) investigated if farming conditions influenced BFR levels in pig and poultry products. In a monitoring study conducted in France from 2013 to 2015, they measured the levels of the eight PBDEs considered to be of primary interest in the previous Opinion in samples from 60 hen egg farms (34 without an open-air range and 26 free-range), 57 broiler farms (27 without an open-air range and 30 free-range) and 42 pig farms without an open-air range in relation to their rearing environments. From each farm, composite samples from either 12 eggs, five broiler pectoral muscles or three pork tenderloins were obtained. The frequencies of detection of at least one PBDE congener were 28% for eggs (median concentration 0.278 ng/g lipid), 72% for broiler muscle (median concentration 0.392 ng/g lipid) and 49% for pig muscle (median concentration 0.403 ng/g lipid). The most frequently detected congeners were **BDE-47**, **-99** and **-209**. The sum of the eight PBDEs exceeded 1 ng/g lipid only in a few cases. The authors concluded that the contamination of free-range eggs and broilers was more frequent than that of conventional ones, suggesting that access to an open-air environment could be an additional source of exposure to PBDEs, although not statistically significant. The authors could not establish any direct relationship between the occurrence of PBDEs in eggs and meat and the characteristics of the farm buildings, such as age, building and insulating materials.

Pajurek et al. (2019) compared the impact of different types of chicken husbandry systems on bioaccumulation of POPs, including the 10 PBDEs considered in the current Opinion. Altogether, 126 egg samples (12 eggs each) were collected from four different rearing systems for laying hens (free range: $n = 44$; organic: $n = 35$; barn: $n = 31$; and battery cage: $n = 16$). The lowest median concentrations for the sum of the 10 PBDEs were found in battery cage (0.43 ng/g lipid) and barn eggs (0.48 ng/g lipid). In the free range and organic eggs the median concentrations for the 10 PBDEs were 0.53 and 0.61 ng/g lipid, respectively. **BDE-209** dominated regardless of the production system. The contribution of the other nine measured congeners to the sum of PBDEs was between 23 and 33%. **BDE-47**, **-99** and **-153** also made up a substantial proportion, especially in the case of organic eggs. The occurrence of **BDE-209** was not correlated with the presence of any other PBDE congener. A correlation between the egg production system and PBDE congeners was only found for **BDE-47** ($p = 0.007776$).

Boucher et al. (2018) extracted congener-specific data published between 2002 and 2015 from 86 articles into a source database representing 32 countries. Geometric mean PBDE concentrations for foods and supplements were derived for 11 congeners (BDE-17, **-28**, **-47**, -66, -85, **-99**, **-100**, **-153**, **-154**, **-183**, **-209**) individually and combined, and used to calculate means for 27 dietary groups. **BDE-47**, **-99**, **-100**, **-153** and **-154** were the most commonly reported congeners (88%–99%), whereas BDE-17, -85 and **-209** were the least frequently reported ones (43%–56%). The availability of congener-specific data varied widely within categories and countries. Based on the group mean values for the sum of 11 PBDEs, the 10 most contaminated groups in decreasing order were: fish oil supplements, poultry liver, poultry fat, oily fish, shellfish, fish oil/plant oil blend supplements, eggs, baked products, poultry meat and red meat fat. The total levels ranged from 164 to 13,862 pg/g ww.

In the past decade, numerous publications focused on PBDE levels in food from specific areas of non-European countries, such as China, USA and South Korea. The studies were mainly performed as fact finding tools to estimate the background PBDE exposure for the general population based on the occurrence levels in food, or were intended to discern the extent of PBDE contamination in dump sites, such as non-proper operated e-waste recycling sites. Depending on the length and extent of use of the different technical PBDE products and the time since their phasing out, which is globally diverse, the PBDE profiles and concentrations substantially vary in food samples from different areas in the world. Dumpsites and non-proper operated e-waste recycling sites are especially problematic, as considerably elevated PBDE levels were detected in food produced in these areas (Zheng et al., 2012; Zeng et al., 2016; Oloruntoba et al., 2019).

In summary, a comparison of the occurrence data reported in the open literature and those submitted to EFSA is hampered due to differences, in particular concerning reporting. Results are given either on lipid weight or wet weight, on

specific congeners, sum of varying numbers of PBDEs, different handling of left-censored data and diverging aggregation of food items. However, where respective results are available, the CONTAM Panel noted that the data that were submitted by European countries on PBDEs in food from official food control are in a comparable concentration range as the results published during the last decade in the peer-reviewed literature.

Data on PBDE metabolites in food are scarce and limited to MeO-BDEs in marine food. As OH-PBDEs, specific MeO-PBDEs can be naturally produced by marine organisms, and can also be metabolites of PBDEs. The limited data indicate that the ratio between PBDEs and MeO-PBDEs differs with higher contributions of MeO-PBDEs in mussels and crabs and lower ratios in fish species, where the parent PBDEs dominate. Moreover, the place and season of sampling may have an influence on the respective ratio. Considering the limited information on origin, levels and fate of MeO-BDEs in food, the CONTAM Panel concluded that the data are insufficient to reliably appraise the significance of MeO-PBDEs for human risk assessment.

3.2.3 | Food processing

In the previous Opinion, and based on the limited data available, it was noted that because PBDEs are chemically stable lipophilic substances, reduction of their content in processed foods was mainly associated with loss of fat, rather than degradation. It was also noted at the time that contact of foods with packaging material contaminated with PBDEs may have resulted in elevated contamination of the respective food (EFSA CONTAM Panel, 2011b).

Since then, additional studies have been published that support this overall conclusion, and others that offer some additional information.

Alves et al. (2017) investigated the effects of cooking (steaming at 105°C) on **BDE-47** and **-100** in nine fish and bivalve species. There was a decrease in PBDEs content of mussels after steaming (e.g. **BDE-47** raw 0.360 ng/g ww; steamed 0.180 ng/g ww, $p < 0.05$), whereas in mackerel no changes were observed after steaming after weight loss was taken into account (e.g. **BDE-100**, raw 0.180 ng/g ww, steamed 0.240 ng/g ww, $p > 0.05$).

Mi, Su, et al. (2017) found that heating of freeze-dried fish (at 200°C for 15 min) did not result in any significant effect on the compositions and content of PBDEs (BDE-17, **-28**, **-47**, -66, -71, -85, **-99**, **-100**, **-138**, **-153**, **-154**, **-183, -190**). The mass of PBDEs in the fish decreased during the frying process, consistent with previous findings that small amounts of PBDEs were evaporated from cooked fish. These results indicated that the water present in fish is related to the mass change of organic contaminants including PBDEs during the cooking processes.

Cunha et al. (2021) investigated the impact of the type of smoking process (natural/liquid; hot/cold) and salt (NaCl or KCl) on PBDEs (**BDE-28**, -37, **-47**, -77, **-99**, **-100**, **-153**, **-154**, **-183**, **-209**), and MeO-PBDEs (2-MeO-BDE-68, 6-MeO-BDE-47, 5-MeO-BDE-47, 4-MeO-BDE-49, 5-MeO-BDE-100, 4-MeO-BDE-103, 5'-MeO-BDE-99, 4'-MeO-BDE-101) in smoked salmon. In general, salmon salted with KCl (25 and 50% of NaCl replacement with KCl) led to a reduction in contamination by PBDEs compared to 100% NaCl smoked salmon. Although higher levels of PBDEs were obtained from salmon processed at elevated temperature, the limited number of samples analysed was insufficient to confirm a statistically significant difference.

Hydrodebromination of **BDE-209** as a result of cooking salmon fillets was investigated by Bendig et al. (2012). Heating of fish fortified with **BDE-209** at typical cooking conditions (200°C, in plant oil) resulted in a decrease in concentration associated with the formation of congeners as a result of debromination. After 15 min, about 25% of **BDE-209** was converted to nona- to octa-brominated congeners. The major transformation route was **BDE-209** → BDE-206 → BDE-196 and -199. Small quantities of heptaBDEs as well as one hexaBDF and a heptaBDF isomers were also detected. However, penta- and tetraBDEs were not observed, and in experiments with **BDE-47**, heating did not produce new transformation products. This route of degradation as a result of heating during cooking was confirmed by Li et al. (2017, English abstract available) and is in line with degradation pathways observed in the environment (**Section 1.3.3.1**).

In another study, Bendig et al. (2013) investigated the fate of three PBDEs (BDE-15, **-47**, **-209**) during the cooking of salmon fillets using a model cooking apparatus and a conventional household microwave oven. The model cooking apparatus consisted of a small glass bowl and a glass beaker with an exhaust fitted with a polyurethane foam filter connected to a water jet pump. It was used to cook the fish (1 g), spiked with the three PBDE congeners, with or without sunflower oil (0.2/0.4 g) for 30 min. Small amounts of the semi-volatile PBDEs were found to evaporate from the fish (**BDE-47** < BDE-15), while the less volatile **BDE-209** was partly transformed to congeners with fewer bromine atoms as a result of debromination. Experiments using a household microwave oven gave similar results, except that no transformation was observed for **BDE-209**.

Aznar-Alemany et al. (2017) evaluated the effect of processing and cooking on contaminants, including PBDEs, in seafood. Fourteen samples were analysed before and after cooking, which involved the addition of culinary salt (2% w/w of edible meat) and steaming at 105°C for 15 mins after wrapping in aluminium foil for fish, and for 5 mins for mussels. When present, all individual PBDEs analysed (**BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**, **-183**, **-209**) concentrated by more than 50% during the cooking process, except **BDE-99**, which was concentrated to a lower extent. MeO-PBDEs (6-MeO-BDE-47, 2-MeO-BDE-68, 5-MeO-BDE-47, 4-MeO-BDE-99, 5-MeO-BDE-100, 4-MeO-BDE-100, 5-MeO-BDE-99, 4-MeO-BDE-101) behaved similarly to the parent compounds in cod, mackerel, mussel and salmon, i.e. concentrations increased. Conversely, the levels of these compounds dropped dramatically in seabream and tuna. There was a tendency that cooking decreased the levels of both PBDEs and MeO-PBDEs in plaice, seabream and tuna, but concentrations increased in mackerel. Overall,

the authors concluded that the steaming process concentrates most contaminants of concern, associated with loss of weight of the samples as they were cooked.

Cruz et al. (2020) investigated PBDEs (**BDE-28**, -**47**, -**99**) and MeO-PBDEs (2′-MeO-BDE-68, 6-MeO-BDE-47, 5-MeO-BDE-47, 4-MeO-BDE-49, 5-MeO-BDE-100) in cooked fish. Hake and Atlantic salmon samples were prepared into burgers, fortified with these compounds and cooked using common household practices such as steaming for 10 min, grilling at 155°C for 3 min, and microwaving at 350 W for 1.5 min. In general, no significant differences ($p > 0.05$) were found between individual burgers, except for **BDE-28** in grilled hake ($p > 0.002$), 6-MeO-BDE-47 in microwaved hake ($p = 0.038$), **BDE-28** in microwaved salmon ($p = 0.001$) and 5-MeO-BDE-100 in microwaved salmon ($p < 0.012$). For hake, cooking led to an overall reduction of all tested congeners, ranging from 0.1% to 17.6% for PBDEs, whereas for MeO-PBDEs it varied from 4.3% to 32.3%. In general, steaming did not lead to a significant decrease of contaminant amounts ($p > 0.05$), whereas both grilling and microwaving provided an average reduction of 30% for 2′-MeO-BDE-68. Overall, these practices resulted in up to 32% loss of contaminants, with significant differences between cooking methods and species. The loss was predominantly associated with removal of lipids.

A study including an investigation into the effects of cooking on the levels of eight PBDEs (**BDE-28**, -**47**, -**99**, -**100**, -**154**, -**153**, -**183**, -**209**), eight OH-PBDEs[55] and 13 MeO-PBDEs[56] in artificially contaminated fish (tilapia) and chicken egg was reported by Zhang et al. (2020). The authors investigated boiling and frying for fish, and frying and steaming for egg. It was shown that thermal degradation or transformation of the target compounds did not occur during boiling and frying of fish.

In a study on the metabolism of **BDE-209** in tilapia and its fate during cooking processes (Dong et al., 2014, English abstract available), it was reported that there were no significant differences in the amounts of PBDEs in tilapia before and after boiling or steaming the fish. However, **BDE-209** was degraded into PBDE congeners with fewer bromine atoms as a result of debromination when fish was fried.

Gallistl et al. (2018) investigated the presence of PBDEs (**BDE-28**/33, -**47**, -**99**, -**153**, -**183**, -190, -**209**) and other contaminants, including PCBs, DPs, decabromodiphenyl ethane (DBDPE) and medium-chain chlorinated paraffins (MCCPs), on the inside of 21 household baking oven doors. PBDEs were detected in 82% of the baking oven samples with concentrations ranging between 6.9 and 246,000 ng/g fat. Only three samples (14%) had concentrations for the sum of PBDEs above 2500 ng/g fat, displaying a congener pattern similar to PentaBDE and OctaBDE, and noting that these samples corresponded to baking ovens produced before the phasing out of these technical products in 2004. The median proportion of **BDE-209** (29%) to the sum of PBDEs was lower than observed in kitchen hood fat deposit samples (median: 50%, Bendig et al., 2013) and dishcloths commonly used in kitchens (median: 55%, Gallistl et al., 2017) in Germany, and was also significantly lower than the value reported for settled kitchen floor dust (median: ~95%, Kuang et al., 2016) from the UK.

In some of these studies, the influence of cooking on the bioaccessibility of PBDEs (defined as the PBDE fraction released from the food matrix into the digestive fluids), was investigated using different *in vitro* digestion models. Zhang et al. (2020) concluded that cooking decreased the bioaccessibility of PBDEs, OH-PBDEs and MeO-PBDEs due to protein denaturation, and that the bioaccessibility of OH-PBDEs in pan-fried egg was greater than for steamed egg. Alves et al. (2017) also reported a decrease in the bioaccessibility of PBDEs in steamed mussels and mullet. Mi, Su, et al. (2017) reported an increase in the bioaccessibility of PBDEs from 26% to 63% in raw fish after the addition of oil, although they observed a decrease from 66% to 40% when fish with added oil was cooked.

In summary, studies conducted since the last EFSA Opinion support previous findings. Most changes in concentrations of PBDEs observed during cooking and processing are associated with changes in lipid content and moisture loss. The main exception to this is that it has been shown that during cooking, **BDE-209** can undergo debromination to produce congeners with fewer bromine atoms, in line with degradation pathways observed in the environment (**Section 1.3.3.1**).

Although only a few studies have covered the behaviour of PBDE metabolites, and they indicate that in general MeO-PBDEs behave in the same way as parent PBDE compounds.

The limited information available indicated that cooking may decrease the bioaccessibility of PBDEs, OH-PBDEs and MeO-PBDEs in *in vitro* digestion models. However, the realism of the models has not been verified.

No new reports of the contamination or migration of PBDEs from packaging material were identified.

3.3 | Dietary exposure assessment for humans

3.3.1 | Current dietary exposure assessment

The CONTAM Panel assessed the dietary exposure to PBDEs (**BDE-28**, -**47**, -**49**, -**99**, -**100**, -**138**, -**153**, -**154**, -**183**, -**209**) following the methodology described in **Section 2.5**. A summary of the PBDEs occurrence data including the number of results and mean concentrations across the FoodEx2 level food categories as used for exposure assessment is presented in **Section 3.2.1**.

[55] 4′-OH-BDE-17, 2′-OH-BDE-28, 3-OH-BDE-47, 5-OH-BDE-47, 6-OH-BDE-47, 2′-OH-BDE-68, 4-OH-BDE-90, 6′-OH-BDE-99.

[56] 2′-MeO-BDE-68, 6-MeO-BDE-47, 3-MeO-BDE-47, 5-MeO-BDE-47, 4-MeO-BDE-42, 4′-MeO-BDE-49, 5′-MeO-BDE-100, 4′-MeO-BDE-103, 4-MeO-BDE-90, 5′-MeO-BDE-99, 4′-MeO-BDE-101, 2-MeO-BDE-123, 6-MeO-BDE-137.

3.3.1.1 | *Mean and high dietary exposure*

The mean and 95th percentile chronic dietary exposure to PBDEs (ng/kg bw per day) was estimated separately for each consumption survey using data recorded at the individual level from the Comprehensive Database (see **Section 2.6**). Due to the methodological differences among the surveys, chronic dietary exposure was estimated separately for each of them.

Tables 38 and **39** show the summary statistics for the assessment of chronic dietary exposure to PBDEs. Detailed mean and 95th percentile dietary exposure estimates calculated for all population groups for each of the 47 dietary surveys are presented in **Annex F1–F10** (Tables F1.2 and F1.3 - F10.2 and F10.3). The total dietary exposure was estimated using the LB and UB PBDEs concentrations from each congener separately for all selected food groups.[57]

The highest mean exposure across the European dietary surveys was estimated for **BDE-209** ranging from 0.17 ('Elderly') to 5.98 ng/kg bw per day ('Toddlers) for the minimum LB and the maximum UB, respectively, with a lowest and highest median of 0.24 ('Elderly') and 4.25 ng/kg bw per day ('Toddlers') for LB and UB, respectively. The highest P95 exposure was estimated for **BDE-209** ranging from 0.34 ('Elderly') to 13.46 ng/kg bw per day ('Toddlers') for the minimum LB and the maximum UB, respectively, with a lowest and highest median of 0.47 ('Elderly') and 7.88 ng/kg bw per day ('Toddlers') for LB and UB, respectively.

The next highest exposure estimate was calculated for **BDE-47** with minimum LB and maximum UB means across European surveys for the age group of 'Adults' and 'Very elderly' of 0.08 and for the age group of 'Toddlers' of 1.80 ng/kg bw per day, respectively. For the P95 exposure, the second highest exposure estimated for **BDE-47** with minimum LB and maximum UB for the age group of 'Infants' of 0.01 and the age group of 'Toddlers' of 3.92 ng/kg bw per day, respectively.

For the other eight congeners considered in the assessment, the maximum average UB exposure was calculated always for the age group of 'Toddlers'.

The highest mean exposure to PBDEs at the LB across all congeners was estimated for the age groups of 'Toddlers' and 'Other children' with the same tendency to decrease moving from the younger to the older age groups. However, 'Infants' were the least exposed age group for the LB scenario for all PBDEs except of **BDE-209**.

The daily mean exposure to PBDEs at the UB generally decreases moving from the younger to the older age groups. 'Toddlers' have the highest exposure to all PBDE congeners. The least exposed age group to **BDE-49** and **-138** was 'Infants', whilst for **BDE-47**, and -**209** was 'Adults', and to **BDE-28**, -**99**, -**100**, -**153**, -**154** and -**183** was 'Elderly'.

Dietary exposure in specific groups of the population, namely 'Pregnant women' and 'Lactating women', were within the range of exposure estimates for the adult population (see **Annex F1** to **F10**, Table F.1.2 and F1.3–F10.2 and F10.3).

In the previous Opinion (EFSA CONTAM Panel, 2011b), a scenario for high and frequent fish consumers was estimated as high consumption of fish meat was considered as a special diet with specific concern for dietary exposure to PBDEs. Given that the Comprehensive Database has sufficient number of data that allow more accurate estimation of high percentiles, in the current Opinion the exposure estimations of PBDEs for high and frequent fish meat and fish offal consumers are represented by the 95th percentile and are reported in Table 39.

Based on the only survey on 'Vegetarians' available in the EFSA Comprehensive food consumption database it can be assumed that the dietary PBDE exposure for this population group is lower than for people consuming a mixed diet. This is because PBDEs are persistent and lipophilic compounds with low water solubility that bioaccumulate in the food chain. Thus, consumption of food of animal origin represents the main route of human dietary exposure to PBDEs. The main contributors of the exposure to PBDEs for 'Vegetarians' were foods included in the category 'Animal and vegetable fats and oils and primary derivatives thereof'. Since uptake of PBDEs by plants from soil is low, the contamination of food of plant origin is generally of minor importance. This is substantiated by the occurrence data on PBDEs in food samples of plant origin submitted by European countries which were almost completely below LOD/LOQ.

In the previous Opinion (EFSA CONTAM Panel, 2011b), due to lack of consumption data, an exposure estimation for 'Elderly' and 'Very elderly' was not possible which precludes a comparison with the current assessment. Similarly, the comparison for the age group 'Infants' would not be reliable as the exposure estimates presented in the previous Opinion were based on only two consumption surveys, and therefore not representative for the European infant population, whereas in the current Opinion 10 surveys on infants were considered. As with the current assessment, in the former Opinion the daily exposure of PBDEs decreased moving from the younger to the older age groups. The highest mean exposure across age groups was estimated for **BDE-209** followed by **BDE-47** as is the case for the current exposure assessment. However, values for both congeners are generally lower in the current Opinion. The CONTAM Panel notes that a comparison of the current data with results from the previous Opinion is hampered by a number of facts, such as improvements in instrumental analysis, different percentage of left-censored data, consideration of further food commodities, more occurrence and consumption data submitted to EFSA, and a higher level of stratification of the food categories and age groups.

[57]For the purpose of this Opinion the age group of 'Infants' covers subjects from 3 to < 12 months of age (see **Section 2.4**).

TABLE 38 Mean chronic dietary exposure (ng/kg bw per day) to PBDEs by age group.

		Infants[a]		Toddlers		Other children		Adolescents		Adults		Elderly		Very elderly	
		LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
BDE-28	**Min**	0.00	0.00	0.01	0.60	0.01	0.40	0.01	0.2	0.00	0.17	0.01	0.15	0.01	0.16
	Median	0.00	0.29	0.02	1.03	0.02	0.7	0.01	0.33	0.01	0.24	0.01	0.25	0.01	0.25
	Max	0.01	0.77	0.06	1.34	0.07	1.01	0.03	0.47	0.03	0.31	0.02	0.29	0.03	0.31
BDE-47	**Min**	0.00	0.00	0.17	0.88	0.18	0.57	0.12	0.31	0.08	0.28	0.09	0.25	0.08	0.27
	Median	0.01	0.32	0.36	1.33	0.32	0.99	0.17	0.49	0.14	0.37	0.13	0.38	0.13	0.40
	Max	0.15	0.75	0.57	1.80	0.51	1.41	0.28	0.72	0.24	0.51	0.29	0.54	0.30	0.58
BDE-49	**Min**	0.00	0.00	0.10	0.33	0.09	0.25	0.05	0.10	0.05	0.11	0.05	0.10	0.06	0.09
	Median	0.02	0.02	0.19	0.49	0.16	0.40	0.10	0.22	0.08	0.17	0.08	0.18	0.08	0.19
	Max	0.12	0.20	0.63	1.05	0.66	0.83	0.25	0.42	0.19	0.34	0.13	0.36	0.31	0.36
BDE-99	**Min**	0.00	0.00	0.10	0.77	0.07	0.45	0.07	0.28	0.04	0.23	0.03	0.20	0.04	0.19
	Median	0.01	0.29	0.23	1.09	0.22	0.86	0.11	0.42	0.09	0.30	0.07	0.30	0.07	0.31
	Max	0.06	0.65	0.35	1.50	0.32	1.23	0.19	0.59	0.15	0.39	0.1	0.34	0.11	0.37
BDE-100	**Min**	0.00	0.00	0.02	0.60	0.01	0.45	0.01	0.21	0.01	0.18	0.01	0.16	0.00	0.18
	Median	0.00	0.29	0.05	1.05	0.04	0.70	0.02	0.35	0.02	0.25	0.03	0.27	0.02	0.27
	Max	0.03	0.77	0.11	1.40	0.11	1.03	0.05	0.48	0.05	0.34	0.06	0.31	0.06	0.34
BDE-138	**Min**	0.00	0.00	0.07	0.17	0.05	0.12	0.03	0.05	0.03	0.04	0.03	0.04	0.03	0.05
	Median	0.01	0.01	0.12	0.23	0.11	0.19	0.07	0.10	0.05	0.07	0.05	0.07	0.05	0.07
	Max	0.09	0.12	0.47	0.57	0.49	0.57	0.20	0.23	0.14	0.16	0.11	0.13	0.23	0.25
BDE-153	**Min**	0.00	0.00	0.01	0.70	0.02	0.58	0.01	0.22	0.01	0.19	0.01	0.17	0.01	0.18
	Median	0.00	0.29	0.03	1.09	0.03	0.76	0.02	0.37	0.02	0.25	0.01	0.25	0.01	0.27
	Max	0.01	0.66	0.05	1.37	0.05	1.10	0.04	0.49	0.03	0.32	0.02	0.30	0.02	0.32
BDE-154	**Min**	0.00	0.00	0.02	0.72	0.02	0.57	0.01	0.23	0.01	0.21	0.01	0.17	0.01	0.18
	Median	0.00	0.30	0.06	1.15	0.05	0.75	0.03	0.39	0.03	0.26	0.02	0.26	0.02	0.28
	Max	0.06	0.79	0.42	1.56	0.46	1.32	0.17	0.50	0.14	0.35	0.09	0.34	0.22	0.46
BDE-183	**Min**	0.00	0.00	0.01	0.71	0.01	0.62	0.00	0.24	0.00	0.20	0.00	0.17	0.00	0.26
	Median	0.00	0.24	0.02	1.27	0.02	0.88	0.01	0.42	0.01	0.28	0.01	0.28	0.01	0.31
	Max	0.01	0.74	0.06	1.54	0.06	1.18	0.03	0.56	0.02	0.40	0.02	0.40	0.03	0.45
BDE-209	**Min**	0.00	0.00	0.71	2.76	0.51	2.08	0.22	1.06	0.21	0.87	0.17	0.77	0.18	0.78
	Median	0.27	0.56	0.91	4.25	0.63	3.10	0.41	1.50	0.27	1.11	0.24	1.08	0.26	1.22
	Max	0.56	2.56	1.16	5.98	0.95	4.52	0.51	2.27	0.37	1.49	0.35	1.59	0.36	1.67

Abbreviations: bw, body weight; LB, lower bound; UB, upper bound.

Note: The values are rounded to two decimals.

[a]For the purpose of this Opinion the age group of 'Infants' covers subjects from 3 to < 12 months of age (see **Section 2.4**).

TABLE 39 95th percentile chronic exposures to PBDEs (ng/kg bw per day) by age group.

		Infants[a,b]		Toddlers[a]		Other children		Adolescents[a]		Adults		Elderly		Very elderly[a]	
		LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
BDE-28	**Min**	0.00	0.62	0.03	1.24	0.04	0.95	0.02	0.42	0.01	0.37	0.01	0.34	0.02	0.45
	Median	0.00	0.92	0.09	2.03	0.06	1.38	0.04	0.69	0.03	0.51	0.03	0.52	0.03	0.50
	Max	0.04	3.08	0.14	2.69	0.15	1.96	0.06	0.92	0.06	0.72	0.04	0.8	0.04	0.62
BDE-47	**Min**	0.01	0.63	0.51	1.9	0.58	1.56	0.29	0.74	0.24	0.55	0.26	0.54	0.27	0.63
	Median	0.03	0.97	1.18	2.59	0.95	2.04	0.53	1.07	0.48	0.93	0.45	0.94	0.39	0.85
	Max	0.94	2.50	1.87	3.92	1.34	3.26	0.88	1.54	0.84	1.39	0.74	1.35	0.67	1.17
BDE-49	**Min**	0.03	0.05	0.27	0.82	0.2	0.67	0.14	0.29	0.13	0.26	0.13	0.27	0.13	0.36
	Median	0.12	0.16	0.48	1.39	0.38	1.03	0.22	0.61	0.19	0.56	0.2	0.55	0.19	0.50
	Max	0.51	0.73	1.24	2.72	1.33	2.34	0.49	1.03	0.38	1.03	0.33	1.22	0.40	0.95
BDE-99	**Min**	0.01	0.63	0.34	1.74	0.23	1.03	0.19	0.66	0.11	0.44	0.10	0.39	0.10	0.51
	Median	0.04	0.92	0.74	2.16	0.57	1.62	0.33	0.86	0.24	0.67	0.21	0.61	0.16	0.58
	Max	0.26	2.15	1.10	2.77	0.86	2.07	0.55	1.19	0.47	0.84	0.3	0.84	0.26	0.7
BDE-100	**Min**	0.00	0.63	0.10	1.24	0.03	0.98	0.02	0.43	0.04	0.39	0.05	0.34	0.01	0.41
	Median	0.01	0.93	0.23	2.05	0.18	1.47	0.10	0.71	0.09	0.53	0.10	0.54	0.10	0.52
	Max	0.23	3.11	0.43	2.8	0.34	2.07	0.19	1.03	0.18	0.79	0.18	0.85	0.16	0.68
BDE-138	**Min**	0.02	0.04	0.18	0.30	0.13	0.24	0.08	0.13	0.07	0.10	0.06	0.08	0.07	0.11
	Median	0.09	0.13	0.29	0.45	0.25	0.37	0.16	0.21	0.12	0.16	0.13	0.15	0.11	0.14
	Max	0.35	0.41	0.90	1.05	0.97	1.07	0.38	0.42	0.28	0.31	0.21	0.23	0.31	0.33
BDE-153	**Min**	0.00	0.63	0.04	1.49	0.05	1.08	0.03	0.45	0.02	0.39	0.02	0.34	0.02	0.42
	Median	0.01	0.92	0.09	2.08	0.07	1.45	0.04	0.76	0.04	0.53	0.03	0.53	0.03	0.50
	Max	0.04	2.18	0.13	2.73	0.10	1.91	0.08	0.94	0.06	0.69	0.04	0.77	0.04	0.66
BDE-154	**Min**	0.00	0.63	0.06	1.53	0.06	1.10	0.03	0.51	0.03	0.43	0.03	0.36	0.04	0.47
	Median	0.00	0.92	0.23	2.06	0.18	1.49	0.12	0.75	0.10	0.58	0.08	0.54	0.08	0.55
	Max	0.31	3.16	0.88	2.91	0.98	2.22	0.36	1.03	0.50	0.79	0.50	0.86	0.28	0.70
BDE-183	**Min**	0.00	0.47	0.02	1.55	0.02	1.17	0.01	0.51	0.01	0.43	0.01	0.38	0.01	0.48
	Median	0.00	0.70	0.04	2.29	0.03	1.68	0.02	0.83	0.02	0.60	0.01	0.58	0.01	0.56
	Max	0.05	3.30	0.12	2.90	0.12	2.09	0.05	1.11	0.04	0.75	0.03	0.81	0.04	0.76
BDE-209	**Min**	0.47	1.15	1.27	5.63	1.00	4.00	0.56	2.27	0.41	1.69	0.34	1.49	0.40	1.50
	Median	0.79	1.67	1.77	7.88	1.25	5.39	0.79	2.89	0.57	2.24	0.47	1.88	0.49	2.20
	Max	1.36	11.83	2.17	13.46	1.82	7.83	1.01	4.17	0.76	3.20	0.72	3.09	0.67	3.43

Abbreviations: bw, body weight; LB, lower bound; UB, upper bound.

Note: The values are rounded to two decimals.

[a]The 95th percentile estimates obtained on dietary surveys/age groups with fewer than 60 observations may not be statistically robust (EFSA, 2011a) and are therefore not included in this table.

[b]For the purpose of this Opinion the age group of 'Infants' covers subjects from 3 to < 12 months of age (see **Section 2.4**).

3.3.1.2 | *Contribution of different food categories to the chronic dietary exposure*

The relative LB and UB contribution (%) of each individual food category to the total mean chronic dietary exposure of the 10 PBDE congeners was estimated across dietary surveys and is presented in **Annex F1–F10** (Table F1.4–F10.4 and Figures F1.1–F10.1).

Dietary exposure reflects the pattern of consumption figures of each age class and the respective country as well as occurrence values. When a high proportion of left-censored data produces a large difference between LB and UB occurrence values, this results in a commensurate uncertainty in dietary exposure estimates. Appraising the contribution of the respective food groups to the total LB exposure is based on measured values not influenced by the percentage and magnitude of the left-censored data. Appraising the contribution of food groups to the total UB dietary exposure should be done with care as the high contribution of certain food groups can be artificially driven by the treatment of the left-censored data.

Table 40 describes the relative contribution (%) of each food category to the overall mean LB exposure to PBDEs as median and range (minimum and maximum) for all age class across all European dietary surveys.

The highest relative contribution (35%) of the mean LB dietary exposure of **BDE-28** was due to the consumption of 'Meat and meat products', followed by 'Fish, seafood, amphibians, reptiles and invertebrates'.

'Fish, seafood, amphibians, reptiles and invertebrates' contributed the most to the dietary exposure of **BDE-47** with a median to the overall LB exposure equal to 46%, followed by 'Meat and meat products' with 31% across European countries and surveys.

The highest relative contribution to the LB dietary exposure of **BDE-49** and **-138** was due to the consumption of 'Animal and vegetable fats and oils and primary derivatives thereof' with 81% and 91%, respectively.

In the case of **BDE-99** and **-153**, the main food category contributing to the LB dietary exposure was 'Meat and meat products' with 69% and 56% respectively. The same food category was the highest source to the exposure of **BDE-183** and **-209** too, but with lower relative contributions of 32% and 44% respectively.

'Fish, seafood, amphibians, reptiles and invertebrates' was the main contributor to the LB exposure of **BDE-100** (74%).

For **BDE-154**, the main food categories that contributed to the LB exposure were 'Animal and vegetable fats and oils and primary derivatives thereof' and 'Fish, seafood, amphibians, reptiles and invertebrates' with almost the same relative contribution to the dietary exposure, with 35% and 34%, respectively.

In the previous Opinion (EFSA CONTAM Panel, 2011b), the relative contribution of the FoodEx (Level 1) categories to the overall mean dietary exposure to PBDEs was presented as minimum and maximum only at the UB for eight congeners (i.e. **BDE-49** and **-138** were not included in the previous assessment). Given that the UB values are mainly driven by the left censored data, a comparison with the UB values from the current Opinion would not be reliable. In addition, and as stated previously, a comparison of the current data with results from the previous Opinion is hampered by a number of facts, such as improvements in analytical methods resulting in a different percentage of left-censored data, consideration of further food commodities, more occurrence and consumption data submitted to EFSA, and a higher level of stratification of the food categories and age groups. Thus, comparison should be interpreted with caution.

TABLE 40 Relative contribution (%) of the FoodEx2 (Level 1) categories to the overall mean dietary exposure to PBDEs (LB) across different surveys and population groups.

	BDE-28			BDE-47			BDE-49			BDE-99			BDE-100		
FoodEx2 level 1	**Min**	**Median**	**Max**	**Min**	**Median**	**Max**	**Min**	**Median**	**Max**	**Min**	**Median**	**Max**	**Min**	**Median**	**Max**
Legumes, nuts, oilseeds and spices	0.0	0.0	0.1	0.0	0.0	0.1				0.0	0.0	0.1	0.0	0.0	0.1
Meat and meat products	0.2	35.1	77.3	0.4	30.5	67.5	0.0	2.8	10.0	2.7	68.8	90.1	0.1	9.5	49.5
Fish, seafood, amphibians, reptiles and invertebrates	1.1	34.5	77.7	2.6	45.5	84.1	0.5	13.9	57.9	0.8	13.7	52.4	22.7	73.8	94.1
Milk and dairy products	0.1	1.9	54.7	0.0	4.6	51.7	0.0	0.9	5.6	0.1	8.0	73.9	0.1	4.8	89.7
Eggs and egg products	0.0	0.9	3.5	0.0	1.8	9.3	0.0	0.3	0.8	0.1	4.1	48.3	0.0	3.9	47.1
Sugar and similar, confectionery and water-based sweet desserts				0.1	0.5	4.5				0.0	0.3	2.1	0.0	0.0	0.3
Animal and vegetable fats and oils and primary derivatives thereof	0.3	17.6	97.2	0.4	6.9	82.1	38.1	80.5	100.0	0.5	2.3	38.3	0.1	2.1	36.7
Food products for young population	0.0	0.0	100.0	0.0	0.0	100.0				0.0	0.0	100.0	0.0	0.0	100.0
Products for non-standard diets, food imitates and food supplements	0.0	0.1	19.8	0.0	0.1	13.9				0.0	0.0	3.2	0.0	0.1	18.2
Composite dishes	0.0	0.7	10.1	0.0	0.5	6.0	0.0	0.2	2.7	0.0	0.3	4.5	0.0	2.5	26.1

	BDE-138			BDE-153			BDE-154			BDE-183			BDE-209		
FoodEx2 level 1	**Min**	**Median**	**Max**	**Min**	**Median**	**Max**	**Min**	**Median**	**Max**	**Min**	**Median**	**Max**	**Min**	**Median**	**Max**
Legumes, nuts, oilseeds and spices				0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.2
Meat and meat products	0.0	3.2	13.1	1.2	55.7	85.2	0.0	5.7	56.0	0.0	31.9	82.5	0.4	43.9	60.4
Fish, seafood, amphibians, reptiles and invertebrates	0.0	2.2	22.8	1.3	18.0	60.1	0.4	33.9	88.2	0.1	5.3	23.6	0.1	4.3	23.8
Milk and dairy products	0.0	0.6	4.2	0.1	8.6	65.9	0.1	1.9	24.4	0.2	10.2	74.2	0.0	16.2	49.7
Eggs and egg products	0.0	0.6	1.9	0.1	7.1	58.7	0.0	1.4	4.5	0.0	9.0	29.4	0.0	11.9	42.0
Sugar and similar, confectionery and water-based sweet desserts				0.0	0.0	0.3				0.1	1.9	12.0	0.8	6.4	28.7
Animal and vegetable fats and oils and primary derivatives thereof	74.1	91.0	100.0	0.4	3.1	49.6	0.2	34.7	98.7	1.5	19.4	86.4	0.4	9.1	29.1
Food products for young population				0.0	0.1	100.0	0.0	0.0	100.0	0.0	0.2	100.0	0.0	1.1	100.0
Products for non-standard diets, food imitates and food supplements				0.0	0.0	3.1	0.0	0.0	20.0	0.0	0.0	0.4	0.0	0.0	0.7
Composite dishes	0.0	0.0	0.9	0.0	0.9	11.5	0.1	15.4	83.3	0.0	0.7	24.3	0.0	0.2	3.3

3.3.1.3 | *Formula fed infants*

For infant formula only scarce data on PBDE contamination were submitted to EFSA. Infant formula reported as solid were reclassified to their liquid form applying a dilution factor of 8 (EFSA, 2018) in alignment with the consumption data.

The number of results for each congener ranged between 5 and 33, and the percentage of left-censored data between 31 and 100%. For **BDE-49** and **-138**, less than six sample results were reported which were all left-censored and thus not further considered in this scenario.

The results for the remaining eight PBDE congeners **BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**, **-183** and -**209** are summarised in Table 41 (as well as in **Annex F1**, **F2**, **F4**, **F5**, **F7**, **F8**, **F9** and **F10**, Tables F1.1, F2.1, F4.1, F5.1, FD7.1, F8.1, F9.1 and F10.1). The table shows the number of samples obtained for each congener together with the respective percentage of left-censored data, and the minimum, mean and maximum levels, calculated as LB and UB concentrations. As illustrated in the table, the differences between the LB and UB concentrations are substantial. The LB concentrations ranged between 0 and 0.006 (**BDE-209**) μg/kg ww, and the UB concentrations between < 0.001 and 0.028 (**BDE-209**) μg/kg ww.

TABLE 41 Lower bound (LB) and upper bound (UB) values in μg/kg for infant formula (liquid and reconstituted to liquid form) submitted to EFSA.

Congeners[a]			LB (μg/kg ww)			UB (μg/kg ww)[a]		
	N	LC (%)	Min	Mean	Max	Min	Mean	Max
BDE-28	33	91	0	0.00000083	0.000011	0.00000088	0.0055	0.017
BDE-47	33	67	0	0.000021	0.00013	0.000025	0.0055	0.017
BDE-99	33	67	0	0.000014	0.000075	0.000025	0.0055	0.017
BDE-100	33	85	0	0.0000014	0.000011	0.00000088	0.0055	0.017
BDE-153	33	70	0	0.0000050	0.000025	0.00000088	0.0055	0.017
BDE-154	33	79	0	0.0000014	0.000010	0.00000088	0.0055	0.017
BDE-183	28	61	0	0.000014	0.000075	0.000013	0.0042	0.016
BDE-209	16	31	0	0.0021	0.0062	0.001	0.0066	0.028

[a]: For **BDE-49** and **-138**, less than six sample results were reported which were all left-censored and thus not further considered in this scenario.

Consumption data of infant formula across European countries are limited. Therefore, the CONTAM Panel used the data published in the Guidance of the EFSA Scientific Committee (SC) on the risk assessment of substances present in food intended for infants below 16 weeks of age (EFSA Scientific Committee, 2017c). For assessing the exposure to substances with a long half-life, which therefore accumulate in the body, the EFSA Guidance recommended to use 170 and 210 mL/kg bw for mean and P95 consumption, respectively, for infants around 2 months (with a body weight of 5 kg[58]). This would lead to daily consumption values of 850 mL for mean consumption, and of 1050 mL for high consumption. The exposure estimates based on these recommended consumption levels and on the minimum, mean and maximum LB and UB concentrations determined in the infant formula samples are shown in Table 42. For the exposure estimation, the occurrence data on the infant formula samples given by the data provider as μg/kg were converted to μg/L assuming a density of 1, which is a small error which gives rise to negligible additional uncertainty in the exposure estimates.

The exposure scenario based on mean infant formula consumption and the mean LB and UB concentrations of the eight PBDEs would result in daily exposure estimates between 0.0001 (**BDE-28**) and 0.35 (**BDE-209**) ng/kg bw at the LB, and between 0.71 (**BDE-183**) and 1.13 (**BDE-209**) ng/kg bw at the UB. The exposure scenario based on P95 infant formula consumption and the mean LB and UB concentrations of the eight PBDEs would result in daily exposure estimates between 0.0002 (**BDE-28**) and 0.43 (**BDE-209**) ng/kg bw at the LB, and between 0.88 (**BDE-183**) and 1.39 (**BDE-209**) ng/kg bw at the UB.

The highest LB and UB daily PBDE exposures through mean and P95 formula consumption were calculated for **BDE-209**, with exposures of 1.05 and 4.76, and 1.30 and 5.88 ng/kg bw, respectively.

[58]According to the EFSA Guidance on selected default values for European infants, aged 0–12 months (EFSA Scientific Committee, 2012).

TABLE 42 Exposure for formula fed infants to eight PBDEs[a] based on the occurrence levels in infant formula submitted to EFSA and mean and P95 consumption values recommended by the EFSA Scientific Committee (2017c).

Exposure estimates, LB mean consumption (ng/kg bw per day)								
	BDE-28	**BDE-47**	**BDE-99**	**BDE-100**	**BDE-153**	**BDE-154**	**BDE-183**	**BDE-209**
Min	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Mean	0.0001	0.0035	0.0023	0.0002	0.0009	0.0002	0.0024	0.3506
Max	0.0019	0.0213	0.0128	0.0019	0.0043	0.0017	0.0128	1.0540
Exposure estimates, UB mean consumption (ng/kg bw per day)								
	BDE-28	**BDE-47**	**BDE-99**	**BDE-100**	**BDE-153**	**BDE-154**	**BDE-183**	**BDE-209**
Min	0.0001	0.0043	0.0043	0.0001	0.0001	0.0001	0.0021	0.1870
Mean	0.9355	0.9388	0.9376	0.9355	0.9361	0.9355	0.7135	1.1263
Max	2.8581	2.8581	2.8581	2.8581	2.8581	2.8581	2.6775	4.7600
Exposure estimates, LB P95 consumption (ng/kg bw per day)								
	BDE-28	**BDE-47**	**BDE-99**	**BDE-100**	**BDE-153**	**BDE-154**	**BDE-183**	**BDE-209**
Min	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Mean	0.0002	0.0044	0.0029	0.0003	0.0011	0.0003	0.0030	0.4331
Max	0.0024	0.0263	0.0158	0.0024	0.0053	0.0021	0.0158	1.3020
Exposure estimates, UB P95 consumption (ng/kg bw per day)								
	BDE-28	**BDE-47**	**BDE-99**	**BDE-100**	**BDE-153**	**BDE-154**	**BDE-183**	**BDE-209**
Min	0.0002	0.0053	0.0053	0.0002	0.0002	0.0002	0.0026	0.2310
Mean	1.1556	1.1597	1.1582	1.1557	1.1564	1.1556	0.8813	1.3913
Max	3.5306	3.5306	3.5306	3.5306	3.5306	3.5306	3.3075	5.8800

[a]As less than six sample results for **BDE-49** and -**138** were reported which were all left-censored, they were not further considered in this estimation.

3.3.1.4 | *Breastfed infants*

For the exposure assessment of breastfed infants, an age of 3 months was selected, equivalent to a weight of about 6.1 kg, with an estimated average daily consumption of 800 mL and a high consumption of 1200 mL of human milk, with a mean fat content of 3.5%. The occurrence data were taken from European pooled milk samples that were collected and analysed as part of the WHO/UNEP field studies between 2014 and 2019. These data were extracted from Table 11 (see **Section 3.1.1.4.1**), which shows the results of all samples that were part of the WHO/UNEP filed studies 2001–2019.

Table 43 shows the minimum, mean, median and maximum concentrations of **BDE-28**, -**47**, -**49**, -**99**, -**100**, -**138**, -**153**, -**154**, -**183** and -**209** in the pooled human milk samples from 2014–2019. Based on the above assumptions, the congener-specific exposure of breastfed infants to the 10 PBDEs was calculated. There is virtually no difference between LB and UB values. As a conservative approach the concentrations are given as UB values.

TABLE 43 Occurrence levels in pooled human milk samples from European countries collected and analysed between 2014 and 2019 within the WHO/UNEP field studies.

PBDEs in pooled human milk samples (μg/kg lipid)										
	BDE-28	**BDE-47**	**BDE-49**	**BDE-99**	**BDE-100**	**BDE-138**	**BDE-153**	**BDE-154**	**BDE-183**	**BDE-209**
N	16	16	7	16	16	16	16	16	16	6
Minimum	0.009	0.185	0.003	0.043	0.057	0.002	0.120	0.006	0.013	0.094
Mean	0.025	0.353	0.007	0.122	0.104	0.007	0.354	0.015	0.035	0.281
Median	0.021	0.326	0.007	0.091	0.091	0.010	0.303	0.012	0.027	0.140
Maximum	0.050	0.750	0.010	0.550	0.180	0.010	0.822	0.050	0.090	0.884

Abbreviations: *N*: number of pooled samples.

The exposure scenario based on average human milk consumption and the median concentrations of the 10 PBDEs would result in an exposure between 0.03 (**BDE-49**) and 1.50 (**BDE-47**) ng/kg bw per day (Table 44). The highest PBDE exposures through average human milk consumption were calculated for **BDE-209**, -**153**, -**47** and -**99** with exposure estimates of 4.06, 3.77, 3.44 and 2.52 ng/kg bw per day, respectively.

For infants with high human milk consumption, the exposures would be around 50% higher, i.e. median exposure estimates between 0.05 (**BDE-49**) and 2.25 (**BDE-47**) ng/kg bw per day, and highest exposure estimates of 6.09, 5.66, 5.16 and 3.79 ng/kg bw per day for **BDE-209**, -**153**, -**47** and -**99**, respectively.

The CONTAM Panel noted that since the analysed human milk samples were pooled samples, it was not possible to estimate specific values for individuals.

TABLE 44 Exposure for breastfed infants to 10 PBDEs based on the occurrence levels in pooled human milk from Europe collected and analysed between 2014 and 2019.

Exposure estimates (ng/kg bw per day, average consumption)										
	BDE-28	**BDE-47**	**BDE-49**	**BDE-99**	**BDE-100**	**BDE-138**	**BDE-153**	**BDE-154**	**BDE-183**	**BDE-209**
Minimum	0.04	0.85	0.01	0.20	0.26	0.01	0.55	0.03	0.06	0.43
Median	0.10	1.50	0.03	0.42	0.42	0.05	1.39	0.06	0.13	0.64
Maximum	0.23	3.44	0.05	2.52	0.83	0.05	3.77	0.23	0.41	4.06
Exposure estimates (ng/kg bw per day, high consumption)										
	BDE-28	**BDE-47**	**BDE-49**	**BDE-99**	**BDE-100**	**BDE-138**	**BDE-153**	**BDE-154**	**BDE-183**	**BDE-209**
Minimum	0.06	1.27	0.02	0.29	0.39	0.01	0.83	0.04	0.09	0.65
Median	0.14	2.25	0.05	0.63	0.63	0.07	2.09	0.08	0.19	0.96
Maximum	0.34	5.16	0.07	3.79	1.24	0.07	5.66	0.34	0.62	6.09

Abbreviation: bw: body weight.

3.3.2 | Previously reported dietary exposure

In 2011, the CONTAM Panel assessed the congener-specific chronic dietary exposure for eight PBDE congeners using the occurrence data submitted to EFSA at that time, and also summarised the studies on dietary assessment available in the peer-reviewed literature until then (EFSA CONTAM Panel, 2011b).

The following paragraphs, which do not claim to be comprehensive, give a short general overview on assessments on human dietary exposure to PBDEs in European countries published in peer-reviewed open literature since the previous EFSA Opinion on PBDEs. Only those studies were considered where the underlying sampling of the food items was from 2010 onwards. In **Appendix G** (Table G.1) these studies are summarised with the underlying occurrence data. A direct comparison of the published data is hampered by the choice of the assessment methodology, the food categories considered, the different number of PBDE congeners measured, and the diverse limits of detection in combination with the respective treatment of the left-censored data.

For exposure estimations, total diet studies (TDS) and duplicate diet studies give valuable information on dietary exposure to food chemicals, as the food sampling is analysed as consumed, thus including potential changes during food processing. These approaches are particularly suitable for estimating chronic dietary exposure (EFSA, FAO, WHO, 2011; WHO, 2019).

Rivière et al. (2019) reported exposure estimations from a total diet study (TDS) covering 705 children aged 1–36 months and including 205 samples among which 36 were common food samples and 169 infant food samples. Among other contaminants eight PBDE congeners were analysed (**BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183** and -**209**). The UB mean exposure to **BDE-209** ranged from 1.12 to 2.62 ng/kg bw per day across age groups. For the sum of the other seven PBDEs (without **BDE-209**), the mean UB exposures ranged from 0.448 to 0.926 ng/kg bw per day.

Duplicate diet studies concerning exposure to PBDEs were for example conducted by Xu, Tay, et al. (2017), Coelho, Sousa, Isobe, Kunisue, et al. (2016), De Filippis et al. (2014) and Bramwell, Harrad, et al. (2017).

Xu, Tay, et al. (2017) collected 24 h duplicate diets from a cohort of 61 Norwegians and analysed them for 9 PBDE congeners and further POPs. While **BDE-47** and -**209** were the most frequently detected PBDEs in the duplicate diet samples with detection frequencies of 57% and 54%, respectively, the detection frequency of the other congeners was low (< 10%). **BDE-209** was the major PBDE congener with a median of 0.045 ng/g ww, followed by **BDE-47** (median 0.010 ng/g ww). The dietary exposure was calculated for each individual participant using the concentrations measured in the respective 24 h duplicate diet samples and individual personal body weight information. Congeners < LOD were assigned the value zero in the exposure estimation. Median exposure estimates (95th Percentiles) for **BDE-47**, -**209** and the sum of 9 PBDEs were estimated as 0.20 (1.4), 0.86 (12), and 1.3 (14) ng/kg bw per day, respectively. No gender differences were observed.

Similar results were reported by Coelho, Sousa, Isobe, Kunisue, et al. (2016) who collected 7-day duplicate diets from 21 volunteers at an academic community in Aveiro/Portugal. The exposure of the sum of the eight PBDEs considered to be of primary interest in the previous Opinion ranged between 0 and 8.7 ng/kg bw per day for the LB and between 1.5 and 11 ng/kg bw per day for the UB, with LB and UB median values of 0.98 and 2.7 ng/kg bw per day, respectively.

Various duplicate diet samples accounting for the diverse eating habits of toddlers (9–12 months), children (4–9 years) and adults (18–64 years) were collected by De Filippis et al. (2014) across Italy, homogenised and pooled into 17 composites depending on the food type for the different age classes. Dietary exposure was estimated from the resulting contaminant levels in composites combined with age-related food consumption data from a national survey. The average LB–UB ranges of dietary exposure to the sum of the same eight PBDE congeners as above for toddlers, children and adults were 23.36 (no range reported), 0.00–7.38 and 0.00–3.4 ng/kg bw and day, respectively. **BDE-209** was not detected in any of the 17 composites. As the contribution of this congener made up ~ 80%–90% to the UB sum of the PBDE concentration, the CONTAM Panel considers the calculated UB exposure an overestimation.

Bramwell, Harrad, et al. (2017) investigated dietary and non-dietary human exposure to BDE-17, -**28**, -**47**, -**49**, -66, -71, -77, -85, -**99**, -**100**, -119, -126, -**138**, -**153**, -**154**, -**183** and -**209** in a cohort of 20 UK adults. The PBDE congeners were measured in 24 duplicate diets, and the exposure estimates compared with occurrence in dust combined with a dust ingestion of 20 mg/day. All PBDEs except **BDE-209** were measurable in all of the duplicate diet samples, and **BDE-209** in 79% of them. PBDE concentrations in the 24 h duplicate diets were converted to daily dietary exposure estimates which ranged from 82 to 1320 pg/kg bw for the sum of the measured PBDEs except **BDE-209**, and < 0.8–1860 pg/kg bw for **BDE-209**. **BDE-209** made up a median of 73% of the total PBDE exposure from diet. While dust was by far the greatest source for total and non-dietary **BDE-209** exposure, diet represented the major contribution to total PBDE exposure for the other measured congeners, making up a median of 85% (see also **Section 3.3.3**).

Based on the results in raw commodities of individual or pooled food commodities, the exposure estimation is mostly performed using a deterministic approach by multiplying the mean PBDE occurrence level in a food type by the mean, maximum or 95th percentiles of the consumption. Less authors perform probabilistic exposure assessments taking into consideration the variability in food consumption between and within individuals and in occurrence of PBDEs in different food commodities. Such an approach considers the whole distribution of exposure, from minimum to maximum and corresponding percentiles.

Pardo et al. (2014) estimated the dietary exposure of PBDEs via fish and seafood in the Region of Valencia (Spain). PBDE levels were determined in a total of 206 samples. Consumption data were extracted from the first Valencian Food Consumption Survey, conducted in 2010. The authors performed a deterministic as well as a probabilistic exposure assessment and compared the two approaches. The analytical determination covered 12 PBDE congeners. **BDE-209** was not included. Using a deterministic approach, the estimated mean LB and UB dietary exposure estimates for the sum of the 12 PBDEs were 0.093 and 0.178 ng/kg bw per day for adults, and 0.101 and 0.196 ng/kg bw per day for children. The related 95th percentiles amounted to 0.389 and 0.551, and 0.377 and 0.72 ng/kg bw per day, respectively. The results of the probabilistic assessment were similar, although in some cases they were slightly lower.

Further results of exposure estimations based on specific food commodities of animal and plant origin from different EU countries performed by deterministic models are depicted in **Appendix G** (Table G.1).

Numerous studies on PBDE exposure in non-European countries were published in the past decade. As already mentioned in **Section 3.2.2**, the PBDE profiles and concentrations in food samples from different areas in the world substantially vary, and thus do the resulting dietary exposures. The exposure is also related to the length and extent of use of the different technical PBDE products and the time since their phasing out, which is globally diverse. Non-proper operated e-waste recycling sites and dump sites are especially problematic, as considerably elevated PBDE exposures were estimated in these areas (Cai et al., 2020; Fan et al., 2021; Hong et al., 2014; Lupton & Hakk, 2017; Minh et al., 2016; Oloruntoba et al., 2019; Sharma et al., 2021; Zeng et al., 2016; Zhixiong et al., 2017).

Taking into account the different methodologies applied for the exposure estimations in combination with the different congeners considered (either congener-specific or sums of varying congeners), and the number and type of food categories contemplated, the CONTAM Panel concluded that the dietary exposure estimates published in the peer reviewed literature are in general accordance with the exposure estimates performed by EFSA based on the occurrence data submitted by the European countries. The CONTAM Panel considered the exposure estimates published in the open literature on OH- and MeO-PBDEs too limited to draw any reliable conclusions.

Several studies focused on the share and importance of dietary vs. non-dietary human exposure to PBDEs. These studies are summarised in **Section 3.3.3**

3.3.3 | Non-dietary sources of exposure

Non-dietary exposure to PBDEs is predominantly from oral exposure of dust, although exposure can also occur via inhalation of gas-phase PBDEs and PBDEs on particles. Dermal exposure has been estimated to provide only a very small relative contribution to the overall exposure for most adults; with smaller molecules achieving faster dermal penetration, and larger molecules demonstrating greater accumulation within the skin tissue (Abdallah et al., 2015). Watkins et al. (2011) measured PBDEs in handwipes and in office dust and found a weak association, but did not estimate dermal exposure as a result of using the wipes. Yu, Ru, et al. (2021) investigated brominated and phosphate flame retardants from interior and surface dust of personal computers as potential sources for human dermal exposure, and found no significant correlation between interior dust and PC surfaces except for **BDE-183**. Exposure assessment results demonstrated a minor contribution from PC dermal contact, compared with hand-to-mouth uptake, to total exposure, meaning that uptake from inhalation of dust is still considered the largest contributor to non-dietary exposure for most of the population.

The previous Opinion identified that house and car dust can be important routes of exposure, especially for children to **BDE-209** (EFSA CONTAM Panel, 2011b). The exposure estimates reported in that Opinion suggested that whilst the ranges of exposure estimated for dust were much greater than the ranges estimated for dietary exposure, they were broadly similar in terms of contribution, although there were differences in relative contributions for different congeners. Children were likely to ingest higher amounts of dust than adults because of, e.g. increased hand to mouth contact.

Since the previous Opinion was published, there have been several reports of PBDEs in dust. Those reporting levels in dust from European countries are summarised in **Appendix B**. Great care needs to be taken when making comparisons, not only because of the differences in congeners measured, but also because of differences in sampling of dust (e.g. use of vacuum, type/power of vacuum, collection time) and in the locations from which dust was collected (e.g. office, home,

car environment). There are also some studies that have attempted to estimate exposure to PBDEs from dust, and these studies are the focus of the following paragraphs.

Roosens et al. (2010) investigated the exposure of the Flemish population to a range of BFRs. The average exposure for the median exposed individuals to the sum of PBDEs (**BDE-47**, **-99**, **-100**, **-153**, **-154**) and **BDE-209** through dust was 0.14 and 1.5 ng/kg bw per day for children less than 1 year of age, and decreased to 0.005 and 0.035 ng/kg bw per day for adults. These estimations were done considering median dust ingestion rates of 42 and 7 mg per day for children and adults, respectively.

Abdallah and Harrad (2014) estimated the exposure of PBDEs from dust and compared this with exposure from other sources and body burden. The average and median exposure estimates from dust to the sum of PBDEs (**BDE-47**, **-99**, **-100**, **-153**, **-154**) were 3.7 and 1.2 ng per day, respectively (note not converted to body weight basis), considering an average adult dust ingestion rate of 20 mg per day. This dust exposure was small compared with the dietary exposure, where both average and median values were 80 ng per day. Exposure from air was lower with values of 1.7 and 0.55 ng per day, respectively. The estimates for **BDE-209** were much higher, being 4270 and 2975 ng per day, for average and median exposure from dust, respectively.

Exposure to PBDEs from house dust and air in Poland was reported by Król et al. (2014). Two exposure scenarios, mean and 95th percentile, were used to assess exposure resulting from ingestion of household dust by toddlers (considering dust ingestion rates of 50 and 200 mg per day, respectively) and for adults (20 and 50 mg per day, respectively). The estimated dust exposure for the sum of PBDEs (**BDE-28**, **-47**, **-99** and **-209**) varied from 21 to 92 ng per day in toddlers, and from 3.7 to 20 ng per day in adults (note that these exposure estimates were not adjusted for body weight).

Cequier et al. (2015) investigated associations between serum concentrations of emerging and legacy halogenated flame retardants in 46 Norwegian women and measured indoor air and dust concentrations of these compounds and compared them with detailed information on diet and household factors. The most abundant PBDEs were **BDE-153** (median 0.82 ng/g lipid) and **BDE-47** (median 0.49 ng/g lipid) which were detected in more than 70% of the samples. In a bivariate analysis, no consistent associations were observed between the biomonitoring data and measured concentrations in indoor air and dust. A multivariate linear regression model showed associations mainly between dietary factors (lamb, margarine and lean fish) and serum levels of **BDE-47**, **-153** and sum 7 PBDEs, showing that in this study group, food plays a more important role in the exposure to PBDEs than indoor air and dust or other household factors.

Sahlström et al. (2015a) estimated exposure of BFRs from diet and dust samples collected in 2009–2010 and compared this to internal concentrations in a Swedish mother-toddler cohort. Octa-decaBDE congener concentrations in serum and faeces of toddlers were significantly correlated to those in in-house dust, while BDE-207 and -208 concentrations in serum of mothers were significantly correlated with the nonaBDEs in house dust. The correlations between house dust and internal concentrations and comparison of the house dust and dietary contributions to the estimated daily exposure estimates suggested that dust exposure played a larger role for octa-decaBDE body burden in toddlers than in their mothers. The estimated median (range) daily exposure of the sum of PBDEs from dust for Swedish mothers ($n = 20$) was 12 (5.5–9300) ng per day, considering a dust ingestion rate of 30 mg per day. For toddlers ($n = 20$) the values were 23 (11–19,000) ng per day, considering a dust ingestion rate of 60 mg per day (note that the values are not on a body weight basis). The results indicated that diet was the most important exposure pathway for tri-octaBDEs in mothers. Dust ingestion was estimated to be the main exposure route for **BDE-209** in mothers and for octa-decaBDE congeners in toddlers.

Coelho, Sousa, Isobe, Kim, et al. (2016) measured a range of contaminants in house dust and found that phosphorus-based flame retardants were found at highest concentrations followed by PBDEs (see **Section 1.3.3**, Figures 2, 3 and 4). Human exposure through dust ingestion was estimated considering dust ingestion rates of 100 mg per day for adults and 200 mg per day for children, which reflect worst-case scenarios. Median exposure estimates to the sum of PBDEs were 0.49 and 5.7 ng/kg bw per day for adults and children, respectively.

Bramwell, Harrad, et al. (2017) estimated PBDE exposure via dust by combining measured dust PBDE concentrations at various sites frequented by study volunteers at different locations where they spent time, e.g. occupation and home environments. The time spent at each location was taken from an activity diary and exposures were estimated considering both average (20 mg per day) and high (50 mg per day) adult dust ingestion rates. Although dust ingestion rates may differ between microenvironments and activities (as well as individuals), for the purpose of this study it was assumed that dust ingestion occurred pro-rata to the proportion of time spent in each microenvironment during the study week. The ranges of PBDE exposure estimates via dust (average and high, respectively) for the study participants was 0.014–1.01 and 0.035–2.52 ng/kg bw per day for the sum of PBDEs, and 0.28–15.9 and 0.7–39.6 ng/kg bw day for **BDE-209**. The study concluded that diet was the major source of PBDEs with 3–7 bromine atoms comprising a median of 85% of the total exposure when using duplicate diet data combined with the average dust ingestion estimate of 20 mg per day. Dust, however, was the greatest source of exposure to **BDE-209**, with median exposure estimates comprising 75% and 88% of the total **BDE-209** exposure for average and high dust ingestion rates, respectively.

Human exposure to a range of flame retardants via dust ingestion from Norwegian and UK indoor environments was reported by Kademoglou et al. (2017). From the nine PBDE congeners analysed (**BDE-28**, **-47**, -66, -85, **-100**, **-153**, **-154**, **-183** and **-209**), **BDE-209** was the most abundant one with median concentrations of 4700 ng/g and 3400 ng/g in UK occupational and house dust, respectively, which was 30- and 20-fold higher than concentrations measured in Norwegian house dust. The worst-case dust exposure scenario was for British toddlers with estimates for the sum of nine PBDEs of 890 ng/kg bw per day, and for **BDE-209** of 820 ng/kg bw per day (considering a high dust ingestion rate of 200 mg per day). Norwegian toddlers showed lower exposure levels.

Exposure to PBDEs from dust was estimated in a study by Tay et al. (2019) to compare external exposure with serum concentrations of a range contaminants in a Norwegian cohort. Average exposure from dust for **BDE-47**, **-153**, -197 and **-209**

were estimated at 0.015, 0.001, 0.001 and 0.023 ng/kg bw per day, respectively, and median exposures were estimated to be 0.007, 0.0007, 0.0005 and 0.014 ng/kg bw per day, respectively, considering an adult dust ingestion of 30 mg per day. The results suggested that exposure via diet was the most important exposure pathway for **BDE-47** and -**209**, being responsible for more than 96% of the total daily exposure of these two PBDEs in the Norwegian cohort.

Sugeng et al. (2020) examined links between toddler behaviour, the home environment, and exposure to flame retardants. The child's behaviour was observed and assessed using a questionnaire. Hand-to-mouth exposure estimates were estimated to be 0.22 and 4.2 ng/kg bw per day for **BDE 209** based on the hand-to-mouth contact frequency and hand wipe **BDE-209** levels for the 50th and 95th percentile, respectively.

Several classes of flame retardant were measured in household dust from Belgium, Italy and Spain by De la Torre et al. (2020). It was found that the contamination pattern was dominated by organo-phosphorus flame retardants (median 12,800 ng/g) followed in decreasing order by PBDEs (229 ng/g), decabromodiphenyl ethane (130 ng/g), 1,2-bis(2,4,6-tribromophenoxy)ethane (1.35 ng/g), hexabromobenzene (0.28 ng/g) and finally pentabromoethylbenzene (0.03 ng/g). PBDEs were quantified > LOQ in all samples with data ranging from 4.32 to 13,073 ng/g. A characteristic PBDE congener pattern was obtained in the three countries, with **BDE-209** as the predominant congener, comprising 75%, 82%, 81% (median for Belgium, Italy and Spain, respectively) followed by **BDE-99** (4%, 3%, 4%), BDE-207 (4%, 3%, 3%), BDE-206 (3%, 3%, 3%) and **BDE-47** (4%, 1%, 2%). Total daily exposure estimates for the sum of PBDEs ranged from 0.04 to 1.30 ng/kg bw per day (median and worst-case scenarios) for adults, and from 0.66 to 16.9 ng/kg bw per day for toddlers.

Besis et al. (2021) measured PBDEs and other contaminants in house dust from Greece and reported concentrations for the sum of 20 PBDEs at 564 ng/g. The authors evaluated the risk by calculating a hazard index for carcinogenic and non-carcinogenic effects in adults and children. In all samples this was less than 1 suggesting a very low level of concern for all age groups.

Jagić et al. (2021) measured PBDEs in house dust samples collected in Croatian households. Concentrations for the sum of PBDEs ranged between 1.1 and 17,662 ng/g dust, with **BDE-99** accounting for ~60% of the total. The estimated daily exposure for the Sum of PBDEs was calculated for toddlers as the most vulnerable population group, and it ranged from 0.003 to 55.04 ng/kg bw per day in the median scenario (considering a dust ingestion of 50 mg per day) and from 0.01 to 110 ng/kg bw per day in the worst-case scenario (considering a dust ingestion of 100 mg per day). The exposure calculated for **BDE-99** in the sample with the highest total PBDE levels was 68.99 ng/kg bw per day in the worst-case scenario.

Exposure to a range of flame retardants from dust was estimated for the Latvian population by Pasecnaja et al. (2021). Highest concentrations were found for phosphorus-based flame retardants, as also reported by Coelho, Sousa, Isobe, Kim, et al. (2016), but PBDEs was the second highest class of those examined. For an average dust ingestion scenario, it was estimated that the median and maximum amounts ingested by toddlers were 18.1 and 110 ng/kg bw per day, respectively (considering a dust ingestion rate of 50 mg/kg bw per day[59]). For adults, the values were 1.24 and 7.83 ng/kg bw per day (considering a dust ingestion rate of 20 mg/kg bw per day). For a high-level dust ingestion scenario, these figures increased to 70.0 and 460 ng/kg bw per day for toddlers (considering a dust ingestion rate of 200 mg/kg bw per day), and to 3.10 and 19.6 ng/kg bw per day for adults (considering a dust ingestion rate of 50 mg/kg bw per day).

Esplugas et al. (2022) investigated emerging and legacy flame retardants in indoor air and dust samples from Tarragona Province (Catalonia, Spain). It was found that organo-phosphorus flame retardants in general showed high concentrations in air and dust and levels of these newer flame retardants exceeded levels of legacy BFRs such as PBDEs. The PBDE congener with the highest mean value was **BDE-47** (0.07 ng/m^3), followed by **BDE-209** (0.046 ng/m^3). **BDE-28** showed the lowest concentrations (0.003 ng/m^3), being significantly ($p < 0.05$) lower than those of the remaining PBDEs, with the exception of **BDE-100** (0.009 ng/m^3). Estimated daily exposure from dust was stated to be 'low' (values not provided).

Another potential oral exposure can arise from unintentional ingestion of parts of plastic toys by small children. Fatunsin et al. (2020) analysed 10 PBDEs (**BDE-28, -47**, -**99**, -**100**, -**153**, -**154** -**183**, -196, -197, -**209**), as well as HBCDDs, TBBPA and other BFRs in 23 plastic samples from 20 new and second-hand children's toys that had been previously shown to be bromine positive by x-ray fluorescence (XRF). PBDEs were the main family detected, with mean levels ranging from 0.12 mg/kg (**BDE-100**) to 160 mg/kg (**BDE-209**). Besides exposure from mouthing, exposure arising from accidental ingestion of plastic from toys can be significant for young children. Straková et al. (2016) analysed several types of plastic toys for PBDEs to examine if the recycling of e-waste plastics may lead to contamination of new products. In total, 47 toy samples from 16 countries were analysed. Forty samples (85%) contained OctaBDE at concentrations between 1 and 108 mg/kg, and the highest concentration in products purchased in a European country was 153 mg/kg. Forty-two samples (89%) contained DecaBDE, and 16 of them at levels greater than 50 mg/kg. The same authors, in a follow-up study, analysed the black parts of 47 consumer goods (toys and hair accessories) bought in the Czech Republic for PBDEs (Strakova et al., 2018). All the samples contained OctaBDE and DecaBDE at 1–513 and 6–2234 mg/kg, respectively. The authors concluded that the results indicate that PBDEs found in e-waste are widely dispersed into children's toys made of recycled plastic containing PBDEs. This finding was supported in a study by Kajiwara et al. (2021) where new consumer products including children's toys purchased mainly from Japan were analysed by XRF and bromine-positive components revealed that 109 pieces (9.6% of the total), mainly those made of black-coloured plastic, contained PBDEs at concentrations ranging between 35 and 10,000 mg/kg.

PBDEs in European dust were compared with levels in other regions by Pasecnaja et al. (2021). Whilst the highest results were found for dust from Europe, the lowest levels were also from Europe.

[59]The CONTAM Panel noted the dust ingestion values used in this study are much higher than the ones use on other studies.

Bramwell et al. (2016) conducted a systematic review on associations between human exposure to PBDEs via diet and indoor dust, and internal dose. One of the topics examined was whether indoor dust exposure or diet was the primary pathway for non-occupational human exposure to PBDEs and whether or not it is time- and site-specific. For penta- and octaBDEs, dietary exposure was found to be similar in both the USA and mainland Europe, so the higher body burdens measured in the USA must be attributable to the higher dust loadings (Frederiksen et al., 2009). In the two included European studies measuring both dust and dietary exposure, diet was reported to provide over 90% of body burden, despite low dietary PBDE concentrations (Fromme et al., 2009; Roosens et al., 2009). Whilst recognising the lack of systematic approach in studies relating to the estimation of exposure to PBDEs from dust, it can be seen that for most of the population this is considerably smaller than exposure from the diet.

In summary, it is difficult to make direct comparisons of the data because of differences in congeners measured, sampling, locations from which dust was collected, etc but it is interesting to note that where studied, phosphorus containing flame retardants generally exceeded concentrations of PBDEs. Young children generally show a higher exposure to PBDEs from dust when compared to adults, due to a higher intake as a result of greater hand-to-mouth contact and due to lower body weight. This is to be considered when total exposure to PBDEs is assessed as exposure from dust can be substantial.

3.4 | Risk characterisation

The Panel calculated the combined MOET and applied a tiered approach for the combined risk assessment for effects of PBDEs in accordance with the EFSA guidance on combined effects of chemical mixtures (EFSA Scientific Committee, 2019) (see **Section 3.1.6.1**).

MOEs for a single congener ca be calculated by dividing their estimated chronic human dietary intakes at the BMDL body burden (see **Section 3.1.5.4**) by the estimated mean and P95 dietary exposure estimates (see **Section 3.3.1**). However, combining MOEs for P95 exposures for multiple congeners at the level of consumption survey or age class was not considered appropriate. This is because survey participants who are highly exposed to one congener will not necessarily be highly exposed to all other congeners. Therefore, to avoid an excessive overestimation of the risk, individual MOEs were calculated for each congener and survey participant. Next, a MOET was calculated for each survey participant as as the reciprocal sum (also known as the harmonic sum, See **Section 3.1.6.1**) of the reciprocals of the MOEs for the individual congeners.[60] Then, in a final step, the MOETs at the mean and P95 of the combined potency-adjusted exposure estimates were derived for each dietary survey and age group. This process was repeated for all tiers and the results across consumption surveys were summarised per age class. MOETs for the mean and P95 combined potency-adjusted exposure estimates are shown in **Tables 45** and **46**, respectively, and details are provided in Annex G.

As described in **Section 3.1.6.2**, a MOET smaller than 25 would raise a health concern.

TABLE 45 Combined margins of exposure (MOETs) across age groups for the mean of the combined potency-adjusted dietary exposure estimates.

	TIER 1													
	Infants		Toddlers		Other children		Adolescents		Adults		Elderly		Very elderly	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Min	–	–	98	4	99	5	121	12	214	13	192	16	202	15
Median	909	9	45	2	50	3	88	7	96	10	131	10	124	10
Max	128	4	30	2	34	2	57	5	74	8	83	9	75	8
	TIER 2													
	Infants		Toddlers		Other children		Adolescents		Adults		Elderly		Very elderly	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Min	–	–	124	4	117	5	153	12	252	15	365	17	258	16
Median	1292	10	54	3	55	4	101	8	111	11	157	11	148	10
Max	167	4	38	2	39	3	62	6	84	9	96	10	95	9
	TIER 3													
	Infants		Toddlers		Other children		Adolescents		Adults		Elderly		Very elderly	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Min	–	–	216	5	173	5	251	15	406	17	417	19	420	18
Median	1092	11	96	3	98	4	175	9	179	12	254	12	242	12
Max	271	5	59	2	57	3	86	7	108	10	157	11	148	10

(Continues)

[60]The reciprocal of an MOE for a congener is the corresponding potency-adjusted exposure (exposure/BMDL) for that congener. So taking the reciprocal sum of the MOEs is equivalent to summing the potency adjusted exposures for the different congeners to obtain the *combined potency-adjusted exposure* and then taking the reciprocal of that to obtain the MOET.

TABLE 45 (Continued)

	TIER 4													
	Infants		Toddlers		Other children		Adolescents		Adults		Elderly		Very elderly	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Min	–	–	2876	621	3480	848	5387	1726	6621	1970	7529	2231	7377	2066
Median	13159	2033	1712	411	2044	556	3723	1134	4972	1506	5332	1499	5253	1454
Max	3748	720	1234	321	1386	425	2521	778	3230	1211	2878	1237	2828	1152

TABLE 46 Combined margins of exposure (MOETs) across age groups for the P95 of the combined potency-adjusted dietary exposure estimates.

	TIER 1													
	Infants		Toddlers		Other children		Adolescents		Adults		Elderly		Very elderly	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Min	711	4	38	2	35	2	28	6	88	6	83	7	88	6
Median	233	3	16	1	20	2	34	4	40	5	50	5	49	5
Max	36	1	12	1	14	1	21	3	31	4	37	3	38	4
	TIER 2													
	Infants		Toddlers		Other children		Adolescents		Adults		Elderly		Very elderly	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Min	960	5	43	2	41	3	65	6	102	7	98	8	109	7
Median	262	3	18	1	22	2	39	4	45	5	57	5	59	6
Max	44	1	13	1	17	1	23	3	32	4	41	4	48	4
	TIER 3													
	Infants		Toddlers		Other children		Adolescents		Adults		Elderly		Very elderly	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Min	1577	5	77	2	67	3	114	7	166	8	157	9	171	8
Median	460	3	35	2	42	2	68	4	77	6	97	6	99	6
Max	80	1	24	1	30	2	40	3	56	5	70	4	81	5
	TIER 4													
	Infants		Toddlers		Other children		Adolescents		Adults		Elderly		Very elderly	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Min	8695	1031	1328	306	1088	439	1983	818	2904	1044	2938	1011	2958	961
Median	3785	684	649	225	858	295	1466	579	1741	731	1919	736	2221	749
Max	805	201	458	156	631	220	937	398	1187	553	1218	558	1378	572

For **Tier 1**, in which the Panel used the lowest Reference Point, expressed as a chronic human dietary intake corresponding to the calculated body burden at the BMDL, for each of the four congeners with data and for the congeners for which no Reference Points were identified the Panel applied the Reference Point of **BDE-47**,

- the MOETs for the mean exposure estimates were all above 25 for the LB estimates, while they were all below 25 for the UB exposures for all age groups.
- the MOETs for the P95 exposure estimates were above 25 for the LB estimates except for Toddlers and Other Children at the Median and Max exposure estimates, and for Adolescents at the Max exposure. For the UB estimates, they were all below 25 for the for all age groups.

For **Tier 2**, in which the Panel included only the four congeners with data, and used their lowest Reference Points to calculate MOEs and subsequently the MOET,

- the MOETs for the mean exposure estimates were all above 25 for the LB estimates, while they were all below 25 for the UB exposures for all age groups.
- the MOETs for the P95 exposure estimates were similar to those in Tier 1; they were above 25 for the LB estimates except for Toddlers and Other Children at the Median and Max exposure estimates, and for Adolescents at the Max exposure. For the UB estimates were all below 25 for all age groups.

Comparing the results of Tier 1 with Tier 2, it was concluded that exposure to the congeners for which there are no toxicological data (**BDE-28**, -**49**, -**100**, -**138**, -**154**, -**183**) does not have a great impact provided that they are not more toxic than **BDE-47**.

For **Tier 3**, in which the Panel included only the four congeners for which Reference Points for neurodevelopment were identified (**BDE-47**, -**99**, -**153**, -**209**), similar to Tier 2,

- the MOETs for the mean exposure estimates were all above 25 for the LB estimates, while they were all below 25 for the UB exposures for all age groups,
- the MOETs for the P95 exposure estimates were above 25 for the LB estimates except for Toddlers at the Max exposure, and they were all below 25 for the UB estimates for all age groups.

For **Tier 4**, in which the Panel included only the three congeners for which Reference Points for neurodevelopment were identified and for which there are sufficient/robust data (**BDE-47**, -**99**, -**209**), the MOETs at the mean and P95 exposure were all well above 25 (typically several orders of magnitude higher) for all age groups.

The CONTAM Panel concluded that estimates of exposure according to **Tier 1**, **2** and **3** raise a health concern at the LB P95 estimates in some surveys of Toddlers, Other children and Adolescent. There are large uncertainties in the estimates of hazard/risk due to the lack of toxicological data on most of the congeners. The estimates indicate no health concern for **Tier 4**. However, the Panel emphasises that **Tier 4** is not representative of dietary exposure to all of the PBDEs considered. Comparing the results from **Tiers 1 to 3** with those of **Tier 4**, demonstrates the importance of the Reference Point for **BDE-153** in its contribution to the MOET. This was the lowest Reference Point but subject to high uncertainty, which was taken into account in the uncertainty analysis (see **Section 3.5**).

Overall, the CONTAM Panel concluded that the resulting MOETs support the conclusion that current dietary exposure to PBDEs across dietary surveys in the European population raises a health concern.

The CONTAM Panel noted that exposure to PBDEs, especially to **BDE-209**, via dust and dermal contact is an additional source of exposure especially for children (see **Section 3.3.3**).

For formula fed infants, estimates of exposure were calculated based on the mean and P95 consumption data of infant formula for assessing the exposure to substances with a long half-life according to the Guidance of the EFSA Scientific Committee on the risk assessment of substances present in food intended for infants below 16 weeks of age (EFSA Scientific Committee, 2017). This was combined with the occurrence data submitted to EFSA on infant formula on the 10 PBDE congeners considered, although **BDE-49** and -**138** were not included since fewer than 6 sample results were reported which were all left-censored (see **Section 3.3.3**). The MOETs were calculated, and for Tier 1, 2 and 3 the estimates of exposure considering the LB occurrence values resulted in MOETs above 25 for mean and P95 consumption of infant formula. These were below 25 when considering the UB estimates. For Tier 4, the MOETs were in all cases above 25. The Panel noted the uncertainty in the exposure estimates due to the large difference between the LB and UB estimates.

For breastfed infants, estimates of exposure were calculated based on average and high human milk consumption and the median concentrations in pooled human milk samples from European countries collected and analysed between 2014 and 2019 within the WHO/UNEP field studies (all quantified values, see **Section 3.3.1**). The MOETs were calculated, and for Tier 1, 2 and 3 the MOETs obtained were all below 25, while for Tier 4 they were above 25. The CONTAM Panel noted that for **BDE-47** and -**99** the Reference Points are based on effects in offspring resulting from in utero and lactational exposure, while for **BDE-153** and -**209** the Reference Points are based on effects resulting from exposure of the offspring by gavage. The Panel also noted that these low MOETs were due to **BDE-153**, and its low Reference Point. Eventually, the body burden is most relevant. It should be noted that it takes three to four half-lives to reach steady-state levels in the body, i.e. 3 years or more for **BDE-99**, 4 or more years for **BDE-47**, and 22 years or more for **BDE-153** in humans. As an alternative approach the body burden in infants resulting from the exposure via human milk can be estimated and compared to the critical body burden. The intake of **BDE-153** during 6 months of breastfeeding can be calculated as follows: 800 mL with 3.5% lipid per day means a daily intake of 28 g lipid per day. At the median, a **BDE-153** level of 0.3 ng/g lipid implies an intake of 8.4 ng per day or 1.5 µg over 6 months. This would result in a worse-case body burden (no elimination, 100% absorption) of 0.25 µg/kg bw (based on a bw of 6 kg). Compared to the body burden at the BMDL of 12.5 µg/kg bw this implies a margin of body burden of 50. It should be noted that body burdens in the children will decrease after breastfeeding ends, due to a much lower exposure via food and growth of the children. Hence, the MOETs as calculated for breastfed infants would be an overestimation of the risk. Still, the MOETs for breastfed infants could only be increased by reducing the concentration of PBDEs in breast milk, by addressing exposure of the future mother.

Comparison of body burdens in adults

As an alternative approach to the risk characterisation based on the MOETs calculated for exposure via the diet, available data on levels in humans were compared with the estimated body burdens at the BMDLs for the various PBDE congeners (See **Section 3.1.5.3**). This was based on levels in human adipose tissue or in human milk, assuming that these reflect the levels in the body.

This was also performed in the previous Opinion on PBDEs in food, where the CONTAM Panel compared the body burden at the BMDLs calculated from animal studies with the estimated body burdens in humans (EFSA CONTAM Panel, 2011b). For this comparison, the Panel at that time identified information on PBDE concentrations in adipose tissue as being most relevant, because they best reflect long-term exposure to PBDEs. The reported concentrations in human adipose tissue were converted to an overall body burden assuming an average fat content in adult women of 25% (van der Molen, 1998).

In the current assessment, and following a similar approach, the CONTAM Panel used the levels reported in adipose tissue from the study of Ploteau et al. (2016) (see **Section 3.1.1.4.4**). These data were obtained from two different types of

adipose tissue from a group of women, reflecting to some extent the range of levels in the population. As the PBDE levels in human milk are likely to be related to the body burden (on a lipid basis) of women of child-bearing age, the reported UB range for PBDEs in human milk (pooled samples) collected in European countries between 2014 and 2019 as part of the WHO/UNEP field studies (see **Section 3.1.1.4.1**) were also converted to overall body burden. The Panel is aware that the body fat content is dependent inter alia on gender, age and physical condition. Deurenberg et al. (2001) reported mean body fat concentrations of 31.2 ± 7.8% and 20.1 ± 7.6% for females ($n = 234$) and males ($n = 182$), respectively. Therefore, for the estimation of the body burdens a fat content value of 31.2% was used. The results are depicted in **Table 47**. The MOET values were calculated by dividing the body burden at the BMDL in rodents by the estimated body burden based on the concentrations in human adipose tissue and human milk.

As shown in **Table 47**, the MOETs based on median human milk levels were larger than 25 for Tier 1, 2, 3 and 4, and as such do not raise a health concern for the median exposure. The CONTAM Panel concluded that this is more consistent with the conclusions based on the MOETs for LB mean dietary exposure calculations than with those based on UB exposure. It is noted that since these were pooled samples, it was not possible to assess the range across the population and it is possible that the MOET will be lower for heavily exposed individuals.

For adipose tissue, the MOETs were below 25 for Tiers 2 and 3 for the Mean, P95 and Max, and for Tier 4 they were below 25 for the P95 and Max. Tier 1 could not be calculated since **BDE-49** and -**138** were not determined. This is consistent with the conclusions based on the MOETs for the UB P95 dietary exposure estimates. The Panel noted the large range of concentrations of **BDE-209** in adipose tissue, in particular the highest concentration which was substantially higher than the maximum values measured in pooled human milk samples when compared on a lipid basis.

To further explore the association between estimated oral exposure and reported levels in human milk and adipose tissue, the CONTAM Panel used the average dietary exposure for adults to estimate the corresponding body burdens in adults based on the one-compartment model, fraction absorbed and half-lives shown in Table 32 (i.e. F_{abs} of 1 for **BDE-47**, -**99**, -**153** and 0.3 for **BDE-209**, $t_{1/2}$ of, respectively, 510, 280, 2700 and 15 days). As shown in Table 38 estimated medians for the mean LB exposure for these PBDEs are 0.14, 0.09, 0.02 and 0.27 ng/kg bw per day. This would result in body burdens of, respectively, 103, 36, 78 and 1.8 ng/kg bw, corresponding to lipid-based concentrations of 330, 117, 250 and 5.6 ng/kg lipid considering a body fat content of 31.2% for women and taking into account that PBDEs mainly accumulate in adipose tissue (see Table 48).

Despite the highest dietary exposure, the estimated body burden for **BDE-209** is much lower due to the short half-life and lower absorption. However, the difference is less clear for the median human milk levels from the WHO/UNEP study, being 326, 91, 303 and 140 ng/kg lipid. These concentrations are very similar to the lipid-based concentrations for **BDE-47**, -**99** and -**153**. However, for **BDE-209**, the median concentration in human milk is 25-fold higher than that calculated for body fat, i.e. 140 vs. 5.6 ng/kg lipid. The median concentrations for omental adipose tissue from the study by Ploteau et al. (2016) were, respectively, 340, 80, 1200 and 2750 ng/kg lipid, the highest levels being for **BDE-209**. For **BDE-47** and -**99** the concentrations were comparable to those estimated from the dietary exposure. For **BDE-153** the concentration was five-fold higher than that estimated, and for **BDE-209** it was 500-fold higher.

Possible explanations for the large underestimation of the **BDE-209** body burden based on the dietary exposure, include a large underestimation of the half-life of this congener in humans. However, the half-life of 15 days is based on observations in people occupationally exposed and followed during a period of low exposure (Thuresson et al., 2006) which is considered to be robust and supported by the study by Zhang et al. (2022). Regarding the differences between human milk and adipose tissue, there may also be differences in the excretion into human milk, being relatively low for **BDE-153** and especially **-209**, implying that human milk levels are poor markers for body burdens of these congeners. However, this is not supported by a study by Antignac et al. (2009), showing similar lipid-based levels in human milk and adipose tissue for a range of PBDEs, including **BDE-209**.

Overall, the body burdens of **BDE-47** and -**99** and -**153** are consistent with the estimated dietary exposure, however this is not the case for **BDE-209** and the most likely explanation for the difference seems to be a significant exposure from additional non-food related sources, e.g. dust (see **Section 3.3.3**).

TABLE 47 Overall body burden and combined margin of exposure (MOET) values for adults estimated on the basis of various human matrices.

A. Human milk[a]

BDE-47		BDE-99		BDE-153		BDE-209		MOET				
Concentration (ng/g lipid)	Body burden (μg/kg bw)	Concentration (ng/g lipid)	Body burden (μg/kg bw)	Concentration (ng/g lipid)	Body burden (μg/kg bw)	Concentration (ng/g lipid)	Body burden (μg/kg bw)		Tier 1	Tier 2	Tier 3	Tier 4
Min: 0.185	0.058	Min: 0.043	0.013	Min: 0.120	0.037	Min: 0.094	0.029	Min:	155	168	250	991
Median: 0.326	0.102	Median: 0.091	0.028	Median: 0.303	0.095	Median: 0.140	0.044	Median: Max:	74	79	110	654
Max: 0.750	0.234	Max: 0.550	0.172	Max: 0.822	0.256	Max: 0.884	0.276		19	21	34	109

B. Adipose tissue[b]

	BDE-47		BDE-99		BDE-153		BDE-209		MOET[c]			
	Concentration (ng/g lipid)	Body burden (μg/kg bw)	Concentration (ng/g lipid)	Body burden (μg/kg bw)	Concentration (ng/g lipid)	Body burden (μg/kg bw)	Concentration (ng/g lipid)	Body burden (μg/kg bw)		Tier 2	Tier 3	Tier 4
Parietal adipose tissue[c]	Median: 0.32	0.100	Median: 0.09	0.028	Median: 1.12	0.349	Median: 1.82	0.568	Median:	16	22	55
	Mean: 0.54	0.168	Mean: 0.16	0.050	Mean: 1.31	0.409	Mean: 3.37	1.051	Mean:	10	15	30
	P95: 1.34	0.418	P95: 0.49	0.153	P95: 2.62	0.817	P95: 6.11	1.906	P95:	5	8	16
	Max: 4.6	1.435	Max: 2.55	0.796	Max: 4.96	1.548	Max: 102.69	32.04	Max:	1	1	1
Omental adipose tissue[c]	Median: 0.34	0.106	Median: 0.08	0.025	Median: 1.2	0.374	Median: 2.75	0.858	Median:	13	17	37
	Mean: 0.66	0.206	Mean: 0.2	0.062	Mean: 1.5	0.468	Mean: 3.43	1.070	Mean:	10	14	29
	P95: 2.66	0.830	P95: 0.65	0.203	P95: 2.91	0.908	P95: 7.91	2.468	P95:	4	7	13
	Max: 4.5	1.404	Max: 2.66	0.830	Max: 5.87	1.831	Max: 13.76	4.293	Max:	2	4	7

Abbreviation: bw: body weight.

In grey, MOET values below 25.

[a]UB range (Min, Max and Median) for **BDE-47**, **-99**, **-153** and **-209** in pooled human milk collected in European countries between 2014 and 2019 as part of the WHO/UNEP field studies (see Table 11).

[b]Data from Ploteau et al. (2016), from French women, collected between 2013 and 2015 for parietal adipose tissue ($n = 99$ samples) and omental adipose tissue ($n = 51$ samples).

[c]Tier 1 could not be calculated since **BDE-49** and **-138** were not determined in the study.

TABLE 48 Estimation of the body burden (based on a one-compartment model) and corresponding concentrations in adipose tissue (considering a body fat content of 31.2%) based on the dietary exposure estimates in adults.

	Dietary exposure (ng/kg bw per day)		Half-life in humans (days)	Absorption (%)	Body burden[a] (ng/kg bw)		Corresponding lipid concentrations[b] (ng/kg fat)		Reported concentrations in omental adipose tissue[c] (ng/kg fat)			Reported concentrations in human milk[d] (ng/kg fat)		
	LB	UB			LB	UB	LB	UB	Median	Mean	P95	Median	Mean	P95
BDE-47	0.14	0.37	510	100	103	272	330	873	340	660	2660	326	185	750
BDE-99	0.09	0.3	280	100	36	121	117	388	80	200	650	91	43	550
BDE-153	0.02	0.25	2700	100	78	974	250	3121	1200	1500	2910	303	120	820
BDE-209	0.27	1.11	15	30	1.8	7	5.6	23	2750	3430	7910	140	90	880

Abbreviation: bw, body weight.

[a]Body burden estimated using the following equation for a 1-compartment approach: Body burden = (F_{abs} × dose)/K_{el}, where dose is the dietary exposure (ng/kg bw per day), K_{el} is the elimination rate constant [ln(2)/(half-life days)] (1/days), and F_{abs} is the fraction of the chemical absorbed into the body.

[b]Estimated assuming 31.2% of fat (Deurenberg et al., 2001).

[c]Calculated from data from Ploteau et al. (2016)

[d]Pooled human milk samples collected in European countries between 2014 and 2019 as part of the WHO/UNEP field studies.

3.5 | Uncertainty analysis

The aim of the uncertainty analysis was to identify and quantify uncertainties affecting the risk assessment for PBDEs in food and combine them to assess the overall certainty of the main conclusions, as recommended in the EFSA Guidance on uncertainty analysis (EFSA Scientific Committee, 2018a). As the risk assessment involved a combination of case-specific approaches for mixture assessment with some standardised elements, e.g. part of the default uncertainty factor of 100 and use of EFSA's Comprehensive Database on consumption, the uncertainty analysis followed the approach for a case-specific assessment (Section 4 of the Guidance).

The combined impact of the identified uncertainties was quantified in a tiered approach, starting with simpler methods (using plausible ranges, see **Section 3.5.4.1**) and proceeding to more refined methods (using plausible ranges and distributions, see **Section 3.5.4.2**) only when needed.

The following sections provide an overview of the main steps of the uncertainty analysis and their results. The details of the methods and results of each step are provided in Annex H, which contains a detailed, standalone description of all parts of the uncertainty analysis.

3.5.1 | Identification of sources of uncertainty

In a first step, sources of uncertainty related to the exposure assessment to PBDEs in food and hazard identification/characterisation were listed and discussed (see Annex H). Subsequently, it was considered which of these were non-standard[61] sources of uncertainty and which would have most impact on the outcome of the exposure and hazard assessments. Standard sources of uncertainty[62] were not considered further in the uncertainty analysis, as these are addressed by standardised elements of the risk assessment procedure used by the CONTAM Panel and the aim was to quantify uncertainty about what the outcome of the risk assessment would be if the non-standard uncertainties were resolved (e.g. by obtaining better data).

3.5.2 | Exposure assessment

The two most important non-standard sources of uncertainty affecting the exposure assessment were left censored data and the lack of occurrence data for some relevant food categories. The potential impact of these sources of uncertainty on exposure estimates for **BDE-47** and Toddlers was explored by a sensitivity analysis using a simplified exposure model, described in Annex H. Results from this were used to inform judgements by four experts quantifying the combined impact of all identified non-standard uncertainties affecting the exposure assessment of **BDE-47**, expressed as a plausible range[63] for the ratios of the 'true'[64] mean and P95 exposures for the EU population of Toddlers to the mid-point of the LB to UB range of the median of the mean exposure estimates from consumption surveys for Toddlers, if all non-standard uncertainties were resolved. The judgements were obtained by a semi-formal structured method of Expert Knowledge Elicitation (semi-formal EKE, Annex B.8 of EFSA Scientific Committee, 2018b), ending with consensus judgements agreed by the four experts.

The consensus plausible range for this ratio for both the mean exposure and the P95 exposure was 0.6 to 1.5, i.e. it was considered with at least 98% certainty[65] that the medians of both the mean and P95 exposure estimates for **BDE-47** and Toddlers would change by a factor between 0.6 and 1.5 relative to the mid-point of the LB to UB range if all the identified non-standard uncertainties were resolved. This plausible range was the experts' assessment of the combined impact of all the identified sources of uncertainty affecting the exposure estimates, including left censored data and the lack of occurrence data for some relevant food categories.

It was judged that the impact of uncertainty on the exposure assessment would be similar for other age groups, estimates (minimum and maximum of individual dietary surveys) and congeners. Subsequently, the elicited plausible range was applied to the exposure estimates for every individual in every survey and for all age groups and congeners, and replaced the LB and UB estimates of exposure in the uncertainty analysis for risk characterisation (see **Section 3.5.4**). Additional uncertainty introduced by applying the elicited plausible range to individual exposure estimates and to other age groups and congeners was considered as part of the assessment of overall uncertainty (see belo).

[61]Non-standard uncertainties are defined by EFSA (2018a) as 'Any deviations from a standardised procedure or standardised assessment element that lead to uncertainty regarding the result of the procedure. For example, studies that deviate from the standard guidelines or are poorly reported, cases where there is doubt about the applicability of default values, or the use of non-standard or 'higher tier' studies that are not part of the standard procedure'.

[62]Standard uncertainties are defined by EFSA (2018a) as 'Sources of uncertainty that are considered (implicitly or explicitly) to be addressed by the provisions of a standardised procedure or standardised assessment element. For example, uncertainties due to within and between species differences in toxicity are often addressed by a default factor of 100 in chemical risk assessment'.

[63]The plausible range was defined as a > 98% probability interval for the impact of the uncertainties, such that the experts judged there is less than 1% probability that the true value is below the lower limit of the range, and less than 1% probability it is above the upper limit.

[64]'True' refers here to what the exposure estimate would be if all the identified non-standard uncertainties were resolved, e.g. by obtaining perfect data on consumption and occurrence.

[65]The impact of uncertainties on each part of the risk assessment was quantified using % probabilities assessed by expert judgement, following EFSA's guidance on uncertainty analysis (EFSA, 2018a). When reporting conclusions, the resulting probabilities are expressed as % certainty for the more probable outcome, following EFSA's guidance on communication of uncertainty (EFSA, 2019).

3.5.3 | Hazard assessment

3.5.3.1 | *Assessment of genotoxicity*

All identified uncertainties affecting the assessment of genotoxicity were assessed by the Panel as having negligible impact on the conclusion (see Annex H). Their combined impact on the conclusion was quantified in a single step, using the semi-formal structured methods of Expert Knowledge Elicitation (semi-formal EKE, Annex B.8 of EFSA Scientific Committee, 2018b).

It was concluded from this with a high level of certainty (> 90%) that, although there is evidence of genotoxicity *in vitro* for some congeners, the 10 congeners considered in the Opinion are either not genotoxic *in vivo* or, if they were genotoxic *in vivo*, this would be by a thresholded indirect mechanism.

3.5.3.2 | *Assessment of neurobehavioural and reproductive/developmental effects*

Neurobehavioural effects and reproductive and developmental effects were identified by the Panel as the critical endpoints for assessing combined risks of PBDEs. Deciding which sources of uncertainty to quantify separately and which to quantify collectively is an important step when planning an uncertainty analysis (Step D in Figure 5 of EFSA Scientific Committee, 2018a). For this assessment, it was decided to quantify uncertainty separately for two of the 10 congeners considered: **BDE-153**, because a breakdown of the MOET calculations for **Section 3.4** indicated this congener contributed most to the combined risk (MOETs); and **BDE-47**, because this contributed more to the combined risk than the other congeners (due to higher exposure). The other two congeners for which hazard data were available (**BDE-99** and **BDE-209**) contributed less to the calculated MOETs, so uncertainty about them was expected to have less impact and it was considered sufficient to take this into account later, when assessing overall uncertainty (**Section 3.5.5**). The Reference Points for the six congeners for which no toxicological data were available (**BDE-28**, -**49**, -**100**, -**138**, -**154**, -**183**) are most uncertain, but as noted in **Section 3.4** they do not have a great impact on the MOET provided that they are not more toxic than **BDE-47**. It was therefore considered most practical to conduct the uncertainty analysis initially for Tiers 3 and 4 of the risk characterisation, which exclude these six congeners, and to take account of their potential contribution collectively when assessing overall uncertainty (see **Section 3.5.5**).

The combined impact of all uncertainties affecting the hazard assessment for **BDE-47** and **-153** was initially quantified as plausible ranges for their Reference Points for neurobehavioural and reproductive/developmental effects, obtained from three experts by semi-formal EKE. The envelope (overall minimum and maximum) of individual judgements from the three experts was taken as an overall plausible range for initial calculations quantifying the impact of the exposure and hazard uncer-

TABLE 49 Overall plausible ranges for neurobehavioural effects and reproductive/developmental effects of **BDE-47** and **-153**, assessed by semi-formal EKE.

	Reference points (expressed as chronic human dietary intake corresponding to the calculated body burden at the BMDL, ng/kg bw per day)		**Overall plausible range for the reference points** (expressed as chronic human dietary intake corresponding to the calculated body burden at the BMDL, ng/kg bw per day)	
Congener	**Neurobehavioural effects**	**Reproductive/developmental effects**	**Neurobehavioural effects**	**Reproductive/ developmental effects**
BDE-47	1097	168	20–3000	5–2300
BDE-153	3.2	NA	1–60	0.1–120

Abbreviations: bw, body weight; NA, not applicable, as no data was identified to establish a Reference Point for reproductive/developmental effects for **BDE-153**.

tainties on risk characterisation (see below). The overall plausible range for each congener and endpoint is shown in Table 49.

An initial assessment of the impact of the uncertainties for exposure and the Reference Points for **BDE-47** and **-153** on the MOETs was obtained by combining the elicited plausible ranges by probability bounds analysis (Section 14.1 of EFSA Scientific Committee, 2018a). This showed that further uncertainty analysis was required to obtain a more refined assessment of the probability of a health concern (see **Section 3.5.4.1**).

It was decided to refine the uncertainty analysis by replacing the plausible ranges for the Reference Points with probability distributions, as it was clear from the earlier steps that the uncertainty of the Reference Points for **BDE-47** and **-153** had a much larger impact on the MOETs than the uncertainty of the exposure estimates. Distributions for these Reference Points were elicited by semi-formal EKE from five experts: the same three as for the plausible range plus two more.

The elicited distributions provided by each of the five experts for each congener and endpoint are shown in Annex H (Figure H.1). Evidence, uncertainties and reasoning identified by the experts as supporting lower or higher values for each Reference Point are also summarised in Annex H. It was decided not to elicit a consensus between the experts for each congener and endpoint but to repeat the subsequent calculations with each expert's distributions in turn. This approach allows the analysis to examine the impact of differences between experts (which are part of the scientific uncertainty) and saves significant meeting time that would otherwise be required to seek a consensus.

3.5.4 | Risk characterisation

Calculations were performed to determine the combined impact of the quantified uncertainties for exposure and the Reference Points for **BDE-47** and **-153** on Tiers 3 and 4 of the risk characterisation, which were focussed on neurobehavioural effects. Tier 3 included four congeners: **BDE-47**, -**99**, -**153** and -**209**. As in **Section 3.4**, Tier 4 included the same congeners except for **BDE-153**, to examine the contribution of this congener to the risk.

Calculations were also performed for modified versions of those Tiers, referred to below as Tiers 3A and 4A, focussed on reproductive/developmental effects. Tier 3A included three congeners (**BDE-47**, -**99** and -**153**) while Tier 4A included only **BDE-47** and -**99**. These modified Tiers were included to assess whether uncertainty about the Reference Point for **BDE-153** might result in a higher probability of concern for reproductive/developmental effects than for neurobehavioural effects. Although a Reference Point for reproductive/developmental effects was also derived for **BDE-209**, this congener was not included in the MOET calculations for Tiers 3A and 4A, but instead was taken into account when assessing the overall uncertainty (see **Section 3.5.5**).

In these calculations, uncertainties affecting exposure for each of the included congeners were quantified by the plausible range obtained in **Section 3.5.2**. Uncertainties affecting the Reference Points for **BDE-47** and **-153** were quantified initially by plausible ranges and subsequently using probability distributions, as described in **Section 3.5.3**. This tiered approach was adopted to determine whether the simpler uncertainty analysis based on plausible ranges would be sufficient, or whether it was necessary to refine the analysis using distributions and Monte Carlo simulation.

Uncertainties affecting the Reference Points for congeners other than **BDE-47** and -**153** were not quantified separately, for the reasons explained in **Section 3.5.3**, and were therefore not included in the calculations. These uncertainties, including the contribution to risk of those congeners that were excluded from Tiers 3, 3A, 4 and 4A, were instead taken into account when assessing overall uncertainty (**Section 3.5.5**).

3.5.4.1 | *Uncertainty analysis using plausible ranges*

Calculation of the MOETs followed the same approach as in **Section 3.4** of the Opinion, replacing the LB and UB estimates of exposure for each of the included congeners with a plausible range based on the elicited factor of 0.6–1.5 applied to the midpoint of the LB and UB (see **Section 3.5.2**) and replacing the Reference Points for **BDE-47** and -**153** with the plausible ranges elicited for them (see **Section 3.5.3**).

The elicited plausible ranges for exposure and the Reference Points were combined by probability bounds analysis to obtain lower and upper probability bounds[66] for the MOETs. This method for combining uncertain quantities is described in section 14.1 of EFSA Scientific Committee (2018a) and in more detail in Annex B.13 of EFSA Scientific Committee (2018b). Its application to the present assessment is described in detail in Annex H, as well as the results of the probability bounds analysis. They show that the range between the lower and upper probability bounds for the MOET extends both below and above 25 for every age group and dietary survey for both the mean and P95 of the combined potency-adjusted exposure estimates in both Tier 3 (neurobehavioural effects) and 3A (reproductive/developmental effects). The only exception to this was the 'minimum' estimate for infants, where the mean exposure was zero. These results imply that, for both neurobehavioural and reproductive/developmental effects of PBDEs, a more refined uncertainty analysis is required to assess the probability of a health concern.

3.5.4.2 | *Uncertainty analysis using plausible ranges and distributions*

A more refined uncertainty analysis was performed by replacing the plausible ranges for Reference Points in the preceding step with probability distributions. The distributions for the Reference Points from five experts were combined with the consensus plausible range for exposure using a combination of Monte Carlo simulation (Section 14.2 of EFSA Scientific Committee, 2018a) and probability bounds analysis. This resulted in lower and upper probability distributions[67] for the MOETs for the mean and P95 of the combined potency-adjusted exposure estimates for each endpoint, Tier (3 and 4 or 3A and 4A), age group, dietary survey and expert. These distributions were then used to derive an approximate probability (lower and upper probability) for each MOET being below 25 in each survey and the minimum, median and maximum probabilities across surveys (when ranked by the probability of the MOET being below 25) for each combination of Tier, age group, exposure level (mean or P95) and expert. Details of the calculation methods and results are presented in Annex H.

An overview and comparison of the calculated probabilities for Adults and Toddlers in Tiers 3 and 3A is presented in Table 50. This shows results for the minimum, median and maximum surveys (when ranked as described above) for the mean and P95 for these two age groups. Each probability range in Table 50 is the envelope (overall minimum and maximum) of the probability ranges for the five experts. These results are from Monte Carlo simulations assuming independence between the distributions for the Reference Points of **BDE-47** and **-153**; potential positive dependencies between them were examined by sensitivity analysis and found to have limited impact. The result shown in bold in Table 50 was taken as the primary focus for the assessment of overall uncertainty in the following section.

[66] A probability bound is a probability or approximate probability for a specified range of values; an approximate probability is a range or bound for a probability (EFSA Scientific Committee, 2018a).

[67] The lower and upper probability distributions result from combining the distributions for the Reference Points of **BDE-47** and **-153** with the lower and upper bounds of the plausible ranges for exposure, respectively. See Annex H for details.

TABLE 50 Calculated lower and upper probabilities (expressed as percentage %) for the MOET being below 25 for reproductive/developmental and neurobehavioural effects in Tiers 3 and 3A at the mean and P95 of the combined potency-adjusted exposure estimates for Toddlers and Adults, for the minimum, median and maximum surveys (when ranked by the probabilities) (Details of how the surveys were ranked are provided in the footnote to **Table H.11** in Annex H, assuming independence between the elicited distributions for the Reference Points of **BDE-47** and **-153.**

		Tier 3A Reproductive/developmental effects			Tier 3 Neurobehavioural effects		
Exposure estimate	**Age group**	**Min**	**Median**	**Max**	**Min**	**Median**	**Max**
P95	**Toddlers**	78–100	82–100	90–100	60–100	67–100	74–100
	Adults	45–88	54–98	62–100	18–86	28–92	37–94
Mean	**Toddlers**	59–100	**69–100**	74–100	34–94	50–99	59–100
	Adults	29–70	35–77	39–83	0–65	4–75	8–81

3.5.5 | Assessment of overall uncertainty

The preceding steps quantified the combined impact on the MOETs of all the uncertainties affecting the Reference Points for **BDE-47** and **-153** and the median estimates of P95 exposure of Toddlers to **BDE-47**, based on the plausible ranges and distributions elicited from the experts. The MOET calculations were limited to four congeners for neurobehavioural effects (**BDE-47**, **-99, -153** and **-209**) and three congeners for reproductive/developmental effects (**BDE-47**, **-153** and **-99**) and did not take into account the potential contribution of other congeners. This is a major additional source of uncertainty in the assessment and was therefore taken into account, together with all other sources of uncertainty identified by the Panel, in the final step of the uncertainty analysis: the assessment of overall uncertainty (Section 16 of EFSA Scientific Committee, 2018a). The supporting evidence provided by the MOETs based on body burdens in adults (**Section 3.4**) was also taken into account in this final step.

The assessment of overall uncertainty focussed mainly on the median probability of a health concern for reproductive and developmental effects at the mean of the combined potency-adjusted exposure estimates for Toddlers at Tier 3A, starting with the median probability range shown in bold in Table 50 (69%–100%) and assessing by semi-formal EKE the impact on this of the additional uncertainties and of the supporting evidence on body burdens. Before judgements for this were elicited, a structured discussion was held to identify additional sources of uncertainty that were not quantified in earlier steps of the uncertainty analysis and to discuss in qualitative terms their potential impact on the MOET. The resulting additional uncertainties are summarised and evaluated in Annex H (Table H.9).

After sharing and discussing individual judgements, the experts agreed that their probabilities for the MOET being less than 25 would be unchanged or increase, compared to the calculated range of 69%–100%, when taking all the additional uncertainties into account. They therefore agreed a consensus judgement of > 70% probability that the MOET for reproductive/developmental effects would be less than 25 at the mean of combined potency-adjusted exposure estimates for the 10 congeners for Toddlers, in the median of the surveys considered, if all the additional uncertainties affecting the assessment were resolved.

The experts then considered more briefly the applicability of their assessment of the additional uncertainties and supporting evidence to the other probabilities shown in Table 50. They agreed that the impact would be similar to that assessed above, i.e. the probabilities for MOET< 25 would generally be equal to or higher than the probabilities shown in Table 50. For example, rounding to the nearest 5% to avoid over-precision, the maximum probability (across surveys) of MOET< 25 for reproductive/developmental effects at the P95 of the combined potency-adjusted exposure estimates for the 10 congeners for Toddlers exceeds 90%; the probabilities for MOET < 25 for neurobehavioural effects are lower than the corresponding probabilities for reproductive/developmental effects (e.g. median probability more than 50% at the mean of the combined potency-adjusted exposure estimates for the 10 congeners for Toddlers and maximum probability more than 75% at the P95 of the combined potency-adjusted exposure estimates for the 10 congeners for Toddlers); and the probability of MOET < 25 for both categories of effects is lower for Adults than for Toddlers but, for reproductive/developmental effects, is still greater than 60% for the maximum survey at the P95 exposure (Table 50).

3.5.6 | Conclusions of the uncertainty analysis

It was concluded with 90%–99% certainty[68] that, although there is evidence of genotoxicity *in vitro* for some congeners, the 10 congeners considered in the Opinion are either not genotoxic *in vivo* or, if they were genotoxic *in vivo*, this would be by a thresholded indirect mechanism.

It was concluded that the risk assessment was affected by considerable uncertainties, including left-censored occurrence data (as indicated by the contrasting MOETs for LB and UB exposures), lack of occurrence data for some relevant food categories, lack of neurotoxicity data for 6 out of the 10 congeners considered, and lack of reproductive/developmental

[68]Probabilities assessed by the uncertainty analysis are reported in conclusions as % certainty for the more probable outcome, following EFSA's guidance on communication of uncertainty (EFSA, 2019).

toxicity data for seven congeners. All of the identified uncertainties were taken into account in a quantitative uncertainty analysis using expert knowledge elicitation. For half of the dietary surveys considered,[69] the Panel concluded with more than 70% certainty that the mean of the combined potency-adjusted exposure estimates for all 10 congeners for Toddlers raises a health concern for reproductive/developmental toxicity effects.

The certainty of a health concern is higher at the P95 of the combined potency-adjusted exposure estimates and in the surveys with higher exposures, e.g. there is a maximum (across surveys) of more than 90% certainty of a health concern for reproductive/developmental effects at the P95 for Toddlers. The probability of a health concern is lower for neurobehavioural effects than for reproductive/developmental effects, e.g. for half of the surveys considered, there is more than 50% certainty at the mean of the combined potency-adjusted exposure estimates for Toddlers. The probability of a health concern is lower for both categories of effects in Adults than in Toddlers, reflecting the differences in exposure between age groups, but for reproductive/developmental effects, is still greater than 60% for the maximum survey at the P95 exposure.

It is noted that these conclusions from the uncertainty analysis are, in effect, a refinement of the assessment provided by the MOETs for the LB and UB exposures in **Section 3.4** of the Opinion. The LB and UB are expected to be extreme estimates of exposure. These are replaced in the uncertainty analysis by more realistic lower and upper plausible limits, obtained by expert judgement based on sensitivity analysis with the simplified exposure model. The assessment in **Section 3.4** results in MOETs below 25 for UB exposures but above 25 for LB exposures. This, together with the high uncertainty of the Reference Point for the most important congener (**BDE-153**), might have made it difficult to reach a conclusion on health concern. The uncertainty analysis improves on this by quantifying the impact of all the identified uncertainties and providing probabilities for the MOETs being below 25, which are much more informative.

4 | CONCLUSIONS

Polybrominated diphenyl ethers (PBDEs) had widespread use as additive flame retardants in the past. They were applied as technical mixtures, termed PentaBDE, OctaBDE and DecaBDE in construction materials, furniture and electric and electronic equipment, generally at concentrations between 5 and 30% by weight. As they were not chemically bound to the plastic or textiles, PBDEs could leach into the environment and consequently had global distribution. The congeners are persistent in the environment and they bioaccumulate at high levels in the food chain. PBDEs are listed in Annex A of the Stockholm Convention,[70] with specific exemptions for use or production. Sensitive analytical methods, predominantly gas chromatography–mass spectrometry-based techniques using isotope-labelled standards, are available for an unequivocal and precise quantitative determination of PBDEs at trace concentrations in environmental, biological and food samples.

As required by the Terms of Reference, the present Opinion focusses on the congeners **BDE-28**, **-47**, **-49**, **-99**, **-100**, **-138**, **-153**, **-154**, **-183** and **-209**. The assessment is an update of the EFSA CONTAM Panel Opinion on PBDEs in Food published by EFSA in 2011. Except **BDE-49** and **-138**, the previous Opinion considered the same congeners as the present assessment. It takes into account the occurrence data in food and biological samples submitted to EFSA after the publication of the previous Opinion, as well as the newly available scientific information of relevance to hazard identification and characterisation.

4.1 | Hazard identification and characterisation

4.1.1 | Toxicokinetics

- In rodents, oral absorption rates and/or bioavaiabilities of **BDE-47** (mice and rats), **-100** (rat), **-154** (rat) from the gastrointestinal tract is almost complete (> 75%) and is lower for **BDE-99** (50% in rat) and **BDE-209** (10%–26% in rat).
- In rodents, PBDE congeners (**BDE-47**, -85, **-99**, **-100** and **-153**) are predominantly distributed to adipose tissue, whereas **BDE-209** is predominantly distributed to highly perfused tissues (e.g. liver).
- PBDEs are maternally transferred to rodent offspring in utero and via lactation.
- In rats and mice PBDEs are mainly metabolised by a CYP-mediated oxidative pathway and by debromination, leading to the formation of OH-metabolites. Glucuronide- and sulfate-conjugate metabolites have also been detected.
- The excretion of PBDEs in rats is mainly via the faeces, whereas urinary excretion is the principal route for mice.
- In humans, transfer of PBDEs and OH-PBDE metabolites from maternal blood to the placenta and human milk has been reported.
- In humans, the main metabolic pathway of PBDEs is CYP-mediated hydroxylation, followed by phase II metabolism with the formation of glucuronide and sulfate conjugates.
- Limited data are available regarding the excretion of PBDEs in humans. Half-lives were estimated using different methodologies. The half-lives were estimated to be in the range of 280–2700 days for **BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154** and **-183**. For **BDE-209**, it was estimated to be 7–18 days.

[69] i.e. for the **median** survey and all those ranked above it.

[70] Annex A of the Stockholm Convention includes chemicals for which parties must take measures to eliminate the production and use. Specific exemptions for use or production are listed and apply only to Parties that register for them.

- Transfer of PBDEs from feed to food of animal origin including milk and eggs, has also been reported in different animal species, i.e. ruminants, pigs, laying hens, broilers, ducks and fish. PBDEs are distributed to a number of tissues and accumulate in tissues with high-fat content.

4.1.2 | Toxicity in experimental animals

- Repeated exposure of rats or mice to **BDE-47** and **-209** induced effects in the liver, e.g. increased liver weight, centrilobular hepatocyte hypertrophy, lipid accumulation/steatosis, changes in serum hepatic chemistry, microsomal enzyme induction. Similar effects, including inflammation and necrosis, were seen in offspring exposed in utero and/or postnatally until weaning. Increases in oxidative stress markers were noted in the liver of rat offspring exposed in utero and during lactation to **BDE-99.**
- Increased thyroid weight, changes in the thyroid hormone system and thyroid follicle structure occurred in adult rats after repeated exposure to **BDE-47** and **-209**. There were also reductions of TT3 and/or TT4 levels with increased serum TSH levels in offspring exposed in utero and during lactation.
- **BDE-47**, -**99** and -**209** affected the reproductive systems of both male and female adult rats and mice. Exposure of offspring to these compounds during gestation and/or lactation caused reproductive toxicity. Changes in serum testosterone and oestradiol levels were observed in adult male rats and mice exposed perinatally or in adulthood.
- **BDE-47** administered to male adult rats or mice resulted in effects on the testes with changes in the organisation of the seminiferous tubules, germ cell loss, decreases in sperm production and motility. Exposure in utero or during lactation until weaning caused the same adverse effects in male offspring of exposed rat dams. Decreased ovarian weight and alteration of folliculogenesis occurred in female rat offspring exposed during gestation.
  Degeneration of gonadal system histology was shown in adult male rats after exposure to **BDE-99**. Administration to pregnant animals resulted in reproductive tract changes in female rats of the F1 generation that were apparent at adulthood, and in changes in reproductive organs in male mice. Incomplete or delayed ossification and internal variations were also observed in rat fetuses exposed during gestation as well as impaired spermatogenesis in male offspring.
- Repeated exposure of adult male rats or mice to **BDE-209** affected testicular histopathology, steroidogenesis and germ cell dynamics resulting in decreased spermatogenesis. Exposure of offspring in utero and/or during lactation resulted in decreased mating and fertility index, and litter size. Embryotoxicity occurred in mice exposed during gestation. In addition, a significant reduction in anogenital distance was reported in mice exposed in utero.
- **BDE-47** and -**209** exerted toxic effects to the immune system, e.g. changes in spleen and thymus, reduction of leucocytes, cytokine production and CD4+ and CD8+ T cells proliferation, inflammation of the gastrointestinal tract.
- **BDE-47**, -**99** and -**209** induced effects on the energy metabolism, such as changes in liver and serum lipids, serum glucose and serum insulin levels. However, contradictory results were reported when comparing studies, even those using the same test substance, making conclusions difficult.
- **BDE-47** induced long-term behavioural impairments in young adult rats or mice exposed in utero and/or during lactation, or at the adult stage, which are related to locomotor activity and spatial learning and memory. **BDE-99**, -**153** and -**209** were also demonstrated to induce the same types of behavioural disorders in rodents exposed during the early phase of brain development or at the adult stage. In addition, the exposure to **BDE-47** or -**99** was identified as being able to induce a reduction in the level of anxiety, and **BDE-99** and -**209** to impair the locomotor coordination and self-reactivity of the animals.
- PBDEs have not been shown to induce gene mutations *in vitro* or *in vivo*.
- *In vitro* tests indicate that some PBDEs (**BDE-47**, **-99**, **-100**, **-153**, **-154** and -**209**) can cause DNA damage (single and double strand breaks).
- Induction of micronuclei was shown *in vitro* in cells expressing xenobiotic-metabolising CYP enzymes (human neuroblastoma cells or V79) exposed to **BDE-47** but not in HepG2 cells. Two metabolites, 6-OH-BDE-47 and 6-MeOH-BDE-47, were also positive for induction of micronuclei *in vitro*.
- *In vivo*, negative results were obtained in micronucleus tests in peripheral blood and bone marrow cells with **BDE-47** and **-209** and the technical product DE-71. The CONTAM Panel noted that while the micronucleus tests do not show evidence of toxicity to the bone marrow, systemic exposure was evident from toxicokinetics and from systemic toxicity and thus these are lines of evidence of bone marrow exposure to the test substance.
- There is evidence that PBDEs can induce DNA damage via an indirect mechanism of action involving, i.e. reactive oxygen species (ROS) production.
- Although there is evidence of genotoxicity *in vitro* for some congeners, there was no evidence for *in vivo* genotoxicity. The CONTAM Panel concluded that the 10 congeners considered in the Opinion are not genotoxic *in vivo*.
- Individual PBDE congeners have not been tested for carcinogenicity. Studies with the technical products DecaBDE and DE-71 showed formation of tumours which were not considered relevant for humans.

4.1.3 | Observations in humans

- The number of epidemiological studies has increased considerably since the previous Opinion, covering a large number of endpoints, including thyroid function and disease, neurodevelopment, lipid and sugar metabolism (diabetes and obesity), cardiovascular effects, effects on male and female reproduction, birth outcomes, effects on the immune system and inflammation and cancer.
- For most of the endpoints assessed, the currently available body of evidence is weak and characterised by a small number of prospective studies, generally short follow-up periods, relatively small sample sizes, considerable heterogeneity in the assessed populations, congeners, exposures and outcomes, and varying methodological quality.
- For cognitive function, there is a growing evidence base stemming from longitudinal studies on the associations between PBDE levels and cognitive function indices that is characterised by a harmonised endpoint assessment through the Wechsler scales. However, statistically significant associations that were replicated in other studies are scarce.
- For attention deficit hyperactivity disorder (ADHD)-related outcomes, although the evidence was enriched with new studies, results are heterogeneous with both positive and null associations reported in relation to prenatal and childhood PBDE levels. Some statistically significant associations were replicated across studies, in particular associations between levels of **BDE-47** and attention deficit subscales, and similarly for Sum PBDE (sum of **BDE-47**, -**99**, -**100** and -**153**).
- For thyroid function, the reported associations are occasionally characterised by an opposite effect direction between and within studies. The prospective data showed mostly non-replicated statistically significant associations for **BDE-47**, -**99**, -**100**, -**153**; only **BDE-47** and -**99** were inversely statistically significantly associated with TSH and TT3 levels in two studies. Statistically significant associations across the whole panel of thyroid function biomarkers were seen for **BDE-47**, and partially for **BDE-99**, but with discordant effect direction in both cases.
- For male fertility, the evidence on the association between PBDE exposure and relevant clinical endpoints is not sufficient, and the same applies for semen quality and sex hormones which are assessed in a larger number of studies but with a high risk of bias and no replication efforts.
- For female reproductive effects, pubertal development in girls was assessed in three studies (one cohort, two cross-sectional studies) with all of them reporting some statistically significant results but with no consistency of effect direction; the proposed delayed pubertal development described in the longitudinal study is not supported by the statistically significant associations with premature pubertal development reported in the two cross-sectional studies.
- For birth outcomes, birth weight was the most studied outcome. Reductions in birth weight and null associations in relation to maternal PBDE levels were reported, and evidence is therefore classified as inconclusive. For other birth outcomes (e.g. birth length, head circumference, gestational age) and outcomes measured in the early years of life (e.g. anogenital distance), there were not enough studies to draw conclusions.
- For obesity, the few statistically significant findings related to prenatal PBDE levels and obesity attributes (e.g. body mass index, waist circumference, % body fat), pointed to an inverse association that is difficult to put into context and integrate with the respective data on Type 2 diabetes or on cardiometabolic risk factors.

4.1.4 | Mode of action

- There is a growing body of evidence that the tested PBDEs and OH-metabolites interfere with mitochondrial calcium homeostasis, leading to oxidative stress and apoptosis in neuronal cells.
  Changes in neurotransmitters (or in expression of related genes) and migration and differentiation of neuronal cells in culture are also observed. The data do not provide a clear picture of how PBDEs affect neurotransmission and synapses. The relative potency of the neurotoxicity of different PBDE congeners is unclear.
- There is a separate and additional line of evidence relating to involvement of the thyroid hormones in neurotoxicity of **BDE-209** although no data are available on similar involvement for other PBDE congeners.
- There is some evidence that PBDEs and their metabolites can act as weak agonists or antagonists of the aryl hydrocarbon receptor (AHR). It is difficult to assess however whether these results were influenced by any contamination with dioxin-like compounds.
- Available evidence suggests that several PBDEs are capable of activating constitutive androstane receptor/pregnane X receptor (CAR/PXR)-dependent gene expression, at least at relatively high exposure levels, and that PXR has higher sensitivity than CAR to PBDEs in mouse. CAR/PXR-dependent expression of biotransformation enzymes would be expected to accelerate metabolism of steroid and thyroid hormones and provides one possible explanation of decreased concentrations of circulating oestradiol, testosterone and T4.
- There is mechanistic evidence that PBDEs, and in particular their OH-metabolites, interfere with the thyroid hormone system by: (i) competing with T4 for thyroid binding proteins and (ii) altering expression and activities of enzymes that metabolise thyroid hormones. This could explain the observed effects of PBDEs on neurodevelopment and reproduction. It remains to be determined how relevant these two mechanisms are for humans.

- There is evidence of the involvement of sex and thyroid hormones, oxidative stress, mitochondrial dysfunction, apoptosis, oxidative damage to DNA, changes in gene expression and epigenetic mechanisms in the generation of adverse effects on reproduction.
- *In vitro* studies on mammalian cells showed that genotoxic effects (mainly DNA strand breaks) induced by **BDE-47**, -**99** and -**209** and their OH-metabolites are primarily mediated by oxidative stress. Based on the data available, the CONTAM Panel concluded that PBDEs can induce DNA damage via an indirect mechanism of action.

4.1.5 | Critical effects and dose–response analysis

- The evidence from the available human data did not provide a sufficient basis for the risk assessment. Thus, the CONTAM Panel considered the data from studies in experimental animals to identify Reference Points for the human hazard characterisation.
- The CONTAM Panel concluded that the neurodevelopmental effects on behaviour and reproductive/developmental effects are the critical effects for the hazard characterisation.
- For **BDE-47**, the lowest $BMDL_{10}$ was 0.023 mg/kg bw per day for reproductive effects (impaired spermatogenesis after repeated exposure), while a $BMDL_{10}$ of 0.15 mg/kg bw per day was obtained for neurodevelopmental effects (impaired spatial learning and memory after repeated exposure).
- For **BDE-99**, the lowest $BMDL_{10}$ was 0.05 mg/kg bw for developmental effects (increased resorption rates in dams following single dose administration on gestational day (GD) 6), while a $BMDL_{10}$ of 0.43 mg/kg bw per day was obtained for neurodevelopmental effects (reduction in the level of anxiety after repeated exposure).
- For **BDE-153**, the Panel identified a $BMDL_{10}$ of 0.11 mg/kg bw for neurodevelopmental effects (impaired learning and memory after single exposure on postnatal day (PND) 10 from the only toxicological study identified for this congener.
- For **BDE-209**, the lowest $BMDL_{10}$ was 0.91 mg/kg bw per day for reproductive effects (decreased sperm motility after repeated exposure), while a $BMDL_{10}$ of 1.59 mg/kg bw per day was obtained for neurodevelopmental effects (impaired learning and memory after repeated exposure).
- Repeated exposure to PBDEs results in increasing concentrations of these chemicals in the body, for this reason the accumulated concentrations in the body or body burden, rather than the daily exposure, is considered as the appropriate dose metric for the risk assessment. Thus, the CONTAM Panel first calculated the body burden at the BMDL, based on the tissue concentrations in rodents reported in the literature.
- Next, the chronic intake that would lead to the same body burden in humans was calculated assuming an absorption of **BDE-47**, -**99** and -**153** in humans of 100%, and of 30% for **BDE-209**, and the median half-lives in humans as reported in the literature.
- For neurodevelopmental effects, this resulted in the following estimated chronic human dietary intakes corresponding to the the body burden at the BMDL, expressed as ng/kg bw per day: 1096 for **BDE-47**, 3575 for **BDE-99**, 3.2 for **BDE-153** and about 5000 for **BDE**-**209**.
- For reproductive effects, this resulted in the following estimated chronic human dietary intakes, expressed as ng/kg bw per day: 168 for **BDE-47**, 38.4 for **BDE-99** and about 3000 for **BDE-209**.
- Assignment of chemicals to an assessment group for combined risk assessment as a mixture is based on whether the chemicals have a common mode of action or a common target/system The four PBDE congeners for which there are experimental data to derive a Reference Point all affect neurodevelopment, and for three of these data are available showing effects on reproduction, forming a scientific basis for inclusion of these four congeners in a common assessment group. The evidence that changes in the thyroid hormone system could be a mode of action in the effects of PBDEs on both neurodevelopment and reproduction further supports a combined risk assessment.
- No studies were available to identify Reference Points for **BDE-28**, -**49**, -**100**, -**138**, -**154** and -**183**. However, mechanistic studies conducted *in vitro* with neural cells with these six congeners indicate that they could share common modes of action with **BDE-47**, -**99**, -**153** and -**209**, and therefore a conservative approach would also include the congeners of interest in the assessment group.
- The Panel concluded that the MOET approach was the most appropriate risk metric for the combined risk characterisation.
- The CONTAM Panel considered that a MOET smaller than 25 would raise a health concern. This would allow for interspecies differences in toxicodynamics and intraspecies differences in toxicokinetics and toxicodynamics.

4.2 | Occurrence and exposure for the European population

4.2.1 | Occurrence in food

- A total of 84,249 analytical results (10,879 samples) generated by either gas chromatography–mass spectrometry (GC–MS) or GC-electron capture detection (GC-ECD) for PBDEs in food fulfilled the quality criteria applied and were used in the assessment.

- The left-censored data accounted for 51% of the occurrence values. Both LOQ and LOD were provided for 21% of all left-censored data, while only LOD or only LOQ were provided for 4% and 75% of the reported left-censored occurrence values, respectively.
- Out of the food categories in which high concentrations of PBDEs were expected, the highest percentage of quantified data was found in 'Fish, seafood, amphibians, reptiles and invertebrates'. The highest mean concentration was reported for 'Fish liver' ranging from 0.002 μg/kg wet weight (ww) for **BDE-138** at the lower bound (LB) to 11.15 μg/kg ww reported for **BDE-47** at the upper bound (UB). The second highest mean concentration was reported for **BDE-100**, again in 'Fish liver', where both LB and UB were 2.47 μg/kg ww.
- For infant formula only few data on PBDE concentrations were submitted to EFSA, and the percentage of left-censored data ranged between 31 and 100%. For **BDE-49** and -**138**, fewer than six sample results were reported, which were all left-censored. The LB concentrations ranged between 0 and 0.006 (**BDE-209**) μg/kg ww, and the UB concentrations between < 0.001 and 0.028 (**BDE-209**) μg/kg ww.
- Occurrence data on PBDEs in European human milk were taken from pooled samples that were collected and analysed as part of the World Health Organisation/United Nations Environment Programme (WHO/UNEP) field studies between 2014 and 2019. The average levels ranged between 0.007 μg/kg lipid (**BDE-49**) and 0.326 μg/kg lipid (**BDE-47**).

4.2.2 | Exposure assessment

- The highest mean exposure to PBDEs at the LB across all congeners was estimated for the age groups of 'Toddlers' and 'Other children', with the tendency to decrease moving to the older age groups. The daily mean exposure to PBDEs at the UB generally decreases moving from the younger to the older age groups with 'Toddlers' having the highest exposure to all PBDE congeners.
- The highest mean exposure across the European dietary surveys was estimated for **BDE-209** followed by **BDE-47**.
  - For **BDE-209** the mean exposure ranged from 0.17 ('Elderly') to 5.98 ng/kg bw per day ('Toddlers') for the minimum LB and the maximum UB, respectively and the highest P95 exposure was estimated for **BDE-209** ranging from 0.34 ('Elderly') to 13.46 ng/kg bw per day ('Toddlers') for the minimum LB and the maximum UB, respectively.
  - For **BDE-47**, the mean exposure ranged from 0.08 ('Adults' and 'Very elderly') to 1.80 ng/kg bw per day ('Toddlers') for the minimum LB and the maximum UB, respectively. The highest P95 exposure ranged from 0.01 ('Infants') to 3.92 ng/kg bw per day ('Toddlers') for the minimum LB and the maximum UB, respectively.
- The lowest exposure for **BDE-49** and -**138** was estimated for 'Infants', whilst for **BDE-47**, and -**209** the lowest exposure was for 'Adults', and for **BDE-28**, -**99**, -**100, -153, -154** and -**183** it was for 'Elderly'.
- Consumption of 'Meat and meat products' and 'Fish, seafood, amphibians, reptiles and invertebrates' contributed the most to the dietary exposure to **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**183** and -**209**. For **BDE-49**, -**138** and -**154** the main food category contributing to the exposure was 'Animal and vegetable fats and oils and primary derivatives thereof'.
- An exposure scenario for formula fed infants resulted in daily exposure estimates for mean consumption between 0.0001 (**BDE-28**) and 0.35 (**BDE-209**) ng/kg bw at the LB, and between 0.71 (**BDE-183**) and 1.13 (**BDE-209**) ng/kg bw at the UB. For P95 infant formula consumption, the daily exposure estimates were between 0.0002 (**BDE-28**) and 0.43 (**BDE-209**) ng/kg bw at the LB, and between 0.88 (**BDE-183**) and 1.39 (**BDE-209**) ng/kg bw at the UB.
- An exposure scenario for breastfed infants, resulted in median daily exposure estimates for average human milk consumption between 0.03 (**BDE-49**) and 1.50 (**BDE-47**) ng/kg bw, and highest exposures estimates for **BDE-209**, -**153**, -**47** and -**99** (4.06, 3.77, 3.44 and 2.52 ng/kg bw per day, respectively). For high human milk consumption, the median exposures were around 50% higher, with estimates between 0.05 (**BDE-49**) and 2.25 (**BDE-47**) ng/kg bw per day, and highest exposure estimates of 6.09, 5.66, 5.16 and 3.79 ng/kg bw per day for **BDE-209**, -**153**, -**47** and -**99**, respectively.
- Exposure to PBDEs, especially to **BDE-209**, via dust and dermal contact is an additional source of exposure especially for children.
- Changes in concentrations of PBDEs during cooking and processing are mainly associated with changes in lipid content and moisture loss. **BDE-209** can undergo debromination to produce congeners with fewer bromine atoms, in line with degradation pathways observed in the environment. The few studies on PBDE metabolites indicate that in general MeO-PBDEs behave in the same way as parent PBDE compounds.

4.3 | Risk characterisation

- The Panel applied four tiers in the combined risk assessment of PBDEs as a sensitivity analysis for the effects of PBDEs:
- As a conservative first tier (**Tier 1**), the Panel used the lowest Reference Points for each of the four congeners with data (**BDE-47**, **-99**, **-153**, **-209**). For the congeners for which no Reference Points were identified (**BDE-28**, -**49**, -**100**, -**138**, -**154**, -**183**), the Panel applied the Reference Point of **BDE-47**, the congener with the most complete and robust toxicological data.

  - As a second tier (**Tier 2**), the Panel included only the four congeners with data, and used their lowest Reference Points.
  - In a third tier (**Tier 3**) the Panel included only the four congeners for which Reference Points for neurodevelopment were identified (**BDE-47**, **-99**, **-153**, **-209**).
  - In a fourth tier **(Tier 4)**, in order to investigate the impact of the lack of data for **BDE-153** and the uncertainties linked to its Reference Point, the Panel including only the three congeners for which Reference Points for neurodevelopment were identified and for which there are sufficient/robust data, i.e. **BDE-47**, **-99**, **-209**.

- For **Tier 1**, the MOETs for the mean exposure estimates were all above 25 for the LB estimates, while they were all below 25 for the UB exposures for all age groups. The MOETs for the P95 exposure estimates were above 25 for the LB estimates except for Toddlers and Other Children at the Median and Max exposure estimates, and for Adolescents at the Max exposure. For the UB estimates, they were all below 25 for all age groups.
- For **Tier 2**, the MOETs for the mean exposure estimates were all above 25 for the LB estimates, while they were all below 25 for the UB exposures for all age groups. The MOETs for the P95 exposure estimates were similar to those in Tier 1; they were above 25 for the LB estimates except for Toddlers and Other Children at the Median and Max exposure estimates, and for Adolescents at the Max exposure. For the UB estimates, they were all below 25 for all age groups.
- Comparing the results of Tier 1 with Tier 2, it was concluded that exposure to the congeners for which there are no toxicological data (**BDE-28**, -**49**, -**100**, -**138**, -**154**, -**183**) does not have a great impact provided that they are not more toxic than **BDE-47**.
- For **Tier 3**, and similar to Tier 2, the MOETs for the mean exposure estimates were all above 25 for the LB estimates, while they were all below 25 for the UB exposures for all age groups. The MOETs for the P95 exposure estimates were above 25 for the LB estimates except for Toddlers at the Max exposure, and they were all below 25 for the UB estimates for all age groups.
- For **Tier 4**, the MOETs at the mean and P95 exposure were all well above 25 (typically several orders of magnitude higher) for all age groups.
- The CONTAM Panel concluded that estimates of exposure according to Tier 1, 2 and 3 raise a health concern at the LB P95 estimates in some surveys of Toddlers, Other children and Adolescents. There are large uncertainties in the estimates of hazard/risk due to the lack of toxicological data on most of the congeners. The estimates indicate no health concern for Tier 4. However, the Panel emphasises that Tier 4 is not representative of dietary exposure to all of the PBDEs considered.
- Comparing the results from Tiers 1 to 3 with those of Tier 4, demonstrates the importance of the Reference Point for **BDE-153** in its contribution to the MOET. This was the lowest Reference Point and the one with the highest uncertainty.
- For formula fed infants, for Tier 1, 2 and 3 the estimates of exposure were above 25 when considering the LB estimates and below 25 when considering the UB estimates. For Tier 4, the MOETs were in all cases above 25. The Panel noted the uncertainty in the exposure estimates due to the large difference between the LB and UB estimates.
- For breastfed infants, the MOETs were calculated, and for Tier 1, 2 and 3 the MOETs obtained were all below 25, while for Tier 4 they were above 25. However, based on the body burden approach, the CONTAM Panel concluded that, the MOETs based on median human milk levels do not raise a health concern for the median exposure.
- An uncertainty analysis was performed. It was concluded with more than 90% certainty[71] that the 10 congeners considered in the Opinion are either not genotoxic *in vivo* or, if they were genotoxic *in vivo*, this would be by a thresholded indirect mechanism.
- The risk assessment was affected by considerable uncertainties, including left-censored occurrence data (as indicated by the contrasting MOETs for LB and UB exposures), lack of occurrence data for some relevant food categories, the uncertainty of the Reference Point for **BDE-153**, the lack of neurotoxicity data for 6 out of the 10 congeners considered, and lack of reproductive/developmental toxicity data for seven congeners.
- All of the identified uncertainties were taken into account in a quantitative uncertainty analysis using expert knowledge elicitation. For half of the dietary surveys considered, the CONTAM Panel concluded with more than 70% certainty that the mean of the combined potency-adjusted exposure estimates for the 10 congeners for Toddlers raises a health concern for reproductive/developmental toxicity effects.
  The certainty of a health concern is higher at the P95 of the combined potency-adjusted exposure estimates and in the surveys with higher exposures, e.g. there is a maximum of more than 90% certainty of a health concern for reproductive/developmental effects at the P95 for Toddlers.
  The probability of a health concern is lower for neurobehavioural effects than for reproductive/developmental effects, e.g. for half of the surveys considered, there is more than 50% certainty at the mean of the combined potency-adjusted exposure estimates for Toddlers. The probability of a health concern is lower for both categories of effects in Adults than in Toddlers, reflecting the differences in exposure between age groups, but for reproductive/developmental effects, is still greater than 60% for the maximum survey at the P95 exposure.
- Overall, the CONTAM Panel concluded that the resulting MOETs support the conclusion that it is likely that current dietary exposure to PBDEs in the European population raises a health concern.

[71]Probabilities assessed by the uncertainty analysis are reported in conclusions as % certainty for the more probable outcome, following EFSA's guidance on communication of uncertainty (EFSA, 2019).

5 | RECOMMENDATIONS

In order to refine the risk assessment and reduce the uncertainties, the CONTAM Panel made the following recommendations:

- As numerous products containing PBDEs are still in use, and end-of-life disposal may result in environmental contamination and consequently their presence in food, surveillance of PBDEs should continue with more sensitive analytical methods, including determination of congeners other than the 10 PBDEs included in the TORs.
- More data on occurrence of PBDEs in infant formula are needed, with more sensitive analytical methods, to enable a more robust exposure assessment for formula fed infants.
- Additional information on human toxicokinetics, e.g. absorption, half-life values and biotransformation of PBDE congeners is needed. More information is needed on the body burden in mothers and in relation to transfer of PBDE to the fetus and during lactation. This information should be used to develop a toxicokinetic model for PBDEs, including excretion into breast milk and placental transfer.
- Information is needed that would allow hazard identification and characterisation for the individual PBDE congeners included in the Terms of Reference for which such data are lacking, in particular for **BDE-153**, and especially related to reproduction/development and neurobehaviour with perinatal exposure. Studies should be conducted with characterised individual congeners of high purity.
- Information to develop adverse outcome pathways is needed, especially related to neurobehaviour, reproduction/development and effects on thyroid function. This would enable prediction of hazard of congeners which have not been studied, and help to refine the integrated assessment.
- Additional effort is needed to align adverse effects observed in humans with endpoints observed in animal studies. Further research should focus on assessment of combined exposure to multiple PBDE congeners and other chemicals.

6 | DOCUMENTATION AS PROVIDED TO EFSA

Malisch R and Schächtele A, 2021. Data provided to EFSA by Rainer Malisch and Alexander Schächtele on the PBDEs-related results of the WHO/UNEP coordinated exposure studies 2001–2019 performed in European countries, and used in **Sections 3.1.1.4.1**, **3.3.1** and **3.4**. Also reported in Schächtele A, Malisch R, Hardebusch B, van Leeuwen R, Moy G, Tritscher A, van Duursen, van den Berg M, Šebková K, Klánová J and Kalina JM, 2023. WHO- and UNEP-coordinated human milk studies 2000–2019: Findings of polybrominated substances (PBDE, HBCDD, PBB 153, PBDD/PBDF). In: Persistent organic pollutants in human milk (eds. Malisch R, Fürst P and Šebková K), Springer Nature, 2023.

ABBREVIATIONS

ADHD	attention deficit hyperactivity disorder
ALH	amplitude of lateral head displacement
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate aminotransferase
BCF	bioconcentration factor
BDNF	brain derived neurotropic factor
BFRs	brominated flame retardants
BMD	Benchmark dose
BMDL	Benchmark dose lower confidence limit
BMDL10	Benchmark dose lower confidence limit for a benchmark response of 10%
BMFs	biomagnification factors
BMI	body mass index
BMR	Benchmark response
bw	body weight
CAR	constitutive androstane receptor
CAS	Chemical Abstracts Service
CYP	cytochrome P450
CONTAM	Panel on Contaminants in the Food Chain
DP	dechlorane plus
dw	dry weight
E2	oestradiol
ECD	electron capture detection
eNOS	endothelial nitric oxide synthase
EQS	Environmental quality standard
ET-1	endothelin-1
EURL	European Reference Laboratory
Fs	furans

GC	gas chromatography
GIC	Groningen Infant COMPARE birth cohort
GSH	glutathione
HBCDDs	hexabromocyclododecanes
ICAM-1	intercellular adhesion molecule 1
InhB	inhibin B
LB	lower bound
LC	liquid chromatography
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LOD	limit of detection
LOEL	lowest-observed-effect level
LOQ	limit of quantification
LPB	lower probability bound
UPB	upper probability bound
MAE	microwave-assisted extraction
MDA	malondialdehyde
MeO-PBDEs	methoxylated PBDEs
MOE	margin of exposure
MOET	combined margin of exposure
MS	mass spectrometry
NIPH	Norwegian Institute of Public Health
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
OH-PBDEs	hydroxylated PBDEs
PAHs	polycyclic aromatic hydrocarbons
PBDD/Fs	polybrominated dioxins and furans
PBDEs	polybrominated diphenyl ethers
PBPK	physiologically based pharmacokinetic
PBT	persistent, bioaccumulative and toxic
PCBs	polychlorinated biphenyls
PCNA	proliferation cell nuclear antigen
POPs	persistent organic pollutants
PXR	pregnane-X-receptor
RBC	red blood cell
ROS	reactive oxygen species
SFE	supercritical fluid extraction
SH group	thiol group
SHBG	sex hormone-binding globulin
SOD	superoxide dismutase
T2D	type 2 diabetes
T3	triiodothyronine
T4	thyroxine
TBARS	thiobarbituric acid reactive substance
TBBPA	Tetrabromobisphenol A
TDS	total diet study
TOF	time-of-flight
TSH	thyroid hormone
TT3	total triiodothyronine
TT4	total thyroxine
UB	upper bound
UNEP	United Nations Environment Programme
UV	ultraviolet
VAP	average path velocity
VCL	sperm curvilinear velocity
WBC	white blood cell
WHO	World Health Organization
ww	wet weight

ERRATUM

The opinion was revised to correct the values of the human chronic dietary intake corresponding to the body burden at the BMDL of BDE-209 for reproductive and neurodevelopmental effects. The overall conclusions were not changed, but amendments to correct the values concerned were made in the following sections: 3.1.5.4 Chronic human dietary intake corresponding to the body burden at the BMDL, 3.4 Risk characterisation (Tables 45 and 46), Section 3.5.4.1 Uncertainty analysis using plausible ranges and distributions (Table 50), Summary, Conclusions, Annex G Calculation of the combined margin of exposure (MOET), Annex H Uncertainty analysis (Tables H.9, H.10, H.11, H.12 and Figure H.2). To avoid confusion, the original version of the output has been removed from the EFSA Journal, and remains available on request.

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CONFLICT OF INTEREST

If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

REQUESTOR

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PANEL MEMBERS

Margherita Bignami, Laurent Bodin, James Kevin Chipman, Jesús del Mazo, Bettina Grasl-Kraupp, Christer Hogstrand, Laurentius (Ron) Hoogenboom, Jean-Charles Leblanc, Carlo Stefano Nebbia, Elsa Nielsen, Evangelia Ntzani, Annette Petersen, Salomon Sand, Dieter Schrenk, Tanja Schwerdtle, Christiane Vleminckx and Heather Wallace.

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APPENDIX A

Overview of the content of common PBDE technical products

TABLE A.1 Composition of technical PBDE products (concentrations in % w/w) (WHO, 1994).

Technical product	tetraBDEs	pentaBDEs	hexaBDEs	heptaBDEs	octaBDEs	nonaBDEs	decaBDE
PentaBDE	24–38	50–60	4–8				
OctaBDE			10–12	44	31–35	10–11	< 1
DecaBDE						< 3	97–98

TABLE A.2 Concentrations (%, w/w) of PBDE congeners in selected **PentaBDE** technical products (La Guardia et al., 2006).

	Technical PentaBDE products	
PBDE congener	**DE-71**	**Bromkal 70-5DE**
BDE-17	0.07	0.05
BDE-28/33	0.25	0.1
BDE-75	< 0.02	ND
BDE-51	< 0.02	ND
BDE-49	0.74	0.36
BDE-48/71	< 0.02	ND
BDE-47[a]/74	38.2	42.8
BDE-68/42	0.53	0.21
BDE-102	0.15	ND
BDE-100	13.1	7.82
BDE-99	48.6	44.8
BDE-97/118	< 0.02	0.12
BDE-85	2.96	2.16
BDE-126/155[a]	0.21	0.67
BDE-154	4.54	2.68
BDE-144	ND	ND
BDE-153	5.44	5.32

Abbreviation: ND, not detected.

[a]Major congener of coeluting pair.

TABLE A.3 Concentrations (%, w/w) of PBDE congeners in selected **OctaBDE** and **DecaBDE** technical products (La Guardia et al., 2006; Environment Canada, 2010).

	Commercial OctaBDE products		Commercial DecaBDE products	
PBDE congener	**DE-79**	**Bromkal 79-8DE**	**Saytex 102E**	**Bromkal 82ODE**
BDE-154	1.07	0.04	ND	ND
BDE-144	0.1	0.12	ND	ND
hexaBDE[a]	< 0.02	ND	ND	ND
BDE-153	8.66	0.15	ND	ND
BDE-139	ND	ND	ND	ND
BDE-140	< 0.02	ND	ND	ND
BDE-138	0.62	ND	ND	ND
BDE-184	< 0.02	< 0.02	ND	ND
heptaBDE[a]	< 0.02	ND	ND	ND
BDE-175/**183**	42	12.6	ND	ND
BDE-191	< 0.02	ND	ND	ND
BDE-180	1.7	ND	ND	ND
BDE-171	1.81	0.17	ND	ND
BDE-201	0.78	< 0.02	ND	ND
BDE-197	22.2	10.5	ND	0.03
BDE-203	4.4	8.14	ND	0.07
BDE-196	10.5	3.12	ND	0.46
BDE-194	< 0.02	ND	ND	ND
octaBDE1[a]	< 0.02	ND	ND	ND
BDE-208	0.19	< 0.02	ND	0.07
BDE-207	11.5	11.2	0.24	4.1
BDE-206	1.38	7.66	2.19	5.13
BDE-209	1.31	49.6	96.8	91.6

Abbreviation: ND, not detected.

[a]Categorised only based on degree of bromination.

APPENDIX B

Levels in dust from European countries

TABLE B.1 Occurrence of PBDEs in dust in European countries.

Reference	Country Sampling place	Sampling year	Median (range), mean (ng/g)		
			PBDEs		BDE-209
D'Hollander et al. (2010)	**Belgium** Homes ($n=43$) Offices ($n=10$)	2008	**BDE-47** **BDE-99** **BDE-100** **BDE-153** **BDE-154** BDE-197 BDE-196 BDE-203	Homes: 27 (4–1214), 104 Offices: 138 (59–10,880), 1256	Homes: 313 (< 5–5295), 590 Offices: 1513 (69–11,574), 443
Kalachova et al. (2012)	**Czech Republic** Homes ($n=25$) Car ($n=27$)	2008–2009	Sum **BDE-28**, **-47**, **-49**, -66, -85, **-99**, **-100**, **-153**, **-154**, **-183** Sum **BDE-28**, **-47**, **-49**, -66, -85, **-99**, **-100**, **-153**, **-154**, **-183**, -196, -197, -203, -206, -207, **-209**	Homes: 44.8 (< LOQ–484.1), 78.3 Car: 3.6 (< LOQ–846.8), 48.8 Homes: 501.0 (84–5896), 896.1 Car: 214.6 (< LOQ–33,728.0), 3722.7	Homes: 375.4 (40.69–5480.9), 724.1 Car: 168.5 (< 5–32,575.2), 3523.2
Thuresson et al. (2012)	**Sweden** Houses ($n=10$) Apartments ($n=34$) Offices ($n=10$) Day-care centres ($n=10$) Cars ($n=4$)	2006	Sum **BDE-28**, **-47**, **-49**, -66, -77, -85, **-99**, **-100**, **-153**, **-154**, **-183**, -207, -203, -197, -206, -207, **-209**	Houses: 510 (53–4000) Apartments: 1400 (13–100,000) Offices: 1200 (800–13,000) Day care centres: 1200 (420–3900) Cars: 1400 (54–30,000)	320 (51–3600) 1100 (< 50–1000,000) 780 (540–12,000) 580 (180–3500) 1300 (50–28,000)
Björklund et al. (2012)	**Sweden** Homes ($n=19$) Vacuum cleaner bags Researcher-collected dust	2008	Sum **BDE-28**, **-47**, **-49**, -66, -85, **-99**, **-100**, **-153**, **-154**, **-183**, -197, -203, -206, -207, -208, **-209**	Vacuum cleaner bags: 380 (170–8000), 540 Researcher-collected dust: 1100 (500–15,000), 1400	Vacuum cleaner bags: 280 (110–6600), 340 Researcher-collected dust: 520 (190–9300), 600
Muenhor and Harrad (2012)	**UK** Home ($n=112$)	2007–2009	**BDE-47** **BDE-99** BDE-17, **-28**, **-47**, **-49**, -66, -85, **-99**, **-100**, **-153**, **-154**	4.1–210 6.8–560 21–1000	NA
Król et al. (2014)	**Poland** Homes ($n=12$)	2012	Sum **BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**, **-183**, **-209**	232 (< MDL–701), 264	219 (7.1–615), 241

TABLE B.1 (Continued)

Reference	Country Sampling place	Sampling year	Median (range), mean (ng/g) PBDEs		BDE-209
Fromme et al. (2014)	**Germany** Homes (vacuum cleaners) ($n = 20$)	2010	Sum **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183**	42 (6–1546), 132	950 (10–3748), 1233
Blanchard et al. (2014)	**France** Homes ($n = 16$–30)	2011	**BDE-28** **BDE-47** BDE-85 **BDE-99** **BDE-100** BDE-119 **BDE-153** **BDE-154**	(< 0.06–< 1.8) 0.07 (< 0.06–0.23) (< 0.06–< 1.8) < 0.06 (< 0.06–0.28) (< 0.06–< 1.8) (< 0.06–< 1.8) (< 0.06–< 1.8) (< 0.06–< 1.8)	< 0.50 (< 0.50–1.7)
Besis et al. (2014)	**Greece** Cars ($n = 30$)	2016	Sum BDE-15, -17, -**28**, -71, -**47**, -66, -77, -**100**, -119, -**99**, -85, -**154**, -**153**, -**138**, -**183**, -181, -203, -207, -206, -**209**	2888 (132–54,666), 9231	2830 (109–37,729), 7624
Sahlström et al. (2015b)	**Sweden** Homes ($n = 27$)	2009–2010	Sum **BDE-28**, -**47**, -**99**, -**100**, -**153**, -196, -197, -203, -206, -207, -208, -**209**	418 (184–310,000), 774	310 (143–310,000), 464
Newton et al. (2015)	**Sweden** Offices ($n = 5$) Apartments ($n = 4$) Stores ($n = 4$) Schools ($n = 2$)	2012	**BDE-47** **BDE-99** **BDE-100** **BDE-153** **BDE-154**	18 (< 0.35–150), 16 38 (< 3.5–200), 32 7.6 (< 0.31–35), 6.2 8.7 (< 0.54–32), 6.9 4.7 (< 0.29–19), 4.2	130 (< 1.3–2600), 90
Lankova et al. (2015). Multi-analyte method for the analysis of various organohalogen compounds in house dust	**Czech Republic** Homes ($n = 18$)	2013	**BDE-47** **BDE-49** BDE-66 **BDE-99** **BDE-153** **BDE-154** **BDE-183** BDE-206 BDE-207	3.44 (< 1–17.8), 2.11 (< 1–3.84) (< 1–14.9) (< 1–8.31) (< 1–4.24) (< 1–2.26) (< 1–7.24) 3.87 (< 5–22.4), 6.89 4.42 (< 5–33.3), 7.11	(< 25–1830)
Coelho, Sousa, Isobe, Kim, et al. (2016)	**Portugal** Homes (vacuum cleaner bags) ($n = 28$)	2010–2011	Sum **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183** Sum **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183**, -**209**	16 (4.5–190), 34 300 (34–9200). 810	270 (24–9200), 780

(Continues)

TABLE B.1 (Continued)

Reference	Country Sampling place	Sampling year	Median (range), mean (ng/g) PBDEs		BDE-209
Tao et al. (2016)	**UK** Homes ($n=45$) Offices ($n=47$)	2013–2015	**BDE-28** **BDE-47** **BDE-100** **BDE-99** **BDE-154** **BDE-153** **BDE-183** Sum **BDE-28**, **-47**, **-100**, **-99**, **-154**, **-153**, **-183**, **-209**	Homes: 0.16 (< 0.03–15), 1.9 Offices: 3.9 2.6 < 0.03–22 Homes: 13 (< 0.04–50), 14 Offices: 83 (7.1–660), 37 Homes: 3 (0.74–16), 4.2 Offices: 18 (1.9–120), 12 Homes: 22 (5–91), 31 Offices: 100 (15–480), 77 Homes: 1.2 (< 0.06–9.3), 2 Offices: 7.7 (0.8–68), 3.9 Homes: 3 (0.025–24), 4.8 Offices: 28 (0.025–190), 9.2 Homes: 3.5 (< 0.13–51), 7.4 Offices: 29 (0.065–220), 9.8 4600 (180–370,000)	Homes: 4500 (160–370,000), 34,000 Offices: 2700 (200–110,000), 9100
Al-Omran and Harrad (2016)	**UK** Home ($n=40$) Living room and bedroom	2013–2014	Sum **BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**, **-183**	53.2 (18.2–116.4), 59.5	2655 (1637–6279), 2986
Kuang et al. (2016)	**UK** Homes ($n=30$) Kitchen Living room	2015	**BDE-28** **BDE-47** **BDE-99** **BDE-100** **BDE-153** **BDE-154** **BDE-183**	Kitchen: 1.2 (< 0.2–150) Living room: 1.0 (< 0.2–55) Kitchen: 7.6 (0.4–940) Living room: 13590 2.4 Kitchen: 17 (2.6–1400) Living room: 33 (4.0–930) Kitchen: 1.7 < 0.2–320) Living room: 3.2 (0.7–1409) Kitchen: 1.7 (0.1–410) Living room: 1.9 (< 0.4–170) Kitchen: 0.4 (< 0.4–180) Living room: 0.7 (< 0.4–60) Kitchen: 1.9 (< 1.0–29) Living room: 4.2 (0.6–120)	Kitchen: 590 (22–32,000) Living room: 1500 (170–170,000)
Bramwell, Harrad, et al. (2017)	**UK** Living rooms ($n=11$) Bedrooms ($n=12$) Vehicles ($n=8$) Workplace ($n=10$)	2011–2012	**BDE-47, -99, -153, -183, -209**	Living rooms: 137 (25.5–1060) Bedrooms: 102 (28.4–7325) Vehicles: 179 (88.1–677) Workplace: 83.6 (16.6–1500)	Living rooms: 2960 (126–106,000) Bedrooms: 3530 (33–107,000) Vehicles: 13,300 (315–137,000) Workplace: 1030 (728–4950)
Al-Omran and Harrad (2017)	**UK** Home ($n=36$) Living room, Bedroom, Vacuum cleaner	2014–2015	Sum **BDE-28**, **-47**, **-99**, **-100**, **-153**, **-154**	Living room: 40.7 (6.8–135), 47.3 Bedroom: 33.5 (8.9–147), 41.4 Vacuum cleaner: 22.4 (12.3–41.5), 24.4	Livingroom: 3066 (466–4184), 2642 Bedroom: 2232 (1175–3944), 2336 Vacuum cleaner: 2462 (1534–3779), 2634

TABLE B.1 (Continued)

Reference	Country Sampling place	Sampling year	Median (range), mean (ng/g)		
			PBDEs		BDE-209
Raffy et al. (2017)	**France** Schools (vacuum cleaning) ($n = 30$)	2009–2010	**BDE-99**	< 40	n.a.
Tay et al. (2017)	**Norway** Homes ($n = 61$)	2013–2014	Sum **BDE-28**, -35, -**47**, -**49**, -66, -77, -85, -**99**, -**100**, -**153**, -**154**, -182, -**183**, -184, -191, -196, -197, -203, -206, -207, -208, -**209**	1200 (160–13,000), 1800	940 (106–8800), 1300
Kurt-Karakus et al. (2017)	**Istanbul/Turkey** *Urban, Semi-urban and Rural location* Office dust, Home dust	2012	Sum BDE-17, -**28**, -**47**, -66, -85, -**99**, -**100**, -**138**, -**153**, -**154**, -**183**, -**209**	*Urban location* Office dust: 2500 (330–32,000), 10,000 Home dust: 2500 (400–2800), 1900 *Semi-urban location* Office dust:1500 (1000–11,000), 4400 Home dust: 1200 (540–2700), 1400 *Rural location* Office dust: NA Home dust: 1800 (420–13,000), 4900	NR
Larsson et al. (2018)	**Sweden** Preschool dust ($n = 100$)	2015	**BDE-47** **BDE-99** **BDE-100** **BDE-153**	7.7 (< 1.5–600), 9.6 9.2 (< 1.4–430), 11 1.6 (< 0.44–120), 2.2 (< 0.30–29)	270 (41–3200), 270
Wemken et al. (2019)	**Ireland** Homes ($n = 29$) Cars ($n = 28$) Offices ($n = 31$)	2016–2017	Sum BDE-17, -**28**, -**47**, -**49**, -66, -**99**, -**100**, -**153**, -**154**, -**183**, -196, -197	Homes: 49 (10–940), 130 Cars: 150 (0.094–690), 200 Offices: 30 (2.8–770), 77	Homes: 13,000 (140–460,000), 58,000 Cars: 26,000 (14–680,000), 82,000 Offices: 3500 (560–150,000), 4200
Drage et al. (2020)	**UK** Houses ($n = 14$)	2019	Sum BDE-17, -**28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183**, -**209**	Houses: 1700 (21–18,000)	Houses: 1600 (21–18,000)
de la Torre et al. (2020)	**Italy** **Spain** **Belgium** Houses in Belgium ($n = 22$), Italy ($n = 22$), Spain ($n = 21$)	2016–2017	Sum **BDE-28**, -**49** + 71, -**47**, -**100**, -**99**, -85, -**154**, -**153**, -184, -**183**, -201, -204 + 197, -203, -196, -208, -207, -206, -**209**	Belgium: 210 (4.32–10,322) Italy: 283 (7.7–2703) Spain: 176 (25.3–13,073)	Belgium: 181 (< 0.86–9854) Italy: 232 (5.36–2470) Spain: 151 (15.1–12,339)

(Continues)

TABLE B.1 (Continued)

Reference	Country Sampling place	Sampling year	Median (range), mean (ng/g)		
			PBDEs		BDE-209
Akcetin et al. (2020)	**Turkey** Car dust samples ($n=62$)	2018	BDE-17 **BDE-28** **BDE-47** BDE-66 BDE-71 BDE-85 **BDE-99** **BDE-100** **BDE-138** **BDE-153** **BDE-154** **BDE-183** Sum PBDEs (including **BDE-209**)	109.8 13.6 14.6 60.7 100.4 40.3 59.5 34.7 79.1 85.3 39.5 71.2 339.6	212.5
Simonetti et al. (2020)	**Italy** Dust samples Houses ($n=2$) Workplaces ($n=3$)	2019	**BDE-47** BDE-66 **BDE-99** **BDE-100** **BDE-153** **BDE-154** **BDE-183** Sum **BDE-28**, -**47**, -**49, -66**, -85, -**100**, -**99**, -**154**, -**153**, -**183**, -197, -**209**	Houses: 19.6 Workplaces: 30.8 Houses: 0 Workplaces: 53.8 Houses: 37.4 Workplaces: 46.3 Houses: 34.2 Workplaces: 29.2 Houses: 0 Workplaces: 16.1 Houses: 6.4 Workplaces: 5.5 Houses: 12.4 Workplaces: 73.7 Houses: 100.6 Workplaces: 986.6 All mean values	Houses: 0 Workplaces: 2368.0
Pasecnaja et al. (2021)	**Latvia** Houses ($n=34$)	2016–2018	Sum BDE-17, -**28**, -**47**, -**49**, -66, -**99**, -**100**, -**153**, -**154**, -155, -**183**, -**209**	Houses: 1600 (468–25,500)	Houses: 1510 (384–25,400)
Dubocq et al. (2021)	**Sweden** House ($n=7$) Office ($n=6$) School ($n=11$) Work environment ($n=6$)	2019	**BDE-28**, -**47**, -85, -**99**, -**100**, -**153**, -**154**, -**183** Only detected congeners: **BDE-99**, **-47**	**BDE-47** House: (< LOQ–138) Office: (< LOQ–83.4) Work environment: (< LOQ–161) **BDE-99** Office: (< LOQ–54.1) School: (< LOQ–40.9)	NA
Jagić et al. (2021)	**Croatia** Homes ($n=10$)	2018–2019	Sum **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183**	Homes: (17,662.4–1.1)	NA
Besis et al. (2021)	**Greece** Homes ($n=21$)	2017	Sum BDE-15, -17, -**28**, -71, -**47**, -66, -77, -**100**, -119, -**99**, -85, -**154**, -**153**, -**138**, -**183**, -181, -203, -207, -206, -**209**	Homes: 427 (50.7–1710), 564	Homes: 366 (40.4–1590) 458
Esplugas et al. (2022)	**Spain** Office ($n=5$) School ($n=5$) Homes ($n=10$)	2019–2020	Sum **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183, -209**	Office, school and homes: 668 (183–2444), 831	Office, school and homes: 660 (142–2368) 774

TABLE B.1 (Continued)

Reference	Country Sampling place	Sampling year	Median (range), mean (ng/g)		
			PBDEs		BDE-209
Strid et al. (2014)	**Sweden** Aircraft: during maintenance work in aircraft Aircraft: during flight (ventilation outlets in aircraft toilets)	2012	Sum **BDE-28**, -**47**, -**99**, -**100**, -**153**, -**154**, -**183**, -**209**	Maintenance: (30–5400) Flight: (2.1–28)	Maintenance: (8.4–1200) Flight: (3.1–11)
Allen et al. (2013)	Aircraft at an international airport ($n = 40$) Floor Vent	2010	**BDE-28**/33 **BDE-47** **BDE-99** **BDE-100** **BDE-153** **BDE-154** **BDE-183**	Floor: 54 (5.3–270) Vent 33 (0.8–140) Floor: 950 (280–17,000) Vent: 3500 (230–19,000) Floor: 950 (330–37,000) Vent: 4200 (360–35,000) Floor: 180 (43–8900) Vent: 630 (45–6100) Floor: 230 (65–5300) Vent: 630 (33–4700) Floor: 120 (33–4700) Vent: 280 (24–3400) Floor: 620 (200–5500) Vent: 390 (76–9100)	Floor: 495,000 (210,000–2,100,000) Vent: 473,000 (190,000–2600,000)

Abbreviations: NA, not analysed; NR, not reported.

APPENDIX C

Literature search to identify studies on PBDEs

Information on physicochemical properties, production and industrial use, environmental fate and levels, analytical methods, previous assessments and legislation was gathered from the previous EFSA Opinion on PBDEs (EFSA CONTAM Panel, 2011b), assessments by international bodies (by checking the original websites of the relevant organisations) and from current EU legislation. Literature searches were also conducted to identify new information in reviews and other peer-reviewed publications, also in the fields of previously reported occurrence data and exposure assessments, food processing and non-dietary exposure. The information was summarised in a narrative way based on expert knowledge and judgement.

Details of the literature search performed are shown in Table C.1 Search strings were run in the databases indicated. The literature searches were performed in August 2019. The outcome of the searches was saved in separate EndNote files and an automatic duplicate detection run. The references were then transferred to DistillerSR (a web-based systematic review software) where another automatic duplicate detection was again made. The selection for relevance based on title and abstract and full text was done by EFSA staff and WG members.

Since that date, the literature was monitored via WoS – Web of Science to identify studies relevant for the risk assessment until the time of endorsement.

TABLE C.1 Details of the literature search.

Databases interrogated	WoS – Web of science, PubMED
Year	2010-date of the search (13 August 2019)
Languages	English
Type of documents	Peer reviewed articles, reviews, books
Key words in the search strings	Polybrominated diphenyl ethers, PBDEs, chemistry, analytical methods, food, dust, dietary exposure, non-dietary, human milk, breast milk, blood, serum, adipose tissue, fat, sediments, water, biota, environment
***N* hits**	A total of 603 references (after duplicate removal in EndNote and DistillerSR) underwent title/abstract screening in Distiller SR and were divided per field of interest: • Analytical methods and chemistry • Environment • Occurrence in food • Dietary exposure • Non-dietary exposure • Human samples
Grey literature	Assessments done by national and international bodies (e.g. in Google or from papers, ECHA, NTP). – if appropriate, dedicated search in Organohalogen Compounds database (extended abstracts from DIOXIN conferences).

APPENDIX D

Studies reporting on the levels of PBDE metabolites in human tissues

TABLE D.1 Studies reporting on the levels of PBDE metabolites in human tissues.

Country Matrix Sampling year	PBDEs	PBDE metabolites	Reference
EUROPEAN COUNTRIES			
The Netherlands Maternal serum (pregnant women) ($n = 90$), Cord blood ($n = 12$) 2001–2002	*Median (range), ng/g lipid* Maternal serum: **BDE-47:** 0.8 (0.04–6.1) **BDE-99:** 0.2 (ND-2.1) **BDE-100:** 0.2 (0.03–1.4) **BDE-153:** 1.6 (0.3–20) **BDE-154:** 0.5 (0.1–3.5) Cord serum: **BDE-47:** 0.5 (0–2.2) **BDE-99:** 0.1 (0–0.4) **BDE-100:** 0.1 (0–0.5) **BDE-153:** 0.9 (0.2–2.2) **BDE-154:** 0.3 (0.1–0.7)	*Median (range), ng/g serum* Maternal serum: **6-OH-BDE-47:** ND Cord serum: **6-OH-BDE-47:** ND	**Meijer et al. (2008)**. Serum concentrations of neutral and phenolic organohalogens in pregnant women and some of their infants in the Netherlands
Belgium Serum (adults) ($n = 274$) 2015	NA	*Mean (SD), pg/mL* **5-OH-BDE-47:** < LOQ (max < LOQ) **5′-OH-BDE-99:** < LOQ (max 8.2) **6-OH-BDE-47:** < LOQ (max 4.5) **2,3,6-TBP**: < LOQ (max < LOQ) **2,4,5-TBP**: < LOQ (max < LOQ) **2,4,6-TBP**: 81,2 (108) **2,3,4,6-Tetrabromophenol**: < LOQ (max 51.1)	**Dufour et al. (2017)**. Determination of phenolic organohalogens in human serum from a Belgian population and assessment of parameters affecting the human contamination

(Continues)

TABLE D.1 (Continued)

Country Matrix Sampling year	PBDEs	PBDE metabolites	Reference
Non-European countries			
Nicaragua (municipal waste disposal site) Serum (children) (***n*** = 10 pools, 131 individual samples in total) 2002	*Range of pools, pmol/g lipid* **BDE-28:** Waste disposal: 1.7–24 Referents: 0.22–0.44 **BDE-47:** Waste disposal: 57–680 Referents: 11–30 BDE-66: Waste disposal: 0.51–12 Referents: 0.29–0.63 BDE-85: Waste disposal: 1.8–35 Referents: 0.26–1.1 **BDE-99:** Waste disposal: 18–309 Referents: 4.2–12 BDE-100: Waste disposal: 16–111 Referents: 2.0–8.4 **BDE-153:** Waste disposal: 15–47 Referents: 2.1–5.3 BDE-154: Waste disposal: 5.1–22 Referents: 1.8–4.3 **BDE-183:** Waste disposal: 1.7–2.5 Referents: 1.0–3.9 **BDE-209:** Waste disposal: 3.1–9.3 Referents: 4.7–16 Sum PBDEs: Waste disposal: 125–1250 Referents: 30–72	*Range of pools, pmol/g lipid* **4′-OH-BDE-17:** Waste disposal: 0.58–13 Referents: 0.27–0.76 **6-OH-BDE-47:** Waste disposal: 4.5–13 Referents: 1.4–2.4 **3-OH-BDE-47:** Waste disposal: 0.33–6.5 Referents: < LOQ–0.32 **4′-OH-BDE-49:** Waste disposal: 0.56–18 Referents: 0.28–0.96 **4-OH-BDE-42:** Waste disposal: 0.56–9.6 Referents: < LOQ–0.32 **4-OH-BDE-90:** Waste disposal: 0.48–54 Referents: < LOQ–0.70 **Sum OH-PBDEs:** Waste disposal: 9.5–120 Referents: 3.1–5.6	**Athanasiadou et al. (2008)**. Polybrominated diphenyl ethers (PBDEs) and bioaccumulative hydroxylated PBDE metabolites in young humans from Managua, Nicaragua

TABLE D.1 (Continued)

Country Matrix Sampling year	PBDEs	PBDE metabolites	Reference
Japan Maternal blood ($n = 16$), Human milk ($n = 8$), Cord blood ($n = 8$), Umbilical cord ($n = 16$) 2005–2006	*Mean (SD), pg/g wet*[a] Maternal blood **BDE-28:** 0.54 (0.94) **BDE-47:** 7.3 (15) **BDE-49:** 0.19 (0.33) **BDE-99:** 1.2 (2.7) **BDE-100:** 1.3 (1.7) **BDE-138:** NR **BDE-153**: 2.9 (0.97) **BDE-154**: 0.084 (0.19) **BDE-183**: < LOQ **BDE-209**: 7.0 (3.7) Human milk: **BDE-28:** 8.1 (10) **BDE-47:** 84 (160) **BDE-49:** 2.5 (3.2) **BDE-99:** 15 (28) **BDE-100:** 11 (12) **BDE-138:** NR **BDE-153:** 13 (5.8) **BDE-154:** 1.0 (1.3) **BDE-183:** 0.10 (0.29) **BDE-209:** < LOQ Cord blood: **BDE-28:** 0.23 (0.28) **BDE-47:** 3.0 (4.6) **BDE-49:** 0.064 (0.12) **BDE-99:** 0.35 (0.62) **BDE-100:** 0.37 (0.44) **BDE-138:** NR **BDE-153:** 0.43 (0.28) **BDE-154:** < LOQ **BDE-183:** < LOQ **BDE-209:** < LOQ Umbilical cord: **BDE-28:** 0.10 (0.16) **BDE-47:** 1.6 (2.0) **BDE-49:** 0.036 (0.067) **BDE-99:** 0.57 (0.80) **BDE-100:** 0.25 (0.24) **BDE-138:** NR **BDE-153:** 0.26 (0.11) **BDE-154:** 0.030 (0.072) **BDE-183:** 0.0038 (0.015) **BDE-209:** NR	Maternal blood **6-OH-BDE-47**: 8.5 (12) **4′-OH-BDE-49**: < LOQ **6′-OH-BDE-49**: < LOQ **6-OH-BDE-99**:< LOQ Human milk: **6-OH-BDE-47**: NA **4′-OH-BDE-49**: NA **6′-OH-BDE-49**: NA **6-OH-BDE-99**: NA Cord blood: **6-OH-BDE-47**: 1.4 (2.0) **4′-OH-BDE-49**: < LOQ **6′-OH-BDE-49**: < LOQ **6-OH-BDE-99**: < LOQ Umbilical cord: **6-OH-BDE-47**: 8.4 (8.1) **4′-OH-BDE-49**: < LOQ **6′-OH-BDE-49**: < LOQ **6-OH-BDE-99**: < LOQ	**Kawashiro et al. (2008)**. Perinatal exposure to brominated flame retardants and polychlorinated biphenyls in Japan

(Continues)

TABLE D.1 (Continued)

Country Matrix Sampling year	PBDEs	PBDE metabolites	Reference
USA Maternal serum (pregnant women occupationally exposued to flame retardants) ($n = 4$), Umbilical cord blood ($n = 16$) 2003–2004	*Mean (SD), ng/g lipid* **BDE-28:** Umbilical cord: 2.3 (1.0) Maternal serum: 0.5 (0.2) Combined: 1.9 (0.8) **BDE-47:** Umbilical cord: 70 (36) Maternal serum: 17 (5.1) Combined: 60 (29) **BDE-99:** Umbilical cord: 22 (11) Maternal serum: 6.3 (1.9) Combined: 19 (8.6) **BDE-100:** Umbilical cord: 12 (5.5) Maternal serum: 3.0 (0.3) Combined: 9.9 (4.4) **BDE-153:** Umbilical cord: 9.4 (4.1) Maternal serum: 6.7 (2.5) Combined: 8.9 (3.2) **BDE-154:** Umbilical cord: 4.6 (2.4) Maternal serum: 1.2 (0.1) Combined: 3.8 (1.9) **Sum PBDEs:** Umbilical cord: 120 (55) Maternal serum: 34 (8.5) Combined: 100 (45)	*Mean (SD), ng/g lipid* **4′-OH-BDE-17:** Umbilical cord: ND Maternal serum: ND Combined: ND **2′-OH-BDE-28**: Umbilical cord: ND Maternal serum: ND Combined: ND **4-OH-BDE-42:** Umbilical cord: 0.9 ± (0.3) Maternal serum: ND Combined: 0.9 ± (0.3) **3-OH-BDE-47:** Umbilical cord: 1.6 (1.1) Maternal serum: 0.1 (0.02) Combined: 1.3 (0.8) **5-OH-BDE-47:** Umbilical cord: 28 (16) Maternal serum: 1.6 (0.5) Combined: 23 (13) **6-OH-BDE-47:** Umbilical cord: 9.9 (4.9) Maternal serum: 0.3 (0.1) Combined: 7.9 (4.0) **4′-OH-BDE-49:** Umbilical cord: 0.9 (0.2) Maternal serum: 0.3 (0.06) Combined: 0.7 (0.2) **5′-OH-BDE-99:** Umbilical cord: 22 (15) Maternal serum: 2.0 (0.6) Combined: 18 (12) **6′-OH-BDE-99:** Umbilical cord: 1.9 (1.0) Maternal serum: 0.3 (0.04) Combined: 1.5 (0.8) **2,4-DBP:** Umbilical cord: 20 (12) Maternal serum: 1.5 (0.5) Combined: 16 (9.6) **2,4,5-TBP:** Umbilical cord: 7.9 (6.0) Maternal serum: 0.2 (0.03) Combined: 6.4 (4.8) **2,4,6-TBP:** Umbilical cord: 5.6 (1.3) Maternal serum: 0.8 (0.3) Combined: 4.6 (1.1) **Sum OH-PBDEs + BPs:** Umbilical cord: 97 (55) Maternal serum: 7.0 (1.7) Combined: 79 (44)	**Qiu et al. (2009)**. Hydroxylated metabolites of polybrominated diphenyl ethers in human blood samples from the United States

TABLE D.1 (Continued)

Country Matrix Sampling year	PBDEs	PBDE metabolites	Reference
South Korea Maternal serum ($n = 26$) Cord blood ($n = 28$) 2008–2009	NA	*Mean (SD), pg/g ww* **6-OH-BDE-47**: Maternal serum: 17.5 (26.3) Umbilical cord serum: 30.2 (27.1) **2′-OH-6′-Cl-BDE-7**: < LOD **6′-OH-BDE-17**: < LOD **4′-OH-BDE-49**: < LOD **2′-OH-6′-Cl-BDE-68**: < LOD **6-OH-BDE-90**: < LOD **2-OH-BDE-123**: < LOD **6-OH-BDE-137**: < LOD	**Wan et al. (2010)**. Hydroxylated polybrominated diphenyl ethers and bisphenol A in pregnant women and their matching foetuses: placental transfer and potential risks
China Blood plasma ($n = 62$ M, 54 F) 2011	*Mean (SD), pg/g lipid* **BDE-47:** M 1400 (860), F 2400 (3200) **BDE-28:** M 2600 (850), F 900 (1100) **BDE-99:** M 970 (730), F 1500 (1800) **Sum PBDEs:** M 9800 (13,000), F 9200 (17,000)	*Mean (SD), pg/g lipid* **6-OH-BDE-47:** M 60 (73), F 56 (61) **5′-OH-BDE-99:** M 16 (24), F 34 (33) **3-OH-BDE-100:** M 27 (44), F 7.1 (9.1) **3-OH-BDE-7:** M 23 (68), F 2.2 (5.1) **6-OH-BDE-85**: M 16 (31), F 3.8 (4.4) **Sum OH-PBDEs**: M 86 (105), F 83 (77) **3-MeO-BDE-47:** M 3100 (4000), F 5700 (9000) **2′-MeO-BDE-28:** M 1000 (900), F 780 (750) **2′-MeO-BDE-68:** M 210 (220), F 310 (250) **4′-MeO-BDE-49:** M 140 (110), F 370 (870) **5-MeO-BDE-47:** M 150 (150), F 140 (160) **6-MeO-BDE-47:** M 100 (110), F 95 (110) **Sum MeO-PBDEs:** M 4900 (4700), F 7800 (9700) **2,4,5-TBP:** M 17 (15), F 30 (18) **2,4,6-TBP:** M 12 (11), F 13 (14) **2,4-DBP:** M 2.0 (1.8), F 5.2 (5.4) **Sum BPs:** M 12 (16), F 17 (27)	**Wang, Chen, et al.** (2012). Hydroxylated and methoxylated polybrominated diphenyl ethers in blood plasma of humans in Hong Kong

(Continues)

TABLE D.1 (Continued)

Country Matrix Sampling year	PBDEs	PBDE metabolites	Reference
China Blood plasma ($n = 100$) Urine ($n = 100$) 2010	*Mean (95% CI), ng/g lipid* Blood plasma: **Sum PBDEs**: 4.45 (3.66–5.41)	*Mean (95% CI), ng/g lipid* Blood plasma: **Sum MeO-BDEs**: 0.42 (0.31–0.56) **Sum OH-BDEs**: 1.88 (1.53–2.29) **Sum BPs**: 1.59 (1.34–1.89) *Mean (95% CI), µg/g creatinine* Urine: **2,4-DBP glucuronide**: 0.32 (0.23–0.44) **2,4-DBP sulfate**: 0.11 (0.08–0.14) **2,4,6-TBP glucuronide**: 0.87 (0.58–1.30) **2,4,6-TBP sulfate**: 0.10 (0.08–0.13)	**Ho et al. (2012)**. Synthesis and characterisation of bromophenol glucuronide and sulfate conjugates for their direct LC–MS/MS quantification in human urine as potential exposure markers for polybrominated diphenyl ethers
USA Maternal/cord serum ($n = 20$ pairs) 2011	*Mean (range), ng/g lipid* Maternal serum: **BDE-28:** 1.02 (0.14–5.85) **BDE-47:** 12.5 (2.53–90.6) **BDE-99:** 3.89 (0.79–26.55) **BDE-100:** 1.50 (0.20–20.48) **BDE-153:** 5.46 (0.79–22.45) **BDE-154:** 0.36 (0.27–2.41) **BDE-209:** 4.28 (2.11–13.97) **Sum PBDEs:** 32.1 (7.46–176) Cord blood: **BDE-28:** 1.66 (0.41–6.76) **BDE-47:** 16.8 (7.29–95.65) **BDE-99:** 6.24 (2.26–25.07) **BDE-100:** 2.44 (0.57–20.14) **BDE-153:** 2.75 (0.58–15.92) **BDE-154:** 0.79 (0.76–1.83) **BDE-209:** 10.51 (6.06–60.93) **Sum PBDEs:** 45.5 (17.9–171)	*Mean (range), ng/g lipid* Maternal serum: **6-OH-BDE-47:** 4.61 (2.50–82.4) **5-OH-BDE-47:** 8.82 (3.40–84.1) **4′-OH-BDE-49:** 2.84 (2.50–12.2) **5′-OH-BDE-99:** 12.88 (8.20–140) **Sum OH-PBDEs:** 32.84 (16.6–231) Cord blood: **6-OH-BDE-47:** 6.60 (2.50–169) **5-OH-BDE-47:** 19.78 (3.40–167.8) **4′-OH-BDE-49:** 3.26 (2.50–21.1) **5′-OH-BDE-99:** 15.57 (8.20–226) **Sum OH-PBDEs:** 49.76 (16.6–446)	**Chen et al. (2013)**. Hydroxylated polybrominated diphenyl ethers in paired maternal and cord sera
Japan Human milk ($n = 9$) Blood serum ($n = 10$) 2005–2006	*Mean (SD), ng/g lipid* Human milk: **BDE-47**: 0.87 (0.74) **BDE-99**: 0.54 (0.51) **BDE-153:** 0.38 (0.18) Serum: **BDE-47**: 1.5 (0.4) **BDE-99**: < LOQ **BDE-153:** < LOQ	*Mean (SD), ng/g lipid* Human milk: **6-OH-BDE-47:** < LOQ **6-MeO-BDE-47:** 0.25 (0.19) **2,4,6-TBP:** 1.17 (0.75) Serum: **6-OH-BDE-47:** 172 (184) **6-MeO-BDE-47:** < LOQ **2,4,6-TBP:** 40.2 (30.1)	**Fujii et al. (2014)**. Dietary exposure to phenolic and methoxylated organohalogen contaminants in relation to their concentrations in breast milk and serum in Japan

TABLE D.1 (Continued)

Country Matrix Sampling year	PBDEs	PBDE metabolites	Reference
Tunisia Human milk ($n = 36$) 2010	*Mean (SD), ng/g lipid* **BDE-28**: 0.59 (0.44) **BDE-47:** 2.09 (1.20) **BDE-99:** 1.12 (0.68) **BDE-66:** 0.19 (0.21) **BDE-100**: 1.50 (0.91) **BDE-138:** 0.07 (0.10) **BDE-154**: 0.67 (0.73) **BDE-153:** 2.01 (1.82) **BDE-183:** 2.49 (1.92) **Sum PBDEs:** 10.74 (5.83)	*Mean (SD), ng/g lipid* **6-MeO-BDE-47**: 0.51 (0.57) **2′-MeO-BDE-68**: 0.27 (0.49) **4′-MeO-BDE-49**: 0.37 (0.61) **5′-MeO-BDE-100**: 0.39 (0.41) **Sum MeO-PBDEs**: 1.52 (1.08)	**Ben Hassine et al. (2012)**. Determination of chlorinated pesticides, polychlorinated biphenyls, and polybrominated diphenyl ethers in human milk from Bizerte (Tunisia) in 2010 **Ben Hassine et al. (2015)**. Methoxylated polybrominated diphenyl ethers (MeO-PBDE) in human milk from Bizerte, Tunisia
USA Adipose tissue ($n = 47$) 2003–2004	*Mean (SD), ng/g lipid* **BDE-28:** 0.31 (0.57) **BDE-47:** 6.00 (10.8) **BDE-85:** 0.33 (0.90) **BDE-99:** 2.27 (5.63) **BDE-100:** 2.22 (5.29) **BDE-119:** 0.03 (0.04) **BDE-153:** 5.78 (12.5) **BDE-154:** 0.96 (1.43) **BDE-183:** 0.07 (0.06) **BDE-206:** 0.69 (3.19) **BDE-207:** 1.20 (4.53) **BDE-208** 0.26 (1.25) **BDE-209** 5.27 (5.06) **Sum PBDEs**: 25.7 (35.3)	*Mean (SD), ng/g lipid* **6-OH-BDE-47**: 0.04 (0.09) **6-OH-BDE-90**: 0.43 (0.76) **Sum OH-PBDEs**: 0.54 (0.88) **2′-MeO-BDE-68**: 0.03 (0.03) **6-MeO-BDE-47**: 0.02 (0.02) **Sum MeO-PBDEs**: 0.07 (0.05) **2,4,6-TBP:** 5.05 (9.74)	**Gao et al. (2015)**. Organobromine compound profiling in human adipose: Assessment of sources of bromophenol
China (Hong Kong) Blood plasma ($n = 100$), Urine ($n = 100$) 2010	*Mean (95% CI),* Plasma *ng/g lipid* **Sum PBDEs**: 4.45 (3.66–5.41)	*Mean (95% CI),* Plasma *ng/g lipid* **Sum MeO-PBDEs**: 0.42 (0.31–0.56) **Sum OH-PBDEs**: 1.88 (1.53–2.29) **Sum BPs:** 1.59 (1.34–1.89) Urine *μg/g creatinine* **2,4-DBP glucuronide:** 0.32 (0.23–0.44) **2,4-DBP sulfate:** 0.11 (0.08–0.14) **2,4,6-TBP glucuronide:** 0.87 (0.58–1.30) **2,4,6-TBP sulfate:** 0.10 (0.08–0.13)	**Ho et al. (2015)**. Urinary bromophenol glucuronide and sulfate conjugates: Potential human exposure molecular markers for polybrominated diphenyl ethers
China Urine (adults) ($n = 10$) Sampling year NR	NA	*Mean (SD), μg/g creatinine [μg/L urine]* **2-BP:** 2.10 (1.58) [2.04 (4.33)] **4-BP:** 3.46 (2.35) [7.55 (8.40)] **2,4-DBP**: 0.66 (0.2) [0.65 (0.90)] **2,4,6-TBP:** 2.35 (0.91) [5.57 (4.05)]	**Feng, Xu, et al.** (2016). Determination of urinary bromophenols (BrPs) as potential biomarkers for human exposure to polybrominated diphenyl ethers (PBDEs) using gas chromatography-tandem mass spectrometry (GC–MS/MS)

(Continues)

TABLE D.1 (Continued)

Country Matrix Sampling year	PBDEs	PBDE metabolites	Reference
USA Serum ($n = 43$) 2008–2010	*Mean (SD), pg/g lipid* **BDE-28/33:** NA **BDE-47:** 13,400 (1000–18,100) **BDE-66:** NA **BDE-99:** 3600 (2600–5100) **BDE-100:** 2500 (1800–3500) **BDE-153:** 3800 (2800–5200) **BDE-154:** 430 (310–620) **BDE 183:** NA **Sum PBDEs:** 27,500 (21,000–35,800)	*Mean (SD), pg/g lipid* **5′-OH-BDE-99:** 62 (34–110) **6-OH-BDE-99:** NA **3-OH-BDE-47:** NA **4′-OH-BDE-49**: 29 (19–46) **6-OH-BDE-47**: NA **2,4,5-TBP:** NA **2,4,6-TBP:** 19,200 (15,700–23,400)	**Butt et al. (2016)**. Development of an analytical method to quantify PBDEs, OH-BDEs, HBCDs, 2,4,6-TBP, EH-TBB, and BEH-TEBP in human serum
China Mother-newborn paired placenta, human milk, fetal cord blood and neonatal urine samples ($n = 30$) 2012	*Median (min, max)* Placenta: *pg/g ww* **BDE-17**: 0.29 (0.02, 1.41) **BDE-28:** 0.44 (ND, 6.21) **BDE-47:** 6.73 (0.93, 36.4) **BDE-85:** ND (ND, ND) **BDE-99:** 0.89 (0.15, 1.77) **BDE-100:** ND (ND, 0.61) **BDE-138**: 0.50 (ND, 3.03) **BDE-153:** 0.64 (0.28, 4.83) **BDE-154**: 0.47 (ND, 1.87) **BDE-183:** 0.45 (ND, 1.85) **BDE-184:** 0.11 (ND, 0.98) **BDE-191:** ND (ND, 0.48) **BDE-196:** 0.50 (ND, 4.46) **BDE-197:** 0.39 (ND, 4.06) **BDE-206:** ND (ND, 0.49) **BDE-207:** ND (ND, 0.37) **BDE-209:** ND (ND, ND) **Sum PBDEs:** 12.7 (4.32, 42.0) Human milk: *pg/g ww* **BDE-17**: 0.35 (0.04, 1.42) **BDE-28:** 1.11 (0.27, 2.44) **BDE-47:** 3.84 (0.48, 8.36) **BDE-85:** ND (ND, 1.99) **BDE-99:** 0.62 (0.12, 5.53) **BDE-100:** 0.19 (ND, 0.55) **BDE-138**: 1.12 (ND, 2.77) **BDE-153:** 1.65 (ND, 7.13) **BDE-154**: 0.47 (ND, 5.87) **BDE-183:** 1.18 (ND, 11.03) **BDE-184:** ND (ND, 0.73) **BDE-191:** ND (ND, 0.47) **BDE-196:** ND (ND, 0.95) **BDE-197:** ND (ND, 0.53) **BDE-206:** ND (ND, 3.92) **BDE-207:** ND (ND, 0.79) **BDE-209:** ND (ND, 0.48)	*Median (min, max)* Placenta: *pg/g ww* **5′-OH-BDE-99:** 18.3 (ND, 59.3) **3-OH-BDE-7:** 2.81 (1.18, 4.31) **6-OH-BDE-47:** 1.72 (ND, 6.99) **2′-OH-BDE-28:** 7.01 (0.34, 79.6) **3-OH-BDE-100:** 2.34 (2.34, 2.34) **4-OH-BDE-90:** 3.75 (1.04, 42.5) **4-OH-BDE-42:** 3.27 (0.67, 50.8) **2′-OH-BDE-7:** 2.21 (ND, 58.9) **6-OH-BDE-85:** 102 (15.0, 189) **2′-OH-BDE-68:** 2.59 (0.87, 44.1) **6-OH-BDE-90:** 1.63 (0.50, 134) **6′-OH-BDE-99:** 1.88 (0.58, 129) **4′-OH-BDE-17:** 0.44 (0.44 0.44) **3-OH-BDE-47:** 1.09 (ND, 15.2) **2′-OH-BDE-66:** 0.34 (0.22, 8.59) **Sum OH-PBDEs:** 41.3 (ND, 654) **2,4-DBP:** 13.6 (ND, 623) **2,4,5-TBP:** 12.4 (0.75, 234) **2,4,6-TBP:** 7.54 (0.39, 178) **Sum BPs:** 56.2 (3.13, 866) Human milk: *pg/g ww* **5′-OH-BDE-99:** 7.07 (1.50, 22.1) **3-OH-BDE-7: 1**2.7 (4.06, 20.3) **6-OH-BDE-47:** 1.84 (0.67, 4.00) **2′-OH-BDE-28:** 13.0 (0.52, 83.0) **3-OH-BDE-100:** 4.95 (2.82, 11.4) **4-OH-BDE-90:** 10.2 (4.28 28.6) **4-OH-BDE-42:** 12.4 (1.75, 31.6) **2′-OH-BDE-7:** 7.55 (0.74, 61.8) **6-OH-BDE-85:** 9.87 (9.87, 9.87) **2′-OH-BDE-68:** 4.23 (1.25, 16.8) **6-OH-BDE-90:** 4.70 (0.53, 16.3) **6′-OH-BDE-99:** 1.89 (0.48, 8.68) **4′-OH-BDE-17:** 2.52 (2.52, 2.52) **3-OH-BDE-47:** 3.73 (0.90, 43.4)	**Chen, Liu, et al.** (2016). Hydroxylated polybrominated diphenyl ethers (OH-PBDEs) in paired maternal and neonatal samples from South China: Placental transfer and potential risks **Chen, Liu, et al.** (2014)**.** Polybrominated diphenyl ethers (PBDEs) in human samples of mother-newborn pairs in South China and their placental transfer characteristics

TABLE D.1 (Continued)

Country Matrix Sampling year	PBDEs	PBDE metabolites	Reference
	Sum PBDEs: 11.4 (3.96, 39.39) Cord blood: *pg/g ww* **BDE-17**: 0.04 (ND, 0.32) **BDE-28:** 0.10 (ND, 0.70) **BDE-47:** 3.82 (ND, 18.16) **BDE-85:** ND (ND, 1.59) **BDE-99:** 0.35 (ND, 1.59) **BDE-100:** ND (ND, 0.88) **BDE-138**: 0.46 (ND, 8.87) **BDE-153:** 0.57 (ND, 12.9) **BDE-154**: 0.45 (ND, 1.83) **BDE-183:** ND (ND, 7.37) **BDE-184:** ND (ND, 0.79) **BDE-191:** ND (ND, 0.57) **BDE-196:** 1.29 (ND, 24.8) **BDE-197:** 1.24 (ND, 23.4) **BDE-206:** ND (ND, 1.12) **BDE-207:** ND (ND, 0.51) **BDE-209:** ND (ND 0.40) **Sum PBDEs:** 9.73 (1.02, 71.3) Urine: *pg/mL* **BDE-17**: 0.03 (ND,0.26) **BDE-28:** 0.09 (ND, 0.46) **BDE-47:** 0.32 (ND, 1.82) **BDE-85:** ND (ND, 0.20) **BDE-99:** 0.05 (ND, 0.55) **BDE-100:** ND (ND, 0.09) **BDE-138**: 0.10 (ND, 0.89) **BDE-153:** 0.16 (ND, 1.29) **BDE-154**: ND (ND, 0.59) **BDE-183:** 0.12 (ND, 1.10) **BDE-184:** ND (ND, 0.08) **BDE-191:** ND (ND, 0.05) **BDE-196:** ND (ND, 2.48) **BDE-197:** ND (ND, 2.34) **BDE-206:** ND (ND, 0.39) **BDE-207:** ND (ND, 0.08) **BDE-209:** ND (ND, 0.05) **Sum PBDEs:** 1.17 (ND, 7.12)	**2′-OH-BDE-66:** 2.08 (0.32, 5.72) **Sum OH-PBDEs:** 62.8 (20.3, 127) **2,4-DBP:** 98.4 (3.41, 522) **2,4,5-TBP:** 27.5 (3.41, 70.2) **2,4,6-TBP:** 7.76 (0.80, 67.0) **Sum BPs:** 129 (19.3, 536) Cord blood: *pg/g ww* **5′-OH-BDE-99:** 35.0 (2.41, 65.5) **3-OH-BDE-7:** 13.5 (0.30, 219) **6-OH-BDE-47:** 7.71 (0.52, 23.3) **2′-OH-BDE-28:** 7.68 (0.65, 117) **3-OH-BDE-100:** 18.2 (7.67, 90.8) **4-OH-BDE-90:** 4.68 (0.72, 65.4) **4-OH-BDE-42:** 7.64 (0.34,117) **2′-OH-BDE-7:** 1.40 (1.40, 1.40) **6-OH-BDE-85:** 6.35 (6.35, 6.35) **2′-OH-BDE-68:** 4.70 (0.56, 31.3) **6-OH-BDE-90:** 4.15 (0.90, 21.0) **6′-OH-BDE-99:** 3.88 (3.88, 3.88) **4′-OH-BDE-17:** 3.36 (0.59, 22.4) **3-OH-BDE-47:** 4.40 (0.76, 67.7) **2′-OH-BDE-66:** 2.63 (0.36, 41.6) **Sum OH-PBDEs:** 75.5 (17.1, 390) **2,4-DBP:** 6.79 (0.45, 177) **2,4,5-TBP:** 16.5 (0.74, 297) **2,4,6-TBP:** 6.67 (0.50, 95.0) **Sum BPs:** 29.4 (2.93, 568) Urine: *pg/mL* **5′-OH-BDE-99:** 14.0 (ND, 138) **3-OH-BDE-7:** 25.6 (1.17, 87.7) **6-OH-BDE-47:** 10.6 (ND, 84.8) **2′-OH-BDE-28:** 1.36 (ND, 4.85) **3-OH-BDE-100:** 5.51 (ND, 102) **4-OH-BDE-90:** 1.21 (ND, 3.09) **4-OH-BDE-42:** 2.16 (ND, 14.8) **2′-OH-BDE-7:** 2.66 (ND, 8.46) **6-OH-BDE-85:** 2.76 (ND, 25.7) **2′-OH-BDE-68:** 7.59 (5.23, 21.6) **6-OH-BDE-90:** 3.98 (ND, 78.7) **6′-OH-BDE-99:** 14.7 (5.18, 29.9) **4′-OH-BDE-17:** 2.53 (1.37, 4.67) **3-OH-BDE-47:** ND (ND, ND) **2′-OH-BDE-66:** 4.98 (1.58, 12.7) **Sum OH-PBDEs:** 71.2 (8.41, 329) **2,4-DBP:** 44.5 (0.65, 916) **2,4,5-TBP:** 23.9 (1.47, 239) **2,4,6-TBP:** 9.74 (0.30, 103) **Sum BPs:** 29.4 (2.93, 568)	

(Continues)

TABLE D.1 (Continued)

Country Matrix Sampling year	PBDEs	PBDE metabolites	Reference
USA Serum ($n = 5$) Sampling year NR	NA	*Range, ng/g lipid* **4-OH-BDE-42:** ND–0.554. **3-OH-BDE-47:** < LOQ–1.07 **5-OH-BDE-47**: < LOQ–3.54 **6-OH-BDE-47:** ND–0.985 **4′-OH-BDE-49:** < LOQ–0.772 **4-OH-BDE-90**: ND–0.274 **5′-OH-BDE-99:** ND–3.82	**Gross et al. (2016)**. Analysis of hydroxylated polybrominated diphenyl ethers (OH-BDEs) by supercritical fluid chromatography/mass spectrometry
Japan Serum (adult women) ($n = 20$) 2007–2009	*Mean (SD), ng/g lipid* **BDE-28:** 0.15 (0.08) **BDE-47:** 1.45 (0.68) **BDE-99:** 0.57 (0.49) **BDE-100:** 0.32 (0.22) **BDE-153:** 1.20 (0.45) **BDE-154:** 0.49 (0.26) **Sum 6 PBDEs:** 4.16 (1.58)	*Mean (SD), ng/g lipid* **6-OH-BDE-47:** 31.4 (22.3) **2′-OH-BDE-68:** 1.43 (1.38) **2′,6-diOH-BDE-68:** 0.12 (0.39) **Sum OH-PBDEs:** 33.0 (23.6) **2′-MeO-BDE-68:** 0.92 (0.79)	**Haraguchi et al. (2016).** Levels, profiles and dietary sources of hydroxylated PCBs and hydroxylated and methoxylated PBDEs in Japanese women serum samples
China (e-waste area) Human milk ($n = 25$ from women who did not directly participate in e-waste recycling operations and had > 20 years residence time in villages heavily involved in e-waste recycling, $n = 21$ from women considered as the control group) 2012–2013	*Mean (SD), ng/g lipid* **BDE-28:** Cases: 1.23 (0.83) Controls: 10.40 (0.43) **BDE-47:** Cases: 3.05 (5.56) Controls: 0.54 (0.41) **BDE-100:** Cases: 0.60 (0.60) Controls: 0.13 (0.14) **BDE-99:** Cases: 1.00 (0.89) Controls: 0.22 (0.18) **BDE-154:** Cases: 2.32 (4.35) Controls: 0.15 (0.08) **BDE-153:** Cases: 8.89 (8.45) Controls: 1.58 (1.26) **BDE-183:** Cases: 1.25 (1.05) Controls: 0.51 (0.48) **BDE-209**: Cases: 7.37 (9.01) Controls: 3.31 (3.94) **Sum PBDEs:** Cases: 25.70 (20.0) Controls: 6.68 (5.61)	**3-OH-BDE-47:** ND **2′-OH-BDE-68:** ND **6-OH-BDE-47**: ND **4′-OH-BDE-49:** ND **4-OH-BDE-42:** ND **6′-OH-BDE-99:** ND **4-OH-BDE-90**: ND **6-OH-BDE-85**: ND	**Li, Tian, et al.** (2017). Accumulation of polybrominated diphenyl ethers in breast milk of women from an e-waste recycling center in China

TABLE D.1 (Continued)

Country Matrix Sampling year	PBDEs	PBDE metabolites	Reference
USA Maternal serum ($n = 85$), Fetal liver ($n = 85$), Placenta ($n = 50$), Cord blood ($n = 22$) 2011–2014	*Mean (SD), ng/g lipid* Maternal serum **BDE-28:** 2.22 (2.17) **BDE-47:** 25.24 (2.02) **BDE-99:** 5.18 (2.70) **BDE-100:** 3.34 (2.80) **BDE-153:** 7.22 (3.04) **Sum PBDEs:** 48.75 (1.96) Fetal Liver **BDE-28:** 0.88 (2.30) **BDE-47:** 14.09 (2.08) **BDE-99:** 3.88 (2.50) **PBDE-100:** 2.52 (2.58) **BDE-153:** 3.72 (3.30) **Sum PBDEs:** 28.34 (1.95) Placenta **BDE-28:** det freq ≤ 50% **BDE-47:** 13.21 (2.04) **BDE-99:** 2.51 (3.13) **BDE-100:** det freq ≤ 50% **BDE-153:** det freq ≤ 50% **Sum PBDEs:** 20.44 (2.05) Cord serum **BDE-28:** 7.97 (1.71) **BDE-47:** 67.08 (1.92) **BDE-99:** det freq ≤ 50% **BDE-100**: 7.92 (2.59) **BDE-153:** det freq ≤ 50% **Sum PBDEs:** 111.12 (19.91)	*Mean (SD), ng/g* Maternal serum **5-OH-BDE-47:** 0.0035 (3.78) **6-OH-BDE-47:** 0.0043 (3.21) **5-OH-BDE-99:** det freq ≤ 50% **4-OH-BDE-49:** det freq ≤ 50% **Sum OH-PBDEs**: 0.015 (2.76) Fetal Liver **5-OH-BDE-47:** det freq ≤ 50% **6-OH-BDE-47:** det freq ≤ 50% **5-OH-BDE-99:** det freq ≤ 50% **4-OH-BDE-49:** det freq ≤ 50% **Sum OH-PBDEs:** 0.0042 (2.16) Placenta **5-OH-BDE-47:** det freq ≤ 50% **6-OHBDE-47:** 0.0014 (2.80) **5-OH-BDE-99:** det freq ≤ 50% **4-OH-BDE-49:** det freq ≤ 50% **Sum OH-PBDEs**: 0.0038 (2.45) Cord serum **5-OH-BDE-47:** 0.0065 (3.27) **6-OH-BDE-47:** det freq ≤ 50% **5-OH-BDE-99:** det freq ≤ 50% **4-OH-BDE-49:** det freq ≤ 50% **Sum OH-PBDEs**: 0.016 (2.51)	**Zota, Mitro, et al.** (2018). Polybrominated diphenyl ethers (PBDEs) and hydroxylated PBDE metabolites (OH-PBDEs) in maternal and fetal tissues, and associations with fetal cytochrome P450 gene expression
USA Serum (pregannt women) ($n = 111$) 2008–2014	*Mean (SD), ng/g* **BDE-28:** 2008–2009: 2.32 (1.68) 2011–2012: 1.18 (2.26) 2014: 2.72 (2.31) **BDE-47:** 2008–2009: 43.1 (1.7) 2011–2012: 25.8 (2.03) 2014: 24.6 (2.02) **BDE-99:** 2008–2009: 11.5 (1.82) 2011–2012: 5.04 (2.78) 2014: 4.89 (2.78) **BDE-100:** 2008–2009: 9.00 (1.86) 2011–2012: 4.6 (2.27) 2014: 2.41 (3.55) **BDE-153:** 2008–2009: 15.5 (1.82) 2011–2012: 10.9 (2.17) 2014: 4.75 (3.81) **Sum PBDEs:** 2008–2009: 85.8 (1.24) 2011–2012: 51.6 (1.29) 2014: 43.6 (1.28)	*Mean (SD), ng/mL* **6-OH-BDE-47:** 2008–2009: 0.025 (2.4) 2011–2012: 0.004 (3.91) 2014: 0.004 (4.04) **5-OH-BDE-47:** 2008–2009: 0.028 (3.5) 2011–2012: 0.004 (5.00) 2014: 0.0021 (5.50)	**Parry et al. (2018).** Polybrominated diphenyl ethers (PBDEs) and hydroxylated PBDE metabolites (OH-PBDEs): A six-year temporal trend in Northern California pregnant women

(Continues)

TABLE D.1 (Continued)

Country Matrix Sampling year	PBDEs	PBDE metabolites	Reference
USA Plasma ($n = 113$) ($n = 29$ e-waste workers, $n = 57$ office workers, $n = 27$ outdoor workers) 2013–2015	*Mean (range), ng/g lipid* **Sum PBDEs**: e-waste: 26.6 (3.6–157.3) Indoor: 27.2 (2.1–45.5) Outdoor: 50.6 (6.6–306)	*Mean (range), ng/g lipid* **4-OH-BDE-17:** e-waste: 1.72 (0.70–6.11) Indoor: 1.24 (0.31–10.4) Outdoor: 1.89 (0.34–9.02) **5-OH-BDE-47:** e-waste: 4.79 (0.27–24.2) Indoor: 3.57 (0.23–53.2) Outdoor: 4.49 (1.10–30.6) **6-OH-BDE-47:** e-waste: 2.06 (0.54–18.0) Indoor: 1.52 (0.48–15.3) Outdoor: 2.58 (0.65–22.6) **5-OH-BDE-99:** e-waste: 1.52 (0.30–7.91) Indoor: 1.50 (0.30–11.8) Outdoor: 2.06 (0.58–8.10) **Sum OH-PBDEs:** e-waste: 8.94 (0.27–67.9) Indoor: 9.12 (0.54–102) Outdoor: 8.11 (0.34–54.4) **4-MeO-BDE-17:** e-waste: 0.97 (0.39–31.7) Indoor: 0.84 (0.28–53.2) Outdoor: 0.78 (0.33–8.63) **4-MeO-BDE-103:** e-waste: 0.76 (0.35–3.17) Indoor: 0.79 (0.33–2.30) Outdoor: 0.91 (0.38–3.01) **Sum MeO-PBDEs:** e-waste: 2.55 (0–33.7) Indoor: 2.48 (0.32–60.4) Outdoor: 3.50 (0–26.2)	**Schultz et al. (2020)**. Occupational and dietary differences in hydroxylated and methoxylated PBDEs and metals in plasma from Puget Sound, Washington, USA region volunteers **Kuo et al. (2019).** Polybrominated diphenyl ethers (PBDEs) in plasma from E-waste recyclers, outdoor and indoor workers in the Puget Sound, WA region

Abbreviations: DPB, dibromophenol; LOQ, limit of quantification; NR, not reported; TBP, tribromophenol.

[a]The following PBDEs were also analysed and reported: BDE-3, -7, -15, -17, -66, -71, -77, -85, -119, -126, -156, -184, -191, -196, -197, -206, -207.

APPENDIX E

Repeated dose toxicity studies in experimental animals

TABLE E.1 Summary of the outcomes of the toxicological studies of the tetraBDE **BDE-47** in experimental animals, excluding studies on neurotoxicity (see Table E.6).

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-47 100% (Accustandard Corp.)	Pregnant Sprague–Dawley rats 30 pregnant rats. After parturition: adjustment to 8 pups per litter M, F (1:1)	Single dose at PND10 Oral (gavage) 0, 1, 5, 10 mg/kg bw Vehicle: corn oil Pups dosed at PND10, tested at 2 months old	No clinical signs of dysfunction, no effect on body weight, body length and tail length Increased relative weight of ovaries at the two highest doses, decreased relative uterus weight in treated animals, decreased relative thyroid weight at the highest dose Decreased concentration of TT4 at the medium dose Increased concentration of **BDE-47** in serum at the two highest doses	LOAEL = 1 mg/kg bw	**He et al. (2011)**. Toxic effect of PBDE-47 in thyroid development, learning and memory, and the interaction between PBDE-47 and PCB153 that enhances toxicity in rats
BDE-47 > 99% (ChemServices)	Wistar rats 5–8 M and 5–8 F per dose group Dams, pups F dosed, offspring tested	Repeated exposure Oral (feed) 0, 3.2, 32 mg/kg feed (corresponding to 0, 0.384, 3.84 mg/kg bw per day[a]) Vehicle: Tween 20 GD1 to PND14	No clinical signs of toxicity Decreased body weight of offspring at the highest dose (at PND7 and PND14) Dose-dependent reductions in TT3 and TT4 levels in dams at PND1, neonates at PND7 and both dams and neonates at PND14 Serum and cortex concentrations of **BDE-47** increased with exposure time in dams but decreased in neonates	LOAEL = 3.2 mg/kg feed (corresponding to 0.384 mg/kg bw per day)	**Wang, Liu, et al. (2011).** Interaction of PFOS and BDE-47 co-exposure on thyroid hormone levels and TH-related gene and protein expression in developing rat brains
BDE-47 Purity and supplier NR	B6 mice 10 animals per dose group Adults (6–8 weeks old) M	Repeated exposure Oral (gavage) 0, 0.0015, 0.045, 30 mg/kg bw per day Vehicle: corn oil 30 days	No effect on body weight, testis weight or sperm morphology Decreased sperm motility. Lower B-type (capacitated) sperm rates. Some seminiferous tubules from mice treated with two highest doses exhibited complete germ cell loss and had a Sertoli cell-only phenotype. The observed germ cell loss may have been caused by increased apoptosis	The Panel noted limitations in the data reporting and in the statistical analysis performed. Therefore no reliable LOAEL could be determined	**Wang et al. (2013).** Adverse effects of 2,2′,4,4′-tetrabromodiphenyl ether on semen quality and spermatogenesis in male mice

(Continues)

TABLE E.1 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-47 100% (Prochem)	BALB/c mice 10 animals per dose group (15 animals in control group) Juvenile (22 days old) F	Repeated exposure Oral (feed) 0, 0.45 mg/kg bw per day 28 days	Increased incidence of vacuolation and pyknotic nuclei in hepatocytes, and lymphocytic infiltration in periportal areas Spleen displayed a significant increase in: – presence of follicular hyperplasia with germinal centre development and lymphocytic infiltration involving the red pulp (spleen). – presence of lymphocyte apoptosis, marker of tissue damage and Hassal's bodies (thymus). – presence of cellular debris in follicular lumen (thyroid).	LOAEL = 0.45 mg/kg bw per day	**Maranghi et al. (2013)**. Dietary exposure of juvenile female mice to polyhalogenated seafood contaminants (HBCD, BDE-47, PCB-153, TCDD): comparative assessment of effects in potential target tissues
BDE-47 ≥ 98.7% (Chemservice)	Sprague–Dawley rats 10 animals per dose group Adult M	Repeated exposure Oral (gavage) 0, 0.001, 0.03, 1 mg/kg bw per day Vehicle: corn oil 8 weeks (6 consecutive days per week)	**Testes**: changes in the normal cellular organisation of the seminiferous epithelium. Increased number of multinucleated giant cells in the lumen at the two highest doses. Abundant vacuolar spaces in the seminiferous epithelium at the highest dose. Decreased number of spermatids and daily sperm production. Decreased testosterone level.	LOAEL = 0.001 mg/kg bw per day	**Zhang, Sun, et al. (2013)**. Cytochrome P450 3A1 Mediates 2,2′,4,4′-Tetrabromodiphenyl Ether-Induced Reduction of Spermatogenesis in Adult Rats.
BDE-47 Purity NR (Chem Service Inc.)	Sprague–Dawley rats 10 animals per dose group Adult M	Repeated exposure Oral (gavage) 0, 0.001, 0.03, 1, 20 mg/kg bw per day Vehicle: corn oil 8 weeks	**Testes**: dose-related decrease relative seminiferous epithelial thickness (statistically significant at the three highest doses), increased apoptotic germ cells adjacent to the basement membrane in the XI–XII stage of spermatogenesis In the three highest dose groups, morphological characteristics of apoptosis (shrinkage of cytoplasm, condensed or marginated chromatin, nuclear debris, aggregation and swelling of mitochondria with a loss of cristae appearing as vacuolated mitochondria) observed	NOAEL = 0.001 mg/kg bw per day	**Huang, Cui, et al. (2015)**. 2,2′,4,4′-Tetrabromodiphenyl ether disrupts spermatogenesis, impairs mitochondrial function and induces apoptosis of early leptotene spermatocytes in rats
BDE-47 Purity not reported (Accustandard Inc.)	Wt, Alb^{Cre}; $Tsc1^{fl/fl}$, and Alb^{Cre}; $Pten^{fl/fl}$, male mice (liver specific KO) on diverse genetic background Young (3–6 weeks old) mice following weaning M	Repeated exposure Oral (gavage) 0, 1 mg/kg bw per day Vehicle: corn oil 6 weeks	**BDE-47** did not affect glucose tolerance, insulin sensitivity, liver somatic index or white adipose tissue in wild type Pten KO mice impaired insulin sensitivity and increased glucose tolerance without a significant difference in fasting glucose concentration compared to the Tsc1 KO and wild type mice	NOAEL = 1 mg/kg bw per day	**McIntyre et al. (2015)**. Polybrominated diphenyl ether congener, BDE-47, impairs insulin sensitivity in mice with liver-specific Pten deficiency
BDE-47 99.9% (AccuStandard Inc.)	Mice $Gclm^{+/+}$ 4–5 animals per dose group Pups (10 days) M	Single dose on PND10 Oral (gavage) 0, 10 mg/kg bw Vehicle: corn oil 1 day	No changes in TT3, TT4, FT3 or FT4	LOAEL = 10 mg/kg bw	**Costa et al. (2015)**. The brominated flame retardant BDE-47 causes oxidative stress and apoptotic cell death *in vitro* and *in vivo* in mice

TABLE E.1 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-47 100% (AccuStandard Corp.)	Sprague–Dawley rats 10 pups per dose group 10-day old pups F	Single dose on PND10 Oral (gavage) 0, 1, 5, 10 mg/kg bw Vehicle: corn oil PND10 to 2 months old	**Ovary**: ovarian coefficient was significantly lower in all BDE-47 treated groups. Thinning of the ovarian granular cell layer and corpus luteum observed at the two lowest doses. Reduction of ovarian granular cell layer, graafian follicles and oocytes and increased corpus luteum observed at the highest dose	LOAEL = 1 mg/kg bw	**Wang et al. (2016)**. Roles of endoplasmic reticulum stress, apoptosis and autophagy in 2,2′,4,4′-tetrabromodiphenyl ether-induced rat ovarian injury
BDE-47	Sprague–Dawley rats 10 rats per group Adults M	Repeated exposure Oral (gavage) 0, 0.001, 0.03, 1 mg/kg bw per day Vehicle: corn oil 8 weeks (6 days per week)	Shallow but dose-dependent increase fasting glucose (significant at all doses). No change serum insulin. No effects on serum cholesterol or triglyceride concentrations. Microvesicular steatosis observed in liver sections of rats treated with 1 mg/kg bw per day but not at lower doses Effects on sugar metabolism was supported by transcriptomics analysis of the liver carried out on rats exposed to 0.03 mg/kg bw per day and the control		**Zhang, Li, Liu, et al. (2016)**. Environmental exposure to BDE47 is associated with increased diabetes prevalence: Evidence from community-based case–control studies and an animal experiment
BDE-47 > 98.7% (Chemservice)	Sprague–Dawley rats Six animals per dose group Adults M	Repeated exposure Oral (gavage) 0, 0.03, 20 mg/kg bw per day With or without high-fat diet Vehicle: corn oil 12 weeks	Accumulation of **BDE-47** in liver and testis **Liver**: micro and macrovesicular steatosis in rats treated with BDE-47 Reduction testosterone concentration in treated animals **Testes**: disruption of the normal cellular organisation of the seminiferous epithelium in treated animals. At the highest dose, significant increase in the number of multinucleated giant cells in the lumen that arose from spermatocytes and aborted meiosis. Abundant vacuolar spaces in the seminiferous epithelium after BDE-47 treatment **Epididymes**: reduction of sperm, particularly in presence of high-fat diet	LOAEL = 0.03 mg/kg bw per day	**Zhang, Yu, et al. (2017)**. High-fat diet aggravates 2,2′,4,4′-tetrabromodiphenyl ether-inhibited testosterone production via DAX-1 in Leydig cells in rats

(Continues)

TABLE E.1 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-47 98% (Toronto Research Chemicals)	Pregnant ICR mice 10–11 animals per dose group Adults F	Repeated exposure Oral (gavage) 0, 0.36, 3.6, 36 mg/kg bw per day Vehicle: ethanol/corn oil (1:9 v/v) Dosing from GD13.5 to GD16.5 (4 days) Sacrifice at GD17.5 for the evaluation of hormonal and gene expression changes. Birth weights monitored between GD18.5 to GD19.5	**Dams**: no effect on liver weight Increased low birth weight at the highest dose Reduction plasma testosterone and progesterone levels at the highest dose Increased rates of stillborn at the two highest doses Decreased growth hormone peptide expression at 3.6 mg/kg bw per day in the placental tissue extracted at GD17.5	NOAEL = 0.36 mg/kg bw per day	**Zhu et al. (2017)**. Exposure to 2,2′,4,4′-tetrabromodiphenyl ether at late gestation modulates placental signalling molecules in the mouse model
BDE-47 100% (AccuStandard Inc.)	CD-1 mice Five dams per dose group Adults (dams) Pups: 21 days F dosed, M pups tested	Repeated exposure Oral (Gavage) 0, 0.2 mg/kg bw per day Vehicle: tocopherol-stripped corn oil GD8 until PND21. Analysed on day 21 and PNW20	No effect on litter size, no effect on dams or pups body weight. No changes in absolute liver weight or adipose tissue	NOAEL = 0.2 mg/kg bw per day	**Khalil, Parker, Mpanga, et al. (2017)**. Developmental Exposure to 2,2′,4,4′-tetrabromodiphenyl ether induces long-lasting changes in liver metabolism in male mice
BDE-47 100% (AccuStandard Inc)	Wistar rats Seven dams per dose group Adults (7 weeks old) F dosed, M offspring tested	Repeated exposure Oral (gavage) 0, 0.2 mg/kg bw per day Vehicle: corn oil GD8 to PND21, analysed on PND120	No effect on litter size. No effect on body weight of dams or pups No changes in serum testosterone on PND120. **Testes**: decrease weight (absolute, relative), decrease sperm production and motility (not statistically significant), significant increase percentage of morphologically abnormal spermatozoa (missing tail or head, misshapen head, bent, coiled, thick, pronged or short tail, and drop-like thickenings in the distal or proximal part of the tail), and increase in spermatozoa head size	LOAEL = 0.2 mg/kg bw per day	**Khalil, Parker, Brown, et al. (2017)**. Perinatal exposure to 2,2′,4′4′ -Tetrabromodiphenyl ether induces testicular toxicity in adult rats

TABLE E.1 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-47 100% (Accustandard Inc.)	Pregnant CD-1 mice 10 animals per dose group 10 months old M offspring (PND300) M offspring	Repeated exposure 0, 1 mg/kg bw per day Prenatal (gestational) oral exposure: from GD8 to delivery, using micropipette Vehicle: tocopherol-stripped corn oil Neonatal oral exposure: from birth to PND21	Prenatal exposure reduced serum triglycerides concentration. Postnatal exposure reduced serum triglyceride concentration and increased liver triglycerides; both prenatal and postnatal exposures increased the liver/serum triglyceride ratio at 10 months. This was associated with an increased expression of lipid importer, Cd36, in liver of mice from both treatment groups Both prenatal (gestational) and neonatal exposure to 1 mg/kg bw per day of BDE-47 resulted in similar changes in expression of metabolic genes in mouse liver at 10 months of age (expression of Cd36 and other lipid transporters and decreased expression of serum lipid-binding proteins)	LOEL = 1 mg/kg bw per day	**Khalil et al. (2018).** Developmental Exposure to 2,2′,4,4′-Tetrabromodiphenyl Ether Permanently Alters Blood-Liver Balance of Lipids in Male Mice
BDE-47 Purity and supplier NR	Pregnant ICR mice Six animals per dose group M offspring	Repeated exposure Oral (gavage) 0, 0.002, 0.2 mg/kg bw per day Vehicle: corn oil From GD6 to PND21 AIN 93 based normal diet or a western high-fat diet (60% calories from fat) for 14 weeks	In utero and lactational exposure to BDE-47 caused a worsening of high-fat diet-induced obesity, hepatic steatosis and hepatic injury; impaired glucose homeostasis and metabolic dysfunction mRNA levels of genes involved in lipid metabolism were significantly altered in the **BDE-47**-treated high-fat diet group. Some changes in expression of lipid metabolism genes and also Cyp2b10 with low fat diet Small but statistically significant decrease in body weight and T4 in the high dose group at PND21 The gut microbiome was perturbed **by BDE-47**, causing diversity reduction, compositional alteration and metabolic changes. These changes were more pronounced for **BDE-47**-treated high-fat diet mice. In mice treated with the high dose **BDE-47** in combination with normal diet, abundance of one singe bacterial genus (*Staphylococcus*) changed. In mice fed the normal diet, **BDE-47** exposure caused increases in faecal bile acid, methionine, succinate, α-glucose, ß-glucose, α-arabinose and α-galactose. Some of these were present at the low dose and showed dose-dependent increase	LOAEL = 0.2 mg/kg bw per day, based on decreased body weight NOAEL = 0.002 mg/kg bw per day, based on hepatic steatosis and injury in offspring exposed in utero and during lactation	**Wang, Yan, et al. (2018).** In utero and lactational exposure to BDE-47 promotes obesity development in mouse offspring fed a high-fat diet: impaired lipid metabolism and intestinal dysbiosis

(Continues)

TABLE E.1 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-47 99.3–99.5% (Cerillant Corp.)	Wistar Han rats Four litters (Six pups each) + dams Adult animals: 11–12 weeks Pups: 22 days F dosed, offspring dosed and tested	Repeated exposure Oral (gavage) 0, 0.1, 15, 50 mg/kg bw per day Vehicle: corn oil Dams dosed GD6–PND21, pups dosed PND12–21, evaluated at PND22	No effect on pup body weight at birth or on littering parameters **Liver**: increase absolute and relative weight at the two highest doses. No effect on levels of triglycerides. Significant increased incidences of centrilobular hepatocellular hypertrophy and fatty change in PND22 pups after exposure to the two highest doses **Thyroid**: dose-related decreases in TT3 and TT4 in M and F pups on PND22. Decrease TT4 levels in dams on PND22. The decreases in TT4 were generally greater in pups than in dams	NOAEL = 0.1 mg/kg bw per day	**Dunnick, Shockley, Pandiri, Kissling, Gerrish, Ton, Wilson, Brar, Brix, Waidyanatha, Mutlu, and Morgan** (2018). PBDE-47 and PBDE mixture (DE-71) toxicities and liver transcriptomic changes at PND 22 after in utero/postnatal exposure in the rat
BDE-47 100% (AccuStandard Inc.)	Sprague–Dawley rats Six animals per dose group Adults M, F (2:1)	Repeated exposure Oral (gavage) 0, 0.1, 1.0, 10 mg/kg per day Vehicle: corn oil From 10 days prior to mating, until weaning of offspring PND21	Significant increase in TT3 levels at the two highest doses and in TT4 levels at all doses Disrupted thyroid follicle structure (expanded thyroid follicles and hyperplastic epithelial cells and shed cell remnants filled in the exhausted follicular lumen) in treated dams	LOAEL = 0.1 mg/kg bw per day	**Li, Liu, et al.** (2018). Perigestational exposure to low doses of PBDE-47 induces excessive ER stress, defective autophagy and the resultant apoptosis contributing to maternal thyroid toxicity
BDE-47 > 99% (AccuStandard Inc.)	Sprague–Dawley rats Nine animals per dose group 2 months old F dosed	Repeated exposure Oral (gavage) 0, 0.1, 1.0, 10 mg/kg bw per day Vehicle: corn oil 10 days before breeding until PND21	**Dams**: Decreased thyroid weights at the two higher doses. Decreased TT3 and TT4 levels Smaller thyroid follicles, immature thyroid follicles lacking follicular units (unorganised arrangement of thyroid cells without follicle formation, their replacement by increased connective tissue). Cell detachment and loss in some disturbed follicles Increase level of TUNEL-positive cells at the two high doses indicating elevated apoptosis-related DNA fragmentation	LOAEL = 0.1 mg/kg bw per day	**Li, Gao, et al.** (2020). Perinatal low-dose PBDE-47 exposure hampered thyroglobulin turnover and induced thyroid cell apoptosis by triggering ER stress and lysosomal destabilisation contributing to thyroid toxicity in adult female rats

TABLE E.1 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-47 99.9% (AccuStandard)	Sprague–Dawley rats 12 animals per dose group Adults F	Repeated exposure Oral (gavage) 0, 0.1, 1.0, 10 mg/kg bw per day Vehicle: corn oil 10 days before mating, throughout gestation and lactation, till weaning of the pups on PND 21 Offspring (4 M, 4 F) observed on PND88	**Adult M:** At 10 mg/kg bw per day: • Increased body weights. Non dose-related decreased relative testis weights at all doses. • Decreased total sperm count and living sperm count. • Decreased (non-significant trend, non-statistically significant) motile sperm count, sperm density and sperm activity. • Lower proportion of sperm with Grade A. • Significant decreases in sperm VCL, VSL and VAP. Decreased mean ALH, BCF, LIN and WOB. Significant influences STR and MAD. • Significant declines in count, motile and density of LM. • Increased TT3 levels at 1.0 and 10 mg/kg/day. No effect on TT4 levels. • Levels of TT3 were negatively correlated with total sperm count, motile sperm count and living sperm count. • Concentrations of TT3 were negatively associated with LIN, WOB, LM count, as well as LM density.	LOAEL = 0.1 mg/kg bw per day	**Li, Gao, et al.** (2021). Impaired sperm quantity and motility in adult rats following gestational and lactational exposure to environmentally relevant levels of PBDE-47: a potential role of thyroid hormones disruption
BDE-47 99.5% (Cerilliant)	Harlan Sprague–Dawley rats Six animals per dose group 7-weeks old M	Repeated exposure Oral (gavage) 0, 0.1, 1, 10, 100, 1000 μM/kg bw per day (corresponding to 0, 0.0485, 0.485, 4.85, 48.5, 485 mg/kg bw per day, as reported by the authors) Vehicle: corn oil 5 days	**Liver**: increased absolute weight. Albumin/globuline ratios significantly decreased at the two higher doses. Significant increase in ALT activity at highest dose. Decrease bile acid concentration at the two highest doses. Centrilobular hepatocyte hypertrophy and significant increase UDP GT1a1 at the two highest doses **Thyroid**: Significant decrease in TT4 and TT3 levels at the two highest doses. No effect on TSH levels	NOAEL = 4.85 mg/kg bw per day	**Shockley et al. (2020).** Comparative toxicity and liver transcriptomics of legacy and emerging brominated flame retardants following 5-day exposure in the rat
BDE-47 ≥ 98.7% Chemservice)	Sprague–Dawley rats Eight animals per dose group 8-week old M	Repeated exposure Oral (gavage) 0, 0.001, 0.03, 1 mg/kg bw (6 days per week, 0, 0.0009, 0.026, 0.86 mg/kg bw per day) Vehicle: corn oil 8 weeks	Statistically significant decrease of plasma TT4 at the highest dose. Statistically significant dose-related decrease in plasma TT3 and increase in rT3 at ≥ 0.026 mg/kg bw per day	NOAEL = 0.0009 mg/kg bw per day	**Wang, Zhu, et al.** (2020). Rno-miR-224–5p contributes to 2,2′,4,4′-tetrabromodiphenyl ether-induced low triiodothyronine in rats by targeting deiodinases

(Continues)

TABLE E.1 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-47 > 95% (AccuStandard)	Sprague–Dawley rats Eight animals per dose group 21-day old M	Repeated exposure Oral (gavage) 0, 0.1, 0.2, 0.4 mg/kg bw per day Vehicle: corn oil 14 days	Significant increased serum testosterone level at 0.4 mg/kg bw per day No effect on serum estradiol level or on T/E2 ratio. Decreased luteinizing hormone level at 0.4 mg/kg bw per day No effect on serum FSH levels Induction of Leydig cell hyperplasia (increased number of CYP11A1-positive Leydig cells) at the highest dose	NOAEL = 0.2 mg/kg bw per day	**Li, Li, et al.** (**2021**). Low dose of fire retardant, 2,2′,4,4′-tetrabromodiphenyl ether (BDE47), stimulates the proliferation and differentiation of progenitor Leydig cells of male rats during prepuberty
BDE-47 Purity NR (Matrix Scientific)	C57BL/6J gpt delta mice Six animals per dose group 7–8 weeks old M	Repeated exposure Oral (gavage) 0, 1.5, 10, 30 mg/kg bw per day, 6 days per week (0, 1.3, 8.6, 25.7 mg/kg bw per day) Vehicle: soybean oil 6 weeks	Testes: degeneration and necrosis of spermatogenic cells at the highest dose, accompanied by seminiferous epithelium thinning. Spermatic granulomas observed at 8.6 mg/kg bw per day and spermatic granulomas accompanied by suppurative inflammation observed at 25.7 mg/kg bw per day Epididymes: sperm reductions at 8.6 and 25.7 mg/kg bw per day	NOAEL = 1.3 mg/kg bw per day	**Xu, Gao, et al.** (**2021**). integrated proteomic and metabolomic analysis of the testes characterises BDE-47-induced reproductive toxicity in mice

Abbreviations: ALH, amplitude of lateral head displacement; ALT, alanine aminotransferase; BAT, brown adipose tissue; BCF, beat cross frequency; bw, body weight; ED, embryonic day; F, females; GD, gestational day; MAD, mean angular displacement; NOAEL, no-observed-adverse-effect level; NR, not reported; LIN, linearity; LM, linear motile sperm; LOAEL, lowest-observed-adverse-effects level; PND, postnatal day; PNW, postnatal week; M, males; STR, straightness; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine; TT3, total triiodothyronine; TT4, total thyroxine; rT3, reverse triiodothyronine; UDP GT1a1, UDP-glucuronosyltransferase 1a1; VAP, average path velocity; VCL, sperm curvilinear velocity; VSL, straight-line velocity; WAT, white adipose tissue; WOB, wobble.

[a]In the absence of specific factors for the conversion of the concentrations in feed into doses per kg bw per day for developmental studies, the conversion has been done using a factor of 0.12 for rats assuming a subacute study duration (EFSA Scientific Committee, 2012).

TABLE E.2 Summary of the outcomes of the toxicological studies of the PentaBDE **BDE-99** in experimental animals, excluding studies on neurotoxicity (see Table E.6).

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/Lo(A)EL	Reference
BDE-99 > 99% (Chemical Plant Cooperation of Kendu)	Sprague–Dawley rats Five animals per dose group Adults (23 days old) M	Repeated exposure Oral (gavage) 0, 120 mg/kg bw per day Vehicle: corn oil Dosing for 5, 15, 30 or 45 days	Time-dependent reduction of gonadal hormone levels and degeneration of gonadal system histology Day 5: no changes Day 15: increased testicular weight, decreases in serum estradiol levels, reduction of PCNA positive expression, damaged sperm in seminiferous tubules Day 30: further increased testicular weight, decreases in serum testosterone and estradiol levels, further reduction of PCNA positive expression, absence of expression of some primary spermatocyte cells, degeneration of seminiferous epithelium Day 45: decreased testicular weight, lower testosterone and estradiol concentrations, severe degeneration of seminiferous epithelium, proliferating cell nuclear antigen (PCNA) expression of only a part of spermatogonial cells	LOAEL = 120 mg/kg bw per day	**Yu and Zhan (2011).** Time-dependent effects of pentabrominated diphenyl ethers on gonadal hormone and genital system histology in male rats
BDE-99 > 99% (Chemical Plant Cooperation of Kendu)	Sprague–Dawley rats 10 animals per dose group Adults (4 weeks old) M	Repeated exposure Oral (gavage) 0, 60, 120, 180 mg/kg per day Vehicle: corn oil 30 days	Dose-related increase in relative testis weight Statistically significant decreases in serum testosterone and estradiol concentrations Degeneration and necrosis in testicular seminiferous tubules. Desquamation of seminiferous epithelium and decreased spermatozoa (more severe at the highest dose) Lower PCNA positive expression cells (significant at the two highest doses)	LOAEL = 60 mg/kg bw per day	**Yuan et al. (2012).** Dose-dependent effects of pentabrominated diphenyl ethers on sexual hormone and histology of male reproductive system in rats
BDE-99 99% (LGC Standards)	Sprague–Dawley rats Eight animals per dose group Adults Dams dosed, fetuses examined F	Repeated exposure Oral (gavage) 0, 0.5, 1, 2 mg/kg bw per day Vehicle: corn oil GD6 to GD19, dams euthanised on GD20	**Dams**: Increase corrected body weight gain during pregnancy at the highest dose **Fetuses**: No signs of external malformations. Dose-related increase in total number of foetuses with skeletal (incomplete bone deposition in parietal and occipital bones of the skull and delayed ossification of floating ribs and caudal vertebrae bones) and internal variations (increase size of heart ventricles and enlargement of the liver) (statistically significant at the highest dose only) Dose-dependent increases of oxidative stress markers in liver (CAT activity and TBARS)	NOAEL = 0.5 mg/kg bw per day	**Blanco et al. (2012).** Gestational exposure to BDE-99 produces toxicity through upregulation of CYP isoforms and ROS production in the fetal rat liver
BDE-99 99% (LGC Standards)	Sprague–Dawley rats Eight animals per dose group Adults F dosed, offspring dosed and tested	Repeated exposure Oral (gavage) 0, 1, 2 mg/kg bw per day Vehicle: corn oil GD6 to PND21	**Pups**: Increased body weight at the highest dose Increased oxidative stress markers in the liver: dose-dependent increases in CAT (significant at highest dose) and SOD (significant at both doses) activity	LOAEL = 1 mg/kg bw per day	**Blanco et al. (2014)**. Perinatal exposure to BDE-99 causes decreased protein levels of cyclin D1 via GSK3beta activation and increased ROS production in rat pup livers

(Continues)

TABLE E.2 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/Lo(A)EL	Reference
BDE-99 > 98% (Glpbio, USA)	ICR mice Eight animals per dose group Adults Dams dosed, male offspring examined	Repeated exposure Oral (gavage) 0, 0.2, 2 and 20 mg/kg bw per day Vehicle: corn oil GD1 to GD21	Decreased body weight on PND35 at the highest dose Statistically significant decrease in anogenital index (AGD/bw) on PND1, 7, 21 and 35 Dose-related increased incidence of cryptorchidism Decreased testicular weight and testicular organ coefficient in treated groups on PND35 Reduction and nuclear fragmentation of spermatogenic cells at 2 and 20 mg/kg bw per day. Short diameter, long diameter and lumen area of seminiferous tubules at 20 mg/kg bw per day were significantly smaller Significantly lower densities of Leydig cells in the treated groups Reductions in serum testosterone levels in all treated groups. Significant increases in serum LH and FSH concentrations at 20 mg/kg bw per day. The ratios of T/LH were found to decrease significantly in all dose groups	LOAEL = 0.2 mg/kg bw per day	**Zhao, Tang, et al. (2021)** Prenatal exposure to environmentally relevant levels of PBDE-99 leads to testicular dysgenesis with steroidogenesis disorders

Abbreviations: bw, body weight; CAT, catalase; F, female; GD, gestational day; M, male; NOAEL, no-observed-adverse-effect level; LOAEL, lowest-observed-adverse-effect level; PCNA, proliferation cell nuclear antigen; PND, postnatal day; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances.

TABLE E.3 Summary of the outcomes of the toxicological studies of the decaBDE **BDE-209** in experimental animals, excluding studies on neurotoxicity (see Table E.6).

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-209 98% (supplier NR)	Sprague–Dawley rats Six animals per dose group 10-day old pups M	Repeated exposure Oral (gavage) 0, 100, 300, 600 mg/kg bw per day Vehicle: corn oil + Tween 80 PND10 to PND42	Significant decreases in TT3 levels at the two highest doses. No effect on TT4. Significant increases in THS levels at the two highest doses **Thyroid**: Significant absolute and relative weight increases at the highest dose. Slightly enlarged colloid in a few acini at the highest dose. Dose-dependent transformation of cuboidal epithelium into squamous epithelium at the two highest doses. Multiple areas of degenerated follicular epithelium and slight attenuation of follicular epithelium at two highest doses **Liver**: Significant absolute and relative weight increases at the highest dose. Hepatocellular fatty degeneration and vascular degeneration, inflammatory foci and necrosis at the two highest doses **Adrenal gland:** Significant increases in absolute and relative weights at the highest dose	NOAEL = 100 mg/kg bw per day	**Lee et al. (2010).** Evaluation of liver and thyroid toxicity in Sprague–Dawley rats after exposure to polybrominated diphenyl ether BDE-209[a]
BDE-209 ≥ 99% (Shanghai Jiachen Chemical Co. Ltd.)	Sprague–Dawley rats 12 animals per dose group 21 days old M	Repeated exposure Oral (gavage) 0, 100 mg/kg bw per day Vehicle: corn oil 90 days	No significant changes in body weight, liver, kidney weights Changes in serum clinical chemistry (AST, ALP, total cholesterol, HDL-cholesterol, creatinine and total bile acids) indicative of hepatotoxicity	LOAEL = 100 mg/kg bw per day	**Wang, Zhang, et al. (2010).** Comparative tissue distribution, biotransformation and associated biological effects by decabromodiphenyl ethane and decabrominated diphenyl ether in male rats after a 90-day oral exposure study
BDE-209 Purity NR (supplier not reported)	C57 mice 10 animals per dose group Adults, offspring F dosed, dams and offspring tested	Repeated exposure Oral (gavage) 0, 150, 750, 1500, 2500 mg/kg bw per day Vehicle: fat emulsion GD7–9 to GD16	**Gestation parameters**: – Increased rate of postimplantation (at three highest doses) and resorptions (at two highest doses). – Dose-related decrease rate of live fetuses/litter (significant at highest dose). **Fetal development**: – Dose-related decreases placenta and brain, liver and heart weights (statistically significant at highest dose). – Decreases fetal weight (statistically significant at three highest doses). – Dose-related decreases in TT3 and TT4 concentrations (significant decreases in TT3 at highest dose, and of TT4 at two highest doses).	NOAEL = 150 mg/kg bw per day	**Chi et al. (2011).** Metabonomic phenotyping reveals an embryotoxicity of deca-brominated diphenyl ether in mice
BDE-209 ≥ 99% (Shanghai Jiachen Chemical Co. Ltd.)	Sprague–Dawley rats 12 animals per group 21 days old M	Repeated exposure Oral (gavage) 0, 10, 50 mg/kg bw per day Vehicle: corn oil 90 days	Decreased body weight gain Increased dose-dependent concentrations of BDE-209 in tissues (liver > kidney > adipose) Increased TT4 levels, significant increases in TT3 levels (not dose-dependent)	LOAEL = 10 mg/kg bw per day	**Wang, Wang, et al. (2011).** Tissue distribution and associated toxicological effects of decabrominated diphenyl ether in subchronically exposed male rats

(Continues)

TABLE E.3 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-209 > 98% (Wake Pure chemical Industries Ltd.)	Sprague–Dawley rats Eight dams per dose group 10 M and 10 F pups per dose group, + 10 M and 10 F for immunotoxicity, + remaining animals kept till PNW11 F dosed, offspring analysed	Repeated exposure Oral (feed) 0, 10, 100, 1000 mg/kg feed, corresponding to: GD10–GD20: 0, 0.7, 7.0, 66.3 mg/kg bw per day PND1–PND9: 0, 1.5, 13.9, 140.4 mg/kg bw per day PND9–PND20: 0, 2.4, 22.8, 224.3 mg/kg bw per day GD10 to PND20 + adult examination on PNW11	**Dams**: Significant increases in thyroid weight (absolute and relative) on PND20 at 10 and 1000 mg/kg feed and a non-significant increase observed at 100 mg/kg feed. TT3 concentrations in M slightly reduced at 1000 mg/kg feed on PND20 **Pups**: Significant increases in absolute and relative liver weight at 10 and 1000 mg/kg feed (absolute) in M, and at 1000 mg/kg feed (absolute and relative) in F No change on onset age of preputial separation, vaginal opening and body weight at time onset of puberty. No effect on oestrous cycle. Significant higher body weight in M at 100 mg/kg feed until PNW11 and also at some time points at 10 mg/kg feed. No effect on body weight in F. Significant increases in body weight in M at 10 and 100 mg/kg feed on PNW11 and non-significant increases in F at 100 mg/kg feed Significant decreases of TT3 and TT4 levels in M on PND20 and PNW11 At PND20: **Thyroid**: Increased thyroid weight at 100 mg/kg feed in M. Diffuse follicular hypertrophy in M on PND20 (statistically significant in incidences and severity at the highest dose) and in F at 10 and 1000 mg/kg feed **Liver**: Diffuse cell hypertrophy associated with increased cytoplasmic eosinophilia in M (statistically significant), and in F at 100 and 1000 mg/kg feed (statistically significant at 1000 mg/kg feed) **Kidney**: Decreases in absolute weights at 100 mg/kg feed in M. Increased cytoplasmic eosinophila in cortical proximal tubular epithelia in M and F (statistically significant in M from 100 mg/kg feed and in F from 10 mg/kg feed) **Brain**: Decreased weight at 10 and 100 mg/kg feed in M, and at 100 mg/kg feed in F (data not shown) **Ovaries**: Increases in interstitial glands cells at 1000 mg/kg feed (not statistically significant) At PNW11: **Thyroid**: Cases of follicular cell hypertrophy in M from 10 mg/kg feed, and 1 case in F at 100 and 1000 mg/kg feed **Brain**: no effects on hippocampal CA1 neurons. Oligodendroglial development-related parameters: significant reduction of the CC area and number of CNPase-positive aligodendrocytes at 100 and 1000 mg/kg feed and slight reductions at 10 mg/kg feed	LOAEL = 10 mg/kg feed (corresponding to a maternal dose of 0.7 mg/kg bw per day)	**Fujimoto et al. (2011).** Impaired oligodendroglial development by decabromodiphenyl ether in rat offspring after maternal exposure from mid-gestation through lactation

TABLE E.3 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-209 98% (Sigma-Aldrich)	Sprague–Dawley rats 20 animals per dose group PND21 F	Repeated exposure Oral (gavage) 0, 300 mg/kg bw per day Vehicle: arachis oil Unclear study design	Decrease in body weight and increase in spleen weight No significant differences in levels of interferonγ and interleukin-4 in exposed rats Decreased proportion of $CD3^+$, $CD4^+$, $CD3^+CD8^+$, $CD3^+CD4^+$, $CD161^+$ and $CD4^+/CD8^+$ T cells in the thymus of exposed dams Levels of serum IgG and IgM significantly decreased Thickened thymus capsule decreases lymphoid tissue in cortex with adipose tissue replacement and increases the size of medulla in thymus. The corticomedullary junction was obscure. Plenty reticular epithelial cells but scarce corpuscles are seen. The sections of spleen showed a decrease in size and number of lymphoid nodules, thinner lymphatic sheath around arteries with less lymphocytes Changes in liver structure and central vein structure. Hepatocyte sinusoids compressed by the swelling hepatocytes with balloon degeneration. Eosinophilic changes and eosinophilic bodies identified in hepatocytes Atrophic changes with decrease in number of follicles and increase amount of fibrotic tissue in ovarian	Unclear study design. Not possible to interpret the results	**Liu et al. (2012).** The PBDE-209 exposure during pregnancy and lactation impairs immune function in rats
BDE-209 Purity NR (Sigma-Aldrich)	Wistar rats Eight animals per dose group Adults M	Repeated exposure Oral (gavage) 0, 0 (DMSO), 1000, 2000, 4000 mg/kg bw per day Vehicle: DMSO 28 days	Decrease water consumption at the highest dose Significant decreases in TT4 and FT4 levels at the two lowest doses compared to controls Significant decreases in FT3 and TT4; FT3, TT4 and FT4; and TT3 at 1000, 2000 and 4000 mg/kg bw per day, respectively, compared to DMSO controls	LOAEL = 1000 mg/kg bw per day	**Curčić et al. (2012)**. Combined effects of cadmium and decabrominated diphenyl ether on thyroid hormones in rats
BDE-209 98% (Sigma-Aldrich)	Wistar rats Eight animals per dose group Age NR (200–240 g) M	Repeated exposure Oral (gavage) 0, 1000, 2000, 4000 mg/kg bw per day (corresponding concentrations in liver: 0.269, 0.569 and 0.859 mg/kg liver weight, respectively). Controls: water and DMSO (vehicle) 28 days	Decrease water consumption at the two highest doses **Liver**: Significant increase in relative liver weight at the lowest dose and significant decrease at two highest doses. (BMD_5 internal dose: 0.224 mg/kg liver weight, corresponding to 971.4 mg BDE-209/kg bw per day) Significant increase of AST at the two highest doses ($BMDL_5$: 0.072 mg BDE-209/kg liver weight, corresponding to 39 mg/kg bw per day) Significant increase γ-GT at lowest dose and highest dose Histopathological changes (edema of hepatocytes, mild hyperemia, small focal haemorrhages, narrowed sinusoids, vacuolar cytoplasm, pathological mitoses, blood vessels dilatation, polymorphonuclear cell infiltration) were seen at all doses	LOAEL = 1000 mg/kg bw per day	**Curčić et al. (2015).** Relationship of hepatotoxicity and the target tissue dose of decabrominated diphenyl ether in subacutely exposed Wistar rats

(Continues)

TABLE E.3 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-209 98% (Sigma-Aldrich)	Wistar rats Eight animals per dose group Adults (200–240 g) M	Repeated exposure Oral (gavage) 0, 1000, 2000, 4000 mg/kg bw per day Vehicle: DMSO 28 days	Statistically significant, but not dose-related, decreases in RBC count. Dose-related increases in WBC (statistically significant at the two highest doses) Statistically significant, but not dose-related, decreases in PLT count at all doses	LOAEL = 1000 mg/kg bw per day	**Curčić et al. (2017)** Interactions between cadmium and decabrominated diphenyl ether on blood cells count in rats-Multiple factorial regression analysis
BDE-209 98% (Sigma-Aldrich)	CD-1 mice Five animals per dose group F dosed, M offspring tested (PND71)	Repeated exposure Oral (gavage) 0, 10, 500, 1500 mg/kg bw per day Vehicle: corn oil Dosed GD0–GD17	Significant increase in mean % sperm morphological abnormalities at the highest dose No effect on sperm count and motility. No significant differences in sperm motion parameters (VCL, VAP, VSL, ALH, BCF) Significant reduction in anogenital distance and anogenital index at the highest dose Pathological lesions in testes, mainly in interstitial cells and/or seminiferous tubules in offspring of exposed groups, specially at the highest dose with severe vacuolation (indicating direct toxicity and apoptosis of sperm or accumulation of hormone precursors) Loss of spermatozoa and spermatids at the highest dose	LOAEL = 10 mg/kg bw per day	**Tseng et al. (2013).** Developmental exposure to decabrominated diphenyl ether (BDE-209): effects on sperm oxidative stress and chromatin DNA damage in mouse offspring
BDE-209 Purity not reported (Tokyo Chemical Industry Co.)	Sprague–Dawley rats 10 animals per dose group Adults M	Repeated exposure Oral (method not stated) 0, 0.05, 1, 20 mg/kg bw/day Vehicle: corn oil 8 weeks	Fasting blood glucose marginally higher in all exposed rats than in the control with no obvious dose–response. Decrease in serum insulin concentrations with no clear dose–response between 0.05 and 20 mg/kg bw per day. Induction of 1257 liver gene transcript changes, and 18 canonical pathways significantly enriched (four involved in immune diseases, including autoimmune thyroid disease) Increase in serum TNF-α at 1 and 20 mg/kg bw per day Reduced glutathione (1 mg/kg bw per day) and SOD (0.05 mg/kg bw per day) in plasma	LOEL = 0.05 mg/kg bw per day, based on increase serum glucose levels	**Zhang, Zhang, et al. (2013).** Mechanism of BDE209-induced impaired glucose homeostasis based on gene microarray analysis of adult rat liver

TABLE E.3 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-209 98% (Wako Pure Chemical Industries, Ltd)	C57BL/6 mice 8–10 animals per dose group Adult (6–8 weeks old) F	Repeated exposure Oral (gavage) 0, 8, 80, 800 mg/kg bw at 2-day intervals (0, 4, 40, 400 mg/kg bw per day) Vehicle: corn oil 10 months	High levels of BDE-209 in the plasma Reduced leukocytes, decreased cytokine (IFN-c, IL-2 and TNF-a) production and lower CD8 T-cell proliferation were observed After 1 or 2 months: significantly lower numbers of monocytes in the peripheral blood at all doses after 1 or 2 months. No significant differences in cytokine production between the controls and BDE-209 exposed mice At month 3: significantly lower numbers of CD4 T, CD8 T and B lymphocytes in the spleen at 40 or 400 mg/kg bw per day After 7 months: the CD8 T cells in the peripheral blood at the highest dose produced less cytokines IFN-c and IL-2. The numbers of both central memory and effector memory CD8 T cells from the peripheral blood were less in mice exposed to BDE-209 at 400 mg/kg bw per day After 27 months: the splenic CD8 T produced much less IFN-c and IL-2. Long-term BDE-209 exposure decreased the polyfunctional CD8 T-cell population in adult mice. Reduced proliferation of CD8 T cells from the BDE-209-exposed mice Lower numbers of antigen-specific CD8 T cells after immunisation with recombinant *L. monocytogenes* expressing ovalbumin (rLm-OVA) and the OVA-specific CD8 T cells had reduced functionality	LOAEL = 4 mg/kg bw per day	**Zeng et al. (2014).** Long-term exposure to decabrominated diphenyl ether impairs CD8 T-cell function in adult mice
BDE-209 97% (Chemtura)	Sprague–Dawley rats Eight animals per dose group 2 months old F	Repeated exposure Oral (gavage) 0, 100 mg/kg bw per day Vehicle: peanut oil 20 days	**Liver**: hepatocellular spotty necrosis and perivasculitis **Kidney**: serious edema **BDE-209** highly accumulated in lipid, ovary, kidney and liver after 20 days' exposure OH- and MeO-PBDEs detected in the rat tissues. A total of 12 different endogenous metabolites showed obvious alterations in urine from the exposed rats	LOAEL = 100 mg/kg bw per day	**Yang et al. (2014).** Alterations of endogenous metabolites in urine of rats exposed to decabromodiphenyl ether using metabonomic approaches
BDE-209 Purity not reported (AccuStandard)	Pregnant Sprague–Dawley rats Eight animals per dose group Adults, offspring F	Repeated exposure Oral (gavage) 0, 0 (vehicle), 1, 5, 10 mg/kg bw per day Vehicle: peanut oil GD0 to GD21	No effect on placental histology. Decreased birth weight at the two highest doses Dose-related increased ET-1 mRNA expression and ET-1 protein in placenta in treated animals. Dose-related reduction eNOS mRNA expression and eNOS protein in placenta in treated animals Increased NO production in placenta at the two highest doses Dose-related increased iNOS mRNA expression and iNOS protein in placenta in treated animals Inhibition of fetal growth, possibly due to vasoconstriction in the placenta via ET-1 upregulation and eNOS downregulation	LOAEL = 1 mg/kg bw per day	**Du et al. (2015).** The effects of PBDE-209 exposure during pregnancy on placental ET-1 and eNOS expression and the birth weight of offspring

(Continues)

TABLE E.3 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-209 98% (Wako pure chemical industries)	C57BL/6 mice 10 animals per dose group 6–8 weeks old F	Repeated exposure Oral (gavage) 0, 800 mg/kg bw at 2-day intervals (0, 400 mg/kg bw per day) Vehicle: corn oil 2 years	Internal dose ~ 200 ng/mL Decreased survival of exposed mice (5/10) compared with control (1/10). The pathological analysis revealed hepatomegaly in the exposed mice. Increased liver, spleen, heart, kidney, ovary and uterus weights **Liver**: histopathological changes: swollen hepatocytes, cytoplasmic vacuolation as well as disruption of hepatic cords, focal infiltration of inflammatory cells **Lung**: extensive inflammation with perivascular and interstitial cellular infiltrates accompanied by the thickening of alveolar walls and the destruction of alveolar septa **Spleen**: significant decrease in number of splenic nodules, the distinction between the white pulp and red pulp was blurry. Large number of megakaryocytes founded in the red pulp, characteristic of extramedullary haematopoiesis **Kidney**: tubular degeneration and dilation, tubular cast formation, shrunken glomeruli with widening of the urinary space and focal infiltrates of inflammatory cells **Ovary**: expanded interstitial spaces in the stroma. Reduction in follicles numbers and preterm luteinization of the follicles No neoplastic lesions observed in this lifetime exposure study in the limited number of experimental mice studied	LOAEL = 400 mg/kg bw per day	**Feng et al. (2015).** Simulating long-term occupational exposure to decabrominated diphenyl ether using C57BL/6 mice: biodistribution and pathology
BDE-209 98% (Wako Pure Chemical Industries, Ltd.)	C57Bl/6 mice 10 animals per dose group 6–8 weeks old F	Repeated exposure Oral (gavage) 0, 800 mg/kg bw, every 2 days (0, 400 mg/kg bw per day) Vehicle: corn oil 10 months	Impaired proliferation and cytokine (IFN-γ, IL-2 or TNF-α) production of CD4 T cells, accompanied by increased T regulatory cells in the blood Weaker antigen-specific CD4 T-cell responses to *Listeria monocytogenes* infection in the mice exposed to BDE-209, suggesting decreased resistance to exogenous pathogens	LOAEL = 400 mg/kg bw per day	**Feng, Zeng, et al. (2016).** Long-term exposure to high levels of decabrominated diphenyl ether inhibits CD4 T-cell functions in C57Bl/6 mice
BDE-209 > 98% (Sigma-Aldrich)	Parkes mice Nine animals per dose group Adults (12–14 weeks) M	Repeated exposure Oral (gavage) 0, 750, 950 mg/kg bw per day Vehicle: corn oil 35 days	Significant reductions in testis and epididymis weights at the highest dose Significant reductions in levels of TT3, TT4 and testosterone at the highest dose Significant reductions in the activities of 3β- and 17β-HSD in testes **Testes**: at the highest dose, non-uniform degeneration changes in the seminiferous tubules (thinning of germinal epithelium, marked depletion of germ cells, exfoliation of germ cells and intraepithelial vacuolation). In severe cases, the epithelium consisted of only a layer of Sertoli cells and few spermatogonia). Significant reduction of the diameter of the seminiferous tubules and the height of the germinal epithelium. Significant reductions in number and viability of spermatozoa in cauda epididymis at the highest dose	NOAEL = 750 mg/kg bw per day	**Sarkar et al. (2016).** Effect of polybrominated diphenyl ether (BDE-209) on testicular steroidogenesis and spermatogenesis through altered thyroid status in adult mice

TABLE E.3 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-209 > 98% (Sigma-Aldrich)	Parkes mice Seven animals per dose group Lactating F dosed, M offspring tested	Repeated exposure Oral (gavage) 0, 500, 700 mg/kg bw per day Vehicle: corn oil PND1–PND28	In pups, Increased serum and intra-testicular levels of 17β-estradiol Increased level of lipid peroxidation Decreased activities of antioxidant enzymes (SOD and CAT) Significant decreases of intratesticular glucose levels Significant decrease in LDH activity Significant decrease in lactate concentration Increased germ cell apoptosis Rise in oxidative stress in testes with increased oestrogen level	LOAEL = 500 mg/kg bw per day	**Sarkar and Singh (2017).** Maternal exposure to polybrominated diphenyl ether (BDE-209) during lactation affects germ cell survival with altered testicular glucose homeostasis and oxidative status through down-regulation of Cx43 and p27Kip1 in prepubertal mice offspring
BDE-209 > 98% (Sigma-Aldrich)	Parkes mice Seven animals per dose group Lactating F dosed, M offspring tested (PND42)	Repeated exposure Oral (gavage) 0, 500, 700 mg/kg bw per day Positive control: 6-propyl-2-thiouracil Vehicle control: corn oil PND1–PND28	No effect on body weight of pups at PND42 Significant decrease in absolute and relative weights of testis and seminal vesicle at PND42 Significant decrease in absolute and relative prostate weights Effect on testicular histopathology (significant increased % of affected seminiferous tubules with centrally displaced germ cells, thinning of germinal epithelium, intraepithelial vacuolation, exfoliation of germ cells, absence of lumen and disorganisation of germ cells), germ cell proliferation (decrease) and steroidogenesis. Down regulation expression of various steroidogenic markers (SF-1, StAR, CYP11A1, 17β-HSD and 3β-HSD) in peripubertal mice offspring. Decreased expressions of maturational markers of Sertoli cells (Cx43, AR and p27Kip1) with a decline in serum thyroid hormone levels (TT3 and TT4) Significant reductions in serum and intra-testicular levels of testosterone at PND42 Significant decreased number of Leydig cells at the lowest dose, and some decrease at the highest dose Impairment of germ cell dynamics	LOAEL = 500 mg/kg bw per day	**Sarkar and Singh (2018).** Inhibition of testicular steroidogenesis and impaired differentiation of Sertoli cells in peripubertal mice offspring following maternal exposure to BDE-209 during lactation suppress germ cell proliferation
BDE-209 > 98% (Sigma-Aldrich)	Parkes mice Seven animals per dose group Lactating F dosed, M offspring tested	Repeated exposure Oral (gavage) 0, 500, 700 mg/kg bw per day Vehicle: corn oil PND1–PND28	In dams: reduction of TT3 and TT4 levels. In M pups: 1. Significant reduction in testis absolute and relative weight at PND28. 2. Significant reduction of TT3 and TT4 levels. 3. Effects on testicular histopathology, steroidogenesis and germ cell dynamics: significant reduction of the diameter of the seminiferous tubules; non-uniform degeneration changes in the seminiferous tubules: decrease in number of spermatogonia and spermatocytes, lumen not properly developed, few round spermatids, in some cases formation of multinucleated giant cells. 4. Significant decreases in activities 3β- and 17β-HSD in testes. 5. Significant reductions in serum and intratesticular levels of testosterone. 6. Impairment of germ cell dynamics.	LOAEL = 500 mg/kg bw per day	**Sarkar et al. (2018).** Maternal BDE-209 exposure during lactation perturbs steroidogenesis, germ cell kinetics and THRalpha1 expression in testes of prepubertal mice offspring

(Continues)

TABLE E.3 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-209 > 98% (Sigma-Aldrich)	Parkes mice 14 animals per dose group Lactating F dosed, M offspring tested on PND42	Repeated exposure Oral (gavage) 0, 500, 700 mg/kg bw per day Vehicle: corn oil PND1–PND28	In M pups: – Histological alterations in epididymis at PND42. Segment I and II: almost normal appearance of epithelium of epididymal duct. In segment III, loss of stainability and only PAS-positive materials in the lumen and vacuole-like spaces in segment IV and V, sperm fragments and PAS-positive materials and vacuole-like spaces. Inflammatory infiltrates in the interstitium of segments IV. – Significant decrease in number of spermatozoa in epididymis. – Significant decrease of spermatozoa motility at the lowest dose only. Significant decrease in sperm viability. – Significant increase in number of morphologically abnormal spermatozoa (tail and head abnormalities). – Significant reduction of sialic level in the epididymis. – Significant increase in total ROS production in testes and epididymis. – High level of lipid peroxidation in testes and epididymis. – Decreased activities of SOD and catalase in testes and epididymis. – Significant decrease in intratesticular glucose level. – Marked decrease in LDH activity and in testicular lactate concentration. Decrease mating index: 100%, 78.57% and 85.71%, respectively. Decrease fertility index: 100%, 81.81% and 83.3%, respectively. Decrease litter size (average): 12.21, 9.01 and 9.97, respectively	NOAEL = 500 mg/kg bw per day	**Sarkar et al. (2019).** Maternal BDE-209 exposure during lactation causes testicular and epididymal toxicity through increased oxidative stress in peripubertal mice offspring
BDE-209 98% (Sigma Aldrich)	Parkes mice 14 pregnant F per dose group Treatment of dams from PND1–PND28 (lactation) Examination of pups (4M + 4F/group) on PND75	Repeated exposure Oral (gavage) 0, 500, 700 mg/kg bw per day Vehicle: corn oil + PTU-treated positive control group	**Testes**: significant decrease of the absolute and relative weights. Modification of testis histoarchitecture: multinucleated giant cells common in majority of degenerate seminiferous tubules, significant decrease of the height of the germinal epithelium in seminiferous tubules, several seminiferous tubules showed degenerative changes (disorganisation of germ cells, intraepithelial vacuolation and thinning of germinal epithelium). Statistically significant decrease in sperm count (not automatic analysis), motility and viability. The number of PCNA-positive cells significantly decreased as well as the proliferation index. **Epididymis**: significant decrease of the absolute and relative weights. **Seminal vesicle**: significant decrease of the absolute and relative weight. **Prostate**: significant decrease in absolute and relative weights. Significant decrease in 3β-HSD and 17β-HSD enzymes activity in the testis Significant decrease in both serum and intra-testicular levels of testosterone Significantly decreased testicular activities of SOD and catalase Significantly high level of lipid peroxidation in testes and marked increase in total ROS production	LOAEL = 500 mg/kg bw per day	**Sarkar and Singh (2021).** Decabromodiphenyl ether (BDE-209) exposure to lactating mice perturbs steroidogenesis and spermatogenesis in adult male offspring

TABLE E.3 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-209 > 98% pure (Sigma Aldrich)	Sprague–Dawley rats 24 animals per dose group F dosed, pups tested GD7, GD13, GD19 and PND1	Repeated exposure Oral (dietary) 0, 1000 mg/kg bw per day Vehicle: not reported F dosed (5 weeks of age, during mating and gestation until delivery)	No difference in the number of foetuses in each rat on GD19 or in the number of pups in each litter on PND1 Significant lower pup birth weight	LOAEL = 1000 mg/kg bw per day	**Zhao et al. (2017).** Correlation between prenatal exposure to polybrominated diphenyl ethers (PBDEs) and infant birth outcomes: a meta-analysis and an experimental study
BDE-209 98% (Sigma-Aldrich)	Albino Wistar rats Six to seven animals per dose group 7 weeks old M	Repeated exposure Oral (gavage) 0, 31.25, 62.5, 125, 250, 500 mg/kg bw per day Vehicle: DMSO 28 days	Increased serum creatinine. Results obtained for serum urea were inconclusive. Relative kidney weight not affected by **BDE-209** exposure Kidney reduced glutathione was elevated but not at the highest dose, while SOD activity was not changed after **BDE-209** exposure Increased levels of TBARS at 125 mg/kg bw per day and above. Total -SH groups were decreased in all exposure groups	LOAEL = 31.25 mg/kg bw per day	**Milovanovic et al. (2018).** Oxidative stress and renal toxicity after subacute exposure to decabrominated diphenyl ether in Wistar rats
BDE-209 Purity not reported (Sigma-Aldrich)	C57BL/6J mice Seven to eight animals per dose group 5 weeks old M	Repeated exposure Oral (drinking water) Mice exposed to the equivalent of three doses of 0, 0.5, 10 μg/kg bw per day (ad libitum) From 5 to 20 weeks of age High-fat diet: 62.2 kcal% fat Normal diet: 9.0 kcal% fat	**BDE-209** exposure in combination with the high-fat diet dose-dependently increased both fasting blood glucose levels compared with vehicle exposure. It had no clear effect in the glucose tolerance test. **BDE-209** exposure significantly reduced mRNA levels of glucose transporter 4 and thyroid hormone receptor alpha in skeletal muscle and mechanistic target of rapamycin complex 2 in brown adipose tissue compared with vehicle exposure under High-fat diet feeding	NOEL = 0.01 mg/kg bw per day, based on increased fasting serum glucose	**Yanagisawa et al. (2019).** Decabromodiphenyl ether exacerbates hyperglycemia in diet-induced obese mice

(Continues)

TABLE E.3 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-209 Purity NR (American Alfa Aesar Company)	ICR mice Eight dams per dose group (each treatment group produced 16 M pups) Dams dosed, M offspring tested M	Repeated exposure Oral (gavage) 0, 100, 300, 500 mg/kg bw per day Vehicle: corn oil GD7–PND21 At PND35 half of the male pups were euthanised. At PND105 the other half of the M mice were euthanised	No effect on breeding success of F1 adults Significant decrease in body weight on PND35 at 100 and 500 mg/kg bw/day, and at 300 mg/kg bw per day at PND105 Significant decrease in absolute testis weight at two highest doses, and relative testis weight at the highest dose Significant decrease epididymis weight at the three dose levels and relative epididymis weight at the medium dose. No effect at PND105 Light microscopy: Histopathological lesions in testis at the two highest doses (vacuolations in spermatogonia, spermatocytes and Leydig cells, disturbed array of germ cells, slightly reduced layers of germ cells, exaggeration of intracellular space) Entrapped sperm cells at PND105. Premature spermatid loss at the lowest dose and absence of spermatids in majority of tubules at the medium dose Vacuolated or swollen mitochondria, pyknotic nuclei and marginal chromatin in exposed F1 mice. Absence of spermatozoa in exposed F1 mice Fewer efferent ductules at the two highest doses on PND105 Impairment of germ cell dynamics. TEM observations demonstrated also ultrastructural changes in blood-testis barrier including Sertoli cells and their junctional complexes and the ultrastructure of the epididymis including sperm	LOAEL = 100 mg/kg bw per day	**Zhai et al. (2019).** An increase of oestrogen receptor alpha protein level regulates BDE-209-mediated blood-testis barrier disruption during spermatogenesis in F1 mice
BDE-209 ≥ 99.5% (Acros Organics)	Sprague–Dawley rats 12 animals per dose group 6 weeks old M	Repeated exposure Oral (gavage) 0, 5, 50, 500 mg/kg bw per day Vehicle: corn oil 28 days	No effect on body weight Significant decreases in TT3, TT4, FT3 and FT4 levels at the highest dose and increased TSH and TRH levels. Decreases in FT3 at medium dose **Thyroid**: Abnormal structures (smaller follicular cavities and disorderly thyroid follicular epithelial cells). Increased height of follicular thyroid follicular epithelial cells, swelling and vacuolation of part of the follicular cells at the lowest dose. Small amount of mast cells infiltration in the follicular stroma and edema in follicular epithelial cells, few exfoliated epithelial cells at the mid dose. At the highest dose, large number epithelial cells swelled, more exfoliated epithelial cells. Plenty spotty necrosis scattering at highest dose. Dose-dependent decreased average colloid area. Modifications of ultrastructure	LOAEL = 5 mg/kg bw per day	**Wang et al. (2019).** A comparison of the thyroid disruption induced by decabrominated diphenyl ethers (BDE-209) and decabromodiphenyl ethane (DBDPE) in rats

TABLE E.3 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-209 Purity NR (J&K Scientific Ltd)	ICR mice 10 animals per dose group 9 weeks old M	Repeated exposure 0, 7.5, 25, 75 mg/kg bw per day Oral gavage 28 days	Increased serum triglycerides and reduced high-density lipoprotein at all doses Increased fasting serum glucose (highest dose only) and insulin (25 and 75 mg/kg bw per day) Small reduction in serum SOD at all doses but without dose–response Qualitative evidence of damage to liver (liver cells cords were arranged disorderly, central venous congestion in hepatic sinuses and diffuse vacuolar degeneration of hepatocytes) and adipose tissue (swelling of fat cells, unclear cell boundaries and damage of the fat cell membrane in dose-dependent manner)	LOEL = 7.5 mg/kg bw per day, based on increased serum triglycerids and reduced high-density lipoprotein	**Zhu et al. (2019).** The effects of decabromodiphenyl ether on glycolipid metabolism and related signalling pathways in mice
BDE-209 > 98% (Acros Organics)	Sprague–Dawley rats 12 animals per dose group 6 weeks M	Repeated exposure Oral (gavage) 0, 5, 50, 500 mg/kg bw per day Vehicle: corn oil 28 days	**BDE-209** caused heart and abdominal aorta morphological and ultrastructural lesions. Congestion of intermuscular capillaries with mild disruption at 5 and 50 mg/kg bw per day and severe fibre disruption with focal hemorrhagic areas between the muscle bundles, and nuclear condensation or dissolution and myocyte swelling at 500 mg/kg bw per day. In the aorta, dose-related increased disarray of elastin networks in the medial layer was observed at the two highest doses, **BDE-209** causes a series of ultrastructure lesions in cardiomyocytes (dose-related) Serum creatine kinase (CK) and lactate dehydrogenase (LDH) were dose-dependently increased with significance at 5 mg/kg bw per day. Lipid peroxidation (MDA) was dose-dependently increased with significance at 5 mg/kg bw per day, and antioxidant enzyme activity changes **BDE-209** induced inflammation, characterised by the upregulation of key inflammatory mediators, including interleukin-1beta (IL-1b), IL-6, IL-10 and tumour necrosis factor alpha (TNFa) Endothelial dysfunction, as evidenced by the endothelin-1 (ET-1) and intercellular adhesion molecule-1 (ICAM-1)	LOAEL = 5 mg/kg bw per day	**Jing et al. (2019).** Cardiovascular toxicity of decabrominated diphenyl ethers (BDE-209) and decabromodiphenyl ethane (DBDPE) in rats

(Continues)

TABLE E.3 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-209 98% (Acros Organics)	Sprague–Dawley rats 12 animals per dose group 6 weeks old M	Repeated exposure Oral (gavage) 0, 5, 50, 500 mg/kg bw per day Vehicle: corn oil 28 days	**Liver**: increase absolute weight at the highest dose, and increase relative weight at the two high doses Statistically significant increase in γGT, significant increase in plasma total bilirubin (TBIL) and indirect bilirubin (IBIL) at the two high doses Increased serum levels of glucose at high dose Mild swelling of the liver cells at low dose and loose and transparent cytoplasm. Extensive damage of the liver at the two high doses: poor lobular structure, disordered hepatic cord and hepatic sinus, and balloon-like edematous hepatocyte, accompanied by feathery necrosis in which the cytoplasm was loose and transparent and the nucleus disappeared, with large lipid droplets in the cytoplasm and inflammatory cells accumulated around the portal vein infiltration Increase liver MDA levels and marked decrease in SOD activities at the two highest doses Increase of inflammatory cytokines tumour necrosis factor-α (TNF-α) and interleukine-6 (IL-6) levels at the two high doses	NOAEL = 5 mg/kg bw per day (based on increased relative liver weight and liver damage)	**Sun, Wang, Liang, et al. (2020).** Hepatotoxicity of decabromodiphenyl ethane (DBDPE) and decabromodiphenyl ether (BDE-209) in 28-day exposed SpragueDawley rats
BDE-209 > 98% (Acros Organics)	Sprague–Dawley rats 12 animals per dose group 6 weeks old M	Repeated exposure 0, 5, 50, 500 mg/kg bw per day Oral (gavage) Vehicle: corn oil 28 days	**Testes**: reduction of sperm cells and pathological changes in seminiferous tubules (seminiferous epithelium deletion, intraepithelial vacuolation and even cell exfoliation), significant decreased sperm number, motility and significantly increased sperm malformation rate (coiled tail, bent neck and irregularly shaped head) at 50 and 500 mg/kg bw per day. Significant increases in MDA content in testis at the two highest doses. T-SOD activity decreases at the highest dose TUNEL staining: significant increases in the number of TUNEL-positive cells per seminiferous tubule at all doses Significant increases in the numbers of senescent cells per seminiferous tubule at all doses	LOAEL = 5 mg/kg bw per day	**Li, Liu, et al. (2021).** BDE-209 and DBDPE induce male reproductive toxicity through telomere-related cell senescence and apoptosis in SD rat

TABLE E.3 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-209 98% (Sigma Aldrich)	Pregnant Sprague–Dawley rats Three animals per dose group Offspring: 3 F1 M selected on PND21/litter (total 9 F1 M) 1 F1 M/litter mated with normal F on PND70 → F2 1 F2 M/litter mated with normal F on PND70 → F3 M offspring observed	Repeated exposure Oral (gavage) 0, 5 mg/kg bw per day (F0 F) Vehicle: corn oil GD0–birth	Significant decreases in body weight on PND25, 31, 34, 37, 40 and 58 in the F1 generation, on PND28 in the F2 generation, and on PND31, 40 and 43 in the F3 generation. Significant decrease in the F1 rats on PND84. No effect on weight of testes, epididymis, seminal vesicles and ventral prostate Significant decreases in anogenital distance on PND25, 49, 52, 67 and 70 in the F1 generation, PND37 and 40 in the F2 generation, and PND31, 34, 52, 55, 64, 67 and 70 in the F3 generation Significant decreases in sperm count of the F1 and F2 generations. Significant reduction in the sperm motility of the F1 offspring. Reduced normal morphology rates of the testis in the offspring of the F2 and F3 generation Increases in the percentage of spermatozoa with bent tails in all generations (F1–F3). Significant increased frequency of multiple abnormal spermatozoa in the F3 generation Significant decreases in serum testosterone levels in the F3 generation No apparent morphological differences including the spermatogenesis, structure of testis, morphology of lumens and seminiferous tubules between the control and exposed groups	LOAEL = 5 mg/kg bw per day	**Hsu et al. (2021)**. Transgenerational effects of BDE-209 on male reproduction in F3 offspring rats
BDE-209 Purity NR (Zhenhuai Biotechnology Co. Ltd)	Balb/c mice 8 weeks old 20 animals per dose group F	Repeated exposure 0, 4, 40, 400 mg/kg bw per day Vehicle: corn oil PND56–76 Analysis after 21-day exposure and after a recovery period of 21 days	On PND77: Decreases in WBC at the highest dose and in lymphocyte percentage at ≥ 40 mg/kg bw per day, increases in the levels of AST from 4 mg/kg bw/day, but not ALP or ALT Decrease in relative spleen (top two doses) and thymus (top dose) weights Significant increases in IgG (at the two lower doses) and Ig M (highest dose) levels. Dose-dependent significant decreases of splenic lymphocyte proliferation. Dose-dependent inhibition of cytokine secretion of IFN-γ and promotion of IL-4 and IL-10 The phagocytic index (α) was significantly decreased at the highest dose Significant increases in MDA activities were measured in liver and spleen (40 and 400 mg/kg bw per day), thymus (400 mg/kg bw per day). Significant decreases in SOD activities in liver and spleen (40 and 400 mg/kg bw per day), thymus (400 mg/kg bw per day) The effects returned to control levels on PND98. However, only partially for promotion of IL-4 and IL-10. The effects on MAD and SOD activities were still significant at the highest dose on PND98. Dose-related increase in IgA at all doses on PND98, which was not seen on PND77	LOAEL = 4 mg/kg bw per day	**Liao et al. (2021).** Short-term exposure of decabromodiphenyl ether in female adult Balb/c mice: immune toxicity and self-recovery

(Continues)

TABLE E.3 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-209 Purity NR (Aladdin, Shanghai, China)	Balb/c mice 6 weeks old 10 animals per dose group M	Repeated exposure 0, 200 mg/kg bw per day Oral (gavage) Vehicle: corn oil 28 days Analysis after 21-day exposure and after a recovery period of 21 days	Decreased body weight gain Damaged intestinal morphology and integrity (reduced height of villi and decreased mucosal layer thickness in the ilium and colon) and increased gut permeability Increased ROS production in the ileum and colon Increased expression of NF-ΚB in ileum and colon, and levels of cytokines (TNF-α, IL-6 and IL21) in serum, indicating intestinal inflammation	LOAEL = 200 mg/kg bw per day	**Shaoyong et al. (2021)**. BDE-209 caused gut toxicity through modulating the intestinal barrier, oxidative stress, autophagy, inflammation, and apoptosis in mice
BDE-209 > 98% (Acros Organics (NJ, USA))	Sprague–Dawley rats 6-week-old 10 animals per dose group M	Repeated exposure 0, 5, 50, 500 mg/kg bw per day Oral (gavage) Vehicle: corn oil 28 days	**Testes**: decrease in sperm quality and quantity at 50 and 500 mg/kg bw per day. The spermatocytes layers sparsely arranged, and mature sperms in the lumen dramatically decreased, vacuolation of seminiferous tubules and exfoliation of spermatogenic cells. Significant decreases in the height of the germinal epithelium at these doses. The mitochondria were slightly swollen, the cristae mildly fractured and vacuolization appeared at 5 and 50 mg/kg bw per day; while at 500 mg/kg bw per day, the mitochondria were swollen and vacuolated; the mitochondrial cristae ruptured or even disappeared Apoptosis of spermatogenic cells was also noted at these doses **Epididymes**: at the two highest doses, sperm concentration and motility significantly reduced and sperm malformations increased resulting in spermatogenesis impairment Testicular glucose level significantly negatively correlated with sperm concentration, but no correlation with motility and malformation rate Triglyceride levels and total cholesterol levels in testes showed significant negative correlations with the sperm concentration and motility, and a positive correlation with the sperm malformation rate, respectively	NOAEL = 5 mg/kg bw per day	**Zhang, Li, et al.** (2021). Decabromodiphenyl ether induces male reproductive toxicity by activating mitochondrial apoptotic pathway through glycolipid metabolism dysbiosis

TABLE E.3 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-209 Purity NR Aladdin Biochemical Tech Co., Ltd	C57BL/6 mice 4-week-old 10 animals per dose group M	Repeated exposure 0, 20, 100, 500 mg/kg bw per day Oral (gavage) Vehicle: corn oil 8 weeks	**Liver:** Statistical increase in liver absolute weight at highest dose Severe histopathological changes: focal infiltration of inflammatory cells and necrotic degeneration Significant increase in AST (all doses) and ALT (at highest dose) concentrations, Dose-dependent increase of pro-inflammatory factors, TNFα and IL-1β Reduction of anti-inflammatory factors IL-4, IL-6 and IL-10 **BDE-209** stimulation-induced ROS production in mice liver (dose-related). Increased MDA concentration (dose-related). Reduction of antioxidant-related enzymes CAT (dose-related), SOD and GSH-Px activities. Dose-related increase in apoptosis	LOAEL = 20 mg/kg bw per day	**Che et al. (2021).** Decabromodiphenyl ether initiates mitochondria-dependent apoptosis by disrupting calcium homeostasis in mice liver
BDE-209 Purity: > 98% AccuStandard Inc	C57BL/6 Mice 8 weeks old Six/group F	Repeated exposure 0, 2, 20, 200 mg/kg bw per day Oral (gavage) Vehicle: corn oil GD0-18	Placenta: Statistically significant decreased weight (all doses), impaired placental vascular development (statistically significant at 200 mg/kg bw per day) and increased placental cell apoptosis (all doses)	LOAEL = 2 mg/kg bw per day	**Zhao et al. (2022).** Gestational exposure to BDE-209 induces placental injury via the endoplasmic reticulum stress-mediated PERK/ATF4/CHOP signalling pathway
BDE-209 Purity: NR	Sprague–Dawley rats 4 weeks old 10/group M	Repeated exposure 0, 5, 50 and 500 mg/kg bw per day Oral (gavage) Vehicle: corn oil 28 days	The intracavernous pressure/mean arterial pressure ratio was used to assess the erectile response Erectile dysfunction observed at the two highest doses. Exposure to these doses induce fibrosis in the corpus cavernosum and decrease endothelial nitric oxide synthase (eNOS) expression In the high dose group, the expression of testosterone significantly decreased The expression levels of caspase-3 in the cavernosum were significantly increased in all treatment groups indicating apoptosis	LOAEL = 5 mg/kg bw per day	Zhou et al. (**2022**). A comprehensive analysis on the relationship between BDE-209 exposure and erectile dysfunction

Abbreviations: ALH, amplitude of lateral head displacement; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCF, beat cross frequency; bw, body weight; CAT, catalase; DMSO, dimethyl sulfoxide; ET-1, endothelin-1; eNOS, endothelial nitric oxide synthase; F, female; GD, gestational day; γ-GT, gamma glutamyl transferase; HDL-cholesterol, high density lipid-cholesterol; 3β- and 17β-HSD, 3β- and 17β-hydroxysteroid dehydrogenase; iNOS, inducible isoform nitric oxide synthase; LDH, lactate dehydrogenase; LOAEL, lowest-observed-adverse-effect level; LOEL, lowest-observed-effect level; M, male; NOAEL, no-observed-adverse-effect level; NR, not reported; PLT, platelets; PND, post-natal day; PNW, post-natal week; RBC, red blood cells; SOD, superoxide dismutase; -SH groups, thiol groups; T3, triiodothyronine; T4, thyroxine; TT3, total T3; TT4, total T4; TEM, transmission electron microscopy; TSH, thyroid hormones.; VAP, average path velocity; VCL, sperm curvilinear velocity; VSL, straight-line velocity; WBC, white blood cells.

[a]This study was cited in the previous EFSA assessment on PBDEs (EFSA CONTAM Panel, 2011b) and it is included again in the current assessment to provide insight into additional observations by the study authors not reported in the previous Opinion.

TABLE E.4 Summary of the outcomes of the toxicological studies of **other PBDEs** (the monoBDE **BDE-3** and the diBDE **BDE-15**) in experimental animals.

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-15 > 99.0% (J&K Company)	ICR mice 10 animals per dose group 6 weeks old M	Repeated exposure Oral (gavage) 0, 1.2 mg/kg bw per day Vehicle: corn oil 28 days	**Liver**: Increases in relative weight. Swelling of the hepatic cells, inflammation, vacuolisation, hepatocellular hypertrophy **Kidney**: Decreases in relative weight Significant decrease in SOD activity Increases in hepatic MDA levels Decreases in GSH levels Significant decreases in GPx activity Significant increases in hepatic copper levels and decreases in liver zinc levels	LOAEL = 1.2 mg/kg bw per day, based on hepatocellular hypertrophy and histopathological effects	**Zhang et al. (2014).** Subacute oral toxicity of BDE-15, CDE-15, and HODE-15 in ICR male mice: assessing effects on hepatic oxidative stress and metals status and ascertaining the protective role of vitamin E
BDE-3 Purity NR (Alfa Aesar)	Sprague–Dawley rats Six animals per dose group 35 days old M	Repeated exposure Oral (gavage) 0, 50, 100, 200 mg/kg bw per day Vehicle: corn oil PND35–56 (21 days)	No effect on body weight. No effect on testis and epididymal weights Dose-dependent decreases in testosterone (statistically significant at the highest dose). No effect on serum LH and FSH levels No alteration of Leydig cell number (no effect on Leydig cell proliferation). No effect on Sertoli cell number. Decreased Leydig cell size and its cytoplasmic size without affecting its nuclear size at the highest dose	NOAEL = 100 mg/kg bw per day	**Chen, Chen, et al. (2018).** 4-Bromodiphenyl ether delays pubertal Leydig cell development in rats
BDE-3 99% (Shanghai Ailex Technology)	C57BL/6J gpt delta mice Six animals per dose group 15 weeks old M	Repeated exposure Oral (gavage) 0, 0.0015, 1.5, 10, 30 mg/kg bw per day Vehicle: corn oil 6 weeks	Dose-dependent decreases in sperm count (statistically significant from 1.5 mg/kg bw per day) Increased rate of tail folding sperm. Slight decrease in germ cells in seminiferous tubules in four M at the highest dose, and mature sperm decreases in epididymis in three M at the highest dose with one M showing cellular debris in lumen and inflammatory cell infiltration in epididymal interstitium	NOAEL = 0.0015 mg/kg bw per day, based on sperm count	**Wei et al. (2018).** Metabolomics coupled with pathway analysis characterises metabolic changes in response to BDE-3 induced reproductive toxicity in mice
BDE-3 Purity NR (Alfa Aesar)	Sprague–Dawley rats Nine animals per dose group Pregnant F exposed Fetuses observed	Repeated dose Oral (gavage) 0, 50, 100, 200 mg/kg bw per day Vehicle: corn oil Dams exposed from GD12 to GD21	No effect on the birth rate, pup number per dam and percent male/female sex ratio of foetuses No effect on body weight of male fetuses Reduced anogenital distance at 100 and 200 mg/kg bw per day Reduction of fetal Leydig cell number at 200 mg/kg bw per day without effect on fetal Leydig cell cluster frequency and Sertoli cell number Significant reduction of serum testosterone levels at all doses Induction of autophagy and apoptosis signalling in fetal testis	NOAEL = 50 mg/kg bw per day	**Li, Ma, et al. (2021).** Exposure to 4-bromodiphenyl ether during pregnancy blocks testis development in male rat foetuses

Abbreviations: bw, body weight; F, female; FSH, follicle-stimulating hormone; GSH, glutathione; GPx, glutathione peroxidase; LH, luteinizing hormone; M, male; MDA, malondialdehyde; NOAEL, no-observed-adverse effect level; NR, not reported; SOD, superoxide dismutase.

TABLE E.5 Summary of the outcomes of the toxicological studies of **PBDE technical products** in experimental animals, excluding studies on neurotoxicity (see Table E.6).

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
DE-71 Congener composition (Lot #1550OI18A): NR Impurities: NR by the study authors, but according to Hanari et al. (2006) for the same Lot number: – PBBs (tri- to decaBBs): 4025 ng/g – PBDFs (tetra- to octaBDFs): 257 ng/g – PBDDs: < LOD of 100–200 ng/g (Great Lakes Chemical Corporation)	Pregnant Long-Evans rats Six M, two F pups F dosed, offspring analysed till PND60	Repeated exposure Oral (gavage) 0, 1.7, 10.2, 30.6 mg/kg per day Vehicle: corn oil GD6 to weaning PND21	**Dams**: Significant hypothyroxinemia: decrease serum TT4 levels on PND22 at the two highest doses. No effect on TT3. Increased serum TSH levels at PND22 (significant at the highest dose) **Offspring**: No effect on M body weight pups (PND4–60). Decrease body weight in F pups at the two highest doses (PND29–58). Decrease body weight in F pups at the lowest dose on PND56 and PND58 Perinatal exposure produced an age-dependent depression in circulating TT4 concentrations between PND4–21 from 10.2 mg/kg bw in M and F. On PND60, TT4 levels returned to control levels in M but were still higher than controls in F. Increased serum TSH levels during postnatal development and then decreased levels in F on PND60 No significant differences in the anogenital distance of M on PND7 (however a 5.5% difference between control and the highest dose group was considered of biological relevance by the authors. Delay in preputial separation and a 20% decrease in mean testosterone concentration at the highest dose on PND60 On PND60, no effect on weights of seminal vesicles, epididymis, testis or ventral prostate lobes No significant effect on PND4 mammary development in F. Abnormally less longitudinal epithelial growth than is typical at the two highest doses, and effect on developmental scores on PND21 PBDE congeners were found in all the rat tissues examined on PND22 (fat tissue, liver, brain, blood)	NOAEL = 17 mg/kg bw per day	**Kodavanti et al. (2010).** Developmental exposure to a commercial PBDE mixture, DE-71: neurobehavioural, hormonal, and reproductive effects[a]
DE-71 Congener composition (Lot #05500F16P): NR Impurities: NR (Wellington Laboratories)	CD®IGS rats 20 pregnant rats F dosed, offspring tested	Repeated exposure Oral (gavage) 0, 60 µg/kg bw per day Vehicle: corn oil Pregnant F0 F from GD1.5 through lactation (except the day of parturition). F1 pups were sacrificed on PND21 or outbred at approximately PND80. Bred F1 F were sacrificed at GD14.5 or at 5 months of age. Bred F1 M were sacrificed at 5 months of age	Lower body weight of F1 F at 80 days and 5 months Increased TT3 and TT4 concentrations at GD14.5 Increased thyroid gland weight at 5 months	LOAEL = 60 mg/kg bw per day	**Blake et al. (2011).** Perinatal exposure to low-dose DE-71 increases serum thyroid hormones and gonadal osteopontin gene expression
DE-71 Congener composition (Lot #I1-9570): BDE-47: 36% BDE-99: 42%–44% Impurities: NR (Cambridge Isotope Lab)	Long-Evans rats 107 dams (3 cohorts, 7 treatment groups per cohort) 11–12 dams per dose group. 1 M and 1 F pups per litter tested. 1 M and 1 F tested for cochlear function at adulthood. Primiparous F dosed, offspring tested	Repeated exposure Oral (onto a cookie) 0, 5.7, 11.4 mg/kg bw per day Vehicle: corn oil Perinatally: Before and during gestation, and during lactation	Decreased TT4 levels in treated groups No effect on cochlear function	LOAEL = 5.7 mg/kg bw per day	**Poon et al. (2011).** Effects of developmental exposure to polychlorinated biphenyls and/or polybrominated diphenyl ethers on cochlear function

(Continues)

TABLE E.5 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
DE-71 Congener composition (Lot #1550OI18A): reported to contain BDE-47, -99, -100, -153 and -154 Impurities: NR by the study authors, but according to Hanari et al. (2006) for the same Lot number: – PBBs (tri- to decaBBs): 4025 ng/g – PBDFs (tetra- to octaBDFs): 257 ng/g – PBDDs: < LOD of 100–200 ng/g (Great Lakes Chemical Corporation)	Long-Evans rats 15 dams per dose group F dosed, offspring tested (M/F)	Repeated exposure Oral (gavage) 0, 1.7, 30.6 mg/kg per day Vehicle: corn oil Exposure: GD6 to PND21, testing on PND21 and PND60 and after 14 and 18 months	In M offspring exposed to high dose TT4 and TT3 levels were reduced on PND21 and recovered to control levels by PND60 when TSH levels were elevated At 14/18 months: hyperosmotic treatment yielded significant changes in systolic blood pressure in exposed rats only (36.1% and 64.7% greater systolic blood pressure responses at 3 h post hyperosmotic injection relative to pretreatment baseline after low and high dose, respectively Impaired osmoregulation in PBDE-treated animals	LOAEL = 1.7 mg/kg bw per day	**Shah et al. (2011).** Altered cardiovascular reactivity and osmoregulation during hyperosmotic stress in adult rats developmentally exposed to polybrominated diphenyl ethers (PBDEs)
DE-71 Congener composition (Lot #7550OK20A): NR by the study authors, but according to Driscoll et al. (2012) for the same Lot number: tetraBDEs: 25%, pentaBDEs: 50%–60%, hexaBDE: 4%–8% Impurities: NR (Great Lakes Chemical Corporation)	Long Evans rats Experiment 1: Four dams per dose group, four M pups per dose group Experiment 2: Five dams per dose group, five M and five F pups per dose group F dosed, F and M pups tested	Repeated exposure Oral (dietary, on a cookie) 1.7, 5, 10, 20, 40, 60 μmol/kg per day (corresponding to 0.96, 2.85, 5.7, 11.4, 22.8, 34.3 mg/kg bw per day) Vehicle: corn oil GD6–PND21	Reduction TT4 levels at doses ≥ 5 μM at PND7 and PND21, at doses ≥ 10 μM at PND14. Maximum reduction was seen at PND21 after the highest dose exposure No effect on body weight at PND7, PND11, PND14 and PND21	NOAEL = 0.96 mg/kg bw per day	**Miller et al. (2012).** Developmental coexposure to polychlorinated biphenyls and polybrominated diphenyl ethers has additive effects on circulating thyroxine levels in rats
DE-71 Congener composition (Lot #2550OA30A): BDE-47: 36% BDE-85: 2% BDE-99: 42% BDE-100: 10% BDE-153: 3% BDE-154: 4% (the remaining 3% consisted of several identified tri-heptaBDEs and some unidentified PBDEs) Impurities: PBDD/Fs: 66 ng/g (Great Lakes Chemical Corporation)	Wistar Han rats 20 dams per dose group 5 M, 5 F pups on PND22 10 M, 10 F per group on week 13 F dosed, measurements in offspring	Repeated exposure Oral (gavage) 0, 50 mg/kg bw per day Vehicle: corn oil Dams exposed GD6–PND21 Offspring dosed from PND12–PND21 and for additional 13 weeks	Increased body weight in M (7%) and decreased body weight (14%) in F on week 13 **Liver**: Hepatocyte hypertrophy (centrilobular and midzonal regions) and hepatocyte cytoplasmic vacuolization (prominent in peripheral regions) on week 13	LOAEL = 50 mg/kg bw per day	**Dunnick et al. (2012).** Characterisation of polybrominated diphenyl ether toxicity in Wistar Han rats and use of liver microarray data for predicting disease susceptibilities

TABLE E.5 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
DE-71 Congener composition (Lot #2550OA30A): BDE-47: 36% BDE-85: 2% BDE-99: 42% BDE-100: 10% BDE-153: 3% BDE-154: 4% Impurities: PBDD/Fs: approx 7×10^{-6}% by weight (Great Lakes Chemical Corporation)	Wistar Han rats Four litters (Six pups each) + dams Adult animals: 11–12 weeks Pups: 22 days F dosed, offspring dosed and tested	Repeated exposure Oral (gavage) 0, 0.1, 15, 50 mg/kg bw per day Vehicle: corn oil Dams dosed GD6–21, pups dosed PND12–21, evaluated at PND22	No effect on pup body weight at birth or on littering parameters, except for a significantly higher litter size at the highest dose **Liver**: increase absolute and relative weight ratios at the two highest doses. Increase trend of serum cholesterol levels in exposed pups on PND22. No effect on levels of triglycerides. Significant increased incidences of centrilobular hepatocellular hypertrophy and fatty changes in PND22 pups after exposure to the two highest doses. Increased mitoses in pups exposed to ≥ 0.1 mg/kg **Thyroid**: dose-related decreases in TT3 and TT4 in M and F pups on PND22. Decrease TT4 levels in exposed dams on PND22. The decreases in TT4 were generally greater in pups than in the dams. Significant dose-related increase trend in TSH levels in M and F pups	LOAEL = 0.1 mg/kg bw per day	**Dunnick, Shockley, Pandiri, Kissling, Gerrish, Ton, Wilson, Brar, Brix, Waidyanatha, Mutlu, and Morgan (2018).** PBDE-47 and PBDE mixture (DE-71) toxicities and liver transcriptomic changes at PND 22 after in utero/postnatal exposure in the rat
DE-71 Congener composition: the authors indicated that DE-71 is composed of six major congeners: BDE-99 > -47 > -100 > -153 > -154 > -85, ranging from 48.60%–2.96% (wet weight) (according to La Guardia et al. (2006)) Impurities: NR > 98% (Cambridge Isotope Laboratories)	B6C3F1 mice Five animals per dose group Adult F	Repeated exposure Oral (gavage) 0, 0.5, 5, 50, 100 mg/kg (total administered dose, TAD, over the course of 28 days) (corresponding to 0, 0.018, 0.18, 1.8, 3.6 mg/kg bw per day) 28 days	Decrease peripheral blood monocyte numbers at 0.018, 0.18 and 1.8 mg/kg bw per day, but not at 3.6 mg/kg bw per day Mitogen-stimulated T- and B-cell proliferation was increased at the highest dose NK cell activity was decreased by the highest dose. The numbers of splenic CD4 + CD8+ cells were decreased at 0.018, 0.18 and 3.6 mg/kg bw per day	LOAEL = 0.018 mg/kg bw per day	**Fair et al. (2012)**. Immune function in female B6C3F1 mice is modulated by DE-71, a commercial polybrominated diphenyl ether mixture
DE-71 Congener composition (Lot #7550OK20A): predominant congeners: BDE-99: 6513 µg/mL BDE-47: 4774 µg/mL BDE-100: 1329 µg/mL (according to Hoppe & Carey, 2007) Same Lot number as Driscoll et al. (2012): tetraBDEs: 25% pentaBDEs: 50%–60% hexaBDE: 4%–8% Impurities: NR (Great Lakes Chemical Corporation)	Wistar rats Eight animals per dose group 1-month-old M	Repeated exposure Oral (gavage) 0, 14 mg/kg bw per day Vehicle: corn oil 3, 14 or 28 days	Fasting plasma glucose, insulin and C-peptide levels were not markedly affected by treatment, but the glucose: insulin ratio was significantly higher in treated compared to control rats Significant decreased PEPCK V_{max} (µmol/min/g liver weight) by 43% and increased liver lipid by 20%. CYP1A, -2B and -3A V_{max} values were enhanced by 5-, 6- and 39-fold, respectively, at both 14 and 28 days in treated rats Significant inverse and temporal correlation between CYP3A and PEPCK V_{max} for the treatment group	LOAEL = 14 mg/kg bw per day	**Nash et al. (2013)**. Polybrominated diphenyl ethers alter hepatic phosphoenolpyruvate carboxykinase enzyme kinetics in male Wistar rats: implications for lipid and glucose metabolism

(Continues)

TABLE E.5 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
DE-71 Congener composition (Lot #3550OC08P): BDE-28: 0.21% BDE-47: 43.10% BDE-85: 1.74% BDE-99: 42.72% BDE-100: 7.95% BDE-153: 1.91% BDE-154 1.96% BDE-183: 0.09% Impurities: – 1,2,3,7,8-pentaBDD: 0.21 ng/g – 1,2,3,4,6,7,8-heptaBDF: 0.81 ng/g (Great Lakes Chemical Corporation)	Sprague–Dawley rats 16 adult rats (8 F, 8 M), 10 pups each litter Adults (35–40 days old) M, F (50:50)	Repeated exposure Oral (gavage) 0, 0.5, 5, 25 mg/kg bw per day Vehicle: corn oil F0: 21 weeks F1: PND22–42 F0 rats were mated and exposure continued through gestation, lactation and postweaning	Dose-dependent increases in total PBDE concentrations in liver and adipose tissue of all F0 and F1 rats. Dose-dependent increase in adipose, liver and milk of individual PBDE congeners concentrations **Dams**: No effect on F0 rats body weight or on maternal body weight gain **Liver**: In M, increased liver weight (absolute and relative) at necropsy at the highest dose. In F, increased absolute liver weight at the two highest doses, relative liver weight not significantly altered by treatment. Hepatocellular hypertrophy of zone 3 hepatocytes in F0 M at two highest doses and in F0 F at the highest dose, consistent with microsomal enzyme induction. Lipid accumulation in M at the highest dose No effect on kidney, ovary, testes, thymus and spleen weights in F0 animals **Thyroid**: Significant decreases in TT4 levels in F0 M at the two highest doses, and in F at the highest dose **Offspring:** No effect on litter size, pup mortality, M/F ratios, M and F anogenital distance. No effect on pup body weight during lactation (PND1–21) **Liver**: In M, increased absolute liver weight at the highest dose and increased relative liver weights at the two highest doses. In F, increased absolute and relative liver weights in F at the two highest doses. Mild hepatocellular hypertrophy in F1 rats at the highest dose **Thyroid**: Decreased TT3 and TT4 levels in F1 M and F at the highest dose **Thymus**: Increased relative thymus weights in F1 F at the mid dose. Increased apoptotic lymphocytes and tangible macrophages in thymic cortex in exposed F1 rats **Spleen**: No effect on spleen weight. Increased proliferation of unstimulated splenocytes in F1 M and F at the highest dose. Decrease B cells area and increase T cells area. Cellular and humoral immune responses to KLH challenge were not altered No effect on kidney, ovary and testes weights in F1 animals	NOAEL = 0.5 mg/kg bw per day	**Bondy et al. (2013)**. Toxicologic and immunologic effects of perinatal exposure to the brominated diphenyl ether (BDE) mixture DE-71 in the Sprague–Dawley rat
DE-71 Congener composition (Lot #7550OK20A): NR by the study authors, but according to Driscoll et al. (2012) for the same Lot number: tetraBDEs: 25% pentaBDEs: 50%–60% hexaBDE: 4%–8% Impurities: NR (Great Lakes Chemical Corporation)	Sprague–Dawley rats Six to nine animals per dose group F dosed, M pups tested	Repeated exposure Oral (onto wafers) 0, 0.1, 1, 10, 30 mg/kg bw per day GD6–PND 21	**Dams**: Small but significant decreased body weight gain at the highest dose. Reduction of TT4 (at two highest doses) and FT4 (at highest dose) **Pups**: Reduction of TT4 and FT4 (at the two highest doses)	NOAEL = 1 mg/kg bw per day	**Bansal et al. (2014)**. Polybrominated diphenyl ether (DE-71) interferes with thyroid hormone action independent of effects on circulating levels of thyroid hormone in male rats

TABLE E.5 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
DE-71 Congener composition (Lot #3550OC08P): NR by the study authors, but according to Bondy et al. (2013) for same Lot number: BDE-28: 0.21%, BDE-47: 43.10%, BDE-85: 1.74%, BDE-99: 42.72%, BDE-100: 7.95%, BDE-153: 1.91%, BDE-154 1.96%, BDE-183: 0.09% Impurities detected: – 1,2,3,7,8-penta BDD: 0.21 ng/g, – 1,2,3,4,6,7,8-heptaBDF: 0.81 ng/g (Chemtura, former Great Lakes Chemical Corporation)	Sprague–Dawley rats 30 animals per dose group 18–23 litters per dose group F	Repeated exposure Oral (on a cookie) 0, 0.3, 3.0, 30 mg/kg per day Vehicle: corn oil GD1–PND 21, offspring tested	No effect on number of litters born, uterine implantation sites, sex ratio or mortality rates. No effect on body weight gain during gestation or lactation. No effect on litter weight gain on PND1–4. Small but significant decrease offspring body weight gain on PND5–40 at the highest dose, but this effect did not persist afterwards. **Liver**: No effect on absolute maternal liver weight but increased relative liver weight at the highest dose. Increased absolute and relative offspring liver weights at two highest doses on PND21. On PND105 increased relative liver weight was still observed at the highest dose, and increased absolute and relative liver weight was still seen in M offspring on PND250. Increased EROD, BROD and PROD activities at highest dose in dams, and at the two highest doses in offspring (transient effects). Increased liver EROD at the lowest dose on PND21. **Thyroid**: Decreased TT3 and TT4 levels in dams at the highest dose and in offspring at two highest doses. Offspring were more sensitive than dams. These effects were transient: levels returned to normal on PND50. Significant increase TSH serum level at the highest dose on PND21. Increase epithelial cell height of thyroid follicles at PND21 at the highest dose. Dose-related increased serum levels of **BDE-47**, **-99**, **-100** and **-153** in dams on PND21.	NOAEL = 0.3 mg/kg bw per day	**Bowers et al. (2015)**. Behavioural and thyroid effects of in utero and lactational exposure of Sprague–Dawley rats to the polybrominated diphenyl ether mixture DE71.
DE-71 Congener composition (Lot #1500K07A and #G550QF65A): NR Impurities: NR (Donated by NIEHS and Indiana University)	Wistar rats (190–230 g) 14 animals per dose group Weanling M	Repeated exposure Oral (gavage) 0, 14 mg/kg bw per day Vehicle: corn oil 28 days	Significant increased absolute and relative liver weight. Increases of hepatic concentrations of **BDE-47**, **-99** and **-100**. Significant reduction in serum glucose after 48 h fast. Increases in β-hydroxybutyrate (marker of fatty acid oxidation) and decreased serum triglycerides. Decreased hepatic lipid content, mild lipid vacuolation in midzonal region. Marked decreases in hepatic glyceroneogenesis.	LOAEL = 14 mg/kg bw per day, based on reduced serum glucose and triglycerids	**Cowens et al. (2015).** Polybrominated Diphenyl Ether (PBDE)-Induced Suppression of Phosphoenolpyruvate Carboxykinase (PEPCK) Decreases Hepatic Glyceroneogenesis and Disrupts Hepatic Lipid Homeostasis.
DE-71 Congener composition (Lot #7550OK20A): NR by the study authors, but according to Driscoll et al. (2012) for the same Lot number: tetraBDEs: 25%, pentaBDEs: 50%–60%, hexaBDE: 4–8% Impurities: NR (Great Lakes Chemical Corporation)	Wistar rats 5 M and 5 F per litter, 32 litters F, M (50/50)	Repeated exposure Oral (gavage) 0, 30 mg/kg bw per day Vehicle: corn oil PND5–22	No effect on body weight or on the weight of thyroid, brain, testes, thymus and spleen. Liver enlargement on PND23, but the effect did not persist on PND70 or PND120. Decreased TT4 level on PND23, but not on PND70 or PND120. Statistically significant increases of liver EROD and PROD activities.	LOAEL = 30 mg/kg bw per day	**de-Miranda et al. (2016)**. Thyroid hormone disruption and cognitive impairment in rats exposed to PBDE during postnatal development

(Continues)

TABLE E.5 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
DE-71 Congener composition (Lot #550OK07A): BDE-85: 2% BDE-47: 36% BDE-99: 42% BDE-100: 10% BDE-153: 3% BDE-154: 4% Impurities: PBDD/Fs: approx 7×10^{-6}% by weight (Great Lakes Chemical Corporation)	B6C3F1 mice 10 M + 10 F per dose group	Repeated exposure Oral (gavage) 0, 0.01, 5, 50, 100, 500 mg/kg bw, 5 days per week, for 14 weeks (0, 0.007, 3.6, 36, 71, 357 mg/kg bw per day) Vehicle: corn oil	Decreased survival of the 357 mg/kg bw groups Significantly decreased mean body weights in M at 71 and 357 mg/kg bw per day, and in F at 357 mg/kg bw per day Small decrease in the circulating red cell mass in the surviving 357 mg/kg bw per day animals (decreases in haematocrit values, haemoglobin concentrations and erythrocyte counts) **Liver**: significant increases in absolute and relative weights in M at 36 mg/kg bw per day and in M and F at 71 and 357 mg/kg bw per day. Significantly increased UDPGT activities in all dosed F groups. Significantly increased EROD activities in F at ≥ 3.6 mg/kg bw per day. Significantly increased A4H activities in M at ≥ 36 mg/kg bw per day and in F at ≥ 3.6 mg/kg bw per day. Significantly increased PROD activities in M and F at ≥ 3.6 mg/kg bw per day Significantly increased incidences of hepatocellular hypertrophy in M at ≥ 36 mg/kg bw per day and in F at 71 and 357 mg/kg bw per day. Significantly increased incidences of hepatocyte necrosis in M and F at 357 mg/kg bw per day and hepatocyte cytoplasmic vacuolisation in M at 357 mg/kg bw per day **Kidney**: significant decreases in absolute weight in M at 357 mg/kg bw per day **Heart**: significant decreases in absolute weights in M and F at 357 mg/kg bw per day **Testes**: decreased absolute weight at 357 mg/kg bw per day. Significantly increased incidence of abnormal residual bodies in the seminiferous tubules at 357 mg/kg bw per day **Epididymis**: significantly decreased left cauda epididymis weight and sperm motility at 71 mg/kg bw per day **Adrenal cortex**: significantly increased incidences of fatty degeneration and hypertrophy of the zona fasciculata in M at 357 mg/kg bw per day **Thymus**: significantly increased incidence of atrophy in M at 357 mg/kg bw per day	NOAEL = 3.6 mg/kg bw per day	**NTP (2016)**

TABLE E.5 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
DE-71 Congener composition (Lot #550OK07A): BDE-85: 2% BDE-47: 36% BDE-99: 42% BDE-100: 10% BDE-153: 3% BDE-154: 4% Impurities: PBDD/Fs: approx 7×10^{-6}% by weight (Great Lakes Chemical Corporation)	F344/*N* rats 10 M + 10 F per dose group	Repeated exposure Oral (gavage) 0, 0.01, 5, 50, 100, 500 mg/kg bw per day, 5 days per week for 14 weeks (0, 0.007, 3.6, 36, 71, 357 mg/kg bw per day) Vehicle: corn oil	Decreased mean body weights in M and F at 357 mg/kg bw per day, and at 71 mg/kg bw per day in F Dose-related decreases in TT4 level on days 4, 25 and 93 in M and F at ≥ 3.6 mg/kg bw per day. Increases in serum TSH concentrations at 71 and 357 mg/kg bw per day groups at 14 weeks Dose-related increases in serum cholesterol concentrations at all time points in M and F administered ≥ 36 mg/kg bw per day Small decrease in circulating red cell mass (decreases haematocrit values and haemoglobin concentrations) at 71 and 357 mg/kg bw per day in M and F at week 14 **Liver**: increased weight (absolute and relative) at ≥ 3.6 mg/kg bw per day; significant increases in UDPGT activities in M and F at ≥ 3.6 mg/kg bw per day; in EROD activities at ≥ 50 mg/kg bw per day in M and at ≥ 3.6 mg/kg bw per day in F; significant dose-related increased PROD activities in M and F at ≥ 3.6 mg/kg bw per day. Significant increased incidences of hepatocellular hypertrophy in M and F at ≥ 3.6 mg/kg bw per day. Increased incidences of cytoplasmic vacuolization of the hepatocytes at 36 mg/kg bw per day in M, and at 71 and 357 mg/kg bw per day in M and F **Thyroid**: increased incidences of thyroid gland follicle hypertrophy in F at ≥ 36 mg/kg bw per day and at 357 mg/kg bw per day in M and F **Kidney**: increased weight at ≥ 36 mg/kg bw per day in M, and at ≥ 3.6 mg/kg bw per day in F **Thymus**: decreased weight at 357 mg/kg bw per day in M and at 36 mg/kg bw per day in F. Atrophy in F at 357 mg/kg bw per day **Testis**: fewer total spermatids per testis and significantly decreased sperm per gram of testis at 71 and 357 mg/kg bw per day. Significantly decreased sperm motility at 357 mg/kg bw per day **Epididymis**: significantly increased incidences of hypospermia, decreased epididymis and cauda epididymis weights, significantly decreased sperm per cauda and sperm per gram of cauda at 357 mg/kg bw per day **Oestrus cycle**: All 357 mg/kg bw per day females failed to cycle and remained in persistent diestrus throughout the examination period **Glandular stomach**: erosion in M at 357 mg/kg bw per day	NOAEL = 0.007 mg/kg bw per day, based on increase absolute and relative liver weight and hepatocellular hypertrophy	**NTP (2016)**

(Continues)

TABLE E.5 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
DE-71 Congener composition (Lot #550OK07A): BDE-85: 2% BDE-47: 36% BDE-99: 42% BDE-100: 10% BDE-153: 3% BDE-154: 4% Impurities: PBDD/Fs: approx 7×10^{-6}% by weight (Great Lakes Chemical Corporation)	Wistar Han rats [Crl:WI(Han) Dams: 62 F0 F in control and high dose group, 52 F0 F in 3 and 15 mg/kg bw per day dose groups Offsprings: 60 F1 M and F in control and high dose group, 50 F1 M and F in 3 and 15 mg/kg bw per day dose groups 10 M and 10 F F1 animals from control and high dose groups sacrificed after 3 months	Repeated exposure Oral (gavage) 0, 3, 15, 50 mg/kg bw (0, 2.1, 10.7, 36 mg/kg bw per day) Dosing of F0 F from GD6–PND21. At PND4 all litters culled to 3 M and 3 F per litter Pups started on direct dosing (same dose as the dam) from PND12–PND21. At PND22 the pups were assigned to the 2-year study (generally 2 M and 2 F from 25 litters to each dose group), and received dosing 5 days per week for 2 years Vehicle: corn oil	Significant decrease in survival in F1 M at highest dose Increased incidences of thinness and significantly decreased mean body weights in high dose F1 F after week 37 Observations after 3 months: **Liver**: at highest dose: – significantly increased absolute and relative weights (M, F). – significantly increased incidences of centrilobular and midzonal hepatocyte hypertrophy and hepatocyte cytoplasmic vacuolation. – significantly increased incidence of fatty changes (M). **Thyroid**: at highest dose: – significantly increased incidences of follicle hypertrophy (M, F). **Kidney**: at highest dose: – significantly increased absolute and relative weight (M). **Testis**: at highest dose: – significantly increased absolute weight. **Thymus**: at highest dose: – significantly decreased absolute weight (F). Observations after 2 years: **Liver**: – significantly increased incidences of eosinophilic foci and fatty changes in M and F at 10.7 and 36 mg/kg bw per day. – significantly increased incidences of centrilobular hepatocellular hypertrophy in M and F at all doses. – significantly increased incidence of nodular cell hyperplasia in F at highest dose. – significantly increased incidence of oval cell hyperplasia in F at highest dose. – cholangiofibrosis occurred in three females at 36 mg/kg bw per day. **Thyroid**: – significantly increased incidence of follicular cell hyperplasia in F at highest dose. – significantly increased incidences of follicle hypertrophy in M at all doses and in F at 10.7 and 36 mg/kg bw per day. **Thymus**: at highest dose: significantly increased incidences of atrophy in M **Kidney**: significantly increased incidences of hydronephrosis in M at 10.7 mg/kg bw per day and in M and F at 36 mg/kg bw per day **Forestomach**: at highest dose: significantly increased incidences of epithelial hyperplasia in M **Uterus**: – significantly increased incidences of squamous metaplasia at 10.7 and 36 mg/kg bw per day **Cervix**: at highest dose: significantly increased incidences of squamous hyperplasia **Prostate**: – significantly increased incidences of chronic active inflammation in M at 10.7 and 36 mg/kg bw per day **Preputial gland duct**: at highest dose: significantly increased incidences of ectasia **Parotid salivary gland**: at highest dose: significantly increased incidences of atrophy and cytoplasmic vacuolisation in M **Adrenal cortex**: at highest dose: significantly increased incidences of focal hyperplasia in F For neoplastic effects see **Section 3.1.2.7**	NOAEL 3 months = 10.7 mg/kg bw per day LOAEL 2 years = 2.1 mg/kg bw per day, based on histopathological effects	**NTP (2016)** **Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Recio, et al. (2018).** Carcinogenic activity of pentabrominated diphenyl ether mixture (DE-71) in rats and mice

TABLE E.5 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
DE-71 Congener composition (Lot #550OK07A): BDE-85: 2% BDE-47: 36% BDE-99: 42% BDE-100: 10% BDE-153: 3% BDE-154: 4% Impurities: PBDD/Fs: approx 7×10^{-6}% by weight. (Great Lakes Chemical Corporation)	B6C3F1 mice 50 M and F per dose group	Repeated exposure Oral (gavage) 0, 3, 30, 100 mg/kg bw, dosing 5 days per week for 105 weeks (0, 2.1, 21, 71 mg/kg bw per day) Vehicle: corn oil	Significant decrease in survival in M and F at 71 mg/kg bw per day, leading to these groups being removed from the study at 18 months Decreases in mean body weights in M and F at 71 mg/kg bw per day after weeks 17 and 21, and in mean body weights in M at 21 mg/kg bw per day after week 87 Occurrences of distended abdomen, which correlated with liver neoplasms **Liver**: – significantly increased incidences of centrilobular hepatocyte hypertrophy in all dosed groups. – significantly increased incidences of eosinophilic foci in F at 21 and 71 mg/kg bw, and significantly increased incidence of clear cell foci in M at 21 mg/kg bw. – significantly increased incidences of fatty changes in F at 21 and 71 mg/kg bw. – significantly increased incidences of focal necrosis in M at 21 mg/kg bw and Kupffer cell pigmentation in all dosed groups. **Thyroid**: significantly increased incidences of follicle hypertrophy in all treated M and in F at 21 and 71 mg/kg bw. **Forestomach**: significantly increased incidences of epithelial hyperplasia in M at 21 and 71 mg/kg bw, and in F at 71 mg/kg bw, and inflammation in M at 30 and 100 mg/kg bw. **Adrenal cortex**: significantly increased incidences of diffuse hypertrophy in M and F at 71 mg/kg bw. **Testis**: significantly increased incidence of germinal epithelium atrophy at 71 mg/kg bw. For neoplastic effects see **Section 3.1.2.7**	LOAEL = 2.1 mg/kg bw per day	**NTP (2016)** **Dunnick, Pandiri, Merrick, Kissling, Cunny, Mutlu, Waidyanatha, Sills, Hong, Ton, Maynor, Recio, et al. (2018).** Carcinogenic activity of pentabrominated diphenyl ether mixture (DE-71) in rats and mice
DE-71 Congener composition (Lot #1550OI18A) Impurities: NR by the study authors, but according to Hanari et al. (2006) for the same Lot number: – PBBs (tri- to decaBBs): 4025 ng/g – PBDFs (tetra- to octaBDFs): 257 ng/g – PBDDs: < LOD of 100–200 ng/g Great Lakes Chemical Corporation (see above)	C57Bl/6N mice F dosed, offspring tested 3–32 animals per dose group	Repeated exposure Dams exposed from 4 weeks pre-conception until weaning PND21 by feeding DE-71 on infused cornflakes 0, 0.1, 0.4 mg/kg bw per day Vehicle: corn oil 10-week dosing regimen (~4 weeks of pre-conception, plus gestation (3 weeks) and lactation (3 weeks)) Offspring were weaned after the lactation period at PND 21. During the last week of the 4-week pre-conception exposure period dams were mated with an untreated C57Bl/6 *N* male	Metabolic endpoints (fasting glycemia, IPGTT, ITT) examined at 1–2 weeks post-weaning and at 5 months after start of exposure for dams and at 4 months for F offspring (F1) **Dams**: slight increase relative liver weight at the low dose only No significantly effect on fasting blood glucose in F0 F F0 exposed to either dose showed significantly elevated blood glucose relative to VEH/CON in the intraperitoneal glucose tolerance test, but the difference was moderate and this occurred only at 30 min time point after glucose injection and the overall effect was not significant. Plasma insulin was reduced in F0 F exposed to 0.4 mg/kg bw per day but there was no effect on their insulin sensitivity following insulin challenge **Offspring**: Slight decrease in body weight in F at low dose only Increase absolute liver weight at the highest dose only In F offspring, 0.1 mg/kg bw per day significantly elevated fasting blood glucose concentration after a 9 h fast, and 0.4 mg/kg bw per day DE-71 elevated fasting blood glucose after an 11 h fast relative to VEH/CON. Blood glucose levels rose rapidly in IPGTT and peaked within 15 min of glucose challenge in the VEH/CON and the HD groups. The peak for low dose group occurred at 30 min. The glycaemia was exaggerated in exposed F1 at 30 and 60 min (0.1 mg/kg bw per day) and at 15 min post injection (0.4 mg/kg bw per day) indicating glucose intolerance. Plasma glucose showed a gradual return to baseline at 60 min post injection in VEH/CON. In contrast, for both exposed F1 groups, the corresponding time was 120 min or 1 h longer. F1 exposed to 0.1 mg/kg bw per day displayed less reduction in glycaemia as compared to VEH/CON at several time points post injection insulin ($t = 15$, 30 min), indicating reduced insulin sensitivity	LOEL = 0.1 mg/kg bw per day, based on increased glucose tolerance and reduced insulin sensitivity on offspring	**Kozlova et al. (2020).** Maternal transfer of environmentally relevant polybrominated diphenyl ethers (PBDEs) produces a diabetic phenotype and disrupts glucoregulatory hormones and hepatic endocannabinoids in adult mouse female offspring

(Continues)

TABLE E.5 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
DE-71 Lot 7550OK20A Congener composition: ~29% BDE-47, ~50% BDE-99, ~9% BDE-100, ~5% BDE-153 and ~4% BDE-154	Pregnant Wistar F rats Study 1: 10 dams/group Study 2: 22 dams/group	Repeated exposure Oral (gavage) Study 1: 0, 20, 40 or 60 mg/kg bw per day from GD7 to PND14 Study 2: 0, 40 or 60 mg/kg/day from GD 7 to PND16 Vehicle: corn oil	Dams: **Liver**: weights (a, r) increased dose-dependently in all exposure groups on PND14 in study 1 (~20% in high dose). By PND27, in study 2, liver weights were similar between groups. **Thyroid**: On GD15, dose-dependent reduction of TT4 (studies 1 and 2) and TT3 levels (study 2). In study 2, no statistically significant effect on TSH concentration, albeit the values appeared more variable at 60 mg/kg bw per day compared to controls. No effect on thyroid weight in the dams on PND27. Offspring: **Liver**: weights were markedly increased (up to ~50%), particularly on PND16 (study 2). By PND27 the increase was less pronounced, demonstrating some recovery after exposure ceased. Increased severity of hypertrophy and vacuolation of hepatocytes with increasing dose in offspring on PND16. Hypertrophy of hepatocytes was localised to the centrilobular areas. No microvesicular vacuolation was observed. **Thyroid**: markedly reduced postnatal TT4 concentrations to 25%–45% of control levels (study 1). On PND16 and PND27, TT3 levels were reduced to ~75%–85% of controls (study 2). DE-71 exposure was discontinued on PND16, but there was only slow recovery in TT4 and TT3 levels between PND16 and PND27. No effect on thyroid weight in female pups on PND16 or in male pups on PND27. In male pups, no changes in the follicular epithelium, follicular morphology, stroma or c-cells were evident in thyroid glands on PND16. Dose-dependent increase in minimal vacuolation of follicular colloid (statistically significant higher incidence at 60 mg/kg bw per day (study 2)	LOAEL = 20 mg/kg bw per day	**Ramhøj et al. (2022).** Developmental exposure to the brominated flame retardant DE-71 reduces serum thyroid hormones in rats without hypothalamicpituitary-thyroid axis activation or neurobehavioural changes in offspring
PentaBDE Congener composition: pentaBDEs: 63.2%, tetraBDEs: 21.4% hexaBDEs: 15.4% heptaBDEs: 0.04% >98% (Aldrich Chemical Co.) **DecaBDE** Congener composition: NR >98% (Aldrich Chemical Co.)	Wistar rats (190–230 g) Five animals per dose group, four animals in control group F	Repeated exposure Oral (gavage) **PentaBDE**: 0, 0 (oil), 2, 8, 40, 200 mg/kg per day **DecaBDE**: 0, 10, 100, 1000 mg/kg per day Vehicle: sunflower oil 7–28 days	**PentaBDE:** Dose-related decreased body weight gain from 8 mg/kg bw per day **Liver**: Increased weight (relative) at the two highest doses and prolonged time of exposure Dose-related increased liver GSH concentration Dose-related increased Glutathione Reductase activity in serum. Increased MDA concentration at the highest dose, small increases at lower doses after 21 days. Dose-related and time dependent decreased TAS in serum. Increased serum ALT and AST levels (indicative of liver damage). Fatty degeneration at the highest dose (steatosis of microvesicular and macrovesicular types). **DecaBDE:** No effect on body weight gain. No effect on liver weight or histopathology	**PentaBDE**: LOAEL = 2 mg/kg bw per day	**Bruchajzer et al. (2010)**. Toxicity of penta- and decabromodiphenyl ethers after repeated administration to rats: a comparative study. [(a)]

TABLE E.5 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
PentaBDE Congener composition: pentaBDEs: 63.2% tetraBDEs: 21.4% hexaBDEs: 15.4% heptaBDEs: 0.04% (the authors stated that its composition corresponded with that of Bromkal 70, DE-71 or Tardex 50) Impurities: NR Supplier: NR	Wistar rats Five animals per dose group, four animals in control group F	Repeated exposure Oral (gavage) 0, oil control, 2, 8, 40, 200 mg/kg bw per day Vehicle: sunflower oil 28 days	**Liver**: dose-dependent increase in ALA-S activity. Increased concentration of total porphyrins. **Urine**: Dose-dependent increase excretion of total porphyrins (tetracarboxyporphyrins predominated). Effect on the heme biosynthesis and porphyrin concentrations.	LOAEL = 2 mg/kg bw per day	**Bruchajzer (2011).** Porphyrogenic effect of pentabromodiphenyl ether after repeated administration to rats.
PentaBDE Congener composition: NR Impurities: NR **DecaBDE** Congener composition: NR Impurities: NR (Wellington Laboratories)	C57BL/6J mice 9 weeks Number of animals: NR F dosed, offspring analysed	Repeated exposure Oral (method not stated) PentaBDE: 0, 50, 100, 200 mg/kg bw per day DecaBDE: 0, 500, 2500, 12,500 mg/kg bw per day Vehicle: corn oil From GD6 to PND21 (5 weeks). Observations on PND21 and PND63.	PentaBDE: Significantly decreases in body weight of offspring on PND21 but Recovery was noted on PND63. **Spleen**: significant decreases in absolute and relative spleen weight in dams and in offspring on PND21 at the two highest doses. Significant decreases in the number of splenocytes in offspring on PND21 at the two highest doses (not significant in dams). Increased splenic T cell proliferation in dams and PND21 offspring but no significant difference in splenic B cell proliferation in all treatment groups. Slight increase in the percentage of total T cells, T helper cells and T cytotoxic cells in splenocytes of PND21 offspring. **Thymus**: significant decreases in absolute and relative weight in offspring on PND21. Significant decreases in the number of thymocytes in offspring on PND21 (not significant in dams). DecaBDE: Increase % WBC and % neutrophils in dams. Decrease in the relative distribution of B cells and increase in the % of macrophages in dams and decrease in PND21 offspring.	PentaBDE: NOAEL = 50 mg/kg bw per day DecaBDE: LOAEL = 0.5 mg/kg bw per day	**Hong et al. (2010).** Polybrominated diphenyl ethers orally administration to mice were transferred to offspring during gestation and lactation with disruptions on the immune system.
OctaBDE Congener composition: octaBDEs: 65.7%, heptaBDEs: 14.8% hexaBDEs: 1.7%, nona-decaBDEs: 17.8% Impurities: NR (Synthesised at the Department of Radiation Chemistry, Technical University of Lodz)	Wistar rats Five animals per dose group, four animals in control group Adults F	Repeated exposure Oral (gavage) 0, 2, 8, 40, 200 mg/kg bw per day Vehicle: sunflower oil 7, 14, 21 or 28 days	After 28 days: **Liver**: lower ALA-S and ALA-D activity, increased concentrations of highly carboxylated porphyrins from the lowest dose. **Urine**: increased, dose-dependent and time-dependent, concentrations of total porphyrins (tetracarboxyporphyrins predominated).	LOAEL = 2 mg/kg bw per day	**Bruchajzer et al. (2012).** Octabromodiphenyl ether-porphyrogenicity after repeated administration to rats.
OctaBDE Congener composition: octaBDEs: 65.7%, heptaBDEs: 14.8%, hexaBDEs: 1.7%, nona-decaBDEs: 17.8% Impurities: NR (Synthesised at the Department of Radiation Chemistry, Technical University of Lodz)	Wistar rats (190–230 g) Five animals per dose group, four animals in control group F	Single and repeated exposure Oral (gavage) Single: 0, 0 (oil), 25, 200, 2000 mg/kg bw Repeated: 0, 0 (oil) control, 0.4, 2, 8, 40, 200 mg/kg bw per day Vehicle: sunflower oil Single dose or 7–28 days	After single or repeated exposure: Impaired redox homeostasis: increased levels of GSH and GSSG and increased concentration of MDA in liver, and reduced TAS in serum. After repeated exposure: increased activity of GST in the liver.	LOAEL = 0.4 mg/kg bw per day	**Bruchajzer et al. (2014).** Selected oxidative stress parameters after single and repeated administration of octabromodiphenyl ether to rats.

(Continues)

TABLE E.5 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
Mixture of PBDEs: BDE-28, -47, -99, -100, -153, -209 (composition not specified)	Wistar rats (adults) 10 animals/dose group Pregnant F	Repeated exposure Oral (dietary: ¼ of a soy-free food treat pellet) 0 and total dose of 105.3 µg PBDE/kg bw per day. Mixture dissolved in ethanol with 10% pure corn oil ranging in concentration from 5.3 to 30.4 mg/kg bw per day, resulting in a total dose of 105.3 mg/kg bw per day Vehicle: corn oil GD6-GD15	Significantly increased fetal mass at GD14 and significantly reduced fetal mass at GD12. TT3 levels in the dosed dams were significantly increased relative to controls at GD14/15 but not at GD12/13. In the placental tissues, there were significant differences in T3 and T4 based on tissue location (e.g. fetal vs maternal). There was a significant decrease in T3 levels in the fetal placental tissue relative to the maternal placental tissue for all control and exposed groups. T3 levels in the maternal and fetal placenta significantly differed from one another based on the GD of the fetus. There was a significant increase in T3 levels in exposed F fetus on GD12/13.		**Ruis et al. (2019).** PBDEs concentrate in the fetal portion of the placenta: implications for thyroid hormone dysregulation.

Abbreviations: ALA-S, aminolevulinic acid synthase; ALA-D, aminolevulinic acid dehydratase; BDDs, brominated dibenzo-*para*-dioxins; BDFs, dibenzofurans; BROD, benzyloxyresorufin-O-dealkylase; bw, body weight; CD4+/CD8+, specific T-cells; EROD, ethoxyresorufin-O-deethylase; PROD, pentoxyresorufin-O-dealkylase; F, female; GD, gestational day; GSH, glutathione; GSSG, oxidised glutathione; GST, total glutathione S-transferase; KLH, keyhole limpet hemocyanin; LOD, limit of detection; M, male; MDA, malondialdehyde; NR, not reported; PND, postnatal day; PEPCK, phosphoenolpyruvate carboxykinase,; PBBs, polybrominated biphenyls; PBDD/FS, polybrominated dibenzo-p-dioxins and dibenzofurans; TAD, total administered doses; TAS, total antioxidant status; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; TT3, total T3; TT4, total T4; WBC, white blood cell.

[a]This study was cited in the previous EFSA assessment on PBDEs (EFSA CONTAM Panel, 2011b) and it is included again in the current assessment to provide insight into additional observations by the study authors not reported in the previous Opinion.

TABLE E.6 Summary of neurotoxicity studies of PBDEs in experimental animals.

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-47					
BDE-47 Purity not specified (Great Lakes Chemical/ Chemtura Corp)	C57BL/6 mice Four to seven M per dose and age of testing 10 day old	Single dose exposure on PND10 Oral (gastric tube) 0, 1, 10, 30 mg/kg bw	Groups of mice culled at age PND15 and PND20 and as adults (PND131–159) for analysis of dopamine and its two metabolites (DOPAC and HVA) in different brain regions Statistically significant increase in dopamine levels in the cortex, regardless of age, in the 10 mg/kg bw groups, but not at 1 and 30 mg/kg bw No **BDE-47** related changes in dopamine in striatum and cerebellum, and in other neurotransmitters (5HT and norepinephrine) in the 3 brain regions studied	No dose–response relationship	**Gee et al. (2011).** Neurochmical changes following a single dose of polybrominated diphenyl ether 47 in mice
BDE-47 100% (AccuStandard Corp)	Sprague–Dawley rats Nine M and nine F per dose group 10 day old Litters limited to eight pups at PND3 max (4 M/4 F)	Single dose exposure on PND10 Oral (gastric tube) 0, 1, 5, 10 mg/kg bw	Spatial learning and memory in a Morris water maze were assessed at age 2 months in six M and six F randomly selected in each group Spatial learning and memory were impaired in a dose-dependent manner (reflected by a significant increase in the latency to perform the test with the dose and a concomitant reduction in the time ratio, respectively)	LOAEL for learning and memory = 1 mg/kg bw	**He et al. (2011).** Toxic effect of PBDE-47 in thyroid development, learning, and memory, and the interaction between PBDE-47 and PCB153 that enhances toxicity in rats
BDE-47 'High purity' (as reported by the authors) (Cambridge Isotope Laboratories)	BALB/c mice Three to seven dams per dose group Adults F dosed, offspring tested Litter limited to five pups at PND5	Repeated exposure GD0–PND18 Oral free access to the food. Two types of food: (i) casein-based diet (CBD) + soy-bean oil (SBO), (ii) CBD + SBO added with fish 15% 0, 6, 1900 µg/kg feed Levels of exposure with the CBD + SBO food correspond to 0.00005, 0.00078, 0.227 mg/kg bw per day during gestation and to 0.00008, 0.00141, 0.421 mg/kg bw per day during lactation Levels of exposure with the fish-added diet correspond to 0.00004, 0.00066, 0.243 mg/kg bw per day during gestation and to 0.00007, 0.00118, 0.402 mg/kg bw per day GD0–PND18	Offspring (two pups per litter) were tested using a modified Fox-battery of tests, including righting reflex, fore-and hind limb grasp and hang-climb ability (PND5–PND11), auditory startle reflex (PND5–PND15), visual placing, cliff drop aversion and grip strength (PND15 and PND18), and hind limb splay (PND18). On PND18, pups and adults were tested for spontaneous behaviour and emotional reactivity in an elevated plus maze No significant behavioural changes except for a lower righting reflex in the **BDE-47** high level group fed with both diets ($p = 0.055$) Changes in gene expression in the whole brain indicated neurodevelopmental effects at the high dose in a casein-based diet, but not in the fish-based diet	NOAEL for neurobehavioural effects = 0.227 mg/kg bw per day	**Haave et al. (2011).** Cerebral gene expression and neurobehavioural development after perinatal exposure to an environmentally relevant polybrominated diphenylether (BDE47)

(Continues)

TABLE E.6 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-47 Purity not specified (AccuStandard Corp)	C57BL/6J mice Adults Four to nine pups per litter (mean = 6 pups/litter), 9–12 litters/group Dams dosed, testing in one M and one F pup randomly selected per litter during weeks 5–17	Repeated exposure Oral (on cornflakes) 0, 0.03, 0.1, 1 mg/kg bw per day From 4 weeks before mating until PND21 (70–80 days in total)	Pups tested for neuromuscular function (week 5, grip strength), locomotor coordination (week 6, ladder walk), gait analysis (week 13) and locomotor activity (weeks 9 and 17). Memory performances were assessed at week 8 in the Barnes maze Impaired performance in the Barnes spatial maze on the first day of training but not on days 2–4 and in the probe trial (day 5), suggesting possible impaired learning when exposed for the first time to the task No significant effects on motor performances	Same effects in the Barnes maze at all doses LOAEL = 0.03 mg/kg bw per day	**Koenig et al. (2012).** Maternal transfer of BDE-47 to offspring and neurobehavioural development in C57BL/6J mice
BDE-47 Purity not reported (AccuStandard)	$Mecp2^{308/+}$ dams mated withwild-type C57BL/6J M mice 77 dams dosed Number of offspring not reported F, M	Repeated exposure Oral (on cornflakes) 0, 0.03, 0.1 (discontinued due to poor reproductive success), 1.0 mg/kg bw per day 10 weeks (4 preconception +3 gestation +3 during lactation) Vehicle: corn oil	Offspring were subjected to a developmental test battery (PND8-18) and then to various behavioural tests at different times up to PND130 Exposure to **BDE-47** was associated with significant decreases in separation distress (ultrasonic vocalisations) in M and F, associated with sociability and learning and memory impairments only in females. No effect on anxiety, social preference, locomotor activity or social interaction in both sexe	Data not presented for the individual doses	**Woods et al. (2012).** Long-lived epigenetic interactions between perinatal PBDE exposure and Mecp2308 mutation
BDE-47 99% (AccuStandard Corp)	Sprague–Dawley rats 16 animals per dose group Adults (7 weeks of age) M	Repeated exposure Oral (gavage) 0, 0.1, 0.5, 1 mg/kg bw per day, + untreated group Vehicle: peanut oil 30 days	Tested for spatial learning and memory performances in a Morris water maze on 5 consecutive days Impaired spatial learning and memory in a significant way to locate the platform at the 4th day of testing and to recover the place of the platform in the probe test at day 5. Both effects occurred in a dose-dependent manner	Effects at all doses LOAEL = 0.1 mg/kg bw per day	**Yan et al. (2012).** Spatial learning and memory deficit of low level polybrominated diphenyl ethers-47 in male adult rat is modulated by intracellular glutamate receptors

TABLE E.6 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-47 100% (AccuStandard Corp)	CD-1 mice Five dams per group, 11–15 pups per litter One (PND21) or three M (after weaning) pups per litter randomly selected were tested F dosed, M pups tested	Repeated exposure Oral (from the tip of a pipette) 0, 0.2 mg/kg bw per day GD8–PND21	One pup per litter tested for spontaneous motor activity on PND21 (open-field), and three other pups for sociability and social dominance/subordination at times up to week 20 Significant reduction in body weight at PNW11 and 16 (not significant at PNW20). No effects on locomotor activity and sociability faced to an unfamiliar individual Litters were not normalised, and a litter size effect was significant throughout the study	LOAEL = 0.2 mg/kg bw per day (based on the reduced body weight) (only dose tested)	**Kim, Colon, Chawla, Vandenberg, and Suvorov (2015).** Endocrine disruptors alter social behaviours and indirectly influence social hierarchies via changes in body weight
BDE-47 > 98% (Chem. Service)	C57BL/6 mice 10 animals per dose group 7-week-old animals M	Repeated exposure Gavage (gavage) 0, 20 mg/kg bw per day Vehicle: corn oil 8 weeks	Tested for spatial learning and memory performances in a Morris water maze on 5 consecutive days and a passive avoidance test for 2 days (one training session and one 24 h-retention session) Impaired spatial learning and memory in a significant way to locate the platform at the 4th day of testing and to recover the place of the platform in the probe test at day 5 Impaired 24h-retention time in the passive avoidance task. No effect on the learning latency during the training session Results improved by hippocampus-specific TDP-43 knockdown in **BDE-47** treated mice	LOAEL = 20 mg/kg bw per day (only dose tested)	**Zhuang et al. (2017).** TDP-43 upregulation mediated by the NLRP3 inflammasome induces cognitive impairment in 2 2′,4,4′-tetrabromodiphenyl ether (BDE-47)-treated mice

(Continues)

TABLE E.6 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-47 > 98% (Chem. Service)	C57BL/6 Mice 10 animals per dose group 7-week-old animals M	Repeated exposure Oral (gavage) 0, 20 mg/kg bw per day Vehicle: corn oil 8 weeks	Tested for spatial learning and memory performances in a Morris water maze on 5 consecutive days and a passive avoidance test for 2 days (one training session and one 24 h-retention session) Impaired spatial learning and memory to locate the platform at the 4th day of testing and to recover the place of the platform at the 5th day of testing (probe test) Impaired 24h-retention time in the passive avoidance task. No effect on the learning latency during the training session. Results improved by hippocampal DJ-1 overexpression and neuroprotective effects against ROS production in **BDE-47** treated mice Exactly the same results observed for controls and **BDE-47** animals as in the previous study (Zhuang et al., 2017)	LOAEL = 20 mg/kg bw per day (only dose tested)	**Zhuang et al. (2018).** Adeno-associated virus vector-mediated expression of DJ-1 attenuates learning and memory deficits in 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47)-treated mice
BDE-47 99.5% (Accustandard Corp)	Sprague–Dawley female rats 15 dams per dose group, 8 pups/litter (four M and four F) One M and one F pups tested per dose group 8-week-old animals	Repeated exposure Oral (gavage) 0, 0.1, 1.0, 10.0 mg/kg bw per day Vehicle: corn oil 10 days prior to mating to PND21 Pups tested on PND88–92	Tested for spatial learning and memory performances in a Morris water maze on 5 consecutive days Impaired spatial learning and memory to locate the platform at the 4th day of testing in 0.1 and 1.0 mg/kg bw per day treated rats and to recover the place of the platform at the 5th day of testing (probe test) in animals exposed to 1.0 and 10 mg/kg bw per day Neuronal loss and apoptosis in the hippocampal CA3 region	LOAEL = 0.1 mg/kg bw per day based on spatial learning deficieny NOAEL = 0.1 mg/kg bw per day based on location platform recovery	**Li, Ma, et al. (2019).** Autophagy impairment contributes to PBDE-47-induced developmental neurotoxicity and its relationship with apoptosis

TABLE E.6 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-47 98% (Toronto Research Chemicals)	BALB/c mice Adult Number of animals per group not specified	Repeated exposure Oral (gavage) 0, 1.0, 10.0, 100.0 mg/kg bw per day Vehicle: corn oil 56 days	No effect on body weight or relative brain weight Loss of hippocampal neurons in DG and CA1. No abnormal histopathological observations concerning both neurons and glial cells in various hippocampal regions Not possible to conclude to a real toxicity of **BDE-47** because no counting results are presented. Not possible to conclude to a potent toxicity related to the dose	Unable to be used to determine a LOAEL/NOAEL	**Liu et al. (2022).** BDE-47 induced PC-12 cell differentiation via TrkA downstream pathways and caused the loss of hippocampal neurons in BALB/c mice
BDE-47 > 99% (Molbase Inc, Shanghai, China)	Sprague–Dawley female rats 15 dams per dose group,1M pup tested per dose group, a different pup/test 8-week-old animals	Repeated exposure Oral (gavage) 0, 50 mg/kg bw per day Vehicle: corn oil GD0-PND21	Animals were tested for self-grooming (PND26), learning performance in a T-maze (PND28), marble-burying (PND32), sociability and social preference in a 3-chamber task (PND36) and locomotor activity in an open-field (PND40) No effects on sociability. A social preference did exist in **BDE-47-**exposed rats but was less marked compared to controls Significant increases in repetitive behaviours (self-grooming, T-maze, marble-burying) and anxiety (central part of the open-field) Significant reduction in dendritic length and branching complexity, and dendritic spine density in the prefrontal cortex	LOAEL = 50 mg/kg bw per day (only one dose tested)	**Li, You, and Wang (2021).** Perinatal exposure to BDE-47 exacerbated autistic-like behaviours and impairments of dendritic development in a valproic acid-induced rat model of autism
BDE-47 > 99.99% (AccuStandard, No BDE-047N, New Haven, USA)	Sprague–Dawley female rats 12 dams per dose group, 5 F pups tested for behaviour per group PND88	Repeated exposure Oral (gavage) 0, 0.1, 1.0, 10 mg/kg bw per day Vehicle: corn oil 10 days prior to breeding-PND21	Animals were tested for activity and anxiety in the open-field at PND88 Significant increases in the total distance travelled and time of locomotion at doses of 1.0 and 10 mg/kg bw per day. Significant dose–response decrease in the distance travelled in the central part of the maze at the same two doses Same significant reduction, but non dose related, in the time spent in the central part of the maze Numerous limitations particularly about the methodology of the study were noted	NOAEL = 0.1 mg/kg bw per day (based on total distance and time of locomotion, and distance travelled in the central part of the maze)	**Qiu et al. (2022).** Perinatal exposure to low-level PBDE-47 programs gut microbiota, host metabolism and neurobehavior in adult rats: An integrated analysis

(Continues)

TABLE E.6 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-99					
BDE-99 Purity NR (LGC Standards S.L.U.)	Sprague–Dawley rats 10 per group Adult M	Repeated dose Gavage 0, 0.6, 1.2 mg/kg bw per day Vehicle: corn oil 45 days	Rats were tested in a Functional Observational Battery in the home cage and a white box consecutively, on days 3, 21 and 44 after the end of exposure. They were assessed for locomotor activity (open-field), early conditioning memory (passive avoidance) and spatial learning and memory (Morris water maze) at the end of the dosing period Performance in only one FOB test, the inverted screen test (rather exploring locomotor coordination and self-reactivity than pure sensitive functions), was impaired on day 3 after the dosing but not at later times, and not in other tests. No effects in behavioural tests or histopathological examination of the brain at the end of the study period Biochemical analyses of brain tissue at the end of the study period indicated changes in antioxidant capacity, mostly in the cerebellum	LOAEL = 0.6 mg/kg bw per day for a transient effect	**Bellés et al. (2010).** Behavioural effects and oxidative status in brain regions of adult rats exposed to BDE-99[a]
BDE-99 99% (LGC Standards)	Sprague–Dawley rats 10 dams per group, litter randomly reduced to two M and two F at PND1 Dams dosed, one M + one F offspring per litter tested for behavioural effects	Repeated exposure Oral (gavage) 0, 1, 2 mg/kg bw per day Vehicle: corn oil GD6 to PND21, except PND0. Pups tested on PND22 and PND23	Testing for locomotor activity (open-field apparatus) and for spatial learning and memory (Morris water maze) were performed on PND22 and PND23–26, respectively No effects on learning and memory performances. Reduction of the level of anxiety in the open-field (higher distance travelled and time spent in the central part of the maze), statistically significant at the highest dose Significant reduction in serum thyroid hormone levels at the same highest dose Significant reduction in the hippocampus gene expression of BDNF at the highest dose	LOAEL = 2 mg/kg bw per day NOAEL = 1 mg/kg bw per day	**Blanco et al. (2013).** Perinatal exposure to BDE-99 causes learning disorders and decreases serum thyroid hormone levels and BDNF gene expression in hippocampus in rat offspring

TABLE E.6 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-99 Purity NR (Promochem)	Sprague–Dawley rats 10 dams per group, 6 M offspring per litter Dams dosed, M offspring tested	Repeated exposure Oral (gavage) 0, 0.2 mg/kg bw per day Vehicle: corn oil GD1 to PND21, except PND0	Offspring assessed for neurobehavioural development from PND3 to PND36 (balancing reflexes, righting reflexe, cliff avoidance and negative geotaxis, every 2 days from PND3 to 21; motor coordination on PND29 and 30 in a rotarod test, 3 trials per day; spatial learning and memory in a Morris water maze on PND34–36, 4 trials per day, no retention test) **BDE-99** had no effects on locomotor reflexes, motor coordination or learning or memory performances	NOAEL = 0.2 mg/kg bw per day (only dose tested)	**Zhao, Zhang, et al. (2014).** Assessment of neurotoxic effects and brain region distribution in rat offspring prenatally co-exposed to low doses of BDE-99 and methylmercury
BDE-99 Purity NR (Stockholm University)	NMRI mice 12 mice from three or four litters per group M	Single dose on PND10 Oral (method not stated) 0, 12 mg/kg bw Vehicle: lecithin and peanut oil	One-hour testing for spontaneous behaviour in a novel home environment (locomotion, rearing and total activity) performed at age 2 months Locomotion, rearing and total activity were significantly reduced during the first 20 min of observation and significantly increased during the third 20 min period. Changes in cholinergic gene transcription in the cortex and hippocampus (significant overexpression of some cholinergic genes in cortex of 2 month-aged mice)	LOAEL = 12 mg/kg bw (only dose tested)	**Hallgren et al. (2015).** More signs of neurotoxicity of surfactants and flame retardants – Neonatal PFOS and PBDE 99 cause transcriptional alterations in cholinergic genes in the mouse CNS
BDE-209					
BDE-209 ≥ 99% (Shanghai Jiachen Chemical Co. Ltd.)	Sprague–Dawley rats 12 animals per group 21 days old M	Repeated exposure Oral (gavage) 0, 10, 50 mg/kg bw per day Vehicle: corn oil 90 days	At the end of the 90 days, open field tests were conducted to assess latency, periphery and centre grids, rearing number and grooming time (latency not defined) Shorter latency at lowest dose, but no effects on other parameters or at the high dose, suggesting the latency finding is not biologically relevant	No consistent effect	**Wang, Wang, et al. (2011).** Tissue distribution and associated toxicological effects of decabrominated diphenyl ether in subchronically exposed male rats

(Continues)

TABLE E.6 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-209 Purity NR (IGC Prochem)	Wild type Tg2576 mice Eight to nine animals per dose group 3 months old M	Repeated exposure Oral (gavage) 0, 20 mg/kg bw per day Vehicle: sunflower oil 15 days	Mice were subjected to testing in a functional observational battery, a light/dark test, a zero maze test and a water maze test at the end of the dosing period Reduction in arousal in the FOB test, reduction of the level of anxiety in the zero maze test whereas no changes were observed in the light/dark apparatus. No significant changes observed between groups in the water maze test excepted those concerning the first probe trial, suggesting that the initial performance of the **BDE-209**-exposed group is worse than that of the control group	LOAEL = 20 mg/kg bw per day (only dose tested)	**Heredia et al. (2012).** Behavioural effects of oral subacute exposure to BDE-209 in young adult mice: a preliminary study
BDE-209 > 98% (University of Stockholm)	NMRI mice 27–40 pups per sex per dose group (six different litters per group) F, M	Single exposure on PND3 Oral (via metal gastric tube) 0, 1.4, 6, 14 μmol/kg bw (corresponding to 0, 1.5, 6.3, 14.6 mg/kg bw per day) Vehicle: egg lecithin, peanut oil	M and F mice were tested for spontaneous behaviour (locomotion, rearing and total activity) and challenged for the cholinergic susceptibility at 2 months of age, and for spontaneous activity alone at 4 months of age. Male mice that have been treated at the two higher dose levels were tested in a Morris water maze at age 5 and 7 months All tested dose levels resulted in altered spontaneous behaviour, impaired habituation (defined as decreasing locomotion, rearing and total activity in response to the diminishing novelty of the test chamber) in both M and F mice aged of 2 and 4 months. Challenging the cholinergic system allowed the performance to be restored. Deficits in learning and memory were observed in the water maze test in mice aged of 5 and 7 months	LOAEL = 1.5 mg/kg bw per day	**Buratovic et al. (2014).** Developmental exposure to the polybrominated diphenyl ether PBDE 209: Neurobehavioural and neuroprotein analysis in adult male and female mice

TABLE E.6 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-209 Purity NR (Beijing J&K Chemicals)	Sprague–Dawley rats 10 dams per dose group, 20 male pups per group F exposed, offspring tested (only male)	Repeated exposure Oral (gavage) 0, 10, 30, 50 mg/kg bw per day Vehicle: arachis oil Control groups: arachis oil and untreated GD1-14	Learning ability assessed in 20 M offspring per group in Morris water maze on 4 consecutive days, starting PND25 There was a dose- and time-related impairment in learning (escape latency) which was statistically significant at 72 and 96 h at 30 and 50 mg/kg bw per day	NOAEL = 10 mg/kg bw per day	**Chen, Li, et al. (2014).** Prenatal exposure to decabrominated diphenyl ether impairs learning ability by altering neural stem cell viability, apoptosis, and differentiation in rat hippocampus
BDE-209 98% (Wako pure chemical industries)	C57BL/6 mice 10 animals per dose group 6–8 weeks old F	Repeated exposure Oral (gavage) 0, 800 mg/kg bw, at 2-day intervals Vehicle: corn oil 2 years	No effect on relative brain weight The hippocampus revealed decreased neurons in the cornu ammonis and dentate gyrus areas, accompanied by lower numerical density and neuronal degeneration Authors also noted abnormailities in behaviour after 6 months, but no details were provided	LOAEL = 400 mg/kg bw per day	**Feng et al. (2015).** Simulating long-term occupational exposure to decabrominated diphenyl ether using C57BL/6 mice: biodistribution and pathology
BDE-209 98% (Sigma-Aldrich)	C57BL6/J mice Litters culled to three M and three F pups at PND1 39 control litters and 42 **BDE-209**-exposed litters Pups F, M	Repeated exposure Oral (from a micropipette) 0, 20 mg/kg bw per day Vehicle: Emulsified in 10% L-α-phospatidylcholine in peanut oil PND1–PND21, tested in adulthood	Tested for forelimb grip strength, motor coordination (rotarod), motor activity (circadian wheel running), and learning and memory (light extinction test) at various timepoints up to PND250. Operant behaviour was challenged with the psychostimulant methylphenidate for the last 5 sessions Exposed M mice showed deficits in grip strength and lever-pressing discrimination, and a higher level of motor activity during the dark phase of the light cycle F mice were less affected, showing only lower activity in a wheel	LOAEL = 20 mg/kg bw per day (only one dose tested)	**Markowski et al. (2017).** Motor deficits, impaired response inhibition, and blunted response to methylphenidate following neonatal exposure to decabromodiphenyl ether
BDE-209 99.5% (Dr Ehrenstorfer GmbH)	Sprague–Dawley rats 10 dams per dose group 10–12 weeks Pup sex not specified for testing	Repeated exposure Oral (gavage) 0, 5, 10, 20 mg/kg bw per day Vehicle: peanut oil Dams dosed GD1 to GD21	Offspring were tested for learning and memory ability in a Morris water maze on PND28–32 Escape latency time in the maze was significantly higher than controls on days 3, 4 and 5 of testing, reflecting impaired learning and memory Results suggest increased hippocampal autophagy, decreased neuron viability and apoptosis	LOAEL = 10 mg/kg bw per day NOAEL = 5 mg/kg bw per day	**Sun et al. (2017).** PBDE-209 exposure damages learning and memory ability in rats potentially through increased autophagy and apoptosis in the hippocampus neuron

(Continues)

TABLE E.6 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
BDE-209 > 98% (Sigma Chemical)	Sprague–Dawley rats 20 animals (10 M and 10 F) per dose group, eight pups per litter (four M and four F) Neonatal (PND5–PND10) F, M (1:1)	Repeated exposure Oral (gavage) 0, 1, 10, 20 mg/kg bw per day Vehicle: peanut oil Dosing from PDN5 to PDN10 (5 days)	Rats were tested for spatial learning and memory in a Morris water maze on PND70–73, and then for spatial working and reference memory in an eight-arm radial maze beginning on PND74 Longer escape latencies and fewer platform crossings in the Morris water maze were observed in a dose-dependent manner at all doses Significantly higher working and reference memory error rates in the eight-arm radial maze were observed at 10 and 20 mg/kg bw per day **BDE-209**	LOAEL = 1 mg/kg bw per day	**Li, Wang, et al. (2017** Neonatal exposure to BDE 209 impaired learning and memory, decreased expression of hippocampal core SNAREs and synaptophysin in adult rats
BDE-209 > 98% (J&K Technology)	Sprague–Dawley rats Eight animals per dose group 11 weeks M	Repeated exposure Oral (gavage) 0, 250, 500, 1000 mg/kg bw per day Vehicle: peanut oil 30 days	Testing in a water maze 7 days after the end of dosing Longer escape latencies and fewer platform crossings in the Morris water maze were observed in a dose-dependent manner at all doses. Swim speed was not affected Significant impairment of memory in the probe trial at the two highest doses Decreased expression of glutamate receptor subunits (NR1, NR2B, Glu-R1) in hippocampus	LOAEL = 500 mg/kg bw per day NOAEL = 250 mg/kg bw per day	**Xiong et al. (2018).** Effect of decabrominated diphenyl ether exposure on spatial learning and memory, the expression and phosphorylation of hippocampal glutamate receptor subunits in adult Sprague–Dawley rats
BDE-209 > 99% (Sigma Aldrich, USA)	ICR mice 12 dams per dose group, mean litter size = 10–13 pups/litter Pregnant mice dosed M + F pups tested	Repeated exposure Oral (gavage) 0, 225, 900 mg/kg bw per day Vehicle: peanut oil GD0-PND21	Significant decreases in litter size and body weight of pups on PND21 at both doses. Significant decrease in brain weight relative to the viscera at the highest dose 12 offspring per dose group were tested for spatial learning and memory ability in Morris water maze on PND21-26, and showed impaired performance at both doses (increased escape latency in both groups at trials 3 and 4, significant impairment of memory in the probe trial at the two doses) Partial neuronal degeneration and necrosis were reported in the hippocampi of top dose pups	LOAEL = 225 mg/kg bw per day	**Qian et al. (2021)**. A preliminary study on the mechanism of the neurosteroid-mediated ionotropic receptor dysfunction in neurodevelopmental toxicity induced by decabromodiphenyl ether

TABLE E.6 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
PBDE technical products					
DE-71 Congener composition (LOT #7550OK20A): tetraBDE: 25% pentaBDE: 50%–60% hexaBDE: 4%–8% Impurities: NR (Great Lakes Chemical Corporation)	Long-Evans rats Eight dams per dose group, three M pups per litter were dosed	Repeated exposure Oral (gavage) 0, 5, 15 mg/kg bw per day Vehicle: corn oil PND6–PND12	Tests for learning and attention performed at various times from PND40 to PND95 No treatment-related changes observed	NOAEL = 15 mg/kg bw per day	**Driscoll et al. (2012).** Acute postnatal exposure to the pentaBDE commercial mixture DE-71 at 5 or 15 mg/kg per day does not produce learning or attention deficits in rats
DE-71 Congener composition (LOT#3550OC08P): NR by the study authors, but according to Bondy et al. (2013) for same Lot number: BDE-28: 0.21% BDE-85: 2% BDE-47: 43% BDE-99: 43% BDE-100: 8% BDE-153: 2% BDE-154: 2% BDE-183: 0.09% Impurities detected: – 1,2,3,7,8-pentaBDD: 0.21 ng/g, – 1,2,3,4,6,7,8-heptaBDF: 0.81 ng/g (Chemtura, former Great Lakes Chemical)	Sprague–Dawley rats 30 dams per dose group 18–23 litters per dose group F	Repeated exposure 0, 0.3, 3.0, 30 mg/kg bw per day Vehicle: corn oil GD1 to PND21 Offspring tested	Tests for effects on motor function (motor activity, beam test), learning and memory (Morris water maze), sensory reactivity (startle), anxiety (emergence latency) and sensorimotor integration were conducted at various times from PND16 to PND450 Small changes in motor activity rearing at PND110 only Acoustic startle responses were increased at PND90 only No other statistically significant effects in behavioural tests Relative brain weight was significantly increased by about 10% at the highest dose on PND21 but not on PND50, PND105 or PND250)	NOAEL for neurobehavioural effects = 3 mg/kg bw per day LOAEL for neurobehavioural effects = 30 mg/kg bw per day (thyroid effects at lower dose)	**Bowers et al. (2015).** Behavioural and thyroid effects of in utero and lactational exposure of Sprague–Dawley rats to the polybrominated diphenyl ether mixture DE71

(Continues)

TABLE E.6 (Continued)

Compound Purity	Species Number of animals Age and gender	Route of administration Exposure doses Study duration	Outcome	NO(A)EL/LO(A)EL	Reference
DE-71 Congener composition (Lot #7550OK20A): NR by the study authors, but according to Driscoll et al. (2012) for the same Lot number: tetraBDEs: 25% pentaBDEs: 50%–60% hexaBDE: 4%–8% Impurities: NR (Great Lakes Chemical Corporation)	Wistar rats Five M and five F per litter, 32 litters F, M (50/50)	Repeated exposure Oral (gavage) 0, 30 mg/kg bw per day Vehicle: corn oil PND5–PND22	Tests for locomotor (open field) at PND42 and PND70, and for hyperactivity and learning (radial maze) at PND100: DE-71 had no effect on motor activity and working memory, but resulted in a reference memory deficit in F only	LOAEL = 30 mg/kg bw per day (only tested dose)	**de-Miranda et al. (2016)**. Thyroid hormone disruption and cognitive impairment in rats exposed to PBDE during postnatal development
DE-71 Congener composition: 0.11% BDE-17 0.24% BDE-28 33.3% BDE-47 2.54% BDE-85 45.3% BDE-99 8.24% BDE-100 0.45% BDE-138 0.92% BDE-139 3.57% BDE-153 3.19% BDE-154 Impurities: NR (Great Lakes Chemical Corporation)	C57Bl/6 *N* mice 45 F per dose group	Repeated exposure Oral (gavage) 0, 0.1, 0.4 mg/kg bw per day Vehicle: corn oil From 3 weeks before mating through gestation to PND21	Dams and female offspring subjected to an extensive battery of behavioural tests during PND28-111 Deficits in short- and long-term social recognition memory were reported in low dose offspring but not in the higher dose offspring or in the dams Short-term novel object recognition memory was compromised in the low-dose, but not high-dose offspring, and in dams at both doses An olfactory habituation/dishabituation tests indicated altered olfactory discrimination in offspring at both doses, but not in the dams No effects on sociability, repetitive behaviour, anxiety or depressive-like behaviour	LOAEL = 0.1 mg/kg bw per day	**Kozlova et al. (2021).** Persistent autism-relevant behavioural phenotype and social neuropeptide alterations in female mice offspring induced by maternal transfer of PBDE congeners in the commercial mixture DE-71
DecaBDE (composite of 3 commercial products) Congener composition: BDE-209: 97.51% nonaBDEs: 2.5% (Albemarle Corporation, Chemtura Corporation, ICL-IP America)	Crl:CD Sprague–Dawley rats 15–30 M, 15–30 F per dose group Adults, F dosed, offspring tested	Repeated exposure Oral (gavage) 0, 1, 10, 100, 1000 mg/kg bw per day Dams dosed from GD6 to PND21 Vehicle: corn oil	Pups tested for developmental landmarks, learning and memory, motor activity and startle response from PND13 180 No neurobehavioural changes in detailed clinical observations, startle response, learning and memory tests, or in motor activity, neuropathological or morphometric measurements	NOAEL = 1000 mg/kg bw per day	**Biesemeier et al. (2011).** An oral developmental neurotoxicity study of decabromodiphenyl ether (DecaBDE) in rats

Abbreviations: BDNF, brain-derived neurotrophic factor; BDDs, brominated dibenzo-*para*-dioxins; BDF, brominated dibenzo furans; bw, body weight; F, females; GD, gestational day; M, males; NOAEL, no observed-adverse-effect level; NR, not reported; LOAEL, lowest observed-adverse-effect level; PND, postnatal day; ROS, reactive oxygen species; TDP-43, TAR-DNA binding protein-43.

[a]This study was cited in the previous EFSA assessment on PBDEs (EFSA CONTAM Panel, 2011b) and it is included again in the current assessment to provide insight into additional observations by the study authors not reported in the previous Opinion.

APPENDIX F

Summary of NOAELs/LOAELs to aid identification of critical effects

TABLE F.1 Summary of NOAELs/LOAELs to aid identification of critical effects.[a]

	Congener	Study design	Effect	NOAEL mg/kg bw (per day)	LOAEL mg/kg bw (per day)	Reference
BDE-47						
Neurodevelopment[b]	**BDE-47**	Neonatal mice (NMRI) Single dose on PND10 0, 0.7, 10.5 mg/kg bw Testing at 2 and 4 months No levels in tissues measured	Alterations in spontaneous behaviour and ↓ habituation	0.7	10.5	Eriksson et al. (2001)
	BDE-47	Neonatal rats (SD) Dosing PND10 0, 1, 5, 10 mg/kg bw Testing at 2 months Levels in serum	Impaired spatial learning and memory	–	1	He et al. (2011)
	BDE-47	Mice F (C57BL/6J) Exposure of dams during gestation and lactation (4 weeks before mating until PND21) 0, 0.03, 0.1, 1 mg/kg bw per day Testing on week 5–17 Levels in blood, brain, fat and milk of dams; in whole fetal homogenate and blood and brain of pups	Impaired memory	–	0.03	Koenig et al. (2012)
	BDE-47	Adult rats F (SD) Exposure of dams during gestation and lactation (10 days prior to mating until PND21) 0, 0.1, 1, 10 mg/kg bw per day Testing on PND88-92 No levels in tissues measured	Spatial learning deficiency	–	0.1	Li, Ma, et al. (2019); Li, Yang, et al. (2019)
	BDE-47	Adult M rats (SD) 30 days dosing 0, 0.1, 0.5, 1 mg/kg bw per day No levels in tissues measured	Impaired spatial learning and memory	–	0.1	Yan et al. (2012)
	BDE-47	Rats (SD) Exposure of dams from 10 days prior to breeding until PND21 (weaning point) 0, 0.1, 1.0, 10 mg/kg bw per day Testing at PND88 No levels in tissues measured	Significant ↑ in total distance travelled and time of locomotion at 1.0 and 10 mg/kg bw per day. Significant dose–response ↓ in the distance travelled in the central part of the maze at the same two doses	0.1	1	Qiu et al. (2022)

(Continues)

TABLE F.1 (Continued)

	Congener	Study design	Effect	NOAEL mg/kg bw (per day)	LOAEL mg/kg bw (per day)	Reference
Developmental and reproductive toxicity	**BDE-47**	Adults M rats (SD) Exposure for 8 weeks 0, 0.001, 0.03, 1, 20 mg/kg bw per day No levels in tissues measured	↓ relative tubular epithelial thickness, ↑ apoptotic germ cells, impaired mitochondrial function	0.001	0.03	Huang, Cui, et al. (2015) here
	BDE-47	Adult M rats (SD) Exposure for 8 weeks 0, 0.001, 0.03, 1 mg/kg bw per day Levels of 3-OH-BDE-47 in plasma, liver, testis	Changes in cell organisation of seminiferous epithelium (giant cells) (at 0.03 mg/kg bw per day). Impaired spermatogenesis (at 1 mg/kg bw per day)	0.001	0.03	Zhang, Zhang, et al. (2013)[c] here
	BDE-47	Adult M rats (SD) Exposure for 12 weeks 0, 0.03, 20 mg/kg bw per day Levels in liver and testis	Changes cellular organisation seminiferous epithelium. Multigiant cells, aborted meiosis (at 20 mg/kg bw per day)	–	0.03	Zhang, Yu, et al. (2017)[d]
	BDE-47	Newborn F rats (SD) Exposure on PND10 0, 1, 5, 10 mg/kg bw per day No levels in tissues measured	↓ ovarian coefficient at age of 2 months, histopathological changes in ovary (at ≥ 5 mg/kg bw per day).	–	1	Wang et al. (2016)
	BDE-47	M offspring rats (Wistar) Exposure of dams during gestation and lactation (GD8-PND21) 0, 0.2 mg/kg bw per day Testing on PND120 No levels measured	↓ Absolute testes weight. ↓ sperm production and motility (not statistically significant), significant ↑ % of morphologically abnormal spermatozoa, and ↑ in spermatozoa head size	–	0.2	Khalil, Parker, Brown, et al. (2017)
	BDE-47	F offspring rats (Wistar) Single dose on GD6 0, 0.14, 0.7 mg/kg bw Testing on PND38 No levels in tissues measured	↓ Ovarian weight, alteration folliculogenesis	–	0.14	Talsness et al. (2008)
	BDE-47	F rats (SD) Exposure of dams before mating, during gestation and lactation up to PND21 0, 0.1, 1, 10 mg/kg bw per day Testing on PND88 No levels in tissues measured	↓ Relative testis weight at all doses (non-dose-related). Effects on sperm (↓ total sperm count, living sperm count, ↓ velocity) (CASA) (statistically significant at 10 mg/kg bw per day)	–	0.1	Li, Gao, et al. (2021)
BDE-99						
Neurodevelopment	**BDE-99**	Neonatal mice (NMRI) Single dose on PND10 0, 0.8, 12 mg/kg bw Testing at 2, 4 or 5 months No levels in tissues measured	Alterations in spontaneous behaviour and ↓ habituation, ↓ performance in Morris swim maze (at 12 mg/kg bw)	–	0.8	Eriksson et al. (2001)
	BDE-99	Neonatal M mice (NMRI) Single dose on PND10 0, 12 mg/kg bw Testing at 2 months No levels in tissues measured	↓ locomotion, rearing and total activity during the first 20 min of observation, and ↑ during the third 20 min period	–	12	Hallgren et al. (2015)
	BDE-99	Perinatal rats (SD) Exposure of dams during gestation and lactation (GD6-PND21) 0, 1, 2 mg/kg bw per day Testing PND22/23 No levels in tissues measured	↓ level of anxiety	1	2	Blanco et al. (2013)
	BDE-99	Adult M rats (SD) Single dose in adulthood 0, 0.6, 1.2 mg/kg bw per day No levels in tissues measured	Impaired performance in exploring locomotor coordination and self-reactivity tests.	–	0.6	Bellés et al. (2010)

TABLE F.1 (Continued)

	Congener	Study design	Effect	NOAEL mg/kg bw (per day)	LOAEL mg/kg bw (per day)	Reference
Developmental and reproductive toxicity	**BDE-99**	F F1G rats examined (Wistar) Single dose on GD6 0, 0.06, 0.3 mg/kg bw Testing on PND90 No levels in tissues measured	F reproductive tract changes at adulthood. ↑ resorptions	–	0.06	Talsness et al. (2005)
	BDE-99	M rat offspring (Wistar) Single dose on GD6 0, 0.06, 0.3 mg/kg bw No levels in tissues measured Testing on PND140	Impaired spermatogenesis	–	0.06	Kuriyama et al. (2005)
	BDE-99	Adult M rats (SD) Exposure for 30 days 0, 60, 120, 180 mg/kg bw per day Testing at 8 weeks No levels in tissues measured	Testis degeneration and necrosis	–	60	Yuan et al. (2012)
	BDE-99	Rats (SD) Exposure of dams during gestation (GD6-19) 0, 0.5, 1, 2 mg/kg bw per day Testing on GD20 (foetuses) No levels in tissues measured	Incomplete or delayed ossification, internal variations	0.5	1	Blanco et al. (2012)
	BDE-99	M mice offspring (ICR) Exposure of dams during gestation (GD1 to GD21) 0, 0.2, 2, 20 mg/kg bw per day Testing on PND1 until PND35 No levels in tissues measured	Changes in reproductive organs: ↓ anogenital index, ↑ cryptorchidism, effects on Leydig and spermatogenic cells	–	0.2	Zhao, Liu, and Pang (2021)
BDE-153						
Neurodevelopment	**BDE-153**	M mice (NMRI) Single dose on PND10 0, 0.45, 0.9, 9 mg/kg bw Testing at 2, 4 and 6 months old No levels in tissues measured	Disruption of spontaneous behaviour, ↓ performance in Morris swim maze (impaired learning and memory)	0.45	0.9	Viberg, Fredriksson, and Eriksson (2003)
BDE-209						
Neurodevelopment	**BDE-209**	Neonatal rats (SD) Single dose on PND3 0, 6.7, 20.1 mg/kg bw Testing up to 6 months No levels in tissues measured	Alterations in spontaneous behaviour indicating ↓ habituation. Alterations in nicotine response (2 months old).	–	6.7	Viberg et al. (2007)
	BDE-209	Neonatal M and F mice (NMRI) Single dose on PND3 0, 1.5, 6.3, 14.6 mg/kg bw Testing up to 7 months No levels in tissues measured	Altered spontaneous behaviour, impaired habituation. Deficits in learning and memory	–	1.5	Buratovic et al. (2014)
	BDE-209	Neonatal M and F mice (C57BL6/J) Exposure PND1–21 0, 20 mg/kg bw Tested in adulthood No levels in tissues measured	Deficits in grip strength, motor activity and some learning measures	–	20 (only dose)	Markowski et al. (2017)
	BDE-209	Neonatal M and F rats (SD) Exposure PND5-10 0, 1, 10, 20 mg/kg bw per day Testing up to PND74 No levels in tissues measured	Impaired learning and memory	–	1	Li, Wang, et al. (2017)
	BDE-209	Rats F (SD) Exposure GD1–GD21 5, 10, 20 mg/kg bw per day Testing on PND28-32 No levels in tissues measured	Impaired learning and memory.	5	10	Sun et al. (2017)
	BDE-209	Mice F (ICR) Dosing GD0–PND21 0, 225, 900 mg/kg bw per day Testing on PND21 No levels in tissues measured	Impaired spatial learning and memory	–	225	Qian et al. (2021)
	BDE-209	Adult rats (SD) Exposure for 30 days 0, 250, 500, 1000 mg/kg bw per day No levels in tissues measured	Impaired spatial learning and memory	250	500	Xiong et al. (2018c)

(Continues)

TABLE F.1 (Continued)

	Congener	Study design	Effect	NOAEL mg/kg bw (per day)	LOAEL mg/kg bw (per day)	Reference
Developmental and reproductive toxicity	**BDE-209**	Adult M rats (SD) Exposure for 28 days 0, 5, 50, 500 mg/kg bw per day No levels in tissues measured	↓ sperm cells and motility (automatic count), ↑ sperm malformations, histopathological changes in seminiferous tubules (at 50 and 500 mg/kg bw per day), apoptosis (at ≥ 5 mg/kg bw per day)	–	5	Li, Liu, et al. (2021)
	BDE-209	Adult M rats (SD) Exposure for 28 days 0, 5, 50, 500 mg/kg bw per day No levels in tissues measured	↓ sperm quantity and quality, degeneration of seminiferous tubules (at 50 and 500 mg/kg bw per day), changes in mitochondria at all doses, ↓ sperm concentration and motility (automatic count), malformations (at 50 and 500 mg/kg bw per day). Apoptosis of spermatogenic cells -> Spermatogenesis impairment.	–	5	Zhang, Li, et al. (2021)
	BDE-209	Adult M mice (Parkes) Exposure for 35 days 0, 950 mg/kg bw per day No levels in tissues measured	↓ weight of testis and epididymis, degeneration of seminiferous tubules, ↓ number and viability of spermatozoa	750	950	Sarkar et al. (2016)
	BDE-209	F mice (C57) Exposure GD7/9-GD16 0, 150, 750, 1500, 2500 mg/kg bw per day Foetuses examined No levels in tissues measured	↑ post-implantation loss (from 750 mg/kg bw per day) and resorptions (from 1500 mg/kg bw per day), ↓ live foetuses/litter, ↓ placenta weight (at 2500 mg/kg bw per day), ↓ fetal weight (from 750 mg/kg bw per day) and brain, liver and heart weight (at 2500 mg/kg bw per day)	150	750	Chi et al. (2011)
	BDE-209	F mice (CD-1) Exposure GD0-17 0, 10, 500, 1500 mg/kg bw per day Offspring examined No levels in tissues measured	Pathological lesions in testis, sperm malformations, ↓ spermatozoa and spermatids (at 1500 mg/kg bw per day), ↓ anogenital distance and index (at 1500 mg/kg bw per day)	10	500	Tseng et al. (2013)
	BDE-209	F mice (Parkes) Exposure of dams during lactation (PND1-28) 0, 500, 700 mg/kg bw per day Offspring examined on PND1, PND28 No levels in tissues measured	↓ Testis weight on PND28, effect on testicular histopathology, steroidogenesis and germ cell dynamics	–	500	Sarkar et al. (2018)
	BDE-209	F mice (Parkes) Exposure of dams during lactation (PND1-28) 0, 500, 700 mg/kg bw per day Offspring examined on PND42 No levels in tissues measured	Testicular and epididymal toxicity: ↓ sperm number and motility (not automatic analysis), ↓ viability, ↑ malformations ↓ mating and fertility index, ↓ litter size	–	500	Sarkar et al. (2019)

TABLE F.1 (Continued)

Congener	Study design	Effect	NOAEL mg/kg bw (per day)	LOAEL mg/kg bw (per day)	Reference
BDE-209	F mice (Parkes) Exposure of dams during lactation (PND1-28) 0, 500, 700 mg/kg bw per day Offspring examined on PND42 No levels in tissues measured	↓ weight (absolute and relative) of testis, seminal vesicle and prostate. Histopathological changes in seminiferous tubules, ↓ germ cell proliferation and steroidogenesis. ↓ Leydig cells	–	500	Sarkar and Singh (2018)
BDE-209	F mice (Parkes) Exposure of dams during lactation (PND1-28) 0, 500, 700 mg/kg bw per day Offspring examined on PND75 No levels in tissues measured	↓ weight (absolute and relative) of testis, epididymis, seminal vesicle and prostate. Histopathological changes in testis: degeneration of seminiferous tubules, multinucleated giant cells, ↓ sperm count (not automatic analysis), motility and viability	–	500	Sarkar and Singh (2021)
BDE-209	F mice (ICR) Exposure of dams during gestation and lactation (GD7-PND21) 0, 100, 300, 500 mg/kg bw per day Offspring examined at PND35, PND105 No levels in tissues measured	↓ weight of testis (from 300 mg/kg bw per day) and epididymis (all doses). Histopathological lesions in testis (from 300 mg/kg bw per day), ↓ or absence of spermatids. Ultrastructural changes in blood-testis barrier. Changes in mitochondria	–	100	Zhai et al. (2019)
BDE-209	Pregnant mice (C57BL/6) Exposure of dams during gestation (GD0-18) 0, 2, 20, 200 mg/kg bw per day Testing on GD18 No levels in tissues measured	Statistically significant ↓ in placental weight (all doses), impaired placental vascular development (at the highest dose) and induced placental apoptosis (at all doses)	–	2	Zhao et al. (2022)

[a]For details on the studies see **Section 3.1.2** and **Appendix E**.

[b]Excludes studies that are not informative about the dose–response, i.e. those that do not identify effects (NOAEL only), those with a single dose level at higher doses than other LOAELs in similar studies, those with more than one dose level but not providing data for the individual doses.

[c]For the study of Zhang, Zhang, et al. (2013), the CONTAM Panel noted the decreased testosterone levels at 0.001 mg/kg be per day, but for the establishment of the critical Reference Point used the LOAEL of 0.03 mg/kg bw per day based in changes in cell organisation of seminiferous epithelium (giant cells), since changes in sex hormones can be considered key events in the Adverse Outcome Pathway, but are not apical outcomes by themselves (see **Section 3.1.5**). In addition, the CONTAM Panel noted the widely spaced dose levels administered in this study, and the fact that the lowest dose tested has not been tested in most studies. Thus, the Panel only considered the LOAEL for the identification of critical effects.

[d]For the study of Zhang, Yu, et al. (2017); Zhang, Yolton, et al. (2017); Zhang, Li, et al. (2017); Zhang, Chang, et al. (2017), the CONTAM Panel noted that in this study only two dose groups were tested, and that the dose of 1 mg/kg bw per day where effects were observed in the previous study was not tested. Thus, the Panel do not consider this study for the identification of critical effects.

TABLE F.2 Summary of NOAELs/LOAELs related to changes in the thyroid hormone system in support of the identification of critical effects.

	Congener	Study design	Effect	NOAEL	LOAEL	Reference
				mg/kg bw (per day)		
BDE-47						
Thyroid hormone system	**BDE-47**	Adult M rats (SD) 8 weeks exposure 0.0009, 0.026, 0.86 mg/kg bw per day No levels in tissues measured	↓ TT3 levels	0.0009	0.026	Wang, Zhu, et al. (2020)
	BDE-47	Offspring M rats (SD) Exposure of dams before mating, and during gestation and lactation up to PND21 + PND12-21 0.1, 1, 10 mg/kg bw per day M offspring examined on PND88 No levels in tissues measured	↓ TT3 and TT4 levels	–	0.1	Li, Gao, et al. (2020)
	BDE-47	Offspring M and F rats (Wistar Han) Exposure of dams during gestation and lactation (GD6-PND21) 0.1, 15, 50 mg/kg bw per day Testing on PND22 Levels in plasma	↓ TT3 and TT4 levels	0.1	15	Dunnick, Shockley, Pandiri, Kissling, Gerrish, Ton, Wilson, Brar, Brix, Waidyanatha, Mutlu, and Morgan (2018)
BDE-99						
Thyroid hormone system	**BDE-99**	Pregnant rats (Wistar) Single dose on GD6 0, 0.06, 0.3 mg/kg bw Levels in adipose tissue and liver	↓ TT4 levels on PND1 in dams	–	0.06	Kuriyama et al. (2007)
	BDE-99	Offspring rats observed on PND22 (Wistar) Dams exposed on GD6 0, 0.06, 0.3 mg/kg bw Levels in adipose tissue and liver	↓ TT4 levels on PND22	0.06	0.3	Kuriyama et al. (2007)
BDE-209						
Thyroid hormone system	**BDE-209**	Adult F rats (SD) Exposed GD10, PND1-20 0, 0.7, 7, 66.3 mg/kg bw per day No levels in tissues measured	↑ thyroid weight on PND20	–	0.7	Fujimoto et al. (2011)
	BDE-209	Adult M rats (SD) Exposed for 28 days 0, 5, 50, 500 mg/kg bw per day No levels in tissues measured	Histopathological changes	–	5	Wang et al. (2019)
	BDE-209	Rats (SD) Exposed PND10-PND42 0, 100, 300, 600 mg/kg bw per day No levels in tissues measured	Follicular degeneration	100	300	Lee et al. (2010)
	BDE-209	Offspring M and F rats (SD) Exposed GD10, PND1-20 0, 0.7, 7, 66.3 mg/kg bw per day No levels in tissues measured	Follicular cell hypertrophy, significant ↓ TT3 levels (on PND20), significant ↓ TT4 levels (on PNW11)	7	66.3	Fujimoto et al. (2011)

APPENDIX G

Summary of the BMD modelling of the critical studies identified

TABLE G.1 Summary of the BMDL modelling of the critical studies (see Annex C for individual BMD reports).[a]

Congener	Reference	Animals/dosing	BMD BMDL-BMDU (mg/kg bw [per day]) All results calculated using bridge sampling[a]	Acceptance criteria satisfied[c] Model fit
BDE-47 (overall LOAEL = 0.03)				
BDE-47	Li, Ma, et al. (2019); Li, Yang, et al. (2019)	Adult rats F (SD) Exposure during gestation and lactation (10 days prior to mating to PND21) 0, 0.1, 1, 10 mg/kg bw per day Testing on PND88-92 No levels measured in tissues	Time spent in target quadrant: BMR 10%: BMD: 0.77 BMDL-BMDU: 0.15–6.62 Distance of target quadrant: BMR 10%: BMD: 3.61 BMDL-BMDU: 0.47–8.63	Yes Best fitting model fits sufficiently well
BDE-47	Zhang, Zhang, et al. (2013) here	Adult M rats (SD) Exposure for 8 weeks 0, 0.001, 0.03, 1 mg/kg bw per day Levels of 3-OH-BDE-47 in plasma, liver and testis	Daily Sperm count: BMR 10%: BMD: 0.11 BMDL-BMDU: 0.023–0.82	Yes None of the models provide an adequate fit do the data
BDE-47	Zhang, Yu, et al. (2017)	Adult M rats (SD) Exposure for 12 weeks 0, 0.03, 20 mg/kg bw per day Levels in liver and testis	No quantitative data for histopathological observations	–
BDE-47	Huang, Cui, et al. (2015) here	Adults M rats (SD) Exposure for 8 weeks 0, 0.001, 0.03, 1, 20 mg/kg bw per day No levels measured in tissues	Epithelial thickness: (SD ~ 5%) BMR 5%: BMD: 5.61 BMDL-BMDU: 0.16–16.56 Apoptotic cells: (SD ~ 18%–40%) BMR 20%: BMD: 8.13 BMDL-BMDU: 0.04–18.1	No None of the models provide an adequate fit to the data
BDE-99 (overall LOAEL = 0.06)				
BDE-99	Blanco et al. (2013)	Perinatal rats (SD) Dosing during gestation and lactation (GD6-PND21) 0, 1, 2 mg/kg bw per day Testing on PND22/23 No levels measured in tissues	Time spent central quadrant: BMR 10%: BMD: 0.67 BMDL-BMDU: 0.43–0.91 Distance travelled: BMR 10%: BMD: 0.75 BMDL-BMDU: 0.49–1.00	Yes Best fitting model fits sufficiently well
BDE-99	Kuriyama et al. (2005) here	M rat offspring (Wistar) Exposure during gestation (GD6) 0, 0.06, 0.3 mg/kg bw Testing on PND140 No levels measured in tissues	Daily sperm production (DSP): BMR 10%: BMD: 0.016 BMDL-BMDU: 0.002–0.045[b] Spermatid: BMR 10%: BMD: 0.017 BMDL-BMDU: 0.002–0.044	Yes DSP: None of the models provide an adequate fit do the data Spermatid: Best fitting model fits sufficiently well
BDE-99	Talsness et al. (2005) here	F F1G rats (Wistar) Exposure during gestation (GD6) 0, 0.06, 0.3 mg/kg bw Testing on PND90 No levels measured in tissues	Resorption dams (*n*) (Quantal): BMR 10%: BMD: 0.19 BMDL-BMDU: 0.05–0.29	Yes Best fitting model fits sufficiently well

(Continues)

TABLE G.1 (Continued)

Congener	Reference	Animals/dosing	BMD BMDL-BMDU (mg/kg bw [per day]) All results calculated using bridge sampling[a]	Acceptance criteria satisfied[c] Model fit
BDE-99	Blanco et al. (2012)	M/F rat foetuses (SD) Exposure during gestation (GD6-19) 0, 0.5, 1, 2 mg/kg bw per day Testing on GD20 No levels measured in tissues	Incomplete ossification occipital skull (quantal): BMR 10%: BMD: 0.54 BMDL-BMDU: 0.20–1.11 Foetuses with internal variations: BMR 10%: BMD: 0.63 BMDL-BMDU: 0.28–0.89 Foetuses with skeletal and internal malformations and variations: BMR 10%: BMD: 0.57 BMDL-BMDU: 0.18–1.52	Yes Best fitting model fits sufficiently well
BDE-99	Zhao, Liu, and Pang (2021)	M mice offspring (ICR) Exposure during gestation (GD1-21) 0, 0.2, 2, 20 mg/kg bw per day Testing on PND1 until PND35 No levels measured in tissues	Cryptorchidism PND35 (quantal): BMR 10%: no response AGI PND21: BMR 10%: BMD: 0.18 BMDL-BMDU: 0.07–0.48	Cryptorchidism: No AGI: Yes AGI: Best fitting model fits sufficiently well
BDE-153 (NOAEL = 0.9)				
BDE-153	Viberg, Fredriksson, Jakobsson, et al. (2003)	M mice (NMRI) Exposure on PND10 0, 0.45, 0.9, 9 mg/kg bw Testing at 2–4-6 months old No levels measured in tissues	Total activity (40–60 min) 6 months: BMR 10%: BMD: 0.33 BMDL-BMDU: 0.11–0.67	Yes Best fitting model fits sufficiently well
BDE-209 (Overall LOAEL = 1)				
BDE-209	Li, Wang, et al. (2017) here	Neonatal M and F rats (SD) Exposure PND5-10 0, 1, 10, 20 mg/kg bw per day Testing up to PND74 No levels measured in tissues	Escape Latency: BMR 10% Day 1: BMD: 4.66 BMDL-BMDU: 0.79–9.18 Day 2: BMD: 1.15 BMDL-BMDU: 0.21–4.61 Day 4: BMD: 0.21 BMDL-BMDU: 0.04–0.81 Platform crossing: BMR 10%: BMD: 4.99 BMDL-BMDU: 1.59–8.44 Reference memory errors: BMR 10%: BMD: 3.87 BMDL-BMDU: 0.90–8.42	Yes Escape Latency: None of the models provide an adequate fit do the data Platform crossing and Reference memory errors: Best fitting model fits sufficiently well
BDE-209	Li, Liu, et al. (2021)	Adult M rats (SD) Dosing 28 days 0, 5, 50, 500 mg/kg bw per day No levels measured in tissues	Sperm cells number: BMR 15% BMD: 223 BMDL-BMDU: 8.01–475 Sperm cells motility: BMR 5% BMD: 3.48 BMDL-BMDU: 0.91–22.55 Sperm cells malformations: BMR 15% BMD: 14.69 BMDL-BMDU: 1.98–167	Sperm cells number: No None of the models provide an adequate fit do the data Sperm cells motility: Yes Best fitting model fits sufficiently well Sperm cells malformation: No None of the models provide an adequate fit do the data

TABLE G.1 (Continued)

Congener	Reference	Animals/dosing	BMD BMDL-BMDU (mg/kg bw [per day]) All results calculated using bridge sampling[a]	Acceptance criteria satisfied[c] Model fit
BDE-209	Zhang, Li, et al. (2021)	Adult M rats (SD) Dosing 28 days 0, 5, 50, 500 mg/kg bw per day No levels measured in tissues	Sperm cells number: BMR 15% BMD: 323 BMDL-BMDU: 24.73–485 Sperm cells motility: BMR 5% BMD: 5.70 BMDL-BMDU: 1.27–34.18 Sperm cells malformations: BMR 15% BMD: 13.85 BMDL-BMDU: 2.16–124	Sperm cells number: Yes Best fitting model fits sufficiently well Sperm cells motility: Yes Best fitting model fits sufficiently well Sperm cells malformation: No None of the models provide an adequate fit do the data

[a]All analyses were performed using Bridge sampling because of the higher level of accuracy with respect to Laplace approximation set as default (Hoeting et al., 1999; Morales et al., 2006; EFSA Scientific Committee, 2022). Extended dose range assumption was not applied in order to avoid confidence intervals falling outside of the dose range tested.

[b]The effects on daily sperm production reported in Kuriyama et al. (2005) were statistically significant compared to control but showed no discernable dose–response. Although the data could be modelled, it was considered not to contain enough information for estimating the BMD and none of the models provide an adequate fit to the data. The $BMDL_{10}$ obtained (0.002 mg/kg bw) is 30 times lower that the lowest non-zero dose tested in the study (0.06 mg/kg bw).

[c]The Acceptance criteria is satisfied if the ratio BMDU/BMDL < 50.

APPENDIX H

Body burden calculations

H.1 | Tissue level approach

For the **tissue level approach**, when strain/species specific tissue concentrations are available following an exposure close to that encountered in the critical study, this approach allows to estimate the body burden more precisely. In this approach, all tissues with reported concentrations (e.g. adipose tissue, liver) are taken into account to calculate the overall body burden. However, this requires information on the morphometry of mice and rats, i.e. organ weights. Several publications reported mean organ weights or % organ weight/body weight in rodents (Iwata et al., 1993; Marino, 2012a, 2012b; Piao et al., 2013; Schoeffner et al., 1999). An overview of the results are shown in Table H.1 and details provided below.

H.1.1. | BDE-47

Following an exposure of 0.05 mg/kg bw of **BDE-47**, the measured concentration at 10 days was 2.30 μg/g adipose tissue and 0.32 μg/g in the skin (Sanders et al., 2006). The total amount in μg in the body is obtained by multiplying all the concentrations reported in different tissues (adipose, liver, skin ….) by the weight of the organs. The overall amount is obtained by adding all the quantities estimated for each organ, leading to a total amount of 55.6 μg or to a body burden in rat of 261 μg/kg bw (considering a body weight of 0.213 kg) (see Table H.2 for details).

Taking the $BMDL_{10}$ of 0.15 mg/kg bw per day for neurodevelopmental effects (Li, Ma, et al., 2019; Li, Yang, et al., 2019), and assuming linearity between dose and concentration in tissues, the resulting body burden at this BMDL was **806.7 μg/kg bw**.

Taking the $BMDL_{10}$ of 0.023 mg/kg bw per day for reproductive effects (Zhang, Zhang, et al., 2013), and assuming linearity between dose and concentration in tissues, the resulting body burden at this BMDL was **123.69 μg/kg bw**.

H.1.2. | BDE-99

Following an exposure of 0.56 mg/kg bw of **BDE-99**, the measured concentration at 10 days was 14.7 μg/g adipose tissue and 2.11 μg/g in the skin (Chen et al., 2006). The total amount in μg in the body is obtained by multiplying all the concentrations reported in different tissues (adipose, liver, skin ….) by the weight of the organs. The overall amount is obtained by adding all the quantities estimated for each organ, leading to a total amount of 457.9 μg or to a body burden in rat of 1896 μg/kg bw (considering a body weight of 0.241 kg) (see Table H.3 for details).

Taking the $BMDL_{10}$ of 0.43 mg/kg bw per day for neurodevelopmental effects (Blanco et al., 2013), and assuming linearity between dose and concentration in tissues, the resulting body burden at this BMDL was **1444 μg/kg bw**.

Following an exposure of 0.56 mg/kg bw of **BDE-99**, the measured concentration at 24 h was 1.12 μg/g adipose tissue and 0.24 μg/g in the skin (Chen et al., 2006). The total amount in μg in the body is obtained by multiplying all the concentrations reported in different tissues (adipose, liver, skin ….) by the weight of the organs. The overall amount is obtained by adding all the quantities estimated for each organ, leading to a total amount of 42 μg or to a body burden in rat of 175 μg/kg bw (considering a body weight of 0.241 kg) (see Table H.4 for details).

Taking the $BMDL_{10}$ of 0.05 mg/kg bw for developmental effects (Talsness et al., 2005), and assuming linearity between dose and concentration in tissues, the resulting body burden at this BMDL was **15.53 μg/kg bw**.

H.1.3. | BDE-153

Following an exposure of 0.643 mg/kg bw of **BDE-153**, the measured concentration at 24 h (after a single dose) was 0.18 μg/g adipose tissue and 0.038 μg/g in the skin (Sanders et al., 2006). The total amount in μg in the body is obtained by multiplying all the concentrations reported in different tissues (adipose, liver, skin ….) by the weight of the organs. The overall amount is obtained by adding all the quantities estimated for each organ, leading to a total amount of 1.32 μg or to a body burden in mice of 73.2 μg/kg bw (considering a body weight of 0.019 kg) (see Table H.5 for details).

Taking the $BMDL_{10}$ of 0.11 mg/kg bw for neurodevelopmental effects (Viberg, Fredriksson, & Eriksson, 2003), and assuming linearity between dose and concentration in **tissues, the resulting body burden at this BMDL was 12.53 μg/kg bw**.

H.1.4. | BDE-209

Following an exposure of 2.9 mg/kg bw of **BDE-209**, the measured concentration at days (after a single dose) was 0.52 μg/g liver and 0.067 μg/g in the skin (Mörck et al., 2003). The total amount in μg in the body is obtained by multiplying all the concentrations reported in different tissues (adipose, liver, skin ….) by the weight of the organs. The overall amount is obtained by adding all the quantities estimated for each organ, leading to a total amount of 11.7 μg or to a body burden in rat of 57.11 μg/kg bw(considering a body weight of 0.205 kg) (see Table H.6 for details).

Taking the $BMDL_{10}$ of 1.6 mg/kg bw per day for neurodevelopmental effects (Li, Wang, et al., 2017), and assuming linearity between dose and concentration in tissues, the resulting body burden at this BMDL was **31.56 μg/kg bw**.

Note: the values in the intermediate calculations have not been rounded.

H.2 | One-compartment approach

Data on absorption and excretion (half-lives) in rodents has not always been reported for both rats and mice and for the different strains (see **Section 3.1.1.1**). For **BDE-47**, no data on the half-life of this congener has been reported in rats. Thus, the elimination rate could not consider in the calculation of the body burden of the two selected studies for this congener, performed with repeated exposure.

Two of the critical studies were single dose administration. Viberg, Fredriksson, and Eriksson (2003) administered a single dose of **BDE-153** on PND10, that corresponds to the start of a critical period in the development of the rodent brain. Talsness et al. (2005) exposed Wistar rats to **BDE-99** on GD6. In those cases, the body burden was not calculated at steady state, but at the first day of administration and the elimination rate was not considered in the calculation of the body burden.

Considering this, the body burden at the BMDL calculated based on the 1-compartment approach resulted in the values shown in Table H.1 and details provided below.

H.2.1. | BDE-47

Taking the $BMDL_{10}$ of 0.023 mg/kg bw per day for reproductive effects (Zhang, Zhang, et al., 2013), and considering an oral bioavailability of this congener of 86% for Sprague–Dawley rats (Örn & Klasson-Wehler, 1998), the body burden at the BMDL was estimated to be 0.020 mg/kg bw per day. The CONTAM Panel did not consider the elimination rate in the calculation of this body burden as this information is only available for mice.

Taking the $BMDL_{10}$ of 0.15 mg/kg bw per day for neurodevelopmental effects (Li et al., 2019), and considering an oral bioavailability of this congener of 86% for Sprague–Dawley rats (Örn & Klasson-Wehler, 1998), the body burden at the BMDL was estimated to be 0.13 mg/kg bw per day. The CONTAM Panel did not consider the elimination rate in the calculation of the body burden as this information is only available for mice.

H.2.2. | BDE-99

Taking the $BMDL_{10}$ of 0.05 mg/kg bw for reproductive effects (Talsness et al., 2005), and considering an oral bioavailability of this congener of 50% in Sprague–Dawley rats (Hakk et al., 2002) (in the absence of data in Wistar rats), the body burden in rats at the BMDL was estimated to be 0.025 mg/kg bw. Since the study was single administration on GD6, and the elimination rate was not applied in the calculation of the body burden.

Taking the $BMDL_{10}$ of 0.43 mg/kg bw per day for neurodevelopmental effects (Blanco et al., 2013), and considering an oral bioavailability of this congener of 86% in Sprague–Dawley rats (Örn & Klasson-Wehler, 1998), and a half-life in this rat strain of 6 days (Hakk et al., 2002), the body burden in rats at the BMDL was estimated to be 1.86 mg/kg bw per day.

H.2.3. | BDE-153

Taking the $BMDL_{10}$ of 0.11 mg/kg bw for neurodevelopmental effects (Viberg, Fredriksson, & Eriksson, 2003), and considering a default oral bioavailability of this congener in mice of 75% (in the absence of data and following the same assumption as in the previous EFSA Opinion, EFSA CONTAM Panel, 2011b), the body burden in mice at the BMDL was estimated to be 0.083 mg/kg bw. As above, this study was also a single administration on PND10, and the elimination rate was not applied in the calculation.

H.2.4. | BDE-209

Taking the $BMDL_{10}$ of 1.59 mg/kg bw per day for neurodevelopmental effects (Li, Wang, et al., 2017), and considering an oral bioavailability of 26% in Sprague–Dawley rats and a half-life in this rat strain of 2.5 days (Sandholm et al., 2003), the body burden at the BMDL was 1.49 mg/kg bw per day.

Taking the $BMDL_{5}$ of 0.91 mg/kg bw per day for reproductive effects (Li, Liu, et al., 2021), and considering an oral bioavailability of 26% in Sprague–Dawley rats and a half-life in this rat strain of 2.5 days (Sandholm et al., 2003), the body burden at the BMDL was 0.85 mg/kg bw per day.

TABLE H.1 Overview of the body burden in rodents at the BMDL using the with the **1-compartment approach** or the **Tissue level approach** and their resulting chronic human dietary intakes corresponding to the calculated body burden at the BMDL (see **Section 3.1.5.4**).

				Body burden in rodents calculated with the 1-compartment approach		Body burden in rodents calculated with the Tissue level approach	
Congener	**Reference**	**BMDL (mg/kg bw per day)**	**Study design**	**BB at BMDL (mg/kg bw)**	**Chronic human dietary intake (ng/kg bw per day)**	**BB at BMDL (mg/kg bw)**	**Chronic human dietary intake (ng/kg bw per day)**
BDE-47	Li et al. (2019)	$BMDL_{10}$ = **0.15**	**Neuro** Sprague–Dawley rats Repeated exposure (10 days prior to mating to PND21) Testing on PND88-92	**0.13** F_{ABS}: 86% SD rats $t_{1/2}$: not applied (no data in rats)	**175.3** F_{ABS}: 100% default $t_{1/2}$: 510 days Trudel et al. (2011)	**0.806** Tissue levels from Sanders et al. (2006)	**1096** F_{ABS}: 100% default $t_{1/2}$: 510 days Trudel et al. (2011)
	Zhang, Sun, et al. (2013)	$BMDL_{10}$ = **0.023**	**Repro** Sprague–Dawley rats Repeated exposure (adults for 8 weeks)	**0.020** F_{ABS}: 86% SD rats. $t_{1/2}$: not applied (no data in rats)	**26.9** F_{ABS}: 100% default $t_{1/2}$: 510 days Trudel et al. (2011)	**0.124** Tissue levels from Sanders et al. (2006)	**168** F_{ABS}: 100% default $t_{1/2}$: 510 days Trudel et al. (2011)
BDE-99	Blanco et al. (2013)	$BMDL_{10}$ = **0.43**	**Neuro** Sprague–Dawley rats Repeated exposure (GD6-PND21) Testing on PND22/23	**1.86** F_{ABS}: 50% SD rats $t_{1/2}$: 6 days SD rats	**4607** F_{ABS}: 100% default $t_{1/2}$: 280 days Trudel et al. (2011)	**1.444** Tissue levels from Chen et al. (2006, 10 days)	**3575** F_{ABS}: 100% default $t_{1/2}$: 280 days Trudel et al. (2011)
	Talsness et al. (2005)	$BMDL_{10}$ = **0.05**	**Developmental** Wistar rats Single dose on GD6 testing on PND90	**0.025** F_{ABS}: 50% from SD rats (no data in Wistar rats) $t_{1/2}$: not applied, single GD6	**61.9** : 100% default $t_{1/2}$: 280 days Trudel et al. (2011)	**0.0155** Tissue levels from Chen et al. (2006, 1 day)	**38.4** F_{ABS}: 100% default $t_{1/2}$: 280 days Trudel et al. (2011)
BDE-153	Viberg, Fredriksson, and Eriksson (2003)	$BMDL_{10}$ = **0.11**	**Neuro** Mice NMRI Single dose on PND10 testing on 2, 4, 6 months old	**0.083** F_{ABS}: 75% default previous Opinion (no data in mice) $t_{1/2}$: not applied, single PND10	**21.2** F_{ABS}: 100% default $t_{1/2}$: 2700 days Trudel et al. (2011)	**0.0125** Tissue levels from Sanders et al. (2006, in mice 24 h)	**3.2** F_{ABS}: 100% default $t_{1/2}$: 2700 days Trudel et al. (2011)
BDE-209	Li, Wang, et al. (2017)	$BMDL_{10}$ = **1.59**	**Neuro** Sprague–Dawley rats Repeated exposure (PND5-10) Testing up to PND74	**1.49** F_{ABS}: 26% SD rats $t_{1/2}$: 2.5 days SD rats	**229,667** F_{ABS}: 30% $t_{1/2}$: 15 days Thuresson et al. (2006), Zhang, Hu, et al. (2022)	**0.0316** Tissue levels from Mörck et al. (2003, day 3)	**4861** F_{ABS}: 30% $t_{1/2}$: 15 days Thuresson et al. (2006), Zhang, Hu, et al. (2022)
	Li, Liu, et al. (2021)	$BMDL_{5}$ = **0.91**	**Reproductive** Sprague–Dawley rats Repeated exposure (28 days)	**0.85** F_{ABS}: 26% SD rats $t_{1/2}$: 2.5 days SD rats	**131,444** F_{ABS}: 30% $t_{1/2}$: 15 days Thuresson et al. (2006), Zhang, Hu, et al. (2022)	**0.0181** Tissue levels from Mörck et al. (2003) (at day 3)	**2782** F_{ABS}: 30% $t_{1/2}$: 15 days Thuresson et al. (2006), Zhang, Hu, et al. (2022)

TABLE H.2 **BDE-47:** Estimation of the body burden based on the tissue concentrations reported in Sanders et al. (2006).

Tissue	Concentration[a] (nmol equivalent/g tissue)	Concentration[b] (ug/g tissue)	Percentage of body weight[c] (%)	Organ weight[d] (g)	Amount (μg)	Total amount (μg)	Body burden (μg/kg)
Blood	0.02	0.01	–	–	–		
Adipose tissue	4.73	2.30	8.67	18.47	42.43		
Liver	0.19	0.09	3.61	7.69	0.71		
Adrenal	1.67	0.81	0.01	0.03	0.02		
Skin	0.65	0.32	15.3	32.59	10.29		
Thyroid	0.87	0.42	–	–	–	56	261
Thymus	1.39	0.68	0.09	0.20	0.13		
Brain	0.06	0.03	0.56	1.20	0.03		
Kidney	0.13	0.06	0.68	1.46	0.09		
Lung	0.11	0.05	0.47	0.99	0.05		
Muscle	0.04	0.02	45.4	96.70	1.88		

[a]Accumulation of **BDE-47** in nmol equivalent/g tissue (male Fisher rats) **following 10 consecutive doses** at 0.1 μmol/kg days (Sanders et al., 2006).
[b]Considering a molecular weight of 458.8 g/mol.
[c]Based on data from Schoeffner et al. (1999), Marino (2012a, 2012b) and Anderson et al. (1993).
[d]Considering a mean body weight of male Fisher rats of 213 g as reported by the authors.

TABLE H.3 **BDE-99:** Estimation of the body burden based on the tissue concentrations reported in Chen et al. (2006).

Tissue	Concentration[a] (nmol equivalent/g tissue)	Concentration[b] (ug/g tissue)	Percentage of body weight[c] (%)	Organ weight[d] (g)	Amount (μg)	Total amount (μg)	Body burden (μg/kg)
Blood	0.18	0.10	–	–	–		
Adipose tissue	26	14.7	8.67	20.9	307		
Liver	2.2	1.24	3.61	8.72	10.8		
Adrenal	3.8	2.15	0.01	0.03	0.07		
Skin	3.8	2.15	15.3	36.9	79.3		
Thyroid	1.6	0.90	0.01	0.02	0.01	458	1896
Thymus	2.4	1.36	0.09	0.22	0.30		
Brain	0.42	0.24	0.56	1.36	0.32		
Kidney	1.1	0.62	0.68	1.65	1.02		
Lung	0.75	0.42	0.47	1.13	0.48		
Muscle	0.94	0.53	45.4	110	58.2		

[a]Accumulation of **BDE-99** in nmol equivalent/g tissue (male Fisher rats) **following 10 consecutive doses** at 1 μmol/kg days from Chen et al. (2006).
[b]Considering a molecular weight of 564.7 g/mol.
[c]Based on data from Schoeffner et al. (1999), Marino (2012a) and Anderson et al. (1993).
[d]Considering a mean body weight of male Fisher rats of 241.5 g as reported by the authors.

TABLE H.4 **BDE-99:** Estimation of the body burden based on the tissue concentrations reported in Chen et al. (2006).

Tissue	Concentration[a] (nmol equivalent/g tissue)	Concentration[b] (ug/g tissue)	Percentage of body weight[c] (%)	Organ weight[d] (g)	Amount (μg)	Total amount (μg)	Body burden (μg/kg)
Blood	0.035	0.02	–	–	–	42	175
Adipose tissue	2	1.13	8.67	20.9	23.6		
Liver	0.37	0.21	3.61	8.72	1.82		
Adrenal	0.9	0.51	0.01	0.03	0.02		
Skin	0.42	0.24	15.3	36.9	8.76		
Thyroid	0.22	0.12	0.01	0.02	0.00		
Thymus	0.8	0.45	0.09	0.22	0.10		
Brain	0.15	0.08	0.56	1.36	0.11		
Kidney	0.36	0.20	0.68	1.65	0.34		
Lung	0.19	0.11	0.47	1.13	0.12		
Muscle	0.12	0.07	45.4	110	7.43		

[a]Accumulation of **BDE-99** in nmol equivalent/g tissue (male Fisher rats) **following 24 h dose** at 1 μmol/kg days from Chen et al. (2006).
[b]Considering a molecular weight of 564.7 g/mol.
[c]Based on data from Schoeffner et al. (1999), Marino (2012a) and Anderson et al. (1993).
[d]Considering a mean body weight of male Fisher rats of 241.5 g as reported by the authors.

TABLE H.5 **BDE-153:** Estimation of the body burden based on the tissue concentrations reported in Sanders et al. (2006).

Tissue	Concentration[a] (nmol equivalent/g tissue)	Concentration[b] (ug/g tissue)	Percentage of body weight[c] (%)	Organ weight[d] (g)	Amount (μg)	Total amount (μg)	Body burden (μg/kg)
Blood	0.40	0.003	–	–	–		
Adipose tissue	27.3	0.18	7.0	1.75	0.31		
Liver	4.0	0.03	4.65	0.84	0.02		
Adrenal	–	–	0.21	0.04	–		
Skin	5.9	0.04	15.3	2.75	0.1		
Thyroid	–	–	–	–	–	1.3	73.2
Thymus	–	–	–	–	–		
Brain	0.60	0.004	1.65	0.30	0.001		
Kidney	0.40	0.003	1.30	0.23	0.001		
Lung	0.50	0.003	0.77	0.14	0.0004		
Muscle	16.8	0.11	45.4	8.17	0.88		

[a]Concentration of **BDE-153** in tissue in % of dose (female mice B6C3F1 mice) **following one single dose** at 1 μmol/kg days from Sanders et al. (2006).
[b]Considering a molecular weight of 643 g/mol.
[c]Based on data from Emond et al. (2013), ILSI (1994), Anderson et al. (1993, data for rats) and Marino (2012b).
[d]Considering a mean body weight of male Fisher rats of 18 g as reported by Sanders et al. (2006).

TABLE H.6 **BDE-209**: Estimation of the body burden based on the tissue concentrations reported in Mörck et al. (2003).

Tissue	Concentration[a] (nmol equivalent/g tissue)	Concentration[b] (ug/g tissue)	Percentage of body weight[c] (%)	Organ weight[d] (g)	Amount (μg)	Total amount (μg)	Body burden (μg/kg)
Blood	0.05	0.05	–	–	–		
Adipose tissue	0.11	0.11	6.48	13.28	1.40		
Liver	0.55	0.53	3.86	7.91	4.17		
Adrenal	1.25	1.20	0.01	0.03	0.30		
Skin	0.07	0.07	15.3	31.4	2.11		
Thyroid	–	–	–	–	–	11.7	57.1
Thymus	0.04	0.04	0.01	0.01	0		
Brain	0.14	0.13	0.32	0.66	0.09		
Kidney	0.17	0.16	0.80	1.64	0.27		
Lung	0.08	0.08	0.43	0.88	0.07		
Muscle	0.04	0.04	45.4	93.1	3.57		

[a]Accumulation of **BDE-209** in nmol equivalent/g tissue (male Sprague–Dawley rat) **following one single dose** at 3 μmol/kg at 3 days from Mörck et al. (2003).
[b]Considering a molecular weight of 959.17 g/mol.
[c]Based on data from Schoeffner et al. (1999), Anderson et al. (1993, data for Fisher rats) and Marino (2012a).
[d]Considering a mean body weight of male Sprague–Dawley rats of 205 g as reported by Mörck et al. (2003).

APPENDIX I

Studies reporting on occurrence and/or exposure to PBDEs in food in European countries in the open literature

TABLE I.1 Studies reporting on the levels of PBDEs in food in European countries, and estimates of the dietary exposure, when reported.

Reference	Country, sampling year	Samples, congeners analysed, occurrence in food and exposure as estimated by the authors
Poma et al. (2018). Occurrence of selected halogenated flame retardants in Belgian foodstuff	Belgium, 2015–2016	Composite food samples ($n = 183$): Fish and fish products ($n = 61$, including fish, crustaceans and molluscs), Meat and meat products ($n = 35$), Milk and dairy products ($n = 38$, including liquid milk, desserts and cheese), Eggs and egg products ($n = 4$), Food for infants/small children ($n = 18$), Animal and vegetable fat ($n = 9$), Grains and grain products ($n = 7$), Potatoes and derived products ($n = 4$), Other food (stock: $n = 4$, food supplements: $n = 1$; vegetables: $n = 2$) 10 PBDEs analysed: **BDE-28**, –**47**, –**49**, –**99**, –**100**, –**138**, –**153**, –**154**, –**183**, –**209** Study performed in response to EC Recommendation on the monitoring of BFRs in food Occurrence data: **Sum 10 PBDEs**: *Mean (SD) [pg/g ww]:* Fish and fish products: 370 (861) Meat and meat products: 689 (1536) Milk and dairy products: 601 (2733) Eggs and egg products: 212 (268) Food for infants and small children: 17 (61) Animal and vegetable fat: < LOD Grains and grain products: 321 (620) Potatoes and derived products: 591 (494) Other food: 182 (250) Exposure estimates: NA
Carlsson et al. (2014). Polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs) and perfluorinated alkylated substances (PFASs) in traditional seafood items from western Greenland	Denmark (Greenland), 2010	Fresh salmon fillet ($n = 6$), smoked salmon fillet ($n = 6$) and smoked halibut fillet ($n = 6$), commercial whale beef ($n = 8$), narwhal mattak (Greenlandic traditional food consisting of blubber and parts of the skin; $n = 6$) and commercial seal meat ($n = 2$). Purchased at the local fish market PBDE analysed: **BDE-28, –47**, –49, –66, –71, –77, –85, **–99, –100**, –119, **–138, –153, –154, –183** Occurrence data: Concentration only shown for **BDE-47**, –**49**, –**99**. **BDE-47** detected in all samples. fresh and smoked salmon: 6 ng/g fat; whale beef: 21 ng/g fat **BDE-49** only detected in smoked salmon: 2 ng/g fat **BDE-99** only detected in smoked and fresh salmon range: 2–4 ng/g fat Exposure estimates: Only for **BDE-47:** considering an intake of food item (in g/day) of fresh salmon (7), Smoked salmon (1.1), smoked halibut (2.7), narwhal (2.6), whale beef (12), seal beef (60) Total daily intake of **BDE-47:** 25 ng per day

TABLE I.1 (Continued)

Reference	Country, sampling year	Samples, congeners analysed, occurrence in food and exposure as estimated by the authors
Venisseau et al. (2018). Occurrence of legacy and novel brominated flame retardants in food and feed in France for the period 2014–2016	France, 2014–2016	*n* = 607 food samples randomly collected in supermarkets, markets and farms: Fish meal (*n* = 15), Fish oil (*n* = 15), Fish (*n* = 114), Crustaceous/Molluscs (*n* = 154), Milk (*n* = 72), Eggs (*n* = 57), Sheep liver (*n* = 28), Meat (*n* = 152, beef, pork, mutton, poultry, rabbit, game) 10 PBDEs analysed: **BDE-28**, –**47**, –77, –**99**, –**100**, –**138**, –**153**, –**154**, –**183**, –**209** Study performed in response to EC Recommendation on the monitoring of BFRs in food Occurrence data: *Median (range) [pg/g ww]:* **BDE-28**: Fish meal: 9.66 (< LOD–24.37); Crustaceous/Molluscs: 0.56 (< LOD–3.91); Sheep liver: 0.023 (< LOD–0.71); Fish oil: 104.52 (6.34–231.3); Milk: 0.011 (< LOD–0.40); Meat: 0.021 (< LOD–0.66); Fish: 2.10 (< LOD–52.06); Eggs: < LOD (< LOD–0.47) **BDE-47:** Fish meal: 135.0 (1.38–473.25); Crustaceous/Molluscs: 13.46 (< LOD–110.8); Sheep liver: 0.77 (< LOD–24.60); Fish oil: 1364.1 (164.53–4102.5); Milk: 0.60 (< LOD–44.61); Meat: 0.66 (< LOD–14.44); Fish: 34.25 (< LOD–2583.2); Eggs: 0.98 (< LOD–16.05) **BDE-99:** Fish meal: 13.17 (0.462–281.5); Crustaceous/Molluscs: 4.15 (< LOD–178.9); Sheep liver: 1.23 (< LOD–17.86); Fish oil: 140.58 (8.38–389.6); Milk: 0.28 (< LOD–75.23); Meat: 0.46 (< LOD–24.01); Fish: 2.72 (< LOD–160.0); Eggs: 1.31 (< LOD–6.41) **BDE-100:** Fish meal: 31.35 (< LOD–166.56); Crustaceous/Molluscs: 3.42 (< LOD–61.22); Sheep liver: 0.31 (< LOD–5.68); Fish oil: 402.46 (26.45–981.6); Milk: 0.075 (< LOD–15.72); Meat: 0.13 (< LOD–6.98); Fish: 11.19 (< LOD–1327.9); Eggs: 0.18 (< LOD–2.11) **BDE-153:** Fish meal: 5.05 (< LOD–27.65); Crustaceous/Molluscs: 0.330 (< LOD–64.07); Sheep liver: 0.78 (< LOD–6.11); Fish oil: 43.68 (3.62–153.6); Milk: 0.062 (< LOD–15.87); Meat: 0.15 (< LOD–5546.71); Fish: 1.50 (< LOD–236.3); Eggs: 0.46 (< LOD–3.13) **BDE 154** Fish meal: 17.58 (< LOD–73.23); Crustaceous/Molluscs: 1.49 (< LOD–38.31); Sheep liver: < LOD (< LOD–2.13); Fish oil: 267.68 (11.34–626.1); Milk: 0.031 (< LOD–10.06); Meat: 0.014 (< LOD–5270.7); Fish: 6.54 (< LOD–541.7); Eggs: < LOD (< LOD–1.04). **BDE-183**: Fish meal: < LOD (< LOD–25.99); Crustaceous/Molluscs: < LOD (< LOD–36.02); Sheep liver: < LOD (< LOD–4.86); Fish oil: 3.41 (< LOD–55.04); Milk: < LOD (< LOD–0.45); Meat: < LOD (< LOD–4744.3); Fish: 0.235 (< LOD–32.80); Eggs: < LOD (< LOD–14.43) **BDE-209:** Fish meal: 171.21 (17.67–1973.0); Crustaceous/Molluscs: 7.63 (< LOD–3940.8); Sheep liver: 29.84 (< LOD–121.9); Fish oil: 709.34 (< LOD–2884.5); Milk: 1.86 (< LOD–49.44); Meat: 11.04 (< LOD–2037.8); Fish: 5.66 (< LOD–107.4); Eggs: 22.34 (1.45–4627.8) Exposure estimates: NA
De Filippis et al. (2014). Exposure to polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), dioxin-like polychlorinated biphenyls (DL-PCBs) and polybrominated diphenyl ethers (PBDEs) through the consumption of prepared meals in Italy	Italy, NR	Duplicate diet study: *n* = 6 meals collected to account for: (1) baby food by toddlers (9–12 months), (2) canteen meals by children attending nursery and primary school (4–9 years old) and by adults (18–64 years old) having lunch at canteen, (3) fast food meals by adults, (4) home-prepared food by adults (duplicate portions), (5) meals that exclude meat, fish and poultry by adults observing a vegetarian lifestyle, (6) Sunday meals consumed at the restaurant by adults 8 PBDEs analysed: **BDE-28**, **–47**, –**99**, –**100**, –**153**, –**154**, –**183**, –**209** Occurrence data: *Levels (UB*: UB with **BDE-209**) [ng/kg]:* Quantified results only for **BDE-47** and -**99**. The remaining congeners were < LOQ. Toddlers' meal: **BDE-47**: 2.02 **BDE-99**: < 1.80 **Sum 8 PBDEs**: LB: 2.02, UB: 15.7, UB*: 87.9 Children meals: **BDE-47**: < 1.72–3.53 **BDE-99**: < 1.41–< 1.72 **Sum 8 PBDEs**: LB 0.00–3.53, UB 13.3–17.2, UB*: 82.1–167.3 Adults' meals: **BDE-47:** < 1.51–5.12 **BDE-99**: < 1.51–5.66 **Sum 8 PBDEs**: LB 0.00–10.78, UB 13.0–26.3, UB*: 74.5–192.1 Exposure estimates: Food consumption data derived from the Italian National Food Survey. For toddlers, the dietary exposure estimated by adding the contributions from baby food and milk formulas. Baby food exposure calculated multiplying the occurrence data derived from the analysis of baby food composite (not including milk formulas) by the average daily food consumption derived from the weight of the baby food composite *Sum 8 PBDEs (LB–UB) [ng/kg bw per day]:* Toddlers: 23.36 Children: 0.00–7.38 Adults: 0.00–3.40

(Continues)

TABLE I.1 (Continued)

Reference	Country, sampling year	Samples, congeners analysed, occurrence in food and exposure as estimated by the authors
Martellini et al. (2016). Occurrence of polybrominated diphenyl ethers (PBDEs) in foodstuffs in Italy and implications for human exposure	Italy, 2011–2012	Meat ($n=42$, cow, pork, chicken, reindeer), Eggs ($n=7$), Dairy products ($n=20$, milk, cheese), Fish ($n=8$, halibut, blue fish, trout), Fish oil ($n=5$), Molluscs ($n=11$, mussels, clams) 22 PBDEs analysed: BDE-7, –15, –17, **–28**, –**47**, –**49**, –66, –71, –77, –85, –**99, –100**, –119, –126, –**138**, –**153, –154,** –156, –**183**, –184, –191, –**209** Occurrence data: *mean (SD), [pg/g ww]:* **Meat** / **Dairy** / **Eggs** / **Molluscs** / **Fish** / **Fish oil** **BDE-28:** 10.7 (12.9) / 3.0 (1.4) / 2.8 (20.1) / 1.3 (0.6) / 10.6 (13.7) / 256 / (24.4) **BDE-47:** 90.5 (188) / 94.6 (61.4) / 58.2 (19.7) / 36.8 (18.9) / 181 (130) / 3439 / (167) **BDE-99:** 45.6 (77.0) / 62.0 (53.3) / 32.6 (13.8) / 18.3 (10.6) / 17.7 (14.0) / 306 / (64.2) **BDE-100:** 9.8 (16.5) / 12.8 (13.7) / 8.2 (4.5) / 6.9 (3.9) / 30.0 (32.2) / 696 / (54.5) **BDE-153:** 7.4 (12.0) / 7.1 (15.1) / 4.7 (2.4) / 12.7 (18.9) / 3.8 (4.8) / 78.6 / (8.9) **BDE-154:** 4.0 (6.3) / 3.5 (26.8) / 2.0 (0.80) / 0.85 (0.49) / 9.8 (12.7) / 290 / (29.9) **BDE-183:** 33.4 (92.7) / 10.8 (6.2) / 18.0 (9.6) / 7.0 (12.5) / 5.5 (5.4) / 105 / (10.2) **BDE-209:** 1257.2 (1859) / 3524 (4698) / 2376 (3318) / 411 (414) / 238 (229) / 1261 / (381) **Sum 22 PBDEs:** 1523 (2199) / 3749 (4711) / 2538 (3346) / 494 (426) / 524 (500) / 7241 / (765) **BDE-209** was the most abundant congener, followed by **BDE-47** and -**99** Exposure estimates: Consumption rate for the general Italian population estimated by the Italian Society for the Human Nutrition and the Nutrition Science Institute of the University of Rome. Body weight assumed to be 70 kg *Sum 22 PBDEs [ng/kg bw per day]:* Meat: 0.49 Dairy products: 7.47 Eggs: 0.18 Fish and mussels: 0.29
Ceci et al. (2021). Brominated and chlorinated contaminants in food (PCDD/Fs, PCBs, PBDD/Fs PBDEs): Simultaneous determination and occurrence in Italian produce	Italy, 2014–2016	$n=61$ food samples: mussels ($n=9$), fresh fish ($n=19$, hake, mullet, sea bream, bogue, red mullet mackerel, sardines, sand steenbras), eggs ($n=6$), poultry ($n=5$), pork ($n=6$), beef ($n=6$), cow's milk ($n=6$), sheep's milk ($n=4$) 8 PBDEs analysed: **BDE-28**, –**47**, –66, –85, –**99**, –**100**, –**153**, –**154**, –**183** Occurrence data: *Mean (range) [ng/g ww]:* **Sum 8 PBDEs:** Mussels: 0.23 (0.18–0.28) Fresh fish: 0.38 (0.03–1.03) Eggs: 0.03 (0.03–0.05) Poultry: 0.07 (0.02–0.22) Pork: 0.18 (0.07–0.36) Beef: 0.07 (0.03–0.22) Cow's milk: 0.04 (0.02–0.08) Sheep's milk: 0.03 (0.01–0.05) Exposure estimates: NA

TABLE I.1 (Continued)

Reference	Country, sampling year	Samples, congeners analysed, occurrence in food and exposure as estimated by the authors
Roila et al. (2021). Risk characterisation and benefit–risk assessment of brominated flame retardant in commercially exploited freshwater fishes and crayfish of Lake Trasimeno, Italy	Italy, 2018–2021	Fish ($n = 74$): carp ($n = 11$), goldfish ($n = 22$), tench ($n = 13$), eel ($n = 12$), perch ($n = 16$) (pools) Crayfish ($n = 16$) (pools) 15 PBDEs analysed: **BDE-28**, –**47**, –**49**, –66, –77, –85, –**99**, –**100**, –**138**, –**153**, –**154**, –**183**, –197, –206, –**209** Occurrence data: *Sum 15 PBDEs [pg/g lipid]:* Carp: LB: 37.94 UB: 7254.82 Goldfish: LB: 97.06 UB: 32,378.43 Tench: LB: 0.00 UB: 10,576.92 Eel: LB: 1797.49 UB: 2955.67 Perch: LB: 630.86 UB: 39,211.11 Crayfish: LB: 8721.43 UB: 81,240.48 The most frequently found congener was **BDE-47**, followed by **BDE-99**, –**100** > **BDE-49**, –**154** > **BDE-153** > **BDE-28**, –66, –77, –85, –197, –207, –**209** > **BDE-138** Exposure estimates: Food consumption based on questionnaire-based dietary survey randomly conducted with inhabitants around Lake Trasimeno ($n = 325$ healthy people from the general population, age range: 19–65 years). The responses to the questionnaire were combined with the food portion size data reported by the Italian dietary surveys. Adult body weight: 70 kg *Sum 15 PBDEs [pg/kg bw per day]:* — *Sum **BDE-47**, –**99**, –**153**, –**209** [pg/kg bw per day]:* Perch: LB: 0.002 UB: 0.146 — LB: 0.002 UB: 0.058 Eel: LB: 0.206 UB: 0.339 — LB: 0.120 UB: 0.171 Tench: LB: 0.000 UB: 0.1556 — LB: 0.000 UB: 0.0613 Goldfish: LB: 0.001 UB: 0.156 — LB: 0.001 UB: 0.061 Crayfish: LB: 0.019 UB: 0.161 — LB: 0.015 UB: 0.068 Carp: LB: 0.001 UB: 0.156 — LB: 0.001 UB: 0.062
Lopez et al. (2018). Occurrence of polybrominated diphenylethers, hexabromocyclododecanes, bromophenols and tetrabromobisphenols A and S in Irish foods	Ireland, 2015	53 food samples: Milk ($n = 12$), Eggs yolk only ($n = 12$), Fish ($n = 10$), Carcass fat (cattle, pigs, lambs, chickens, $n = 12$), Liver (bovine, porcine, ovine, equine, avian, $n = 7$) 17 PBDEs analysed: BDE-17, **–28**, **–47**, –**49**, –66, –71, –77, –85, **–99, –100**, –119, –126, –**138**, **–153, –154, –183, –209** (Sum 10 PBDEs: sum of **BDE-28**, –**47**, –**49**, –**99**, –**100**, –**138**, –**153**, –**154**, –**183**, –**209** Study performed in response to EC Recommendation on the monitoring of BFRs in food Occurrence data: *Mean (range) [μg/kg ww]:* Fish: **Sum 17 PBDEs** 0.59 (0.02–1.37) **Sum 10 PBDEs**: 0.56 (0.02–1.29) Milk: **Sum 17 PBDEs**: 0.02 (0.01–0.05) **Sum 10 PBDEs**: 0.02 (0.01–0.05) Eggs yolk: **Sum 17 PBDEs**: 0.38 (0.03–0.96) **Sum 10 PBDEs**: 0.38 (0.03–0.96) Carcass fat: **Sum 17 PBDEs**: 0.26 (0.04–1.28) **Sum 10 PBDEs**: 0.26 (0.04–1.28) Liver: **Sum 17 PBDEs**: 0.01 (0.002–0.03) **Sum 10 PBDEs**: 0.01 (0.002–0.03) **BDE-47**, –**99** and -**100** were the most abundant congeners (detected in > 50% of the samples) Exposure estimates: NA

(Continues)

TABLE I.1 (Continued)

Reference	Country, sampling year	Samples, congeners analysed, occurrence in food and exposure as estimated by the authors
Zacs et al. (2021). Polybrominated diphenyl ethers (PBDEs), hexabromocyclododecanes (HBCDD), dechlorane-related compounds (DRCs), and emerging brominated flame retardants (EBFRs) in foods: The levels, profiles, and dietary intake in Latvia	Latvia, 2016–2019	*n* = 144 food samples randomly collected from local retail markets: Meat (*n* = 25, pork, beef, poultry, lamb), Milk and dairy products (*n* = 39, milk, cheese, butter, whey powder, milk protein, cream, sour cream), Fish and fish products (*n* = 44, Baltic herring and sprats, trout, tunafish, Atlantic mackerel, Atlantic salmon, Atlantic herring, canned cod liver samples), Plant origin (*n* = 22, bread, cereal, vegetable oil, dark chocolate), Eggs (*n* = 14) 13 PBDEs analysed: BDE-17, –**28**, –**47**, –**49**, –**99**, –**100**, –**138**, –139, –**153**, –**154**, –155, –**183**, –**209** Occurrence data: *Mean (min-max) [ng/kg wet weight]:* Meat: **Sum 13 PBDEs:** 34.2 (4.78–96.7) **BDE-209**: 12.1 (1.4–54.1) Fish: **Sum 13 PBDEs**: 620 (67.6–1910) **BDE-209**: 23.3 (0.56–154) Cod liver: **Sum 13 PBDEs**: 3484 (803–11,088) **BDE-209**: 46.2 (11.6–119) Eggs: **Sum 13 PBDEs**: 54.8 (17.3–105) **BDE-209**: 34.1 (7.44–95.2) Milk and milk products: **Sum 13 PBDEs:** 11.3 (0.32–139) **BDE-209**: 1.68 (0.03–10.1) Bread and cereals: **Sum 13 PBDEs:** 79.5 (3.71–482) **BDE-209**: 38.4 (2.43–277) Vegetable oils: **Sum 13 PBDEs**: 121 (20.1–346) **BDE-209**: 66 (4.37–212) Chocolate: **Sum 13 PBDEs**: 52.6 (27.8–77.4) **BDE-209:** 30.8 (12.0–49.6) Fat of animal origin: NA Fish and cod liver samples showed the highest PBDE levels. The remaining food categories showed lower mean levels (< 100 ng/kg wet weight). In fish, the most important contributors to the exposure were **BDE-47**/–**49** (up to 65%). In other food product groups, **BDE-99** also contributed significantly, as well as **BDE-209**, except in the fish food categories Exposure estimates: The food consumption data from the EFSA Comprehensive Food Consumption database (EFSA, 2011a, 2015). Body weight: 72 kg for the general population *[ng/kg bw per day]:* Meat and meat products: **Sum 13 PBDEs**: 0.11 **BDE-209:** 0.04 Fish: **Sum 13 PBDEs**: 0.27 **BDE-209:** 0.01 Fish products (including cod liver): **Sum 13 PBDEs**: 0.34 **BDE-209:** 0.004 Eggs: **Sum 13 PBDEs**: 0.01 **BDE-209:** 0.01 Milk and milk products: **Sum 13 PBDEs**: 0.05 **BDE-209:** 0.01 Bread and cereals: **Sum 13 PBDEs**: 0.36 **BDE-209:** 0.17 Oils and fats: **Sum 13 PBDEs**: 0.08 **BDE-209:** 0.04 Sweets (including chocolate): **Sum 13 PBDEs**: 0.02 **BDE-209:** 0.01 Total exposure: **Sum 13 PBDEs**: 1.22 **BDE-209**: 0.29
Carlsson et al. (2016). Perfluoroalkylated substances (PFASs) and legacy persistent organic pollutants (POPs) in halibut and shrimp from coastal areas in the far north of Norway: Small survey of important dietary foodstuffs for coastal communitie	Norway, 2008–2012	Fish and seafood purchased from local fishermen and fishmarkets, and caught from coastal waters close to Tromsø: halibut, shrimps (peeled and unpeeled) 11 PBDEs analysed: **BDE-28**, –32, –35, –37, –**47**, –**49**, –71, –**99**, –**100**, –**153**, –**154** Occurrence data: Shrimps: **BDE-47** (median 2.8 ng/g fat) was the dominant congener in the unpeeled shrimp samples, followed by **BDE-100** and -35 (both 0.5 ng/g fat). Concentrations of **BDE-47** and Sum 11 PBDEs were significantly higher in the unpeeled shrimps compared to the peeled shrimps Halibut: **BDE-47** was the major contributor (median 11.3 ng/g fat), followed by **BDE-100** (3.5 ng/g fat) and -**154** (1.1 ng/g fat) Exposure estimates: NA

TABLE I.1 (Continued)

Reference	Country, sampling year	Samples, congeners analysed, occurrence in food and exposure as estimated by the authors
Xu, Yi, et al. (2017); Xu, Tay, et al. (2017). Assessment of dietary exposure to organohalogen contaminants, legacy and emerging flame retardants in a Norwegian cohort	Norway, 2013–2014	24 h duplicate diet ($n = 61$) 9 PBDEs analysed: **BDE-28**, **–47**, –66, –85, **–100**, –**153**, **–154**, **–183**, **–209** Occurrence data: *Mean, Median [ng/g ww]:* **BDE-28**: 0.0003, < LOQ **BDE-47**: 0.014, 0.0094 BDE-66: 0.0002, < LOQ **BDE-100**: 0.0003, < LOQ **BDE-209**: 0.12, 0.046 **BDE-47** and **-209** had the highest detection frequencies (57% and 54%, respectively). The remaining congeners had detection frequencies < 10%. The authors indicated that the high concentrations of **BDE-209** observed in the food samples '*might be attributed to contamination during the cooking process, and/or dust particles adhering to the food*' Exposure estimates: Dietary intake was calculated for each individual participant using the levels measured in the 24-h duplicate diet samples and the individual personal body weight information *Median (P95) (LB) [ng/kg bw per day]:* **BDE-47**: 0.20 (1.4) **BDE-209**: 0.86 (12) **Sum 9 PBDEs**: 1.33 (14)
Nøstbakken et al. (2018). Factors influencing risk assessments of brominated flame-retardants; evidence based on seafood from the North East Atlantic Ocean	Norway, 2006–2016	$n = 9211$ wild and farmed fish (whole, muscle or liver): Atlantic cod (farmed and wild), Atlantic halibut (wild), Atlantic salmon (farmed and wild), Blue Whiting (wild), Capelin (wild), Common ling (wild), European eel (wild), European hake (wild), European plaice (wild), Greenland Halibut (wild), Herring (wild), Northern shrimp (wild), Polar cod (wild), Rainbow trout (farmed), Rose fish (wild), Saithe (wild), Tusk(wild) 10 PBDEs analysed: **BDE-28**, –**47**, –66, **–99**, **–100**, –119, –**138**, **–153**, **–154**, **–183** Sum 7 PBDEs = sum of **BDE-28**, –**47**, –**99**, –**100**, –**153**, –**154**, –**183** Occurrence data: Levels of Sum PBDEs in individual fillet samples ranged from the ΣUB LOQs in Atlantic cod fillet to 39.5 μg/kg in Atlantic halibut I-cut. The concentrations in liver ranged from UB 0.2 to 143 μg/kg, both extremes measured in samples from Atlantic cod The main contributor to the Sum PBDEs in all species analysed was **BDE-47** (65% of the total), followed by **BDE-100** (12%), **–154** (6%), –**99** (5%). **BDE-28**, –**153** and **-183** represented < 3.5% each. The relationship between **BDE-47** and UB Sum PBDEs showed a significant linear regression ($r^2 = 0.9908$), enabling the authors to use **BDE-47** as marker for Sum PBDEs Exposure estimates: Maximum daily consumption of fish (in kg) to not exceed JECFAs or US-EPA recommended maximum values provided in the supplementary material of the original paper
Pajurek et al. (2019). Poultry eggs as a source of PCDD/Fs, PCBs, PBDEs and PBDD/Fs	Poland, NR	$n = 126$ egg samples collected from various layer chicken rearing systems (free range, organic, barn, battery cage). Aggregated samples from 12 individual eggs (yolk and white) were analysed 10 PBDEs analysed: **BDE-28**, –**47**, –**49**, –**99**, –**100**, –**138**, –**153**, –**154**, –**183**, –**209** Occurrence data: *Sum 10 PBDEs: Mean (SD), median (min–max) [ng/g lipid]:* Free range ($n = 31$): 1.08 (2.08) Organic ($n = 31$): 1.07 (1.86) Barn ($n = 25$): 0.94 (1.55) Battery cage ($n = 12$): 0.52 (0.43) **BDE-209** was the most abundant congeners regardless of the production system. **BDE-47**, –**99** and **-153** also made up a significant proportion, especially in the case of organic eggs Exposure estimates: NA

(Continues)

TABLE I.1 (Continued)

Reference	Country, sampling year	Samples, congeners analysed, occurrence in food and exposure as estimated by the authors
Pietroń et al. (2019). Exposure to PBDEs associated with farm animal meat consumption	Poland, 2015–2017	Meat samples ($n = 199$): muscles from sheep, cow, pigs, chicken, turkey, horse, ostrich, rabbit, farm deer 10 PBDEs analysed: **BDE-28**, –**47**, –**49**, –**99**, –**100**, –**138**, –**153**, –**154**, –**183**, –**209**

Occurrence data:

Median [pg/g ww]:

	Sheep	Cow	Pig	Chicken	Turkey	Horse	Ostrich	Rabbit	Farm deer
BDE-28:	1.21	0.46	0.55	0.18	0.12	0.61	0.63	0.25	0.22
BDE-47:	2.95	2.77	2.48	1.98	1.61	10.8	2.35	3.82	2.98
BDE-49:	1.35	0.53	0.61	0.21	0.14	0.44	0.70	0.27	0.18
BDE-99:	5.92	1.22	1.34	1.15	0.91	3.63	2.06	1.62	0.93
BDE-100:	2.59	0.69	0.79	0.29	0.27	0.87	0.92	0.62	0.29
BDE-138:	1.48	0.71	0.67	0.22	0.13	0.74	0.78	0.30	0.20
BDE-153:	3.7	0.69	0.80	0.26	0.20	0.89	1.15	0.53	0.39
BDE-154:	1.32	0.43	0.51	0.17	0.13	0.54	0.56	0.33	0.19
BDE-183:	1.99	0.79	0.77	0.25	0.19	0.73	1.23	2.74	0.22
BDE-209:	14.2	10.2	9.21	8.67	7.97	13.4	16.8	16.5	6.68
Sum 10 PBDEs:	46.7	19.7	19.8	13.1	11.7	41.8	29.8	26.9	11.6

BDE-209 was the most abundant congener followed by **BDE-47** and -**99**. **BDE-99** contribution was higher than **BDE-47** only in sheep and ostrich muscles. The contributions of the other congeners were < 5%. Sheep samples contained a higher amount of **BDE-153** and -**100** with 10.6% and 6.9% contribution, respectively

Exposure estimates:

Consumption scenario: 100 g of meat per day by adults.

Median [ng per day]:

Sheep: **BDE-47**: 0.30 (2.1) **BDE-99**: 0.59 (4.88) **BDE-153**: 0.37 (2.51) **BDE-209**: 1.42 (49.96)
Cow: **BDE-47**: 0.28 (1.64) **BDE-99**: 0.12 (3.29) **BDE-153**: 0.07 (1.02) **BDE-209**: 1.02 (3.68)
Pig: **BDE-47**: 0.25 (1.01) **BDE-99**: 0.13 (0.25) **BDE-153**: 0.08 (0.25) **BDE-209**: 0.92 (66.31)
Chicken: **BDE-47**: 0.20 (0.49) **BDE-99**: 0.11 (0.31) **BDE-153**: 0.03 (0.31) **BDE-209**: 0.87 (9.29)
Turkey: **BDE-47**: 0.16 (0.57) **BDE-99**: 0.09 (0.22) **BDE-153**: 0.02 (0.22) **BDE-209**: 0.80 (35.46)
Horse: **BDE-47**: 1.08 (17.8) **BDE-99**: 0.36 (2.62) **BDE-153**: 0.09 (2.62) **BDE-209**: 1.34 (8.90)
Ostrich: **BDE-47**: 0.23 (0.58) **BDE-99**: 0.21 (0.28) **BDE-153**: 0.11 (0.28) **BDE-209**: 1.68 (3.48)
Rabbit: **BDE-47**: 0.38 (0.69) **BDE-99**: 0.16 (0.19) **BDE-153**: 0.05 (0.19) **BDE-209**: 1.65 (2.68)
Farm deer: **BDE-47**: 0.30 (0.38) **BDE-99**: 0.09 (0.06) **BDE-153**: 0.04 (0.06) **BDE-209**: 0.67 (0.81)

The highest exposure to **BDE-47** was related to the consumption of horse meat. The highest **BDE-99** and -**153** intake was due to the consumption of sheep meat. Ostrich meat showed the largest amount of **BDE-209**. In the case of meat consumption containing the highest concentrations of the congeners (P95), the highest theoretical intake of **BDE-47**, –**99** and -**153** occurred in horse meat. In the case of **BDE-209** dietary intake, the pork was the main source

TABLE I.1 (Continued)

Reference	Country, sampling year	Samples, congeners analysed, occurrence in food and exposure as estimated by the authors
Pietroń et al. (2021). Polybrominated diphenyl ethers (PBDEs) in raw milk from different animal species and in infant formula. Occurrence and risk assessment	Poland, 2015–2018	*n* = 87 raw non-processed milk samples from Polish farms: cow's milk (*n* = 30), sheep's milk (*n* = 22) and goat's milk (*n* = 35) *n* = 16 infant formula 10 PBDEs analysed: **BDE-28**, –**47**, –**49**, –**99**, –**100**, –**138**, –**153**, –**154**, –**183**, –**209** Study performed in response to EC Recommendation on the monitoring of BFRs in food Occurrence data: *Sum 10 PBDEs, Mean (SD) [ng/g fat]* Cow milk: 0.23 (0.09) Goat's milk: 0.46 (0.35) Sheep's milk: 1.00 (2.4) Infant formula: 0.44 (0.21) In the raw milk, the most frequently detected congeners were **BDE-47**, –**99**, –**153** and -**209**. **BDE-209** was the predominant congener constituting at least 38%. In infant formula, **BDE-209** was the predominant congener. Median concentrations of **BDE-99** and -**209** in infant formula were higher than those in cow's milk. **BDE-28**, –**49**, –**138**, –**154** and -**183** were < LOQ in all samples Exposure estimates: Consumption raw milk: 2 dietary intake scenarios: (i) consumption of one glass (250 mL) of any type of milk, (ii) average milk and dairy product consumption by adults, and the recommended consumption by children. Assumed that 90% of consumed milk came from cows, 5% from sheep and 5% from goats. Consumption infant formula: from producers. Average body weight: 70, 23.1 and 6 kg for adults, children and infants, respectively Consumption of one glass of milk: *Sum 10 PBDEs, Median (P95) [ng]*: Cow: 1.78 (3.25) Goat: 3.20 (12.46) Sheep: 4.24 (55.27) Infant formula: 3.83 (6.56) Average consumption by adults and children, *Sum 10 PBDEs, Median (P95) [ng/kg bw per day]:* Infants: **BDE-28**: 0.015 (0.015) **BDE-47:** 0.114 (0.281) **BDE-49:** 0.051 (0.051) **BDE-99:** 0.145 (0.351) **BDE-100:** 0.051 (0.056) **BDE-138:** 0.026 (0.026) **BDE-153:** 0.010 (0.059) **BDE-154:** 0.051 (0.051) **BDE-183:** 0.051 (0.051) **BDE-209:** 1.939 (3.311) Sum 10 PBDEs: 2.421 (3.793) Children: **BDE-28**: 0.005 (0.009) **BDE-47:** 0.061 (0.161) **BDE-49:** 0.017 (0.019) **BDE-99**: 0.027 (0.076) **BDE-100**: 0.018 (0.022) **BDE-138**: 0.009 (0.009) **BDE-153**: 0.006 (0.019) **BDE-154**: 0.017 (0.018) **BDE-183**: 0.017 (0.019) **BDE-209**: 0.197 (0.605) Sum 10 PBDEs: 0.397 (0.928) Adults: **BDE-28:** 0.001 (0.001) **BDE-47:** 0.010 (0.025) **BDE-49:** 0.003 (0.003) **BDE-99:** 0.004 (0.012) **BDE-100:** 0.003 (0.003) **BDE-138:** 0.001 (0.001) **BDE-153:** 0.001 (0.003) **BDE-154:** 0.003 (0.003) **BDE-183:** 0.003 (0.003) **BDE-209:** 0.031 (0.095) Sum 10 PBDEs: 0.062 (0.145) The most exposed age group to Sum 10 PBDEs were infants. The highest intake was estimated for **BDE-209** and the lowest for **BDE-153**

(Continues)

TABLE I.1 (Continued)

Reference	Country, sampling year	Samples, congeners analysed, occurrence in food and exposure as estimated by the authors
Falandysz et al. (2019). PBDEs in cod (Gadus morhua) liver products (1972–2017): Occurrence and human exposure	Poland, 2017	Canned cod liver products: 'Cod livers in own oil', 'Pate - cod livers and vegetables' 17 PBDEs analysed: BDE-17, –**28**/33, –**47**, –**49**, –66, –71, –77, –85, –**99**, –**100**, –119, –126, –**138**, –**153**, –**154**, –**183**, –**209** Occurrence data: *Sum 17 PBDEs [ng/g lipid]:* 'Cod livers in cod liver oil': 16.7 (LB) 'Pate, cod liver and vegetables': 40.2 (LB) Exposure estimates: Estimated for **BDE-47**, –**49**, –**99** and -**100**. For the canned food, portions of 105–150 g, 52–75 g and 26–37 g were used for adults, teenagers and children, respectively. Body weights: 70 kg for adults, 56 kg for adolescents, 26 kg for children *Exposure to canned cod livers [ng/kg bw per week]:* **BDE-47 BDE-49 BDE-99 BDE-100 Sum 4 PBDEs** Adults: 8.5–12.2 3.6–5.1 0.36–0.51 2.4–3.4 17.6–25.1 Teens: 5.3–7.6 2.2–3.2 0.22–0.32 1.5–2.1 10.9–15.7 Children: 5.7–8.1 2.4–3.4 0.24–0.34 1.6–2.3 11.7–16.7
Coelho, Sousa, Isobe, Kim, et al. (2016). Brominated flame retardants and organochlorine compounds in duplicate diet samples from a Portuguese academic community	Portugal, NR	7-day duplicate diet ($n = 21$ volunteers) 9 PBDEs analysed: **BDE-28**, –**47**, –**99**, –**100**, –**153**, –**154**, –**183**, –**209** and other PBDE congeners (not specified) Occurrence data: *Mean (range) [ng/g ww]:* **Sum all PBDEs**: LB: 0.049 (< LOD–0.23) UB: 0.38 (0.30–0.63) **Sum 8 PBDEs** (w/o **BDE-209**): LB: 0.046 (< LOD–0.22) UB: 0.099 (0.059–0.28) **Sum tri- to heptaBDEs** (w/o **BDE-209**): LB: 0.0024 (< LOD–0.021) UB: 0.046 (0.037–0.060) **BDE-209** had the highest detection frequency (66.7%) and concentration (median (range): 0.031 (< LOD–0.22) ng/g), followed by **BDE-47** and -**99** that were detected in 19.0% and 9.5% of the samples, with values ranging from < LOD–0.014 ng/g and < LOD–0.010 ng/g, respectively Exposure estimates: Daily intakes estimated considering that a person ingests daily 1867.2 g of food (data relative to the food ingestion rate in 2012, set by the National Institute of Statistics, Portugal), and the participants' body weights reported in the FFQ *Median (range) [ng/kg bw per day]*: **Sum all PBDEs**: LB: 1.1 (0–9.1) UB: 11 (6.8–24) **Sum 8 PBDEs:** LB: 0.98 (0–8.7) UB: 2.7 (1.5–11) **Sum Tri-hepta-BDEs** (w/o **BDE-209**): LB: 0 (0–0.79) UB: 1.4 (0.80–2.2)

TABLE I.1 (Continued)

Reference	Country, sampling year	Samples, congeners analysed, occurrence in food and exposure as estimated by the authors
Menezes-Sousa et al. (2021). Polybrominated diphenyl ethers and their methoxylated congeners in Douro river estuary biota: Seasonal occurrence and risk assessment	Portugal, 2019–2020	*n* = 273 samples of seafood from the Douro estuary collected seasonally (spring, summer, autumn and winter): Mussels, Crabs, Macroalgae, Grey mullet, Flounder, Sea bass 5 PBDEs analysed: **BDE-28**, –**47**, –**99**, –**153**, –**154**, –**183** 8 MeO-PBDes analysed: 2′-MeO-BDE-68, 6-MeO-BDE-47, 4-MeO-BDE-49, 5-MeO-BDE-47, 4-MeO-BDE-103, 5-MeO-BDE-100, 4′-MeO-BDE-101, 5′-MeO-BDE-99 Occurrence data: *Mean (SD) [ng/g]:* **Spring** Microalgae: Sum 5 PBDEs: < LOD Sum 8 MeO-PBDEs: 0.08 (0.11) Mussel: Sum 5 PBDEs: 0.52 (0.26) Sum 8 MeO-PBDEs: 1.34 (0.51) Crab: Sum 5 PBDEs: 1.76 (0.54) Sum 8 MeO-PBDEs: 5.66 (3.15) Grey mullet: Sum 5 PBDEs: 0.61 (1.24) Sum 8 MeO-PBDEs: 0.004 (0.02) Flounder: Sum 5 PBDEs: 0.14 (0.21) Sum 8 MeO-PBDEs: 0.01 (0.06) Sea bass: Sum 5 PBDEs: 0.86 (1.14) Sum 8 MeO-PBDEs: < LOD **Summer** Microalgae: Sum 5 PBDEs: < LOD Sum 8 MeO-PBDEs: 1.04 Mussel: Sum 5 PBDEs: 1.39 Sum 8 MeO-PBDEs: 4.97 Crab: Sum 5 PBDEs: 3.15 Sum 8 MeO-PBDEs: 2.57 Grey mullet: Sum 5 PBDEs: 0.22 (0.22) Sum 8 MeO-PBDEs: 0.03 (0.06) Flounder: Sum 5 PBDEs: 0.01 (0.02) Sum 8 MeO-PBDEs: 0.001 (0.006) Sea bass: Sum 5 PBDEs: 0.14 (0.29) Sum 8 MeO-PBDEs: 0.09 (0.09) **Autumn** Ulva sp.: Sum 5 PBDEs: < LOD Sum 8 MeO-PBDEs: 0.42 Fucus sp.: Sum 5 PBDEs: < LOD Sum 8 MeO-PBDEs: 0.16 Mussel: Sum 5 PBDEs: 2.24 Sum 8 MeO-PBDEs: 3.87 Crab: Sum 5 PBDEs: 1.48 (1.36) Sum 8 MeO-PBDEs: 1.72 (1.59) Grey mullet: Sum 5 PBDEs: 1.51 (3.61) Sum 8 MeO-PBDEs: 0.06 (0.1) Flounder: Sum 5 PBDEs: 0.02 (0.05) Sum 8 MeO-PBDEs: < LOD Sea bass: Sum 5 PBDEs: 0.05 (0.08) Sum 8 MeO-PBDEs: 0.51 (0.36) **Winter** Ulva sp.: Sum 5 PBDEs: < LOD Sum 8 MeO-PBDEs: 0.27 Fucus sp.: Sum 5 PBDEs: < LOD Sum 8 MeO-PBDEs: < LOD Mussel: Sum 5 PBDEs: 3.75 Sum 8 MeO-PBDEs: 2.45 Crab: Sum 5 PBDEs: 1.04 (1.15) Sum 8 MeO-PBDEs: 2.86 (3.27) Grey mullet: Sum 5 PBDEs: 0.68 (0.84) Sum 8 MeO-PBDEs: < LOD Flounder: Sum 5 PBDEs: 0.27 (0.31) Sum 8 MeO-PBDEs: 0.02 (0.11) Sea bass: Sum 5 PBDEs: 0.03 (0.11) Sum 8 MeO-PBDEs: 0.11 (0.27) **BDE-28**, –**47** and -**99** detected and quantified in all mussel samples. In crabs, **BDE-47** was the most abundant congener. In all three fish species, **BDE-47** and -**99** were the most frequent congeners, and in flounder, the only quantified congener was **BDE-47**. In macroalgae, MeO-PBDEs were detected in Ulva sp. in all seasons, while in Fucus sp. samples, only 2′-MeO-BDE-68 and 4′-MeO-BDE-101 were quantified. In fish, sea bass showed the highest levels of of MeO-PBDEs, followed by grey mullet and flounder. Crabs and mussels showed higher levels in comparison to other species Exposure estimates: Consumption data from the Portuguese consumption rate for flounder and sea bass only *Mean (SD) [ng/kg bw per day]:* Sum PBDEs: Bass: 0.49 (0.8) Flounder: 0.2 (0.3) **BDE-47**: Bass: 0.063 (1.0) Flounder: 0.03 (0.04) **BDE-99**: Bass: 0.002 (0.003) Flounder: 0.002 (0.003) **BDE-153**: Bass: 0.003 (0.004) Flounder: 0.0004 (0.0007) Sum 8 MeO-PBDEs: Bass: 0.51 (0.85) Flounder: 0.05 (0.07)

(Continues)

TABLE I.1 (Continued)

Reference	Country, sampling year	Samples, congeners analysed, occurrence in food and exposure as estimated by the authors
Pardo et al. (2014). Probabilistic risk assessment of the exposure to polybrominated diphenyl ethers via fish and seafood consumption in the Region of Valencia (Spain)	Spain, 2007–2012	*n* = 206 fish and seafood samples (25 species) from local markets and supermarkets: Sardine and pilchard, Anchovy, Salmon and trout, Mackerel, Tuna, Cod and whiting, Hake, Flounder, Carp, Blue whiting, Pagel, Swordfish, Monkfish, Turbot, Perch, Rays, Whiting, Jurel, Gilthead bream, Sea bream, Prawns, Squid, Octopus, Cuttlefish, Mussel 12 PBDEs analysed: **BDE-28**, –**47**, –**49**, –66, –**99**, –**100**, –119, –139, –**153**, –**154**, –155, –**183** Occurrence data: *Sum PBDEs per fish species, LB, UB [pg/g ww]:* Sardine and pilchard (*n* = 8): 32.2, 151.1 Anchovy (*n* = 6): 0.0, 120.0 Salmon and trout (*n* = 11): 366.6, 472.8 Mackerel (*n* = 8): 136.7255.2 Tuna (*n* = 12): 0.0120.0 Cod and whiting (*n* = 11): 10.0150.0 Hake (*n* = 8): 0.8120.6 Flounder (*n* = 6): 90.0150.0 Carp (*n* = 7): 12.8132.0 Blue whiting (*n* = 6): 0.0120.0 Pagel (*n* = 5): 1.3121.0 Swordfish (*n* = 12): 18.4235.5 Monkfish (*n* = 7): 0.0120.0 Turbot (*n* = 12): 0.0 70.0 Perch (*n* = 9): 0.0120.0 Rays (*n* = 6): 0.0120.0 Whiting (*n* = 8): 0.0120.0 Jurel (*n* = 12): 10.9131.1 Gilthead bream (*n* = 9): 44.9163.1 Sea bream (*n* = 8): 78.8197.5 Prawns (*n* = 5): 0.0120.0 Squid (*n* = 8): 0.0120.0 Octopus (*n* = 7): 0.0120.0 Cuttlefish (*n* = 9): 0.0120.0 Mussel (*n* = 6): 0.0120.0 *Total per congener LB, UB [pg/g ww]:* **BDE-28**: 65.9, 313.2 **BDE-47**: 356.1, 581.4 **BDE-49**: 45.1, 264.6 **BDE-66**: 46.9, 264.7 **BDE-99**: 180.5, 473.4 **BDE-100**: 223.6, 509.9 **BDE-119**:0.0, 220.0 **BDE-139**: 0.0, 220.0 **BDE-153**: 0.0, 250.0 **BDE-154**: 55.3, 303.1 **BDE-155**: 0.0, 220.0 **BDE-183**: 0.0, 250.0 **Sum 12 PBDEs**: 803.4, 3790.2 **BDE-47** was the most abundant congeners (% contribution to the total: 14%–37%). PentaBDEs (**BDE-99** and -**100**) and hexaBDEs (**BDE-153** and -**154**) accounted for 24%–42% and 6%–14%, respectively Exposure estimates: A questionnaire-based dietary survey conducted in 2010 in the same area from where fish and seafood samples were collected: dietary data collected through a 24-h recall, that included 1478 subjects (195 children, 1281 adults). Only the fish group was further considered by the authors. Adults: 16–95 years old, 71.2 kg bw. Children: 6–15 years old, 43.5 kg bw *Mean (LB, UB), P95 (LB, UB) [ng/kg bw per day]:* *Deterministic intake Sum 12 PBDEs:* Adults: Mean: 0.093, 0.178 P95: 0.389, 0.551 Children: Mean: 0.101, 0.196 P95: 0.377, 0.720 *Probabilistic intake Sum 12 PBDEs:* Adults: Mean: 0.068 (0.057–0.082), 0.137 (0.124–0.158) P95: 0.267 (0.220–0.322), 0.569 (0.496–0.649) Children: Mean: 0.103 (0.054–0.148), 0.180 (0.115–0.244) P95: 0.315 (0.181–0.619), 0.722 (0.571–0.957) The highest mean dietary exposure was due to **BDE-47** (0.039–0.064 ng/kg bw per day), followed by **BDE-49** (0.007–0.022 ng/kg bw per day)
Trabalón et al. (2017). Human exposure to brominated flame retardants through the consumption of fish and shellfish in Tarragona County (Catalonia, Spain)	Spain, NR	Fish and shellfish collected at supermarkets: sole, hake, sardine, tuna, codfish, shrimp, salmon, mackerel, squid, mussel 8 PBDEs analysed: **BDE-28**, –**47**, –**99**, –**100**, –**153**, –**154**, –**183**, –**209** 8 MeO-PBDEs analysed: 5-MeO-BDE-47, 6-MeO-BDE-47, 4-MeO-BDE-49, 2′-MeO-BDE-68, 5′-MeO-BDE-99, 5-MeO-BDE-100, 4-MeO-BDE-101, 4-MeO-BDE-103 Occurrence data: *[ng/g ww]:* Hake: **Sum PBDEs**: 0.9 **Sum MeO-PBDEs**: 0.3 Sole: **Sum PBDEs**: 1.2 **Sum MeO-PBDEs**: 0.4 Cod: **Sum PBDEs**: 0.8 **Sum MeO-PBDEs**: 0.3 Shrimp: **Sum PBDEs**: 0.6 **Sum MeO-PBDEs**: 0.4 Squid: **Sum PBDEs**: 0.6 **Sum MeO-PBDEs**: 0.3 Salmon: **Sum PBDEs**: 1.3 **Sum MeO-PBDEs**: 0.3 Tuna: **Sum PBDEs**: 0.8 **Sum MeO-PBDEs**: 1.0 Mackerel: **Sum PBDEs**: 0.7 **Sum MeO-PBDEs**: 0.4 Sardine: **Sum PBDEs**: 0.4 **Sum MeO-PBDEs**: 0.3 Mussel: **Sum PBDEs**: 0.6 **Sum MeO-PBDEs**: 1.5 **BDE-47** was the predominant congener (congener-specific concentrations are provided in the original paper). **BDE-100**, –**183** and -**209** were < LOD in all samples. **BDE-154** was identified only in mackerel, but < LOQ. The levels of MeO-PBDEs were comparatively lower than those of PBDEs. 2-MeO-BDE-68, 6-MeO-BDE-47 and 5-MeO-BDE-100 were the predominant congeners, while 5-MeO-BDE-47, 4-MeO-BDE-49, 4-MeO-BDE-103, 5-MeO-BDE-99 and 4-MeO-BDE-101 were < LOD in all samples Exposure estimates: Consumption data were collected from a nutritional survey conducted in Catalonia, Spain, between 2002 and 2003 Results for PBDEs and MeO-PBDEs exposure estimates are provided only in Figures for LB, MB and UB for children, adults and elderly

TABLE I.1 (Continued)

Reference	Country, sampling year	Samples, congeners analysed, occurrence in food and exposure as estimated by the authors
Pardo et al. (2020). Polybrominated diphenyl ethers in foods from the Region of Valencia: Dietary exposure and risk assessment	Spain, 2010	*n* = 32 food items (3200 samples, 320 composite samples): Vegetable oils (Olive oil, sunflower oil), Meat and meat products (Chicken, pork, beef, lamb, rabbit, hamburger, sausages, cured ham, cooked ham, cured sausage, foie-grass, offal), Eggs (chicken), Milk and dairy products (Cow milk, cheese, yogurt, custards, smoothies, butter), Fish and seafood (Tuna, albacore tuna, squid, cuttlefish, crustacean, mussel, salmon and trout, hake, sardine and anchovy, swordfish, salty fish, smoked fish, seabream, seabass, canned fish) 13 PBDEs analysed: **BDE-28**, –**47**, –**49**, –66, –**99**, –**100**, –**138**, –139, –**153**, –**154**, –155, –**183**, –**209** Occurrence data: *Sum 13 PBDEs, Mean [pg/g ww]:* Vegetable oils (*n* = 20): 503 Milk and dairy products (*n* = 60): 247 Meat and meat products (*n* = 120): 224 Fish and fish products (*n* = 120): 464 Eggs (*n* = 10): 229 **BDE-47** was the most abundant congener in fish and seafood, meat and meat products, and vegetable oils, and **BDE-99** in eggs, and milk and dairy products Exposure estimates: Consumption data obtained from a dietary survey conducted and validated by the Public Health Directorate of Valencia between 2010 and 2011. Information on food intake collected through 24 h recalls from 1484 subjects (196 young people 6–15 years of age, mean bw = 43.5 kg, and 1288 adults 16–95 years of age, mean bw = 73.2 kg) *Sum 13 PBDEs, Mean (P95) [ng/kg bw per day]:* Young people (6–15 years old): LB: 0.482 (1.449) UB: 3.456 (7.622) Adults (> 15 years old): LB: 0.253 (0.885) UB: 1.443 (3.239)
Sahlström et al. (2015a). Estimated intakes of brominated flame retardants via diet and dust compared to internal concentrations in a Swedish mother-toddler cohort	Sweden, 2010	Market basket study: Five food categories: Fish, Meat, Vegetable oils, Dairy products, Eggs (4 homogenates for each food category) 10 PBDEs analysed: **BDE-28**, –**47**, **–99**, –**100,** –**153**, –197, –206, –207, –208, –**209** Occurrence data:

(pg/g ww)	Fish (*n* = 4)	Dairy (*n* = 4)	Veg. oils (*n* = 4)	Meat (*n* = 4)	Eggs (*n* = 4)
Lipid %	12	4.5	67	12	10
BDE-28	23	< 0.19	< 1.1	< 0.19	< 0.19
BDE-47	294	4.0	20	7.6	< 1.7
BDE-99	< 21	< 6.1	< 38	< 6.1	< 21
BDE-100	< 20	< 0.68	< 4.2	< 5.8	< 20
BDE-153	11	< 0.63	< 3.9	< 0.63	1.7
BDE-197	< 5.2	6.4	< 32	< 5.3	< 5.2
BDE-206	< 1.6	< 1.6	< 9.8	2.1	< 1.6
BDE-207	0.33	0.27	4.9	3.0	0.61
BDE-208	0.36	< 0.21	4.5	1.5	< 0.21
BDE-209	< 3.6	5.3	42	4.6	13

Exposure estimates:
Estimated median (range) daily intake (ng per day) of BFRs from diet for Swedish mothers and toddlers (*n* = 20)
BDE-28: mothers: 0.89 (0.12–1.9) Toddlers: 0.42 (0.058–0.91)
BDE-47: mothers: 14 (3.3–27) Toddlers: 6.4 (1.5–12)
BDE-99: mothers: not calculated Toddlers: not calculated
BDE-100: mothers: not calculated Toddlers: not calculated
BDE-153: mothers: 0.72 (0.44–1.1) Toddlers: 0.34 (0.21–0.54)
BDE-209: mothers: 2.7 (0.93–6.0) Toddlers: 1.3 (0.44–2.8)

(Continues)

TABLE I.1 (Continued)

Reference	Country, sampling year	Samples, congeners analysed, occurrence in food and exposure as estimated by the authors
Boon et al. (2016). Dietary exposure to polybrominated diphenyl ethers in the Netherlands. RIVM Letter report 2016–0037	The Netherlands, 2011–2013	Cereal products, fruits, margarine, nuts and seeds, prepared pasta, prepared rice, potato products, vegetable oils, vegetables and wine, cow's milk, eggs, meat, fish and shellfish 5 PBDEs analysed: **BDE-47**, –**99**, –**100**, –**153**, –**183** Occurrence data: The report gives occurrence data on the five PBDEs in numerous food items within several different food categories, such as 12 meat types. Due to the multitude of results, for further information the reader is referred to the original publication Exposure estimates: Food consumption data derived from the Dutch National Food Consumption Survey *Median [ng/kg bw per day]:* **BDE-47**: 2–6 years old: 0.10 (0.09–0.12) 7–69 years old: 0.05 (0.05–0.06) **BDE-99**: 2–6 years old: 0.10 (0.10–0.11) 7–69 years old: 0.05 (0.04–0.05) **BDE-100**: 2–6 years old: 0.02 (0.02–0.02) 7–69 years old: 0.01 (0.01–0.01) **BDE-153**: 2–6 years old: 0.03 (0.02–0.04) 7–69 years old: 0.02 (0.01–0.02) **BDE-183**: 2–6 years old: 0.04 (0.03–0.07) 7–69 years old: 0.02 (0.02–0.03)
Simsek et al. (2021). Comparison of selected lipophilic compound residues in honey and propolis	Turkey, 2019	Region A: *n* = 20 honeydew honey samples, 20 propolis samples. Region B: *n* = 20 blossom honey samples, 20 propolis samples 9 PBDEs analysed: **BDE-28**, –**47**, –66, –85, –**99**, –**100**, –**153**, –**154**, –**183** Occurrence data: Only BDE-85 found in one propolis samples (region B) (mean = 1.78 ng/g) Exposure estimates: NA
Aydin et al. (2019). Organohalogenated pollutants in raw and UHT cow's milk from Turkey: a risk assessment of dietary intake	Turkey, NR	*n* = 15 samples of raw cow's milk, 15 samples of UHT cow's milk 5 PBDEs analysed: **BDE-47**, –**99**, –**100**, –**153**, –**154** Occurrence data: Raw cow's milk UHT cow's milk **BDE-47**: 2.14 (< LOD–2.87) 11.20 (< LOD–20) **BDE-100**: 0.86 (< LOD–1.35) 4.81 (< LOD–6.67) **BDE-99**: 2.43 (< LOD–5.52) 1.11 (< LOD–1.33) **BDE-154**: 3.54 (< LOD–9.67) 1.15 (< LOD–1.67) **BDE-153**: 3.58 (< LOD–9.46) 5.74 (< LOD–10) **Sum PBDEs**: 9.51 (< LOD–20.22) 6.99 (< LOD–20) Exposure estimates: Sum PBDEs (*μg/kg bw per day*): Raw cow's milk UHT cow's milk Adults: 0.64 0.56 Children: 1.68 1.46

TABLE I.1 (Continued)

Reference	Country, sampling year	Samples, congeners analysed, occurrence in food and exposure as estimated by the authors
Bramwell, Harrad, et al. (2017). Predictors of human PBDE body burdens for a UK cohort **Bramwell, Mortimer, et al. (2017).** UK dietary exposure to PCDD/Fs, PCBs, PBDD/Fs, PBBs and PBDEs: comparison of results from 24-h duplicate diets and total diet studie	UK, 2011–2012	24-h Duplicate diet study: *n* = 20 volunteers Total diet study: *n* = 986 retail food samples purchased from national supermarkets, symbol retailers and independent retailers in 12 UK locations. Samples split into 20 representative food groups: Bread, Cereals, Carcass meat, Offal, Meat products, Poultry, Fish and seafood, Fats and oils, Eggs, Sugar and preserves, Green vegetables, Potatoes, Other vegetables, Canned vegetables, Fresh fruit, Fruit products, Milk, Milk and dairy products, Nuts 16 PBDEs analysed: BDE-17, **–28, –47**, **–49**, –66, –71, –77, –85, **–99**, **–100**, –119, –126, **–138**, **–153**, **–183**, **–209** Occurrence data: *Mean (range) [ng/g lipid]:* Duplicate Diet study: **BDE-47:** 0.18 (0.04–0.86) **BDE-99**: 0.14 (0.03–0.44) **BDE-153**: 0.03 (0.01–0.10) **BDE-183**: 0.02 (0.003–0.08) **BDE-209**: 0.85 (< 0.001–3.13) Sum tri-heptaBDEs: 0.5 (0.10–1.40) TDS *[pg/kg ww]:* Bread: **BDE-47:** 5 **BDE-99:** 6 **BDE-153:** 2 **BDE-209:** < 200 Cereals: **BDE-47:** 6 **BDE-99:** 8 **BDE-153:** 2 **BDE-209:** < 190 Carcass meat: **BDE-47:** 18 **BDE-99:** 22 **BDE-153:** 7 **BDE-209:** < 130 Offal: **BDE-47:** 7 **BDE-99:** 9 **BDE-153:** 3 **BDE-209:** < 120 Meat products: **BDE-47:** 18 **BDE-99:** 19 **BDE-153:** 4 **BDE-209:** < 140 Poultry: **BDE-47:** 5 **BDE-99:** 6 **BDE-153:** 1 **BDE-209:** 220 Fish and seafood: **BDE-47:** 134 **BDE-99:** 23 **BDE-153:** 7 **BDE-209:** 170 Fats and oils: **BDE-47:** 37 **BDE-99:** 35 **BDE-153:** 8 **BDE-209:** < 390 Eggs: **BDE-47:** 13 **BDE-99:** 16 **BDE-153:** 5 **BDE-209:** 90 Sugar and preserves: **BDE-47:** 121 **BDE-99:** 62 **BDE-153:** 7 **BDE-209:** 1950 Green vegetables: **BDE-47:** 2 **BDE-99:** 1 **BDE-153:** 0.2 **BDE-209:** 50 Potatoes: **BDE-47:** 5 **BDE-99:** 5 **BDE-153:** 1 **BDE-209:** 50 Other vegetables: **BDE-47:** 5 **BDE-99:** 8 **BDE-153:** 1 **BDE-209:** 50 Canned vegetables: **BDE-47:** 1 **BDE-99:** 0 **BDE-153:** < 1 **BDE-209:** 20 Fresh fruit: **BDE-47:** 1 **BDE-99:** 1 **BDE-153:** 0.2 **BDE-209:** 140 Fruit products: **BDE-47:** 1 **BDE-99:** 1 **BDE-153:** 0.4 **BDE-209:** 30 Milk: **BDE-47:** 2 **BDE-99:** 2 **BDE-153:** 0.5 **BDE-209:** 120 Milk and dairy products: **BDE-47:** 23 **BDE-99:** 25 **BDE-153:** 6 **BDE-209:**20 Nuts: **BDE-47:** 6 **BDE-99:** 5 **BDE-153:** 1 **BDE-209:** 100 Exposure estimates: *[pg/kg bw per day]:* Duplicate Diet, Average LB: **BDE-47:** 92 **BDE-99:** 100 **BDE-153**: 20 **BDE-209**: 708 **Sum PBDEs** (w/o **BDE-209**): 274 Duplicate Diet, Average UB: **BDE-47:** 92 **BDE-99:** 100 **BDE-153**: 20 **BDE-209**: 751 **Sum PBDEs** (w/o **BDE-209**): 292 Duplicate Diet, P97.5 LB: **BDE-47:** 204 **BDE-99:** 263 **BDE-153**: 53 **BDE-209**: 1770 **Sum PBDEs** (w/o **BDE-209**): 634 Duplicate Diet, P97.5 UB: **BDE-47:** 204 **BDE-99:** 263 **BDE-153**: 53 **BDE-209**: 1770 **Sum PBDEs** (w/o **BDE-209**): 646 TDS, Average UB: **BDE-47:** 200 **BDE-99:** 140 **BDE-153**: 30 **BDE-209**: 2560 **Sum PBDEs** (w/o **BDE-209**): NR TDS, P97.5 UB: **BDE-47:** 410 **BDE-99:** 250 **BDE-153**: 60 **BDE-209**: 5030 **Sum PBDEs** (w/o **BDE-209**): NR **BDE-209** was the congener contributing most to both the Duplicate Diet and TDS exposure. It was followed by **BDE-47** in the TDS, and by **BDE-99** in the Duplicate Diet

(Continues)

TABLE I.1 (Continued)

Reference	Country, sampling year	Samples, congeners analysed, occurrence in food and exposure as estimated by the authors
Zhihua et al. (2018). Spatial analysis of polybrominated diphenylethers (PBDEs) and polybrominated biphenyls (PBBs) in fish collected from UK and proximate marine waters	UK and proximate marine waters (North Atlantic regions around Norway, the Irish Sea, and the European coastal North Atlantic regions, including the North Western coast of France, Biscay and the Algarve), 2013–2014	*n* = 135 samples of fish (edible muscle tissues): sardines (*n* = 15), sprats (*n* = 12, whole fish), sea bass (*n* = 25), mackerel (*n* = 27), herring (*n* = 14), grey mullet (*n* = 25), turbot (*n* = 13), others (*n* = 4) 17 PBDEs analysed: BDE-17, –**28**, –**47**, –**49**, –66, –71, –77, –85, –**99**, –**100**, –119, –126, –**138**, –**153**, –**154**, –**183**, –**209** Sum 10 PBDEs: Sum of **BDE-28**, –**47**, –**49**, –**99**, –**100**, –**138**, –**153**, –**154**, –**183**, –**209** Occurrence data: *Sum 10 PBDEs: Mean (Min, Max) [ng/kg ww]:* Sardines: **Sum measured PBDEs**: 535 (159, 2206) **Sum 10 PBDEs**: 497 (133, 2118) Mackerel: **Sum measured PBDEs**: 1206 (169,3636) **Sum 10 PBDEs**: 1096 (141, 3381) Herring: **Sum measured PBDEs**: 2140 (808, 8906) **Sum 10 PBDEs**: 2039 (757, 8635) Grey Mullet: **Sum measured PBDEs**: 1198 (147, 5422) **Sum 10 PBDEs**: 1094 (77, 5360) Sprat: **Sum measured PBDEs**: 1301 (383, 4620) **Sum 10 PBDEs**: 1236 (354, 4560) Sea Bass: **Sum measured PBDEs**: 2033 (297, 5747) **Sum 10 PBDEs**: 1972 (270, 5641) Turbot: **Sum measured PBDEs**: 367 (87, 859) **Sum 10 PBDEs**: 332 (64, 792) Others: **Sum measured PBDEs**: 169 (100, 293) **Sum 10 PBDEs**: 146 (78, 268) Exposure estimates: NA
Aznar-Alemany et al. (2017). Occurrence of halogenated flame retardants in commercial seafood species available in European markets	Seafood consumed in Europe (Spain, Denmark, Portugal, Italy, the Netherlands, France, Ireland, Greece), 2014–2015	*n* = 42 commercial seafood samples: cod (3), mackerel (11), monkfish (4), mussel (10), Nile perch (1), plaice (1), salmon (3), seabream (2), shrimp (1) and tuna (6) 8 PBDEs analysed: **BDE-28**, –**47**, –**99**, –**100**, –**153**, –**154**, –**183**, –**209** 8 MeO-PBDEs analysed: 5-MeO-BDE-47, 6-MeO-BDE-47, 4′-MeO-BDE-49, 2′-MeO-BDE-68, 5′-MeO-BDE-99, 5′-MeO-BDE-100, 4′-MeO-BDE-101, 4′-MeO-BDE-103 Occurrence data: *Sum PBDEs (mean (range)) [ng/g lipid]:* Cod: 107 (< LOD–317) Mackerel: 42.6 (< LOD–188) Monkfish: 27.7 (< LOD-151) Mussel: 52.7 (6.10–141) Plaice: 55.3 Salmon: 10.3 (3.98–18.0) Seabream: 179 (2.94–356) Tuna: 7.4 (< LOD–38.0) Nile perch: < LOD Shrimp: < LOD *Sum MeO-PBDEs (mean (range)) [ng/g lipid]* Cod: 1.73 (ND–4.55) Mackerel: 19.8 (< LOD–56.7) Monkfish: NQ Mussel: 13.0 (NQ–44.2) Plaice: NQ Salmon: 6.16 (NQ–12.9) Seabream: 73.2 (NQ–144) Tuna: 108 (NQ–305) Nile perch: NQ Shrimp: < LOD Exposure estimates: Estimated for **BDE-47** and -**99** only, using the concentrations of the raw samples and based on the overall seafood consumption pattern of adults from Belgium, Ireland, Italy, Portugal and Spain. For each country, a distribution was fitted to the consumption data of each species and of body weight using @RISK *Mean (SD) [μg/kg bw per day]:* BE: **BDE-47**: LB: 0.00017 (0.00013). UB: 0.00018 (0.00013) **BDE-99**: LB: 0.00011 (0.000085). UB: 0.00012 (0.000088) ES: **BDE-47**: LB: 0.00048 (0.00022). UB: 0.00049 (0.00022) **BDE-99**: LB: 0.00034 (0.00017). UB: 0.00035 (0.00017) IE: **BDE-47**: LB: 0.00017 (0.00014). UB: 0.00018 (0.00014) **BDE-99**: LB: 0.00011 (0.00011). UB: 0.00012 (0.00011) IT: **BDE-47**: LB: 0.00038 (0.00018). UB: 0.00038 (0.00018) **BDE-99**: LB: 0.00027 (0.00014). UB: 0.00029 (0.00015) PT: **BDE-47**: LB: 0.00057 (0.00027). UB: 0.00058 (0.00027) **BDE-99**: LB: 0.00034 (0.00019). UB: 0.00035 (0.00019)
Chiesa et al. (2018). Levels and distribution of PBDEs and PFASs in pork from different European countries	Austria, Denmark, France, Germany, The Netherlands, Italy, Poland, Spain, 2016–2017	Pork muscle samples (*n* = 77): from AU (*n* = 7), DK (*n* = 8), FR (*n* = 8), DE (*n* = 10), NL (*n* = 8), IT (*n* = 20), PL (*n* = 8), ES (*n* = 8) 7 PBDEs analysed: **BDE-28**, –33, **–47**, **–99**, **–100**, **–153**, **–154** Occurrence data: PBDEs detected in 3 out of 77 samples: 1 sample from DE, 1 sample from NL and 1 sample from IT. In the sample from DE all congeners were detected with a concentration range of 0.53–0.77 ng/g ww. In the sample from NL only **BDE-153** was detected (0.53 ng/g ww) and in the sample from IT only **BDE-100** (0.62 ng/g ww) Exposure estimates: NA

TABLE I.1 (Continued)

Reference	Country, sampling year	Samples, congeners analysed, occurrence in food and exposure as estimated by the authors
Boucher et al. (2018). A global database of polybrominated diphenyl ether flame retardant congeners in foods and supplements	32 countries, 2002–2015	Data from 86 articles: Fish and Shellfish, Red Meat and Poultry, Eggs and Dairy, Fats and Oils, Vegetables and Fruits, Nuts, Seeds and Legumes, Cereals, Grains and Baked Products, Beverages and Other Foods, Dietary Supplements 11 PBDEs analysed: BDE-17, –**28**, –**47**, –66, –85, –**99**, –**100**, –**153**, –**154**, –**183**, –**209** Occurrence data: The 10 most contaminated groups (Sum 11 PBDEs levels: 164–13,862 pg/g ww) in decreasing order were: Fish oil supplements, Poultry liver, Poultry fat, Dark or oily fish, Shellfish, Fish oil/plant oil blend supplements, Eggs, Baked products, Poultry meat and Red meat fat The 10 least contaminated groups (Sum 11 PBDEs levels: 0–71 pg/g ww) in ascending order were: Beverages, Plant oil supplements, Fruits, Other foods, Vegetables, Dairy products, Vegetable fats and oils, Mixed dishes, Dairy fat and Processed meats The remaining 7 groups had total PBDE levels from 72 (Nuts and seeds) to 149 (Poultry skin) pg/g ww Exposure estimates: NA

Abbreviations: LB, lower bound; LOD, limit of detection; LOQ, limit of quantification; NA, not available; NR, not reported; SD, standard deviation; TDS, total diet study; UB, upper bound.

ANNEXES

Annex A – Protocol for the risk assessments for human health related to the presence of brominated flame retardants (BFRs) in food

The Annex is provided as a separate pdf file containing the risk assessment protocol applied by the CONTAM Panel to update the previous risk assessments of brominated flame retardants (BFRs) in food, and is available under the Supporting Information section on the online version of the Scientific output.

Annex B – Occurrence data on PBDEs in food submitted to EFSA and dietary surveys per country and age group available in the EFSA Comprehensive Database, considered in the exposure assessment

The Annex is provided as a separate Excel file containing the occurrence data submitted to EFSA and dietary surveys per country and age group, and is available on the EFSA Knowledge Junction community on Zenodo at: https://doi.org/10.5281/zenodo.10517475

Annex C – Levels in human tissues from non-European countries

The Annex is provided as a separate pdf file containing tables compiling the studies on levels on PBDEs in human tissues from non-European countries, and is available under the Supporting Information section on the online version of the Scientific output.

Annex D – Epidemiological studies on PBDEs

The Annex is provided as a separate pdf file containing tables compiling the epidemiological studies on PBDEs, and is available under the Supporting Information section on the online bersion of the Scientific output.

Annex E – Benchmark dose analysis

The Annex is provided as a separate pdf file containing the results of the benchmark dose (BMD) analysis and is available under the Supporting Information section on the online bersion of the Scientific output.

Annex F – Chronic dietary exposure to PBDEs and the contribution of different food groups to the dietary exposure

The Annex is provided as a separate excel file containing the chronic dietary exposure assessment to PBDEs per survey and the contribution of different food groups to the dietary exposure, and is available on the EFSA Knowledge Junction community on Zenodo at: https://doi.org/10.5281/zenodo.10518801

Annex G – Calculation of the combined margin of exposure (MOET)

The Annex is provided as a separate excel file containing the calculations of the combined margin of exposure (MOET) for the risk characterisation of PBDEs, and is available on the EFSA Knowledge Junction community on Zenodo at: https://doi.org.10.5281/zenodo.12657178

Annex H – Uncertainty analysis

The Annex is provided as a separate pdf file containing a detailed, standalone description of the methods and results of each step of the uncertainty analysis, and is available under the Supporting Information section on the online version of the Scientific output.

Annex I – Outcome of the public consultation

The Annex is provided as a separate pdf file containing the comments received during the public consultation and the replies by the CONTAM Panel, and is available under the Supporting Information section on the online version of the Scientific output.