TECHNICAL REPORT

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# Assessment of endocrine disrupting properties in EFSA Conclusions on the Pesticides Peer Review

## European Food Safety Authority

## Abstract

Regulation (EC) No 1107/2009 introduced new criteria for the approval of pesticide active substances, including hazard based exclusion criteria with regard to certain classification criteria, environmental concerns, and endocrine disrupting properties. The Regulation specifies criteria for substances with carcinogenic, mutagenic or toxic for reproduction properties (CMR), Persistent Organic Pollutants (POPs) and substances that are persistent, bioaccumulable and toxic (PBTs) including those very persistent and very bioaccumulable. The Regulation also calls for specific scientific criteria for the determination of endocrine disrupting properties, and pending the adoption of these criteria, enacts the so-called 'interim criteria', based on classification considerations and 'toxic effects on the endocrine organs'. Since 2014, EFSA has published 15 Conclusions on new active substances and 26 on applications for renewal that explicitly summarise the assessment of potential endocrine effects under Regulation (EC) No 1107/2009. For 24 active substances, including 3 microbial pesticide active substances, the available information has not led to the detection of specific concerns, however in the case of two substances EFSA has recommended additional studies to confirm this conclusion. Hazard or risk based concerns have been identified from the available information for 15 substances. An overview of the outcome of the assessments of the interim criteria and the concerns identified regarding endocrine disrupting properties in EFSA Conclusions on the Pesticides Peer Review is presented. The number of substances assessed to date is insufficient to conduct a statistical analysis however a wide range of options is already evident. For some substances the interim criteria were not met, but EFSA highlighted evidence extracted from the regulatory studies or scientific publications suggesting possible concerns, and recommended the need for additional studies to finalise the assessment of the potential endocrine mediated adverse effects. With this approach, the EFSA Conclusions offer risk managers, stakeholders and citizens a transparent assessment of the available evidence, offering information that can be used to support the decision making process.



**Key words:** pesticides, peer-review, EFSA Conclusion, endocrine disrupting properties

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## Summary

Regulation (EC) No 1107/2009 introduced new criteria for the approval of pesticide active substances, including hazard based exclusion criteria with regard to certain classification criteria, environmental concerns, and endocrine disrupting properties. The Regulation specifies criteria for substances with carcinogenic, mutagenic or toxic for reproduction properties (CMR), Persistent Organic Pollutants (POPs) and substances that are persistent, bioaccumulable and toxic (PBTs) including those very persistent and very bioaccumulable. The Regulation also calls for specific scientific criteria for the determination of endocrine disrupting properties, and pending the adoption of these criteria, enacts the so-called 'interim criteria', based on classification in accordance with the provisions of Regulation (EC) No 1272/2008, and 'toxic effects on the endocrine organs'.

The EFSA Conclusions present the properties of the substance, in particular the toxicological and ecotoxicological profiles, including the assessment of potential endocrine effects, based on the available data. Since 2014, EFSA has published 15 Conclusions on new active substances and 26 on applications for renewal that explicitly summarise the assessment of potential endocrine effects under Regulation (EC) No 1107/2009. For 24 active substances, including 3 microbial pesticide active substances, the available information has not led to the detection of specific concerns, however in the case of two substances EFSA has recommended additional studies to confirm this conclusion. Hazard or risk based concerns have been identified from the available information for 15 substances. These concerns are related to the application of the interim criteria, the identification of relevant adverse effects which could be related to endocrine mechanisms or both.

An overview of the outcome of the assessments and the concerns identified regarding endocrine disrupting properties in EFSA Conclusions on the Pesticides Peer Review is presented. Expressing the results of the scientific assessments on potential endocrine related effects is very complex, and some EFSA conclusions have been republished with editorial modifications for clarifying the results. Considering the interest in this area and the EFSA role in risk communication the EFSA Pesticides Unit has compiled in this document the recent assessments offering an overview of over thirty pesticides active substances.

The number of substances assessed to date is insufficient to conduct a statistical analysis however a wide range of options is already evident. Although the number of substances is still too limited for allowing a statistical assessment, some differences between the application of the criteria and the outcome of the detailed scientific assessment presented in the EFSA conclusions have been identified, as could be expected for regulatory interim criteria. A number of active substances meet the interim criteria for the identification of endocrine disrupting properties and possible endocrine-mediated adverse effects were observed in mammals, while in one case the first interim criterion is met although the scientific evidence suggests that it is unlikely the substance to be endocrine disruptor in mammals (false positive). In addition, for some substances the interim criteria were not meet, but EFSA considers that some adverse effects, identified from the regulatory studies or scientific publications, could be linked to endocrine mediated mechanisms (false negatives), and therefore EFSA highlighted possible concerns and recommended the need for additional studies to finalise the assessment of the endocrine effects. With this approach, the EFSA Conclusions offer risk managers, stakeholders and citizens a transparent assessment of the available evidence, offering information that can be used to support the decision making process.

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# 1. Introduction

Regulation (EC) No 1107/2009[1] introduced new criteria for the approval of pesticide active substances, including hazard based exclusion criteria with regard to certain classification criteria ('CMR': carcinogenicity, mutagenicity and toxicity for reproduction), environmental concerns ('POP': Persistent Organic Pollutants; and 'PBT': persistent, bioaccummulable and toxic properties), and endocrine disrupting properties. The application of hazard based approaches requires comparison of the available information with the specific criteria. The Regulation specifies criteria for CMR, POPs and PBTs, and calls for specific scientific criteria for the determination of endocrine disrupting properties. Pending the adoption of these criteria, the regulation enacts the so-called 'interim criteria', based on classification considerations and 'toxic effects on the endocrine organs'.

EFSA is required to give a Conclusion in the light of current scientific and technical knowledge on the properties of the active substance and whether it can be expected to meet the approval criteria, covering the risk to human health, animal health and the environment according to the so-called "Uniform Principles" for assessing pesticide active substances and products as well as the abovementioned hazard based criteria.

# 2. EFSA Conclusions on the Pesticides Peer Review

The EFSA Conclusions present the properties of the substance, highlighting in particular the toxicological and ecotoxicological/environmental profiles, which include the scientific assessment of potential endocrine related adverse effects, based on the available data. The information available to EFSA and used for this scientific assessment combines several sources; basically:

- the dossier prepared by the applicant,
- the draft risk assessment prepared by the rapporteur Member State,
- the additional information collected during the EFSA peer-review process which includes a public consultation and several commenting rounds with the risk assessors experts in the Member States, and
- the complementary information available to EFSA and the Member States' networks, which includes general scientific knowledge, relevant information from previous assessments by EFSA and other risk assessment bodies, related grants and procurements including systematic literature reviews, etc.

The different information sources include both regulatory studies mostly conducted under Good Laboratory Practices and scientific peer-review publications. The outcome of the scientific assessment is then compared with the hazard based criteria, and also used in the hazard characterisation and risk assessment.

Regarding endocrine effects, following the scientific assessment methodology, EFSA evaluates the available evidence during the peer-review, focusing on observed adverse effects which are plausibly linked to endocrine modes of action and evidence from *in vitro* mechanistic studies, as well as other information sources such as evidence from closely related substances. The scientific assessment is conducted in line with the Opinion of the EFSA Scientific Committee (EFSA SC, 2013) and the OECD developments following the Conceptual Framework for Testing and Assessment of Endocrine Disrupting Chemicals (OECD, 2012). The outcome of the scientific assessment is then compared with the hazard based criteria, in particular regarding the assessment of 'toxic effects on endocrine organs' which is part of the second interim criteria, and also used in the hazard characterisation and risk assessment to identify critical areas of concern as well as issues that could not be finalised. The need for additional information with the identification of data gaps is also presented.

The EFSA Conclusions include specific sections where health or environmental concerns are listed, in order to facilitate communication of the assessment to risk managers, stakeholders and the public. 'Critical areas of concern' are identified where hazard or risk based concerns were ascertained from

[1] Regulation (EC) No 1107/2009 of 21 October 2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1–50.

the available information, with regard to the approval criteria. 'Issues not finalised' are concerns due to indications of a relevant hazard or risk but where the available information is insufficient to establish a conclusion; and which trigger lacking information to be identified as a 'data gap'. Other issues including minor deficiencies and less relevant data gaps are also presented in the Conclusion but not highlighted as concerns in Section 9 of the Conclusion. This approach has been established by EFSA, following a discussion with the European Commission and the Member States, in order to offer risk managers, stakeholders and the public a clear communication of the risks and concerns identified for each pesticide active substance.

# 3. Overview of the assessment of endocrine disrupting properties

Since 2014, EFSA has published 15 Conclusions on new active substances (NAS) and 26 on applications for renewal (AIR) that explicitly summarise the assessment of potential endocrine effects under Regulation (EC) No 1107/2009. For 24 active substances the available information has not led to the detection of specific concerns (see Appendix A). This list includes 3 microbial pesticide active substances, for which the classification according to the CLP Regulation is not applicable. In the case of two substances EFSA has not detected concerns but has recommended additional studies to confirm this conclusion (Appendix B).

Hazard or risk based concerns, including potential concerns due to issues not finalised, have been identified from the available information for 15 substances (Appendix C).

The hazard based concerns are based in all cases on the regulatory interim criteria, complemented, in some but not all cases, by the identification of adverse effects with plausible endocrine mediated mechanisms. The interim regulatory criteria are based on the classification for reproductive and carcinogenic effects. The criteria are applied by EFSA covering both the actual classification as well as proposed classifications during the EFSA peer-review. In the conclusions, EFSA has considered the current harmonised classification under the CLP Regulation[2] and the EFSA assessment regarding the substances that "have to be classified"; when available the opinion of the Committee for Risk Assessment of the European Chemicals Agency was also considered. Both cases are specified in the respective EFSA Conclusions.

The potential concerns related to issues not finalised are related to the identification, during the scientific assessment, of relevant adverse effects for which the available information did not allow to rule out an endocrine mediated mode of action.

For a number of further EFSA Conclusions under Regulation (EC) No 1107/2009, the assessment was limited in scope to either applications for amendment to the conditions of approval or to specific mandates under Article 21 of the Regulation. These conclusions do not provide an assessment of endocrine effects and the substances have been listed in Table 1 only for completeness. Conclusions adopted under the previous legal framework, not requiring the specific assessment of endocrine effects as approval criteria, have not been included in this report.

An overview of the outcome of the assessments of the interim criteria and the concerns identified regarding endocrine disrupting properties in EFSA Conclusions on the Pesticides Peer Review is presented in Table 1. Summaries of the assessment of endocrine disrupting properties for the relevant EFSA Conclusions are given in Appendices A to C.

[2] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 OJ L 353, 31.12.2008, p. 1-1355.

**Table 1:** Overview of the assessments of endocrine disrupting properties for active substances in the EU Pesticides Peer Review. EFSA Conclusions in chronological order categorised by identification of data gaps, concerns identified and other EFSA Conclusions on applications for amendment and under Article 21 of Regulation (EC) No 1107/2009.

| Active substance | Critical area of concern identified, section 9.2[a] | Critical area of concern identified, section 9.2[a] | Concern identified for an issue not finalised, section 9.1[d] | Other comments |
|---|---|---|---|---|
| | First interim criteria[b] | Second interim criteria[c] | | |
| **Active substances where no concerns and no data gaps were identified specific to the assessment of endocrine disrupting properties in the EFSA Conclusion (see Appendix A)** | | | | |
| Cerevisane | – | – | – | – |
| *Isaria fumosorosea* strain Apopka 97 | – | – | – | – |
| Sulfoxaflor | – | – | – | – |
| Sulfosulfuron | – | – | – | – |
| Fenhexamid | – | – | – | – |
| Pyridate | – | – | – | – |
| Cyantraniliprole | – | – | – | – |
| Prosulfuron | – | – | – | – |
| COS-OGA | – | – | – | – |
| Esfenvalerate | – | – | – | – |
| Halauxifen-methyl | – | – | – | – |
| Flumetralin | – | – | – | – |
| 3-decen-2-one | – | – | – | – |
| Cyhalofop | – | – | – | – |
| Metsulfuron-methyl | – | – | – | – |
| Ferric phosphate | – | – | – | – |
| *Pepino mosaic* virus strain CH2, isolate 1906 | – | – | – | – |
| Florasulam | – | – | – | – |
| Metalaxyl-M | – | – | – | – |
| Pyraflufen-ethyl | – | – | – | – |
| Rescalure | – | – | – | – |
| *Trichoderma atroviride* strain SC1 | – | – | – | – |

| Active substance | Critical area of concern identified, section 9.2[a] | Critical area of concern identified, section 9.2[a] | Concern identified for an issue not finalised, section 9.1[d] | Other comments |
|---|---|---|---|---|
| | First interim criteria[b] | Second interim criteria[c] | | |
| Mandestrobin | – | – | – | – |
| Famoxadone | – | – | – | – |
| **Active substances where no concerns were identified regarding endocrine disrupting properties, however where data gaps have been identified specific/relevant to the assessment of endocrine disrupting properties (see Appendix B)** | | | | |
| Thiabendazole | – | – | – | – |
| Triasulfuron | – | – | – | – |
| **Active substances where concerns have been identified regarding endocrine disrupting properties (see Appendix C)** | | | | |
| Iprovalicarb | – | – | On the basis of the pattern of tumours observed in the long-term toxicity study in rats, it cannot be excluded that iprovalicarb is an endocrine-disruptor. | – |
| Bentazone | – | Not finalised. The data gap is relevant for the interpretation of the interim criterion for the determination of potential endocrine disrupting properties. | An endocrine-mediated mode of action could not be ruled out regarding the critical effects observed in the developmental toxicity study in rats (increased post implantation loss, reduced number of live foetuses and retarded foetal development), a data gap for the Level 2/3 tests currently indicated in the OECD Conceptual Framework was identified, and the assessment could not be finalised. | EFSA proposes classification as toxic for reproduction category 2 |
| Lambda-cyhalothrin | – | – | An endocrine-mediated mode of action could not be ruled out regarding the brain morphological changes observed in the developmental neurotoxicity study (and possible sperm effects, which have to be clarified in the first place) and the potential for endocrine disrupting effects could not be finalised. | – |
| Acibenzolar-S-methyl | – | EFSA proposes classification as toxic for reproduction category 2, and effects that may be linked to | An endocrine-mediated mode of action could not be ruled out regarding the morphometric | The data gap for the OECD level 2/3 tests is relevant for the interpretation of the interim criteria |

| Active substance | Critical area of concern identified, section 9.2[a] | Critical area of concern identified, section 9.2[a] | Concern identified for an issue not finalised, section 9.1[d] | Other comments |
|---|---|---|---|---|
| | First interim criteria[b] | Second interim criteria[c] | | |
| | | endocrine organs (resulting in impaired development of the cerebellum) have been identified. | changes in the cerebellum of foetuses in the developmental neurotoxicity study. | |
| Flumioxazin | – | Flumioxazin is classified as toxic for reproduction (category 1B) and toxic effects were observed in endocrine organs (prostate, testes, epididymidis, gestation index, live born pups). | An endocrine-mediated mode of action could not be ruled out regarding reproductive organ abnormalities, reduced gestation index and reduction in live born pups in the two-generation study. | Flumioxazin has harmonised classification and labelling as toxic for reproduction category 1B |
| Amitrole | – | Amitrole is classified as toxic for reproduction category 2 and toxic effects were observed in endocrine organs (thyroid). | – | EFSA proposes classification as toxic for reproduction category 1B, H360 'May damage the unborn child' Endocrine disrupting properties can be inferred from the observation of adverse effects on thyroid in mammals and birds. |
| Flutianil | EFSA proposes classification as carcinogen category 2 and toxic for reproduction category 2. | EFSA proposes classification as toxic for reproduction category 2 and adverse effects on endocrine organs across different species and timelines were observed. | – | An endocrine-mediated mode of action could not be ruled out regarding the adverse effects that have been observed on endocrine organs. |
| 2,4-D | – | – | Adverse effects on endocrine organs have been observed in apical studies that may be endocrine-mediated, which should be further clarified to assess their relevance on the developing offspring. | – |
| Terpenoid blend QRD-460 | Not finalised | Not finalised | Not finalised | A critical area of concern was identified (section 9.2) as the toxicological database was considered incomplete and not sufficient to identify the hazard of the active substance and no reference values could be established. |
| Pymetrozine | Pymetrozine has harmonised classification as carcinogen category 2 and EFSA proposes classification | EFSA proposes classification as toxic for reproduction category 2, and adverse effects on endocrine organs | – | An endocrine-mediated mode of action could not be ruled out regarding adverse effects observed |

| Active substance | Critical area of concern identified, section 9.2[a] | Critical area of concern identified, section 9.2[a] | Concern identified for an issue not finalised, section 9.1[d] | Other comments |
|---|---|---|---|---|
| | First interim criteria[b] | Second interim criteria[c] | | |
| | as toxic for reproduction category 2 | across different species and timelines were observed. | | in mammalian toxicity studies. |
| Flupyrsulfuron (variant evaluated flupyrsulfuron-methyl-sodium) | EFSA proposes classification as carcinogen category 2 and toxic for reproduction category 2 | – | – | Flupyrsulfuron-methyl-sodium is unlikely to be an endocrine disruptor in mammals according to the current scientific state-of-play. |
| Tricyclazole | – | – | On the basis of effects on reproductive organ weights and sexual maturation in mammals, it cannot be excluded that tricyclazole is an endocrine disruptor. Additionally, some observations on reproductive organs of birds and increased vitellogenin level in fish were also noted. | – |
| Benzovindiflupyr | – | – | Considering the effects observed in the reproductive system of the two-generation reproductive toxicity study (reduced percentage of normal sperm in males of the P generation, reduced number of growing follicles and corpora lutea, and increased incidence of lactational diestrus in females of both P and F1 generations, delay of sexual maturation in offspring, while an increased incidence of hypertrophy of the adrenal zona glomerulosa was observed in adult females and increased incidence of cell hypertrophy in the pars distalis of the pituitary were observed in adult males at the top dose), it cannot be excluded that benzovindiflupyr is an endocrine disruptor. | – |
| Thifensulfuron- | – | EFSA proposes classification as toxic | An endocrine-mediated mode of | |

| Active substance | Critical area of concern identified, section 9.2[a] | Critical area of concern identified, section 9.2[a] | Concern identified for an issue not finalised, section 9.1[d] | Other comments |
|---|---|---|---|---|
| | First interim criteria[b] | Second interim criteria[c] | | |
| methyl | | for reproduction category 2 and toxic effects were observed in endocrine organs (i.e. mammary gland tumours in long-term toxicity study in rats) | action regarding the occurrence of mammary gland tumours observed in the long-term toxicity study in rats cannot be excluded | |
| Isoproturon | Isoproturon has harmonised classification as carcinogen category 2 and EFSA proposes classification as toxic for reproduction category 2 | EFSA proposes classification as toxic for reproduction category 2 and the effects observed on fertility and overall reproductive performance might be endocrine-mediated | – | Results from reproductive toxicity studies indicated that isoproturon may be an endocrine disrupting compound in mammals |
| **Other EFSA Conclusions: Applications for amendment to the conditions of approval under Regulation (EC) No 1107/2009** | | | | |
| Fluazifop-P | Assessment limited to an application for amendment to the conditions of approval. No reference to endocrine effects. | | | |
| Fenazaquin | Assessment limited to an application for amendment to the conditions of approval. No reference to endocrine effects. | | | |
| Acrinathrin | Assessment limited to an application for amendment to the conditions of approval. No reference to endocrine effects. | | | |
| Fenpyroximate | Assessment limited to an application for amendment to the conditions of approval. No reference to endocrine effects. | | | |
| Tebuconazole | Assessment limited to an application for amendment to the conditions of approval. In an addendum to the DAR some information is presented but was not peer-reviewed by EFSA. | | | |
| **Other EFSA Conclusions: Article 21 of Regulation (EC) No 1107/2009** | | | | |
| Chlorpyrifos as regards the conclusions of human health assessment | Assessment limited to the conclusions of human health assessment. Specific concerns on genotoxicity, endocrine disruption and developmental neurotoxicity are indicated in the EFSA conclusion. | | | |
| Imidacloprid as regards the risk to aquatic organisms | Assessment limited to the risk to aquatic organisms. No reference to endocrine effects in the EFSA Conclusion. | | | |
| Neonicotinoids (clothianidin) as regards the risk to bees | Assessment limited to the risk to bees. No reference to endocrine effects in the EFSA Conclusion. | | | |
| Neonicotinoids (thiamethoxam) as regards the risk to bees | Assessment limited to the risk to bees. No reference to endocrine effects in the EFSA Conclusion. | | | |
| Neonicotinoids (imidacloprid) as | Assessment limited to the risk to bees. No reference to endocrine effects in the EFSA Conclusion. | | | |

| Active substance | Critical area of concern identified, section 9.2[(a)] | Critical area of concern identified, section 9.2[(a)] | Concern identified for an issue not finalised, section 9.1[(d)] | Other comments |
|---|---|---|---|---|
| | First interim criteria[(b)] | Second interim criteria[(c)] | | |
| regards the risk to bees | | | | |

(a): An issue is listed as a critical area of concern if there is enough information available to perform an assessment for the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 of the European Parliament and of the Council and as set out in Commission Regulation (EU) No 546/2011, and if this assessment does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.
An issue is also listed as a critical area of concern if the assessment at a higher tier level could not be finalised due to a lack of information, and if the assessment performed at the lower tier level does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.
An issue is also listed as a critical area of concern if, in the light of current scientific and technical knowledge using guidance documents available at the time of application, the active substance is not expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council.

(b): Regulation (EC) No 1107/2009 Annex II, Point 3.6.5, Paragraph 3: "Pending the adoption of these criteria, substances that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogenic category 2 and toxic for reproduction category 2, shall be considered to have endocrine disrupting properties."

(c): Regulation (EC) No 1107/2009 Annex II, Point 3.6.5, Paragraph 4: "In addition, substances such as those that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 2 and which have toxic effects on the endocrine organs, may be considered to have such endocrine disrupting properties."

(d): An issue is listed as 'could not be finalised' if there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 of the European Parliament and of the Council and as set out in Commission Regulation (EU) No 546/2011 and if the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).
An issue is also listed as 'could not be finalised' if the available information is considered insufficient to conclude on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council.

# 4. Conclusions

The EFSA conclusions consider independently both interim criteria, informing risk managers, stakeholders and citizens on observations related to toxic effects on endocrine organs even when the first criterion is met. The assessment is complemented with a scientific evaluation of all available information, which cover regulatory guideline studies, scientific peer-review publications and complementary information sources. The number of substances assessed to date is insufficient to conduct a statistical analysis however a wide range of options is already evident. For instance, in the case of flupyrsulfuron, the first interim criterion is met due to the proposed classification, but the information suggested the substance to be unlikely an endocrine disruptor in mammals. Regarding the second criteria, the term "toxic effects on endocrine organs" has been interpreted, in line with the current scientific knowledge, to include adverse structural or functional alterations observed in organs involved in hormonal control resulting in adverse alterations in the regulation of endocrine systems. It is important to mention that in all cases where the second interim criteria is met according to the EFSA evaluation, the complementary scientific assessment indicates that endocrine mediated mechanisms cannot be ruled out regarding some adverse effects. In addition, for several substances the interim criteria were not met, but EFSA highlighted evidence extracted from the regulatory studies or scientific publications suggesting possible concerns, and recommended the need for additional studies to finalise the assessment of the endocrine effects. With this approach, the EFSA Conclusions offer risk managers, stakeholders and citizens a transparent assessment of the available evidence, offering information that can be used to support the decision making process.

# References[3]

EFSA SC (EFSA Scientific Committee), 2013. Scientific Opinion on the hazard assessment of endocrine disruptors: scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment. EFSA Journal 2013;11(3):3132., 84 pp., doi: 10.2903/j.efsa.2013.3132

OECD (Organisation for Economic Co-operation and Development), 2012. Guidance document on standardised test guidelines for evaluating chemicals for endocrine disruption, No. 150 ENV/JM/MONO(2012)22, 24 August 2012.

[3] All Conclusions are available in the EFSA Journal and the links are provided in the appendices.

## Abbreviations

| | |
|---|---|
| AIR | Annex I Renewal |
| AIR II | Annex I Renewal for a second group of active substances in accordance with Commission Regulation (EU) No 1141/2010 |
| CMR | carcinogenicity, mutagenicity and reprotoxicity |
| DAR | draft assessment report |
| EDSP | U.S. Environmental Protection Agency Endocrine Disruptor Screening Program |
| NAS | new active substance |
| OECD | Organisation for Economic Co-operation and Development |
| PBT | Persistent Bioaccumulative and Toxic |
| POP | Persistent Organic Pollutant |
| RMS | rapporteur Member State |

# Appendix A – EFSA Conclusions where no concerns and no data gaps were identified specific to the assessment of endocrine disrupting properties

1. **Cerevisane** (cell walls of Saccharomyces cerevisiae strain LAS117; NAS)
Conclusion approved: 7 February 2014
EFSA Journal 2014;12(6):3583 doi:10.2903/j.efsa.2014.3583
http://www.efsa.europa.eu/en/efsajournal/pub/3583.htm

The active substance is an inert derivate of the yeast *Saccharomyces cerevisiae* strain LAS117 corresponding to the cell walls of the yeast. *Saccharomyces cerevisiae* is the most widely used yeast in industrial/commercial food and beverage production and it is consumed as a nutritional supplement. EFSA considered *Saccharomyces cerevisiae* safe for consumers having a presumption of safety status. No human safety concerns are expected from the use of this substance as a plant protection product. Based on the toxicological profile, no health based reference values need to be set.

2. ***Isaria fumosorosea* strain Apopka 97** (AIR II)
Conclusion approved: 28 April 2014
EFSA Journal 2014;12(5):3679 doi:10.2903/j.efsa.2014.3679
http://www.efsa.europa.eu/en/efsajournal/pub/3679.htm

Microbial pesticide active substance.

3. **Sulfoxaflor** (NAS)
Conclusion approved: 12 May 2014
EFSA Journal 2014;12(5):3692 doi:10.2903/j.efsa.2014.3692
http://www.efsa.europa.eu/en/efsajournal/pub/3692.htm

Interim criteria negative.

It is unlikely that sulfoxaflor is an endocrine disruptor in mammals. However in the ecotoxicology section, although no specific concerns were identified from the available studies, no firm conclusion could be made from the available information and it was concluded that overall, insufficient information was available to perform an assessment of whether sulfoxaflor has endocrine disrupting properties that may cause adverse effects on non-target organisms.

A data gap was identified for a search of the scientific peer-reviewed open literature however no specific concerns or data gaps were identified regarding endocrine disrupting properties.

4. **Sulfosulfuron** (AIR II)
Conclusion approved: 26 June 2014
EFSA Journal 2014;12(7):3764 doi:10.2903/j.efsa.2014.3764
http://www.efsa.europa.eu/en/efsajournal/pub/3764.htm

Interim criteria negative.

It is noted that no recognised endocrine disrupting effects are observed *in vivo* and it is considered unlikely that any of the *in vitro* tests reported in the level 2 of the OECD Conceptual Framework would add any relevant information; therefore sulfosulfuron is unlikely to be an endocrine disruptor in mammals according to the current scientific state-of-play.

No specific concerns on the potential for endocrine disruption have been identified from the available ecotoxicological data set on birds and fish. However, no firm conclusion can be drawn from the available information, as in general, these studies alone are not sufficient to investigate all the relevant mechanisms and they may not be sufficient to detect all adverse effects which could be caused by an endocrine mechanism.

5. **Fenhexamid** (AIR II)
Conclusion approved: 27 June 2014
EFSA Journal 2014;12(7):3744 doi:10.2903/j.efsa.2014.3744
http://www.efsa.europa.eu/en/efsajournal/pub/3744.htm

Interim criteria negative.

It was noted that positive *in vitro* findings are reported in the published literature, however no recognised endocrine disrupting effects are observed *in vivo* and it is considered unlikely that any of the *in vitro* tests reported in the level 2 of the OECD Conceptual Framework would add any relevant information; therefore fenhexamid is unlikely to be an endocrine disruptor in mammals according to the current scientific state-of-play. No specific concerns on the potential for endocrine disruption have been identified from the available ecotoxicological data set on birds and fish.

6. **Pyridate** (AIR II)
Conclusion approved: 18 July 2014
EFSA Journal 2014;12(8):3801 doi:10.2903/j.efsa.2014.3801
http://www.efsa.europa.eu/en/efsajournal/pub/3801.htm

Interim criteria negative.

Thyroid toxicity effects were observed in short-term, long-term and reproductive toxicity studies in rats. The RMS assessed thyroid toxicity effects according to the OECD Conceptual Framework for testing and assessment of endocrine disrupting chemicals and concluded that they were not endocrine-mediated thyroid effects, and the experts at the Pesticides Peer Review Experts' Meeting agreed. Furthermore, no specific concerns on the potential for endocrine disruption have been identified from the available ecotoxicological data set on birds and fish.

7. **Cyantraniliprole** (NAS)
Conclusion approved: 13 August 2014
EFSA Journal 2014;12(9):3814 doi:10.2903/j.efsa.2014.3814
http://www.efsa.europa.eu/en/efsajournal/pub/3814.htm

Interim criteria negative.

It is noted that no recognised endocrine disrupting effects are observed *in vivo* and it is considered unlikely that any of the *in vitro* tests reported in the level 2 of the OECD Conceptual Framework would add any relevant information; therefore cyantraniliprole is unlikely to be an endocrine disruptor in mammals according to the current scientific state-of-play.

8. **Prosulfuron** (AIR II)
Conclusion approved: 18 August 2014
EFSA Journal 2014;12(9):3815 doi:10.2903/j.efsa.2014.3815
http://www.efsa.europa.eu/en/efsajournal/pub/3815.htm

Interim criteria negative.

In mammals, no recognised endocrine disrupting effects were observed *in vivo* and it is considered unlikely that any of the *in vitro* tests reported in the level 2 of the OECD Conceptual Framework would add any relevant information; therefore prosulfuron is unlikely to be an endocrine disruptor (in mammals) according to the current scientific state-of-play. No specific concerns on the potential for endocrine disruption have been identified from the available ecotoxicological data set on birds and fish.

9. **COS-OGA** (NAS)
Conclusion approved: 1 October 2014
EFSA Journal 2014;12(10):3868 doi:10.2903/j.efsa.2014.3868
http://www.efsa.europa.eu/en/efsajournal/pub/3868.htm

No specific reference to endocrine effects. Overall no toxicological concern was identified on the components of COS-OGA and therefore no reference values were set.

10. **Esfenvalerate** (AIR II)
Conclusion approved: 17 October 2014
EFSA Journal 2014;12(11):3873 doi:10.2903/j.efsa.2014.3873
http://www.efsa.europa.eu/en/efsajournal/pub/3873.htm

Interim criteria negative.

Data from a literature search and from *in vivo* and *in vitro* assays conducted for US EPA's Endocrine Disruptor Screening Programme (EDSP) (Tier 1 Battery) were provided during the peer review. Esfenvalerate did not exhibit any evidence of endocrine mediated effects in the EDSP's assays, including studies for androgen receptor binding, aromatase, oestrogen receptor binding, oestrogen receptor transcriptional activation, Hershberger, female pubertal, male pubertal, steroidogenesis and uterotrophic assessment.

In an article identified during the first expert meeting, delayed vaginal opening and hormonal changes were observed in prepubertal female rats. In its evaluation, the RMS noted that the described study had some limitations such as missing investigations of the systemic toxicity. In a second discussion (Peer Review Meeting 118), the experts agreed that these effects were overruled by the studies submitted to US EPA (EDSP battery), where the investigated end points would have been affected by the hormonal changes observed in the Pine study. Additionally, no effect was observed on the time of vaginal opening in the US EPA study (GLP and guideline).

Esfenvalerate is unlikely to have endocrine disrupting properties in mammals. This conclusion is based on the absence of adverse effects in the US EPA's EDSP assays and in the regulatory studies. However no firm conclusion can be drawn regarding birds and fish (21-day amphibian metamorphosis and 21-day fish assay available).

11. **Halauxifen-methyl** (NAS)
Conclusion approved: 17 November 2014
EFSA Journal 2014;12(12):3913 doi:10.2903/j.efsa.2014.3913
http://www.efsa.europa.eu/en/efsajournal/pub/3913.htm

Interim criteria negative.

Results from reproductive toxicity studies did not indicate an endocrine disrupting potential in mammals. In long-term toxicity studies rats and mice showed hypertrophy of the zona glomerulosa cells in the adrenal cortex. The RMS proposed that adrenal effects were not due specifically to endocrine disruption and were secondary to halauxifen renal toxicity. EFSA considered this proposal plausible but mechanistic data are not available.

Some effects which can be linked to a potential endocrine disruption mode of action were observed in the fish reproduction assays. However, these effects were considered to be covered by the presented aquatic risk assessment. Halauxifen-methyl did not indicate an endocrine disrupting potential in mammals; however, no firm conclusion can be drawn regarding fish and birds.

12. **Flumetralin** (NAS)
Conclusion approved: 19 November 2014
EFSA Journal 2014;12(12):3912 doi:10.2903/j.efsa.2014.3912
http://www.efsa.europa.eu/en/efsajournal/pub/3912.htm

Interim criteria negative.

Flumetralin is proposed by the EFSA peer review to be requiring classification as toxic for reproduction category 2.

It was considered that malformations, such as fused sternebrae, and testicular polyangiitis would typically not be considered as related to an endocrine-mediated mode of action. No recognised

endocrine disrupting effects are observed *in vivo* and it is considered unlikely that any of the *in vitro* tests reported in the level 2 of the OECD Conceptual Framework would add any relevant information; therefore flumetralin is unlikely to have endocrine disrupting effects in mammals according to the current scientific state-of-play. No specific concerns on the potential for endocrine disruption have been identified from the available ecotoxicological data set on birds and fish, however no firm conclusion can be drawn.

13. **3-decen-2-one** (NAS)
Conclusion approved: 2 December 2014
EFSA Journal 2015;13(1):3932 doi:10.2903/j.efsa.2015.3932
http://www.efsa.europa.eu/en/efsajournal/pub/3932.htm

Interim criteria negative.

Considering the limited toxicological data package and the presence of positive genotoxicity results, EFSA considers that no reliable reference values can be set for (3E)-3-decen-2-one.

Pending on the conclusion about the genotoxic potential of (3E)-3-decen-2-one and considering the limited data available, a potential for endocrine activity might not have been detected and may need to be further assessed according to the OECD Conceptual Framework.

In the ecotoxicology section, with regard to the endocrine disruption potential, no firm conclusion can be drawn regarding mammals, fish and birds.

14. **Cyhalofop** (variant evaluated cyhalofop-butyl; AIR II)
Conclusion approved: 5 December 2014
EFSA Journal 2015;13(1):3943 doi:10.2903/j.efsa.2015.3943
http://www.efsa.europa.eu/en/efsajournal/pub/3943.htm

Interim criteria negative.

The available studies do not provide any indication of a potential endocrine-mediated effect. Therefore cyhalofop-butyl is unlikely to be an endocrine disrupting compound in mammals. No specific concerns on the potential for endocrine disruption have been identified from the available ecotoxicological data set on birds and fish, however no final conclusion can be drawn.

15. **Metsulfuron-methyl** (AIR II)
Conclusion approved: 5 December 2014
EFSA Journal 2015;13(1):3936 doi:10.2903/j.efsa.2015.3936
http://www.efsa.europa.eu/en/efsajournal/pub/3936.htm

Interim criteria negative.

It is noted that no recognised endocrine disrupting effects were observed *in vivo* and it is considered unlikely that any of the *in vitro* tests reported in the level 2 of the OECD Conceptual Framework would add any relevant information; therefore metsulfuron-methyl is unlikely to be an endocrine disruptor in mammals according to the current scientific state-of-play. However, no firm conclusion can be drawn on birds and fish.

16. **Ferric phosphate** (AIR II)
Conclusion approved: 15 December 2014
FSA Journal 2015;13(1):3973 doi:10.2903/j.efsa.2015.3973
http://www.efsa.europa.eu/en/efsajournal/pub/3973.htm

Interim criteria negative.

There are no indications that ferric phosphate might have endocrine disruption properties in mammals, however no firm conclusion can be drawn regarding birds and fish.

17. ***Pepino mosaic* virus strain CH2, isolate 1906** (NAS)
Conclusion approved: 18 December 2014
EFSA Journal 2015;13(1):3977 doi:10.2903/j.efsa.2015.3977
http://www.efsa.europa.eu/en/efsajournal/pub/3977.htm

Microbial pesticide active substance.

18. **Florasulam** (AIR II)
Conclusion approved: 22 December 2014
EFSA Journal 2015;13(1):3984 doi:10.2903/j.efsa.2015.3984
http://www.efsa.europa.eu/en/efsajournal/pub/3984.htm

Interim criteria negative.

No recognised endocrine disrupting effects were observed *in vivo* and it is considered unlikely that any of the *in vitro* tests reported in the level 2 of the OECD Conceptual Framework would add any relevant information. It is unlikely that florasulam is an endocrine disruptor in mammals; however, no firm conclusion can be drawn regarding fish and birds.

19. **Metalaxyl-M** (AIR II)
Conclusion approved: 19 January 2015
EFSA Journal 2015;13(3):3999 doi:10.2903/j.efsa.2015.3999
http://www.efsa.europa.eu/en/efsajournal/pub/3999.htm

Interim criteria negative.

Regarding the scientific assessment of the potential endocrine disruptive properties of metalaxyl-M, no recognised endocrine disrupting adverse effects were observed in the apical studies and *in vitro* and *in vivo* investigations performed with metalaxyl according to the U.S. Environmental Protection Agency Endocrine Disruptor Screening Program (EDSP), gave no indications of potential endocrine activity of the substance. Therefore metalaxyl-M is unlikely to be an endocrine disruptor in mammals according to the current scientific state-of-play.

The RMS summarised two additional studies in the revised RAR which relate to the assessment of the potential for endocrine disruption (amphibian metamorphosis assay and fish short-term reproduction assay). These studies were not included in the dossier and therefore could not be used for the assessment of the endocrine disruption properties of metalaxyl-M in non-target organisms. Therefore, on the basis of the information available no firm conclusion regarding endocrine disruption in fish and birds could be reached. It is, however, noted that the RMS raised a concern that, on the basis of the results of the fish short-term reproduction assay, endocrine mediated effects could not be excluded.

20. **Pyraflufen-ethyl** (AIR II)
Conclusion approved: 22 January 2015
EFSA Journal 2015;13(2):4001 doi:10.2903/j.efsa.2015.4001
http://www.efsa.europa.eu/en/efsajournal/pub/4001.htm

Interim criteria negative.

No recognised endocrine disrupting effects were observed in the available toxicological studies and it is considered unlikely that any of the *in vitro* tests reported in the level 2 of the OECD Conceptual Framework would add any relevant information. Therefore, pyraflufen-ethyl is unlikely to be an endocrine disruptor in mammals according to the current scientific state-of-play; however, no firm conclusion can be drawn regarding fish and birds.

21. **Rescalure** (NAS)
Conclusion approved: 5 February 2015

EFSA Journal 2015;13(2):4031 doi:10.2903/j.efsa.2015.4031
http://www.efsa.europa.eu/en/efsajournal/pub/4031.htm

Interim criteria negative.

No data are available to demonstrate that rescalure is not carcinogenic, reproductive toxicant or endocrine disruptor, however no further data are required since the predicted exposure from the use as a pesticide will not exceed the natural background exposure levels.

In the ecotoxicology section, no data were available to address the potential endocrine activity of rescalure. However, by considering that the exposure from the representative use was in the range of natural occurrence, no further data are needed.

22. ***Trichoderma atroviride* strain SC1** (NAS)
Conclusion approved: 20 April 2015
EFSA Journal 2015;13(4):4092 doi:10.2903/j.efsa.2015.4092
http://www.efsa.europa.eu/en/efsajournal/pub/4092.htm

Microbial pesticide active substance.

23. **Mandestrobin** (NAS)
Conclusion approved: 22 April 2015
EFSA Journal 2015;13(5):4100 doi:10.2903/j.efsa.2015.4100
http://www.efsa.europa.eu/it/efsajournal/pub/4100.htm

Interim criteria negative.

The experts noted that some effects in reproductive studies could be considered as potentially endocrine mediated, however mechanistic data *in vitro* demonstrated that there was no interaction with oestrogen and androgen receptors as well as no influence on testosterone and oestradiol production. Some effects related to reproductive organs were also observed at high dose levels where systemic toxicity was evident. As a conclusion, the experts considered that mandestrobin is unlikely to be an endocrine disruptor in mammals.

No specific concerns on the potential for endocrine disruption have been identified from the available ecotoxicological data set on birds and fish. However no firm conclusion can be drawn regarding endocrine effects.

24. **Famoxadone** (AIR II)
Conclusion approved: 3 July 2015
EFSA Journal 2015;13(7):4194 doi:10.2903/j.efsa.2015.4194
http://www.efsa.europa.eu/en/efsajournal/pub/4194

Interim criteria negative.

Famoxadone is not classified or proposed to be classified as carcinogenic or toxic for the reproduction category 2. Although a firm conclusion regarding endocrine activity of famoxadone cannot be drawn due to the lack of sensitive investigations referred to above, as no recognised endocrine disrupting effects were observed *in vivo*, it is considered unlikely that the Level 2 and 3 tests of the OECD Conceptual Framework (OECD, 2012) would add relevant information and famoxadone is unlikely to be an endocrine disruptor in mammals according to the current scientific state-of-play. However no firm conclusion can be drawn regarding fish and birds.

# Appendix B – EFSA Conclusions where no concerns were identified regarding endocrine disrupting properties, however where data gaps have been identified specific/relevant to the assessment of endocrine disrupting properties

1. **Thiabendazole** (AIR II)
Conclusion approved: 23 October 2014
EFSA Journal 2014;12(11):3880 doi:10.2903/j.efsa.2014.3880
http://www.efsa.europa.eu/en/efsajournal/pub/3880.htm

Interim criteria negative.

Limited information from the scientific peer-reviewed open literature was identified that indicates a potential for endocrine-mediated effects of thiabendazole which should be further investigated. Relevant scientific peer-reviewed open literature on the potential endocrine activity of thiabendazole, reported as being available, was not provided in the dossier. No investigations have been provided to clarify a possible endocrine-mediated mode of action of thiabendazole. In particular, the Level 2 tests, currently indicated in the OECD Conceptual Framework (OECD, 2012), are missing.

Data gaps were identified in the EFSA Conclusion for 1.) Investigation of the potential for endocrine-mediated effects of thiabendazole (Level 2 tests currently indicated in the OECD Conceptual Framework), and 2.) scientific peer-reviewed open literature on the active substance, and its relevant metabolites, that should include literature on the potential endocrine activity of thiabendazole, reported as being available.

2. **Triasulfuron** (AIR II)
Conclusion approved: 12 December 2014
EFSA Journal 2015;13(1):3958 doi:10.2903/j.efsa.2015.3958
http://www.efsa.europa.eu/en/efsajournal/pub/3958.htm

Interim criteria negative.

The most frequently occurring tumours were noted in the endocrine tissues and mammary gland. No investigations have been provided to clarify a possible endocrine-mediated mode of action of triasulfuron. In particular, the Level 2 tests, currently indicated in the OECD Conceptual Framework, are missing. For the ecotoxicological assessments, no studies were available to address the potential endocrine activity of triasulfuron. Pending on the outcome of the data gap further ecotoxicological tests might be necessary to address the potential endocrine disrupting properties of triasulfuron.

A data gap was identified for investigation of potential endocrine-mediated effects of triasulfuron.

# Appendix C – EFSA Conclusions where concerns have been identified regarding endocrine disrupting properties

1. **Iprovalicarb** (AIR II)
Conclusion approved: 17 March 2015
EFSA Journal 2015;13(4):4060 doi:10.2903/j.efsa.2015.4060
http://www.efsa.europa.eu/en/efsajournal/pub/4060.htm

Interim criteria negative.

Iprovalicarb is proposed by EFSA to be classified as carcinogenic category 2 (no harmonised classification currently available).

Results from long-term toxicity studies in rats indicated that endocrine disruptor mediated effects for iprovalicarb cannot be ruled out. According to the majority of experts (the RMS disagreed) the pattern of tumours observed in rats could be hormone-mediated. The applicant did not provide mechanistic data investigating this mode of action; in particular the Level 2 tests currently indicated in the OECD Conceptual Framework are missing.

For the ecotoxicological assessments, no other studies were available to address the potential endocrine activity of iprovalicarb. Pending on the outcome of the data gap in Section 2, further ecotoxicological tests might be necessary to address the potential endocrine disrupting properties of iprovalicarb.

A data gap was identified for mechanistic data to rule out an endocrine mediated mode of action for the pattern of tumours observed in rats.

A concern was identified for an issue not finalised (section 9.1) as on the basis of the pattern of tumours observed in the long-term toxicity study in rats, it cannot be excluded that iprovalicarb is an endocrine-disruptor.

2. **Bentazone** (AIR II)
Conclusion approved: 8 April 2015
EFSA Journal 2015;13(4):4077 doi:10.2903/j.efsa.2015.4077
http://www.efsa.europa.eu/en/efsajournal/pub/4077.htm

The interim criteria assessment is dependent on an outstanding data gap leading to a concern for an issue not finalised.

Bentazone is proposed by the EFSA peer review to be classified as toxic for reproduction category 2 (no classification regarding this endpoint is included in the current harmonised classification).

Published literature did not identify receptor-mediated (anti)oestrogenic or (anti)androgenic activity *in vitro*. However, the available data are not sufficient to clarify the potential endocrine activity of bentazone. An endocrine-mediated mode of action could not be ruled out regarding the critical effects observed in the developmental toxicity study in rats (increased post implantation loss, reduced number of live foetuses and retarded foetal development). For the ecotoxicological assessments, no specific studies were available to address the potential endocrine activity of bentazone. Pending on the outcome of the data gap, further ecotoxicological tests might be necessary to address the potential endocrine disrupting properties of bentazone.

A data gap was identified for Level 2/3 tests currently indicated in the OECD Conceptual Framework to address the potential for endocrine-mediated mode of action regarding the developmental effects observed in a developmental toxicity study in rats (increased post implantation loss, reduced number of live foetuses and retarded foetal development in the absence of clear maternal toxicity suggesting that classification as reprotoxic category 2 may be appropriate). This data gap is relevant for the interpretation of the interim criteria for the determination of potential endocrine disrupting properties. The RMS disagrees with the data gap, considering unlikely that the increased post implantation loss, reduced number of foetuses and retarded foetal development are caused by an endocrine mediated effect.

A concern was identified for an issue not finalised (section 9.1) as an endocrine-mediated mode of action could not be ruled out regarding the critical effects observed in the developmental toxicity study in rats (increased post implantation loss, reduced number of live foetuses and retarded foetal development), a data gap for the Level 2/3 tests currently indicated in the OECD Conceptual Framework was identified, and the assessment could not be finalised. The data gap is relevant for the interpretation of the interim criteria for the determination of potential endocrine disrupting properties.

3. **Lambda-cyhalothrin** (AIR II)
Conclusion approved: 23 April 2014
EFSA Journal 2014;12(5):3677 doi:10.2903/j.efsa.2014.3677
http://www.efsa.europa.eu/en/efsajournal/pub/3677.htm

Interim criteria negative.

*In vitro* studies from the open literature describe interactions of lambda-cyhalothrin with receptors of the endocrine and immune systems. Considering sperm effects reported in the published literature in mice treated with low doses of lambda-cyhalothrin (tested in a formulation) and the brain morphological changes in the developmental neurotoxicity study, the available data are not sufficient to clarify the potential endocrine activity. In particular, some of the validated tests indicated in the OECD Conceptual Framework are not available. In the ecotoxicology section, insufficient information was available to perform an assessment of whether lambda-cyhalothrin has endocrine disrupting properties that may cause adverse effects on non-target organisms.

Data Gaps were identified 1.) to clarify whether the sperm effects reported in mice have an impact on the outcome of the risk assessment; and 2.) for tests according to the OECD Conceptual Framework to screen the potential endocrine activity.

A concern was identified for an issue not finalised (section 9.1) as an endocrine-mediated mode of action could not be ruled out regarding the brain morphological changes observed in the developmental neurotoxicity study (and possible sperm effects, which have to be clarified in the first place) and the potential for endocrine disrupting effects could not be finalised.

4. **Acibenzolar-S-methyl** (AIR II)
Conclusion approved: 7 May 2014
EFSA Journal 2014;12(8):3691 doi:10.2903/j.efsa.2014.3691
http://www.efsa.europa.eu/en/efsajournal/pub/3691.htm

Interim criteria negative.

Acibenzolar-S-methyl is proposed to be classified as toxic for reproduction category 2 and effects that may be linked to endocrine organs (resulting in impaired development of the cerebellum) have been identified. An endocrine-mediated mode of action could not be ruled out regarding the morphometric changes in the cerebellum of foetuses in the developmental neurotoxicity study. The available toxicological data was not sufficient to clarify the potential endocrine activity; in particular the Level 2 tests indicated in the OECD Conceptual Framework were not available. A data gap was identified for the Level 2/3 tests indicated in the OECD Conceptual Framework, noting that further tests might be necessary pending on the outcome. This data gap is relevant for the interpretation of the interim criteria.

A concern was identified for an issue not finalised (section 9.1) as an endocrine-mediated mode of action could not be ruled out regarding the morphometric changes in the cerebellum of foetuses in the developmental neurotoxicity study.

5. **Flumioxazin** (AIR II)
Conclusion approved: 04 June 2014
EFSA Journal 2014;12(6):3736 doi:10.2903/j.efsa.2014.3736
http://www.efsa.europa.eu/en/efsajournal/pub/3736.htm

Flumioxazin is classified as toxic for reproduction category 1B, in accordance with the provisions of Regulation (EC) No 1272/2008, and toxic effects were observed in endocrine organs (prostate, testes, epididymidis, gestation index, live born pups), and therefore the second interim provision of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 indicates that flumioxazin may be considered to have endocrine disrupting properties, leading to a critical area of concern.

Results from the two-generation reproductive toxicity study indicated that the substance may be an endocrine disrupting compound in mammals. Effects that may be associated with endocrine disruption were an increased incidence of reproductive organ abnormalities (i.e. reduced weight of prostate, testes and epididymidis), reduced gestation index and reduction in live born pups at 18.9 mg/kg bw per day. As all the endpoints are apical, it is difficult to discern mechanism of action from this study alone. Available data are then not sufficient to rule out an endocrine-mediated mode of action

The Conclusion identified a data gap for the level 2 tests indicated in the OECD Conceptual Framework, noting that further testing might be necessary based on the outcomes.

A concern was identified for an issue not finalised (section 9.1) as an endocrine-mediated mode of action could not be ruled out regarding reproductive organ abnormalities, reduced gestation index and reduction in live born pups in the two-generation study.

Critical areas of concern were identified (section 9.2) as 1.) flumioxazin has harmonised classification and labelling as toxic for reproduction category 1B; and 2.) flumioxazin may be an endocrine disruptor according to the interim criteria since it has toxic effects on reproductive organs.

At time of drafting the Conclusion, ECHA was reassessing the classification and labelling of flumioxazin. The ECHA RAC subsequently reconfirmed flumioxazin as toxic for reproduction category 1B. A further application for reclassification has been submitted and, as of June 2015, ECHA is awaiting further data submission.

6. **Amitrole** (AIR II)
Conclusion approved: 19 June 2014
EFSA Journal 2014;12(7):3742 doi:10.2903/j.efsa.2014.3742
http://www.efsa.europa.eu/en/efsajournal/pub/3742.htm

Amitrole is classified as toxic for reproduction category 2 and toxic effects were observed in endocrine organs (thyroid). It should be noted that EFSA is proposing classification in category 1B H360 'May damage the unborn child'. Data gaps were identified in the EFSA Conclusion, including the concern related to effects of amitrole on the thyroid glands of birds; and the concerns for potential endocrine mediated effects in fish.

Critical areas of concern were identified (section 9.2) as 1.) the peer review proposed a classification for amitrole as toxic for reproduction category 1B, H360 'May damage the unborn child'; and 2.) amitrole may be considered to have endocrine disrupting properties according to the interim criteria since as is classified as toxic for reproduction category 2 and toxic effects were observed in endocrine organs (thyroid).

The relevant mammalian NOAEL is based on thyroid effects and endocrine disrupting properties can also be inferred from the observation of adverse effects on thyroid in birds.

7. **Flutianil** (NAS)
Conclusion approved: 28 July 2014
EFSA Journal 2014;12(8):3805 doi:10.2903/j.efsa.2014.3805
http://www.efsa.europa.eu/en/efsajournal/pub/3805.htm

The EFSA Peer Review experts suggested classification of flutianil as carcinogenic category 2 and reproductive toxicant (for the development) category 2 (no harmonised classification is available); furthermore, adverse effects have been observed on endocrine organs in different species and timelines (seminiferous tubules atrophy, testes softening and atrophy in mice, seminiferous tubules atrophy and cellular infiltrate of prostate in dogs, reduced number of implantation sites and pups

delivered, increased histopathological findings and increased uterus weight, decreased ovary weight and atrophy, and carcinogenic effect on the pancreatic islet system in rats).

An endocrine-mediated mode of action could not be ruled out regarding the adverse effects that have been observed on endocrine organs in different species and timelines and a data gap was identified for the Level 2 tests indicated in the OECD Conceptual Framework, noting that further tests in the toxicological and ecotoxicological areas might be necessary pending on the outcome.

A critical area of concern was identified (section 9.2) with regard to the interim provisions for active substances that shall be considered to have endocrine disruption properties considering the suggested classification of flutianil as carcinogen category 2 and reproductive toxicant (for the development) category 2 by the EFSA peer review (no harmonised classification is available), and that flutianil produced adverse effects on endocrine organs across different species and timelines.

8. **2,4-D** (AIR II)
Conclusion approved: 7 August 2014
EFSA Journal 2014;12(9):3812 doi:10.2903/j.efsa.2014.3812
http://www.efsa.europa.eu/en/efsajournal/pub/3812.htm

Interim criteria negative.

*In vivo* studies provide evidence for endocrine effects produced by 2,4-D exposure on the thyroid hormone system, i.e. decreased levels of T4 and T3 and increased TSH levels, correlated with increased thyroid weight and macroscopic observation of (thyroid) masses at higher dose levels (150 mg/kg bw per day), and histopathological findings (increased incidence of parafollicular cell nodular hyperplasia). There was no indication of potential androgenic, anti-androgenic, oestrogenic or correlated adverse effects on the reproduction and reproductive organs in an extended one-generation study (the results of which were however not completely available to the peer review). Considering the known correlation of the thyroid hormone concentrations with adverse effects on other organ systems, such as the brain development and its relevance to humans, a data gap is identified for the complete set of measurements included in the extended one-generation study. It is further noted that increased adrenal weight and cortical hypertrophy were observed in a 90-day study in rats treated with 100 mg/kg bw per day and higher dose levels, which may indicate an effect on the HPA axis, however the current state of science is limited regarding possible effects in *in vivo* studies that are not tailored to test the adrenal function. Therefore a data gap for a steroidogenesis assay has been identified.

A data gap was identified considering the uncertainties regarding the endocrine disruption potential of 2,4-D, the complete study results from the extended one-generation and a steroidogenesis assay study should be submitted, noting that further toxicological and ecotoxicological tests might be necessary.

A concern was identified for an issue not finalised (section 9.1) as adverse effects on endocrine organs have been observed in apical studies that may be endocrine-mediated, which should be further clarified to assess their relevance on the developing offspring (issue not finalised).

9. **Terpenoid blend QRD-460** (NAS)
Conclusion approved: 20 August 2014
EFSA Journal 2014;12(10):3816 doi:10.2903/j.efsa.2014.3816
http://www.efsa.europa.eu/en/efsajournal/pub/3816.htm

No valid studies were submitted for defining the endocrine disruption potential. Overall, the toxicological data package was considered too limited to set reference values.

A data gap was identified for the toxicological profile, including endocrine disrupting potential.

A critical area of concern was identified (section 9.2) as the toxicological database was considered incomplete and not sufficient to identify the hazard of the active substance and no reference values could be established.

10. **Pymetrozine** (AIR II)
Conclusion approved: 22 August 2014
EFSA Journal 2014;12(9):3817 doi:10.2903/j.efsa.2014.3817
http://www.efsa.europa.eu/en/efsajournal/pub/3817.htm

Pymetrozine has harmonised classification as carcinogen category 2. Pymetrozine is proposed by the EFSA peer review experts to be classified as reproductive toxicant category 2 (H361f Suspected of damaging fertility and H361d Suspected of damaging the unborn child).

An endocrine-mediated mode of action could not be ruled out regarding adverse effects observed in mammalian toxicity studies, and a data gap has been identified for the Level 2 tests indicated in the OECD Conceptual Framework, noting that further tests in the toxicological and ecotoxicological areas might be necessary pending on the outcome.

A critical area of concern was identified (section 9.2) with regard to the interim provisions for active substances that shall be considered to have endocrine disrupting properties on the basis that pymetrozine has harmonised classification as carcinogen category 2 and the EFSA peer review proposed classification as reproductive toxicant category 2, and that pymetrozine produced adverse effects on endocrine organs across different species and timelines.

It is noted that the scientific assessment for potential endocrine disruption properties of pymetrozine could not be finalised.

11. **Flupyrsulfuron** (variant evaluated flupyrsulfuron-methyl-sodium; AIR II)
Conclusion approved: 22 October 2014
EFSA Journal 2014;12(11):3881 doi:10.2903/j.efsa.2014.3881
http://www.efsa.europa.eu/en/efsajournal/pub/3881.htm

Flupyrsulfuron-methyl-sodium was proposed to be classified as carcinogen category 2 (H351) and as reproductive toxicant category 2 by the Pesticides Peer Review experts' meeting and by EFSA, respectively.

No recognised endocrine disrupting effects were observed *in vivo* and it is considered unlikely that any of the *in vitro* tests reported in the level 2 of the OECD Conceptual Framework would add any relevant information; therefore flupyrsulfuron-methyl-sodium is unlikely to be an endocrine disruptor in mammals according to the current scientific state-of-play, however no firm conclusion can be drawn regarding birds and fish.

A critical area of concern was identified (section 9.2) with regard to the interim provisions for active substances that shall be considered to have endocrine disrupting properties based on the proposed classification as carcinogen category 2 and reproductive toxicant category 2.

12. **Tricyclazole** (NAS)
Conclusion approved: 11 February 2015
EFSA Journal 2015;13(2):4032 doi:10.2903/j.efsa.2015.4032
http://www.efsa.europa.eu/en/efsajournal/pub/4032.htm

Interim criteria negative.

Results from short-term and reproductive toxicity studies indicated that tricyclazole may be an endocrine disrupting compound in mammals. Effects that may be associated with endocrine disruption were mainly reproductive organ weight changes and effects on sexual maturation. The effects on sexual maturation were also observed in animals showing decreased body weight gain, but the dose levels were lower than the dose exhibiting reproductive organ weight changes. As all the endpoints are apical, it is difficult to discern mechanism of action from these studies alone. Available data are then not sufficient to rule out an endocrine-mediated mode of action; in particular the Level 2 tests currently indicated in the OECD Conceptual Framework are missing. Pending on the results of these tests, further studies might be required.

It is noted that some indications for potential effects of tricyclazole on reproductive organs (i.e. ovary regression, small testis) were also noted from the available long-term studies on birds in high doses.

However, these findings did not allow a firm conclusion to be drawn. A fish study from the open literature indicated an increased vitellogenin level at a low concentration (considerably below the LC50 or the available reproductive NOEC). Seven or 14 days after the exposure period the vitellogenin level in fish was still significantly higher than in the control fish. Some shortcomings of this study were noted by the RMS, who considered this study as not reliable. Overall, it was concluded that potential endocrine disruption properties of tricyclazole was indicated by the available data and there were not enough evidence to exclude this potential hazard to non-target organisms. Therefore a data gap was identified for further investigations of the potential endocrine disruption properties of tricyclazole. It is noted that the conclusions on potential endocrine disrupting properties and the data gap has not been agreed by the RMS.

The data gap was identified for investigation of potential endocrine-mediated effects of tricyclazole, following the OECD Conceptual Framework for terrestrial vertebrates and for aquatic organisms.

A concern was identified for an issue not finalised (section 9.1) since, on the basis of effects on reproductive organ weights and sexual maturation in mammals, it cannot be excluded that tricyclazole is an endocrine disruptor. Additionally, some observations on reproductive organs of birds and increased vitellogenin level in fish were also noted.

13. **Benzovindiflupyr** (NAS)
Conclusion approved: 6 March 2015
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Interim criteria negative.

In a two-generation reproductive toxicity study, effects on the reproductive system, characterised by reduced percentage of normal sperm in males of the P generation, reduced number of growing follicles and corpora lutea, and increased incidence of lactational diestrus in females of both P and F1 generations were observed at parental toxic doses (reduced parental and offspring's body weight/body weight gain, and liver toxicity). Delay of sexual maturation was also observed in offspring, while an increased incidence of hypertrophy of the adrenal zona glomerulosa was observed in adult females and increased incidence of cell hypertrophy in the pars distalis of the pituitary were observed in adult males at the top dose. Although the reduced body weight may be an explanation for part of the reproductive effects observed, the majority of experts agreed that there was insufficient evidence demonstrating that the mode of action was not endocrine-mediated and a data gap was identified for the Level 2 tests currently indicated in the OECD Conceptual Framework, noting that further tests might be necessary pending on the outcome. The RMS did not support this data gap.

For the ecotoxicological assessments, no further studies were available to address the potential endocrine activity of benzovindiflupyr. Pending on the outcome of the data gap, further ecotoxicological tests might be necessary to address the potential endocrine disrupting properties of benzovindiflupyr.

A data gap was identified for Level 2 tests currently indicated in the OECD Conceptual Framework, to address the potential for endocrine-mediated mode of action regarding the reproductive effects observed in a two-generation reproductive toxicity in rats (reduced percentage of normal sperm in males of the P generation, reduced number of growing follicles and corpora lutea, and increased incidence of lactational diestrus in females of both P and F1 generations, delay in sexual maturation and histopathological findings -hypertrophy- in the pituitary and adrenals). Pending on the outcome further tests might be necessary.

A concern was identified for an issue not finalised (section 9.1) on the basis of the effects observed in the reproductive system of the two-generation reproductive toxicity study (reduced percentage of normal sperm in males of the P generation, reduced number of growing follicles and corpora lutea, and increased incidence of lactational diestrus in females of both P and F1 generations, delay of sexual maturation in offspring, while an increased incidence of hypertrophy of the adrenal zona glomerulosa was observed in adult females and increased incidence of cell hypertrophy in the pars distalis of the pituitary were observed in adult males at the top dose), it cannot be excluded that benzovindiflupyr is an endocrine disruptor.

14. **Thifensulfuron-methyl** (AIR II)
Conclusion approved: 6 July 2015
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http://www.efsa.europa.eu/en/efsajournal/pub/4201

Thifensulfuron-methyl is proposed to be classified as toxic for reproduction category 2 by the EFSA peer review. Toxic effects were observed in endocrine organs (i.e. mammary gland tumours in long-term toxicity study in rats). With regard to the scientific assessment, results from long-term toxicity studies in rats indicated that endocrine mediated effects for thifensulfuron-methyl cannot be ruled out. Mammary gland tumours observed in rats could be hormone-mediated. The applicant did not provide mechanistic data investigating the mode of action; in particular the Level 2 tests currently indicated in the OECD Conceptual Framework (OECD, 2012), and analysed in the EFSA Scientific Opinion on the hazard assessment of endocrine disruptors (EFSA Scientific Committee, 2013) are missing. Although during the experts' meeting mammary gland tumours were considered not relevant for classification and labelling purposes but treatment-related for the risk assessment, EFSA considered the lack of mechanistic data on the possible endocrine-mediated mode of action for mammary gland tumours observed in rats as a data gap and identified it as an issue that could not be finalised. The RMS did not agree.

A data gap for mechanistic data to rule out an endocrine mediated mode of action for mammary gland tumours observed in rats was identified.

A concern was identified for an issue not finalised (section 9.1) as an endocrine-mediated mode of action regarding the occurrence of mammary gland tumours observed in the long-term toxicity study in rats cannot be excluded.

A critical area of concern was identified (section 9.2) with regard to the interim provisions for active substances as thifensulfuron-methyl may be considered to have endocrine disrupting properties according to the interim criteria for the determination of endocrine disrupting properties since it has toxic effects on endocrine organs and it is proposed to be classified as toxic for reproduction category 2 by the EFSA peer review, requiring consideration by risk managers.

15. **Isoproturon** (AIR II)
Conclusion approved: 28 July 2015
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http://www.efsa.europa.eu/en/efsajournal/pub/4206

Isoproturon has harmonised classification as carcinogenic category 2 and is proposed to be classified as toxic for reproduction category 2 by the EFSA peer review. Results from the reproductive toxicity studies indicated that isoproturon may be an endocrine disrupting compound in mammals. Effects on fertility and overall reproductive performance in the two-generation reproductive toxicity studies in rats might be endocrine-mediated. Scientific literature indicated that isoproturon might have mild anti-estrogenic and anti-androgenic activity. Available data are not sufficient to rule out an endocrine-mediated mode of action; in particular the Level 2 tests, which are currently indicated in the OECD Conceptual Framework and analysed in the EFSA Scientific Opinion on the hazard assessment of endocrine disruptors, are missing.

For the ecotoxicological assessments, one peer reviewed paper was available in RAR concerning the potential endocrine activity of isoproturon. The available study used a recombinant yeast screen to detect receptor mediated (anti-) estrogenic and (anti-) androgenic activity; cultured Xenopus oocytes were used to measure effects on the ovulatory response and ovarian steroidogenesis. Some antiestrogenic and antiandrogenic activities were reported in the study, along with inhibited ovulation without altering hormone levels. This *in vitro* study was considered as relevant supporting information, but the reported results are not considered strong evidence of endocrine disruption activity. Further ecotoxicological tests might be necessary to address the potential endocrine disrupting properties of isoproturon.

A data gap was identified for investigation of potential endocrine-mediated effects of isoproturon, following the OECD Conceptual Framework, using a stepwise approach from Level 2 for mammalian toxicology

A critical area of concern was identified (section 9.2) with regard to the interim provisions as isoproturon is classified as carcinogenic category 2 and proposed to be classified as toxic for reproduction category 2 and therefore the interim provisions concerning human health for the consideration of endocrine disrupting properties are met. With regard to the scientific risk assessment, results from reproductive toxicity studies indicated that isoproturon may be an endocrine disrupting compound in mammals.