Cumulative risks from combined exposure to multiple pesticide residues in fruit and vegetables

Project Kennis- en modelkoppelingen voor borging voedselveiligheid in de groenten en fruit sector

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Summary

Cumulative intake of mixtures of pesticide residues through consumption of fruits and vegetables can lead to health risks that are not controlled under the current EU system using only the maximum residue limit (MRL) and acute reference dose (ARfD) for single substances on single food products. In a collaboration between the European Commission, the European Food Safety Authority and member states, methods have been developed to implement Regulation (EC) No 1107/2009 that states that plant protection products should not have harmful health effects, also taking into account possible cumulative and synergistic effects. These methods have been implemented in the Monte Carlo Risk Assessment (MCRA) software which is available for national and European public institutions to perform pesticides mixture risk assessment.

This report describes a web portal that was developed to allow cumulative risk assessment by the Dutch private vegetable and fruit sector organised in the Foundation Food Compass using MCRA with the monitoring data collected in the Food Compass database.

A case study was performed to combine Food Compass monitoring data from the years 2013-2020 with consumption data of children from the Dutch national food consumption survey. The main interest was to assess the risk of cumulative exposure due to the combined intake of multiple pesticide residues in their diet. If potential risks were observed, it was of interest to know which residues and foods contributed to such risks and if there were trends over the period of the monitoring. The results of the cumulative assessments were compared to an analysis of limit value exceedances at the level of single measurement results.

The results presented in this report are provisional due to insufficient availability of data. Some of the analytical scopes in the Food Compass database could not be linked appropriately to the active substance groups used for cumulative risk assessment. Food processing steps, such as peeling or juicing of citrus fruits, are expected to reduce residue levels, but the collection of processing factors to account for this in the calculations was incomplete. Limit values are sometimes changed, and recently artificially low limit values were introduced in the sectoral system to generate alerts for substances which have been classified as genotoxic. Such data will then also have an artificial impact on the cumulative assessments.

The conventional analysis of single residue measurements showed that 1-3% of residue levels exceeded the MRL throughout the period 2013-2020. However, the frequency of conservatively estimated exceedances of the ARfD using the PRIMo 3.1 model decreased from around 3% to below 1% in the same period. It was also found that ARfD exceedances did often occur without an associated MRL exceedance.

The cumulative assessments indicated that the probability of a critical acute exposure was estimated to be in the range 0.1- 0.4% during the period 2013-2019 (the results for 2020 were affected by an artificial low ARfD value and are therefore not useful to estimate real risk). Nevertheless, the main identified risk drivers were occurrences of chlorpyrifos and chlorpyrifos-methyl in some citrus fruit products such as juices for which no account of processing effects was included in the assessment due to lack of validated data. Including validated processing factors for citrus fruit products as they are consumed in practice will result in more realistic critical probabilities which are expected to be lower. It is planned to update the current trend analysis in further work.

1 Introduction

1.1 Overview and aim of the study

A case study was performed to combine Food Compass monitoring data from the years 2013-2020 with consumption data of Dutch children. The main interest is to find if there could have been cumulative exposure due to the combined effects of multiple pesticide residues in their diet. If so, it was of interest to know which residues and foods contributed to such risks and if there were trends over the period of the monitoring. The results presented in this report are provisional due to insufficient availability of certain data.

This case study is part of a project to use private sector pesticide residue monitoring data for cumulative risk assessment using public food consumption data and the publicly developed Monte Carlo Risk Assessment (MCRA) web platform. For linking private and public data the IPGF portal was developed in the context of a public-private partnership project between WUR Biometris, financed from public means, and Food Compass, who contributed the monitoring data. IPGF is the abbreviation of 'Impactanalyse Pesticiden in Groenten en Fruit' ('Impact analysis Pesticides in Fruit and Vegetables').

The primary stakeholders of this work are the project partners WUR Biometris and Foundation Food Compass. WUR Biometris aims to build up expertise regarding the linkage of knowledge (seen as data) and models across the internet in an interoperable manner, and to promote the distribution of knowledge about performing cumulative risk assessments using the MCRA software. Food Compass aims to be able to perform EU compatible cumulative risk assessments on Food Compass samples per period, compare results across periods (trend analysis), to use the results for risk communication to Food Compass and GroentenFruit Huis colleagues, and possibly to Food Compass participants and/or retail representatives regarding the health impact of cumulative pesticide exposure. A secondary objective is to prepare for analyses at the sample level by Food Compass participants in the context of quality control or early warning systems.

The longer-term aim is to create better links between private and public knowledge management systems in the interest of open and transparent risk assessment.

1.2 Development of a web portal to link private and public data

The IPGF web portal is developed to analyse the concentration levels of substance residues found on the fresh fruit and vegetable samples recorded by Food Compass and assess the human health risk associated with consumption of fruits and vegetables with such residue concentration levels. Users of the portal are able to evaluate the substance residue concentration levels of Food Compass samples and 1) compare these levels with legal residue limits (MRLs), 2) compare these levels with non-statutory retail requirements, and 3) evaluate the potential human health risk from exposure to these concentration levels using different assessment models. The latter comprises both the single-substance, deterministic IESTI calculations, and more realistic multi-substance, probabilistic cumulative exposure and risk calculations as available in MCRA. In addition, users are able to evaluate the trends of the substance residue concentration levels and their potential associated impact on human health over time.

The IPGF portal retrieves the Food Compass concentration data from the Food Compass database, which can be done via the Food Compass web API. These

concentration data are validated, curated, and linked with other data as a prerequisite for performing the analyses. E.g., linking of food codes and curation of analytical scopes. Therefore, the portal includes a data management module to allow for data inspection and, if needed, data curation of some identified data types.

The potential users of the IPGF portal are Food Compass and GroentenFruit Huis staff members, Food Compass participants (for single sample analyses), and interested stakeholders in the Netherlands or in Europe. To allow usage by a broad audience, the portal has been developed in English.

2 Data

2.1 Monitoring data (Food Compass)

Food Compass monitoring data for the years 2012-2020 were obtained from the Food Compass Web API in December 2021. The samples used in the case study were gathered from all Food Compass sampling programs: "Monitoring (M)", "EWRS (X)", "NVWA (N)", "Bedrijfseigen monster (E)" and "Aanvullend monster (A)".

Food Compass food sample reports were retrieved for each batch and aligned with the known laboratory scopes. The latter is required because the sample reports contain only information on the positive substance concentrations and not the substance measurements that were below the detection limit. The Laboratory scope lists provide information on all substances measured by a given analytical method, including the applicable detection limits. The import step also contains some validation and curation steps to detect and, if possible, restore inconsistencies between the known laboratory scopes and the reported sample substance concentrations. Inconsistencies are reported as critical or non-critical measurement inconsistencies (reflecting individual substance measurements within a sample) and inconsistencies in linking the reported analysis methods with the known analytical scopes.

For the cumulative exposure assessments, the imported samples are converted to the MCRA concentration data format. The table below shows the results of the sample imports forming the concentration data for the batch exposure assessments.

Table 1 Food samples of the batches imported from Food Compass.

Year	Total samples	Number of sampled food products	Samples[1] with invalid analytical scopes	Samples[1] with invalid measurements	Samples with non-critical measurement inconsistencies	Samples available for cumulative analyses	Samples with positive concentrations for cumulative analyses
2013	4376	171	259	470	390	4329	2622
2014	3771	158	424	396	394	3626	2389
2015	3732	166	134	514	408	3650	2270
2016	3244	160	105	351	420	3226	2129
2017	3372	160	640	446	329	3366	2014
2018	2165	147	354	343	267	2120	1321
2019	1710	156	460	286	228	1564	1051
2020	1472	143	263	238	182	1387	959

[1] These samples may still contain valid data for other analysis methods/substances.

Residue monitoring data were listed with 3 laboratories. The complete list of 37 laboratories had in total 675 different laboratory scopes.

2.2 Catalogues of substances and food products (GroentenFruit Huis)

2.2.1 Substances

The substance catalogue was downloaded from the GroentenFruit Huis WebAPI on 01-12-2021. Substances are identified by GroentenFruit Huis codes, which are mostly the same as CAS codes but are adapted in some cases. The substance catalogue was

adapted and stored in the IPGF portal by mapping the GroentenFruit Huis codes to CAS codes and then to EFSA PARAM codes. The final substance catalogue has 1411 entries.

2.2.2 Foods

The food catalogue was downloaded from the GroentenFruit Huis WebAPI on 01-12-2021. The food catalogue was adapted and stored in the IPGF portal by mapping to EFSA MATRIX codes which were used as modelled foods for cumulative assessments. The final food catalogue has 495 entries.

2.3 Limit values (GroentenFruit Huis)

A database with MRL and ARfD values for substance/food combinations is maintained at the GroentenFruit Huis portal and is periodically synchronised with the EU Pesticide database.

For the sample calculations, the GroentenFruit Huis web service is used to get the MRL for positive substance concentrations of the samples.

Acute Reference Dose (ARfD) values used in this study both for single sample calculations and batch calculations were a combination of values obtained from the GroentenFruit Huis web service on 01-12-2021 (the most recent values) and values that were obtained from earlier versions of the GroentenFruit Huis acceptance environment. All ARfD values were labelled with a 'Valid from' date. Some examples are shown in Table 2.

In the regulatory system, ARfD values are only set for active substances that are supposed to have no health effects below a certain threshold. ARfD values are not derived for active substances with known or presumed health effects due to a non-threshold mode of action, such as substances that are carcinogenic, mutagenic, or toxic for reproduction (CMR substances). In practice, this means that such active substances are or will be excluded from the market. However, some of these substances were allowed in previous years and are therefore found in historical monitoring data. To obtain a clear alert for current use, GroentenFruit Huis has decided to include an artificial very low value for such substances. Relevant for the current case study, an artificial low ARfD of 0.0001 mg/kg bw/day was set for Chlorpyrifos and Chlorpyrifos-methyl per 13-11-2020.

Table 2. Examples Acute Reference Doses for selected substances.

Substance code	Substance name	ARfD (mg/kg bw/day)	valid from
133062	captan	0.3	11-07-2008
101213	chlorprofam	0.5	02-03-2004
2921882	chlorpyrifos	0.005	07-04-2014[2]
2921882	chlorpyrifos	0.0001[1]	13-11-2020
5598130	chlorpyrifos-methyl	0.1	21-10-2005
5598130	chlorpyrifos-methyl	0.0001[1]	13-11-2020
16672870	ethephon	0.05	02-12-2008
35554440	imazalil	0.05	04-03-2010
91465086	lambda-cyhalothrin	0.005	01-04-2016[2]
2032657	methiocarb	0.013	07-02-2007
60207901	propiconazole	0.3	17-07-2003
60207901	propiconazole	0.1	19-06-2019
175013180	pyraclostrobin	0.03	10-03-2004
107534963	tebuconazole	0.03	25-09-2008

[1] 0.0001 mg/kg bw/day is an artificial low value meant to generate ARfD exceedance signals if this substance is found. The substance has been declared to be genotoxic mutagenic and therefore is no longer allowed according to the interpretation by NVWA.

[2] Is some cases the earliest Valid from date available was later than the starting date of the trend analysis, i.e. 01-01-2013. In those cases the earliest available ARfD value was used.

2.4 Additional data for CRA used in MCRA

2.4.1 Overview data for cumulative risk assessment

The data required for cumulative risk assessments in MCRA originate from different sources. The IPGF portal feeds parts of the data to MCRA, for example the concentration data, and specifies the data to be used for calculation jobs. Some data are already available at MCRA and can be used in assessments by just referencing these datasets, for example the consumption data used for the assessments. The table below summarizes that data needs for performing the cumulative risk assessments.

Table 3 Data for cumulative risk assessment in MCRA.

Data type	Data	Coding systems	Data origin	Recoding needed
Foods (and processing types)	All food products measured in the concentration data and all food products with consumptions in the Raw Primary Commodity consumption data.	EFSA MATRIX food product codes with processed foods coded with FoodEx2 facet codes for the processing types.	MCRA	*No*
Substances	All FC substances with additional PARAM codes from CAG definitions and residue definitions	Substance codes following the FC CAS coding system.	IPGF portal / original data at GroentenFruit Huis	*No*
Effects	Acute organ level CAGs, derived from Nielsen et al. (2012).	Custom effect coding system used in the CAGs dataset.	MCRA	*No*
Active substances (assessment group memberships)	Acute organ level CAGs, derived from Nielsen et al. (2012).	Substance codes following the FC CAS coding system and the custom effect coding system used in the CAGs dataset.	MCRA	EFSA PARAM to FC Cas
Consumptions	RPC consumption data of: • NL VCP child population 2005-2006 (2-6yr) • NL VCP general population (age 7-69) 2007-2010 • NL VCP elderly population (70+ yr) 2010-2012	EFSA MATRIX food product codes with processed foods coded with FoodEx2 facet codes for the processing types.	MCRA	*No*
Concentrations (background)	FC concentration data (specific sample selection unknown)	EFSA MATRIX food product codes obtained by mapping of the FC food codes. Substance codes following the FC CAS coding system.	IPGF portal / original data at FC	FC food codes to EFSA MATRIX codes
Residue definitions	Residue definitions from EFSA/RIVM-FPA	Substance codes following the FC CAS coding system.	IPGF portal	EFSA PARAM to FC Cas

Processing factors	Import of RIVM processing factors	EFSA MATRIX food product codes. FoodEx2 facet codes for the processing types. Substance codes following the FC CAS coding system.	IPGF portal / original data at MCRA	EFSA PARAM to FC Cas
Unit variability factors	EFSA/RIVM-FPA Tier II unit variability factors	EFSA MATRIX food product codes. FoodEx2 facet codes for the processing types.	MCRA	*No*
Food translations	Food translations containing the RPC yield factors for processed foods	EFSA MATRIX food product codes. FoodEx2 facet codes for the processing types.	MCRA	*No*
Hazard characterisations	ARfDs from GroentenFruit Huis	Substance codes following the FC CAS coding system.	IPGF portal / original data at GroentenFruit Huis	*No*

2.4.2 Health effects and assessment groups data

Cumulative exposure assessments were performed for 15 adverse effects at organ level, with cumulative assessment groups (CAGs) of varying sizes. These CAGs were proposed by Nielsen et al. (2012) in a scientific opinion for the EFSA Panel on Plant Protection Products and their Residues (PPR). It should be noted, that EFSA has started a process for more data collection and an updated definition of CAGs, but this has until now resulted in just three CAGs for acute effects (EFSA 2019c, 2020). For illustrative purposes the 15 CAGs from Nielsen et al. (2012) were selected in the context of this case study.

An MCRA effects and assessment groups dataset is created from the CAGs proposed by Nielsen et al. (2012). The acute Effects and CAGs at CAG level 1 (organ level) will be used for the analyses. I.e., an analysis will be done for each level 1 effect/CAG. The CAG dataset is available on a share in MCRA and a local copy of this data is maintained within the portal for administration/quality checking.

Table 4 Health effects and assessment groups for cumulative risk assessment.

Effect	Description	Substances in CAG	Substances with missing ARfD	Index substance
Adrenal	Adverse effects on the adrenal gland	10		fosthiazate (98886443)
Bone	Adverse effects on the bone marrow	9		bromoxynil (1689845)
Cardiovascular	Adverse effects on the cardiovascular system	10		formetanate (22259309)
Developmental	Adverse developmental effects	110	fenoxaprop-P-ethyl	oxamyl (23135220)
Eye	Adverse effects on the eye	39		oxamyl (23135220)
Haematological	Adverse effects on the haematological system	68	fenoxaprop-P-ethyl	methomyl (16752775)
Kidney	Adverse effects on the kidney	47	fenoxaprop-P-ethyl	oxamyl (23135220)
Liver	Adverse effects on the liver	100	fenoxaprop-P-ethyl	dinocap (39300453)
Muscle	Adverse effects on the muscle	10		fosthiazate (98886443)
Nervous	Adverse effects on the nervous system	54		oxamyl (23135220)

Parathyroid	Adverse effects on the parathyroid	5		methconazole (125116236)
Skeleton	Adverse effects on the skeleton	3		tetraconazole (112281773)
Spleen	Adverse effects on the spleen	9		tetraconazole (112281773)
Thyroid	Adverse effects on the thyroid	32		dinocap (39300453)
Urinary	Adverse urinary effects	14		flusilazole (85509199)

2.4.3 Consumption data

Assessments use the consumption data from three Dutch food surveys (VCP) for three different subpopulation the child population (2-6yr) 2005-2006, the general population (age 7-69) 2007-2010, and the elderly population (70+yr) 2010-2012. In the current report only the consumption data for children have been used to have a first demonstration of the results. The data has been provided by RIVM to EFSA and has been provided again by EFSA in the form of raw primary commodity consumption data (RPC, EFSA 2019a), meaning that the consumptions are expressed in terms of the raw (measured) food products.

A number of modelled foods found in the foods catalogue did not match/align with the RPF consumption data and were therefore not included in the cumulative assessments (Table 5).

Table 5 Modelled/measured foods not matched with the consumption data.

Modelled food (MATRIX) code	Modelled food name
P0252030A	Chards/beet leaves
P0163050A	Granate apples/pomegranates
P0161060A	Kaki/Japanese persimmons
P0110040A	Limes
P0231040A	Okra (lady's fingers)
P0161050A	Carambolas
P0162040A	Prickly pears
P0213050A	Jerusalem artichokes
P0213060A	Parsnips
P0213090A	Salsifies
P0213110A	Turnips
P0232990A	Other cucurbits with edible peel
P0233990A	Other cucurbits with inedible peel
P0255000A	Witloofs/Belgian endives
P0840020A	Ginger
P0163040A	Papayas
P0260030A	Peas (with pods)
P0252020A	Purslanes
P0130030A	Quinces
P0270070A	Rhubarbs
P0251060A	Roman rocket/rucola
P0212020A	Sweet potatoes
P0256100A	Tarragon

The RPC consumption datasets are available for use on a share on MCRA and a reference to these dataset is sufficient for using it is an MCRA cumulative exposure analysis from the IPGF portal.

2.4.4 Processing factor data

The EFSA database of processing factors prepared by Scholtz et al. (2018) serves as the basis of the processing factors used in this case study. However, this dataset contains only a limited amount of substance-food combinations. In this project, we noticed in initial assessments that imazalil on citrus fruits was identified as an important risk driver, but that peeling of citrus fruits is expected to remove most of the imazalil residues. More processing factors are available in a Dutch database maintained at RIVM in the last updated version of 2020[1], but the latter database is not organised using the harmonised substance and food codes at EFSA and could therefore not be used automatically. For the analyses reported here, the EFSA processing factor data were extended with processing factors for imazalil in citrus food as were available from the RIVM database.

For preparing the dataset, the EFSA PARAM codes used by the original processing factors dataset of Scholtz et al. (2018) were mapped to the Food Compass substance coding system (based on CAS) using the mapping as available in the internal substances catalogue.

A data share in MCRA contains this generated dataset processing factor dataset, which can be referenced for use in cumulative exposure assessments in MCRA.

2.4.5 Unit variability data

The same unit variability are used as used in the Tier II calculations in van Klaveren et al. (2019a) and EFSA (2020a). It should be noted that these studies focused on a subset of 30 food products and no unit variability factors are available for the food products not considered by these studies. The unit variability factors dataset is available for use on a share on MCRA and a reference to this dataset is used within the cumulative exposure analyses in MCRA.

2.4.6 Residue definition data

The cumulative exposure assessments are performed at the level of so-called active substances, which are the substances that are associated with the effects and CAGs and for which potency information is assumed to be available. Substance conversions are used for converting measured substance concentrations (such as sum-substance measurements) to active substance concentrations. The substance conversions are obtained from the Food Compass substances hierarchy, which is included in the substances catalogue.

For each sum-substance that is linked to one or more active substances, substance conversion rules are added to map concentration values of the sum-substances to active substance concentrations. These conversion rules specify the proportion of measurements of the sum-substance measurements that can be assumed to translate exclusively to a concentration of each active substance, and a conversion factor to translate the concentration of the sum-substance to a concentration of the active substance. Due to a lack of data, a conversion factor of 1 is assumed for all rules and equal proportions of 1/n are assumed for all active substances linking to the sum-substance, with n being the total number of substances linking to the sum-substance. As an example, consider the dithiocarbamates substances in the table below. The sum-substance (dithiocarbamaten (som als CS2)) links to four active substances. For these active substances, four substance conversion rules are created. Each with a proportion of 0.25 and a conversion factor of 1 (see table below).

Table 6 Example: the substance hierarchy of the dithiocarbamates in the substances catalogue.

Substance code	Substance name	Type	EFSA PARAM code	Is sum (Y/N)	Sum substance code

[1] https://www.rivm.nl/en/chemkap/fruit-and-vegetables/processing-factors, last update 11 June 2020

75150	carbondisulfide (CS2)	BreakdownProduct	RF-0151-005-PPP	N	90000075150
8018017	mancozeb	BreakdownProduct	RF-0151-004-PPP	N	90000075150
9006422	metiram	BreakdownProduct	RF-0151-002-PPP	N	90000075150
12427382	maneb	BreakdownProduct	RF-0151-003-PPP	N	90000075150
90000075150	dithiocarbamaten (sum as CS2)	Residue	RF-0151-001-PPP	Y	

Table 7 Example: substance conversion rules for dithiocarbamates as generated from the substances hierarchy.

idMeasuredSubstance	idActiveSubstance	ConversionFactor	IsExclusive	Proportion
90000075150	75150	1	TRUE	0.25
90000075150	9006422	1	TRUE	0.25
90000075150	8018017	1	TRUE	0.25
90000075150	12427382	1	TRUE	0.25

For each cumulative exposure assessment, a substance conversions dataset is created in this way, uploaded to MCRA, and used in the assessment.

2.4.7 Food translation data (reverse yield factors)

The food consumptions of the food survey are specified at the level of processed raw commodities. Within the cumulative exposure assessments, these consumptions are linked to the measured (raw) food products using food translations. The food translations do not only qualitatively link the processed foods to the unprocessed/raw foods, but also include weight correction factors to translate consumed food amounts to equivalent modelled food amounts. For the RPC consumption data, the translations data consists of the weight correction factors due to processing.

The food translation dataset is available for use on a share on MCRA and a reference to this dataset is sufficient for using it is an MCRA cumulative exposure analysis from the IPGF portal.

3 Method

3.1 Single substance-food assessments

In the business-as-usual scenario, risk assessment by Food Compass focuses on the inspection of individual concentration values in the Food Compass monitoring data.

3.1.1 MRL exceedance

Residue levels for single substances in crop samples are compared to the MRL for that substance in that crop and exceedances are reported. The %MRL calculation is delegated to the GroentenFruit Huis web service. For each positive substance concentration of each sample, the GroentenFruit Huis web service is used to compare the measured concentration to the MRL as stored in the GroenFruit Huis portal in the form of a percentage (%MRL).

3.1.2 ARfD exceedance

The exposure of the substance via consumption of the crop can be estimated using the IESTI model according to the PRIMo 3.1 specification (EFSA 2019b) and compared to the ARfD as stored in the GroenFruit Huis portal using the ARfD% application of GroentenFruit Huis[2].

The %ARfD calculation is delegated to the GroentenFruit Huis web service, which computes the %ARfD with the consumption amounts and nominal bodyweights of the critical population and the currently active ARfD value. For the retrospective analyses in the IPGF portal, it is also desirable to compute the %ARfD for historical samples, using the then-present ARfD value. Therefore, the %ARfD value received from GroentenFruit Huis is recomputed for historical samples by dividing by the currently active ARfD and multiplying with the ARfD active during the period of sampling.

In the GroentenFruit Huis tool, artificial low ARfD values were included for some genotoxic substances such as chlorpyrifos and chlorpyridos-methyl (see section 2.3). Moreover, for these cases all processing factors were removed from the calculation in the tool.

3.1.3 MRL and ARfD exceedance

In practice, Food Compass is using MRL exceedance as a first screening and ARfD exceedances are registered for those samples where MRL was exceeded.

3.2 Probabilistic cumulative risk assessments

Cumulative effects from mixtures of pesticide residues can lead to health risks that are not controlled under the current EU system using only the MRL and ARfD for single substances. In a collaboration between the European Commission, the European Food Safety Authority and member states methods have been developed to assess cumulative exposure and risk (van Klaveren et al. 2019ab; EFSA 2020ab). These methods have been implemented in MCRA (van Klaveren et al. 2019ab).

In the current study we consider risk for acute health effects as might result from consuming fruit and vegetables from the Dutch market against a background of other dietary consumptions of Dutch children. Specifically, we apply the EC Tier 2 method as was proposed by the European Commission in 2018 and was subsequently adopted by

[2] For GroentenFruit Huis members, available at https://groentenfruithuis.nl/dashboard under Tools - Voedselveiligheid.

EFSA. For a full description of the probabilistic method for acute health effects see van Klaveren et al. (2019a). Here we only provide a short summary.

Health effects can be grouped according to hierarchical levels. RIVM and EFSA have thus far applied cumulative risk assessments for four specific phenomenological effects, two neurological effects and two effects on the thyroid (level 2; van Klaveren et al. 2019ab, EFSA 2020ab), but have also investigated cumulative risk assessments at the corresponding organ levels, neurological and thyroid (level 1; te Biesebeek et al., 2021). In this case study, cumulative modelling is applied for 15 cumulative assessment groups (CAGs) defined at level 1 by Nielsen et al. (2012).

3.2.1 General

The exposure and risk assessment are computed in an acute MCRA risk assessment using the hazard index as the risk metric. Dietary exposures are computed in principle according to EC 2018 Tier 2 settings; meaning that simulated substance residues are generated using a sample-based approach, processing factors are used in the calculation, and unit-variability is accounted for in a beta-binomial model using a realistic estimates nature.
The active substances of the assessment are obtained from data, with a further restriction to only the substances for which an ARfD is available. The hazard characterisations are formed by ARfDs obtained from GroentenFruit Huis, which apply to the critical effect that are used as a proxy for specific (organ / CAG level 1) effects in the cumulative exposure assessments. This is similar to the approach followed by te Biesebeek et al. (2021). For each exposure assessment, the most toxic substance (i.e., the substance with the lowest ARfD) was selected as reference substance.
Options are available to run the cumulative exposure and risk assessments with or without uncertainty. More specifically, there are two options for uncertainty analysis: an uncertainty-test option using only 10 uncertainty analysis cycles (bootstrap cycles), using a reduced population size of 10.000 simulated individuals in the uncertainty cycles, and an uncertainty-full option with 100 bootstrap cycles simulating 100.000 individuals in each bootstrap run.

3.2.2 Concentration modelling and occurrence frequencies

Concentration modelling is done according to the EC 2018 Tier 2 specifications. Thus, sample-based concentration modelling is done, non-detects are replaced by 1/2 x LOR and missing values are imputed using occurrence frequency estimates.
Occurrence patterns and frequencies are computed the same way as in the EC 2018 Tier 2 method, except that no substance authorisation data to restrict use percentage up-scaling to authorised uses was used. This is because authorised uses data was not sufficiently available to use this option.

3.2.3 Extrapolation of food samples

No extrapolation was done of food samples for foods with a limited amount of samples (data poor foods) from other foods (data rich foods). The reason for this is that the extrapolation rules were not sufficiently available.

3.2.4 Substances conversion

Substances conversion rules are used to translate measured substance concentrations (e.g., of sum substances) to active substance concentrations. The residue definitions are obtained from the sum-substance hierarchy information of the Food Compass substances catalogue. However, substance authorisation information is not included in the substance conversion, since this information was not sufficiently available.

Note that samples can have multiple sample analyses, measured using different analytical methods. Because of this, it may be possible that there are multiple (conflicting) substance measurements for the same substance if the substance is by both analytical methods. This may also occur indirectly (via active substance

allocation) when one analytical method reports the active substance concentration directly and another analytical method reports a sum-substance concentration that translates that active substance.

As an example, consider the following example:

- A sample can be analysed with both LC-MS and GC-MS.
- The LC-MS method measures bromoxynil(sum), translating to bromoxynil (as) and bromoxynil-octanoate.
- The GC-MS method measures bromoxynil (as) and bromoxynil-octanoate directly.
- Hence, active substance allocation leads to two (possibly conflicting) concentration values for the active substances bromoxynil (as) and bromoxynil-octanoate on the same sample.

If active substance allocation leads to multiple allocated measurements for the same substance on the same sample, then the following procedure is implemented rules for resolving these inconsistencies:

- If all measurements are non-detect, then select the measurement with the smallest LOR.
- If any of the measurements is positive or zero, then take the mean of all positive/zero measurements.

Note that these rules are quite generic and would work quite well also in case there are many measurements for the same active substance. In practice, one would expect only a few (two).

3.3 Software: the MCRA platform

The cumulative risk calculations were performed using the Monte Carlo Risk Assessment (MCRA) portal, version 9.1[3]. MCRA 9, also known as the EuroMix Toolbox, is a program for Monte Carlo Risk Assessment, developed for RIVM by Wageningen University & Research, Biometris to facilitate RIVM's tasks for the Dutch food safety authority (NVWA) and for cooperation in international projects (EFSA, EC Research). MCRA 9 was developed in the EuroMix project and in collaborations with EFSA.
For acute dietary risk assessment of pesticides, MCRA provides functionality to link consumption data from a dietary survey and residue occurrence data. Consumption of individual-days are randomly combined with residue levels for all consumed foods to produce an estimate of the exposure distribution. Scaled against the ARfD of a substance the exposure distribution can be expressed as a distribution of the hazard quotient (in MCRA termed hazard index, HI), with values above 1 indicating potential risk. For cumulative assessments all residue levels of the substances in an assessment group are scaled by their relative potency factor (RPF) with respect to a selected index substance. Scaled exposures are summed, and the sum is scaled to HI by dividing by the ARfD of the index substance.

The consumption data and the files defining health effects and cumulative assessment groups are available in MCRA for the Food Compass user. Many refinements of the assessment are possible, and some are part of the EC Tier 2 method in this case study. This requires additional data on processing factors, unit variability factors and residue definitions. These data are also available in MCRA to the Food Compass user.

The use of MCRA requires a high level of understanding and some degree of experience. To allow the use of MCRA functionality from other more easily accessible entry points (such as the IPGF platform, see next section), an application programming interface (API) was created to allow MCRA calculations to be delivered as a web service (WebAPI). For example, external programs can ask MCRA which data is available, send

[3] The offical version of MCRA 9.1 can be found at https://mcra.rivm.nl. In the current report calculations were made using the test verison of MCRA 9.1 at WUR, which is in principle the same version as available at RIVM.

specific data to MCRA, ask MCRA to perform a specific calculation and to send back the results.

3.4 Software: the IPGF portal

All analyses of this case study were performed using a beta version of the IPGF web portal (version 2.0.0-beta.1). As mentioned, IPGF portal is a web platform specifically to designed to perform human health risk analyses on the Food Compass concentration data. It does so by linking this concentration to other data and delegating model calculations to specific modelling services, such as MCRA for cumulative risk assessment and the GroentenFruit Huis web service for IESTI and MRL calculations.

The e-infrastructure of the IPGF portal is depicted in the figure below. The platform can be used to collect data from and delegate calculations to different external web services via Web APIs. These web services are the Food Compass web service, the GroentenFruit Huis web service, and the MCRA web service. Each service is used for different purposes, which is illustrated in the platform service infrastructure diagram of Figure 2. Establishing connections with these services and linking the data from multiple sources is therefore a key aspect of this portal.

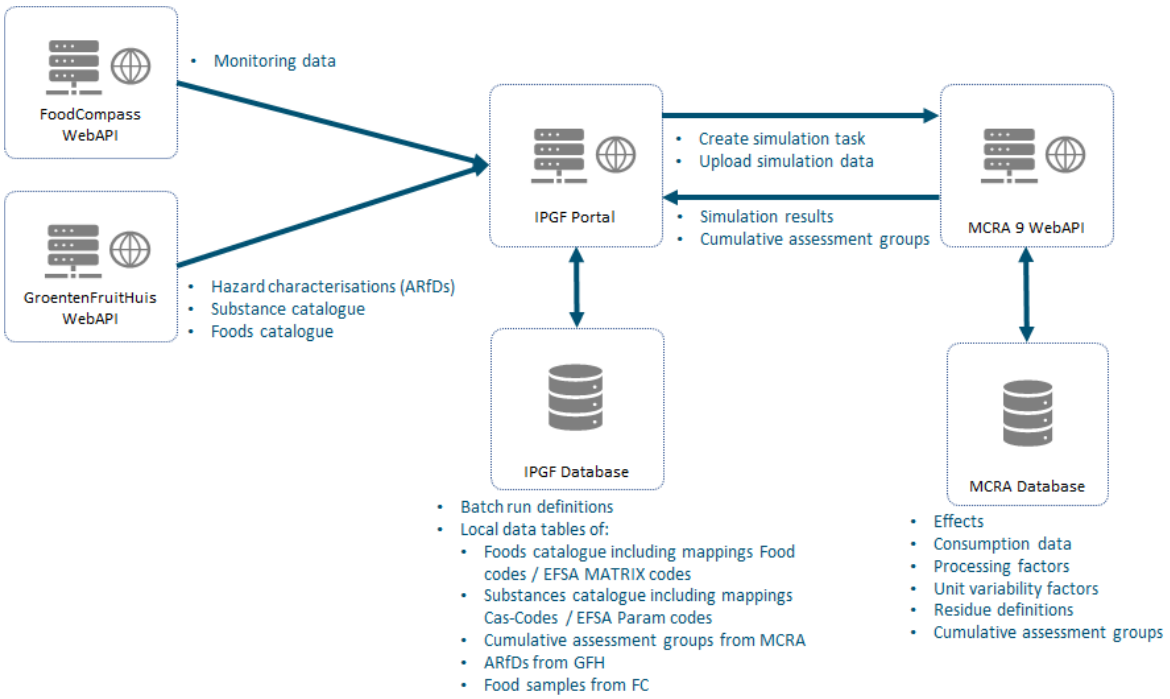


Figure 1 Illustration of the e-infrastructure of the communication and data exchange between the IPGF Portal and other web services.

The portal presents three types of analyses to analyse the food samples from Food Compass:

- **Single sample analyses:** analysis of individual samples, either entered manually or selected from all available samples in the FC data (findable by sample report number). This type of analyses can be performed by all users of the portal.
- **Sample collection (batch) analyses:** analysis of a collections of samples. Consider all samples in a specified time period (e.g. the year 2019). Batches can be defined (by means of a start date, end date, etc.) and run by administrators of the portal. All users are able to evaluate the results of batch analyses.
- **Batch comparison analyses:** comparison of (risk) indicators of different batch analyses. Particularly intended to visualize trends in time.

For the present case study, the batch analysis and the batch comparison analysis are used. Figure 2 shows a screenshot of the batch overview page. On this page, main information about the batch and the analysis status is shown and from this page the user can browse to the various batch result report pages. Figure 3 shows a screenshot of the cumulative exposure assessment results of this batch. For each health effect, it shows the cumulative exposure and confidence intervals at a specified percentile, and the probability of critical exposure (POCE), with its confidence intervals. As a last example, Figure 4 shows the main results of multiple batches combined in an overview table, which is part of the batch comparison analyses.

In the case study of this report, a batch analysis was done for each year from 2013 to 2020 and the results were extracted from the batch analysis reports and the batch comparison report.

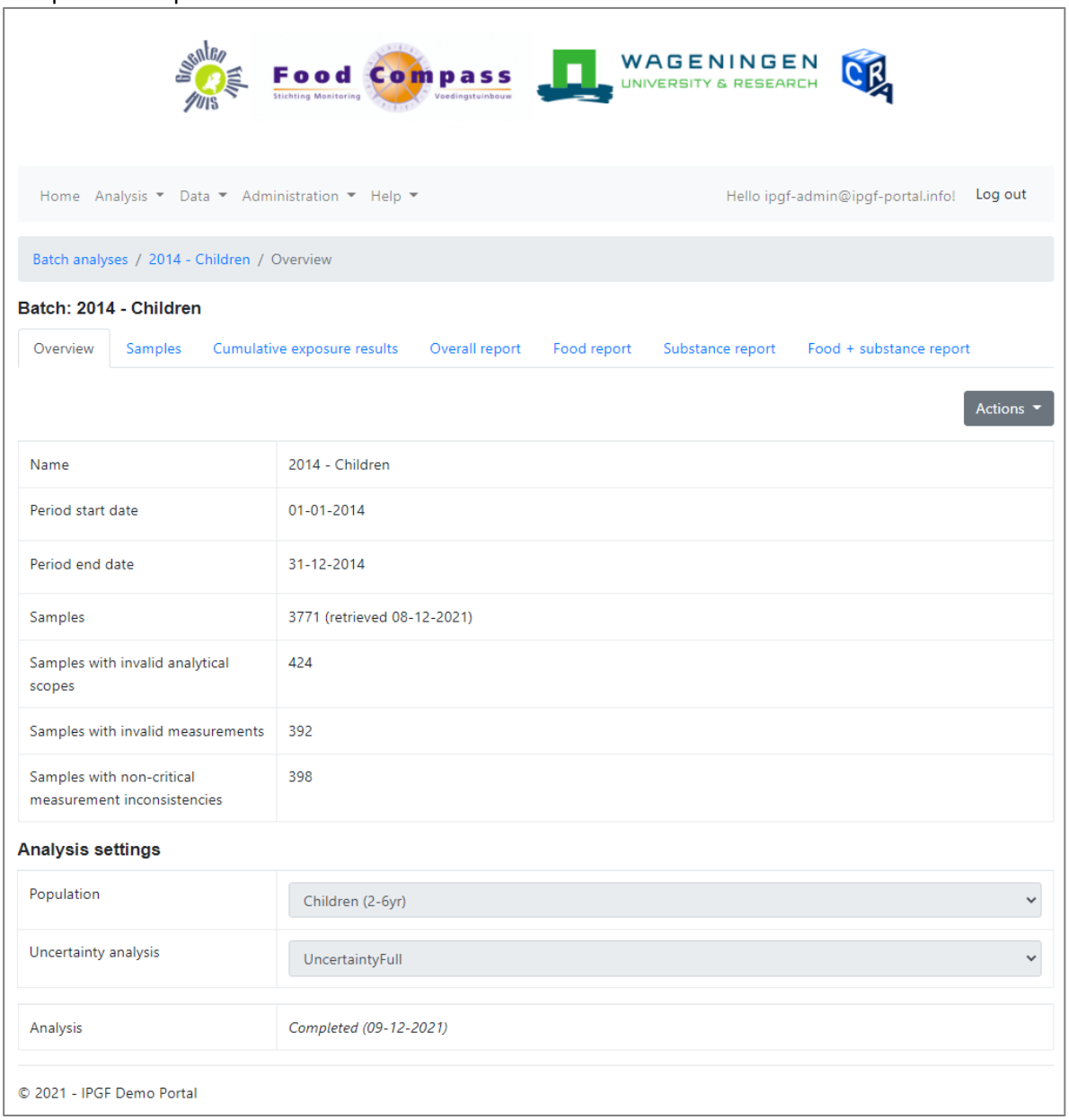


Figure 2 Screenshot of the IPGF web portal. This is the batch analysis overview page of the batch "2014 - Children".

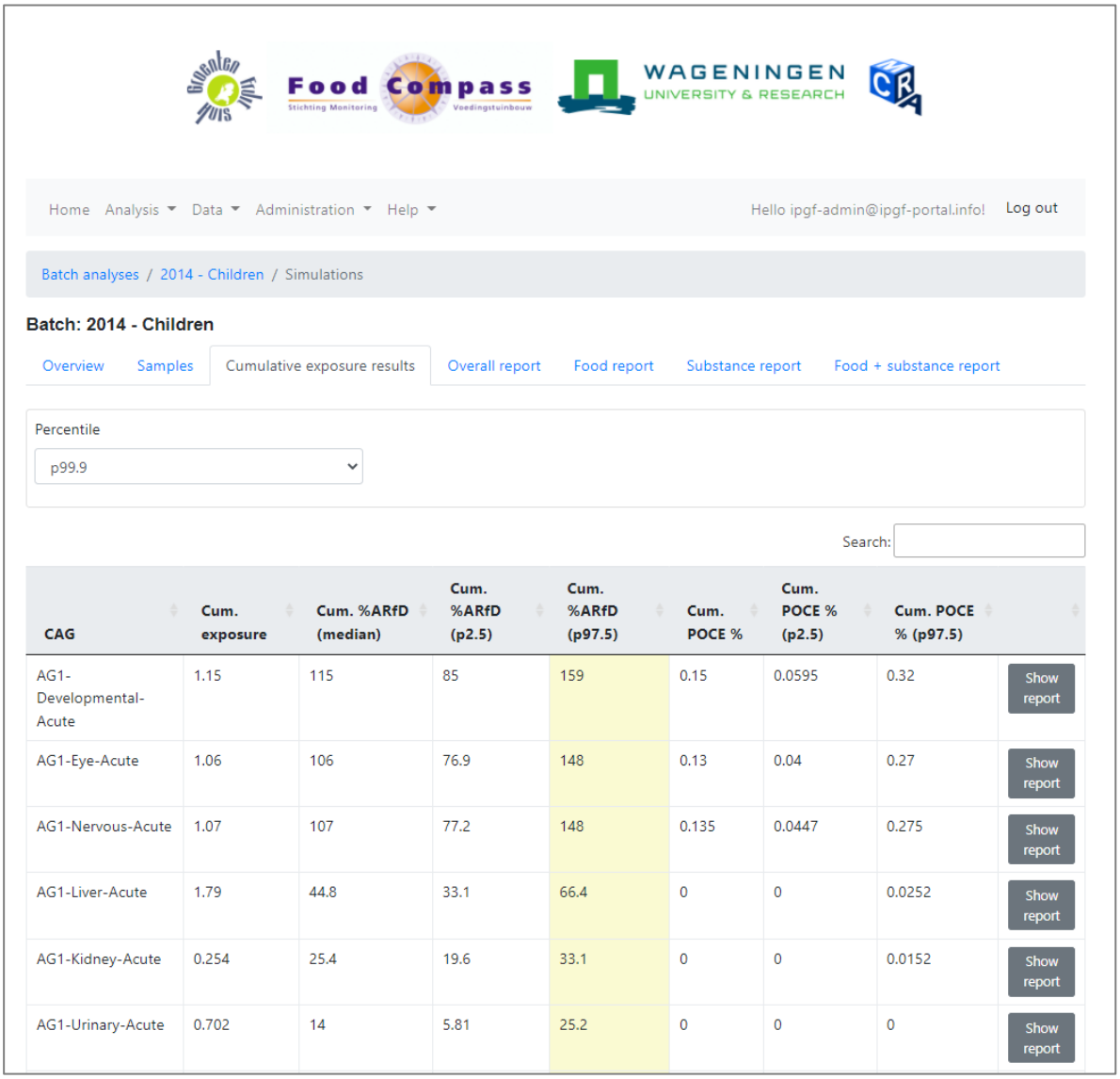
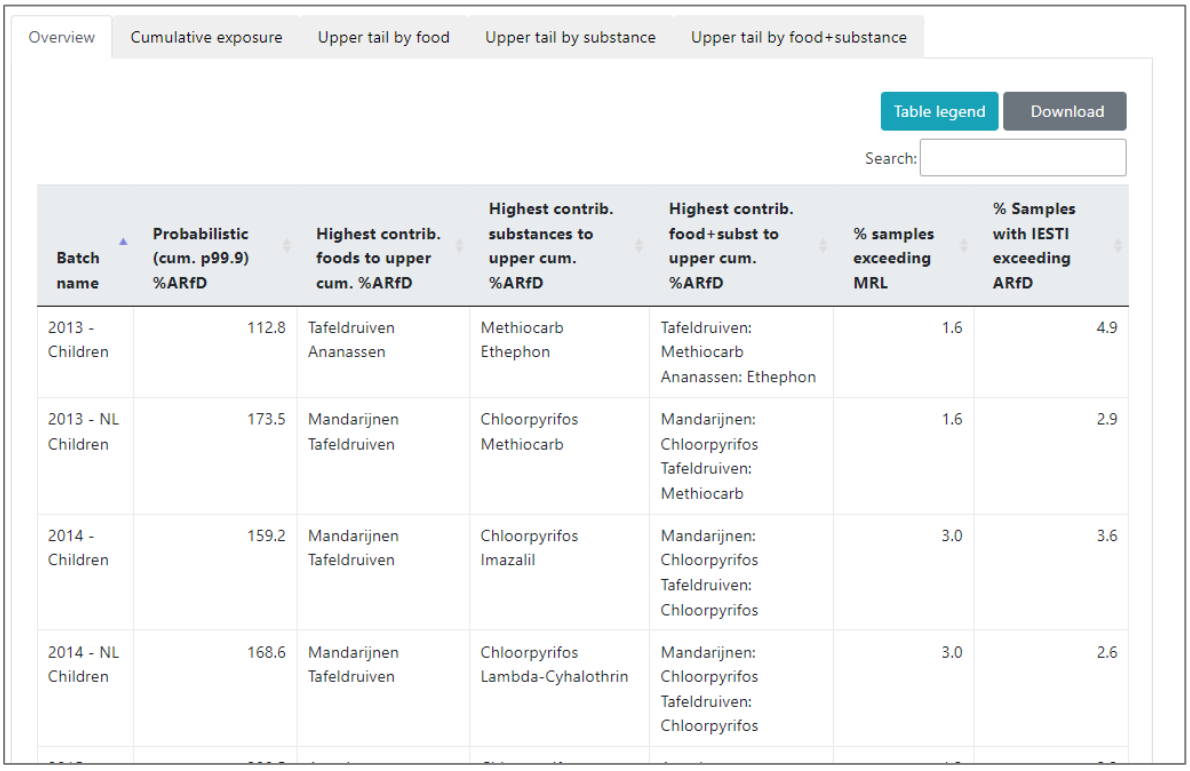


Figure 3 Screenshot of the provisional cumulative exposure results report of a batch analysis in the IPGF portal.



Batch name	Probabilistic (cum. p99.9) %ARfD	Highest contrib. foods to upper cum. %ARfD	Highest contrib. substances to upper cum. %ARfD	Highest contrib. food+subst to upper cum. %ARfD	% samples exceeding MRL	% Samples with IESTI exceeding ARfD
2013 - Children	112.8	Tafeldruiven Ananassen	Methiocarb Ethephon	Tafeldruiven: Methiocarb Ananassen: Ethephon	1.6	4.9
2013 - NL Children	173.5	Mandarijnen Tafeldruiven	Chloorpyrifos Methiocarb	Mandarijnen: Chloorpyrifos Tafeldruiven: Methiocarb	1.6	2.9
2014 - Children	159.2	Mandarijnen Tafeldruiven	Chloorpyrifos Imazalil	Mandarijnen: Chloorpyrifos Tafeldruiven: Chloorpyrifos	3.0	3.6
2014 - NL Children	168.6	Mandarijnen Tafeldruiven	Chloorpyrifos Lambda-Cyhalothrin	Mandarijnen: Chloorpyrifos Tafeldruiven: Chloorpyrifos	3.0	2.6

Figure 4 Screenshot of the batch comparison report, combining the results of multiple batches in an overview table.

4 Results

4.1 Trend analysis for Dutch children 2013-2020

4.1.1 Single-substance assessments, business as usual

The percentages of samples with exceedance of the MRL or with a calculated IESTI exceeding the ARfD is shown for the years 2013-2020 in Table 8 and Table 9 and in Figure 5. Large numbers, i.e. 31-41 different foods and 45-72 different substances were involved in the MRL exceedances. Smaller but still quite large numbers, i.e. 5-22 different foods and 3-22 different substances were involved in the ARfD exceedances.

The conventional analysis of single residue measurements showed that 1-3% of residue levels exceeded the MRL throughout the period 2013-2020, without a clear trend.

The most notable change was the gradual decrease of the ARfD exceedance frequency using the PRIMo 3.1 model from around 3% in earlier years to 0.7 % in the latest year. Another interesting observation is the low frequency of samples with both MRL and ARfD exceedances (always below 0.5%), meaning that ARfD exceedances may also occur without an accompanying MRL exceedance in the same sample.

Table 8. Single substance assessments: Concentration exceeding MRL.

Year	Number of samples	% of samples with concentration >MRL for any substance	Number of foods with at least one MRL exceedance	Number of substances with at least one MRL exceedance	Number of food/ substances combinations with at least one MRL exceedance
2013	4376	1.6	37	60	84
2014	3771	3.0	39	67	94
2015	3732	1.3	34	57	76
2016	3244	3.0	39	72	116
2017	3372	2.2	41	57	82
2018	2165	2.6	37	58	71
2019	1710	3.3	39	55	76
2020	1472	3.0	31	45	61

Table 9. Single substance assessments: IESTI exceeding ARfD.

Year	Number of samples	% of samples with IESTI > ARfD for any substance	Number of foods with at least one ARfD exceedance	Number of substances with at least one ARfD exceedance	Number of food/substances combinations with at least one ARfD exceedance	% of samples with concentration > MRL and IESTI > ARfD for any substance
2013	4376	2.9	16	11	31	0.2
2014	3771	2.6	20	22	40	0.4
2015	3732	3.2	22	14	31	0.4
2016	3244	2.5	15	14	28	0.3
2017	3372	1.9	13	10	20	0.1
2018	2165	2.2	9	10	13	0.4
2019	1710	0.9	5	3	5	0.3
2020	1472	0.7	9	9	13	0.5

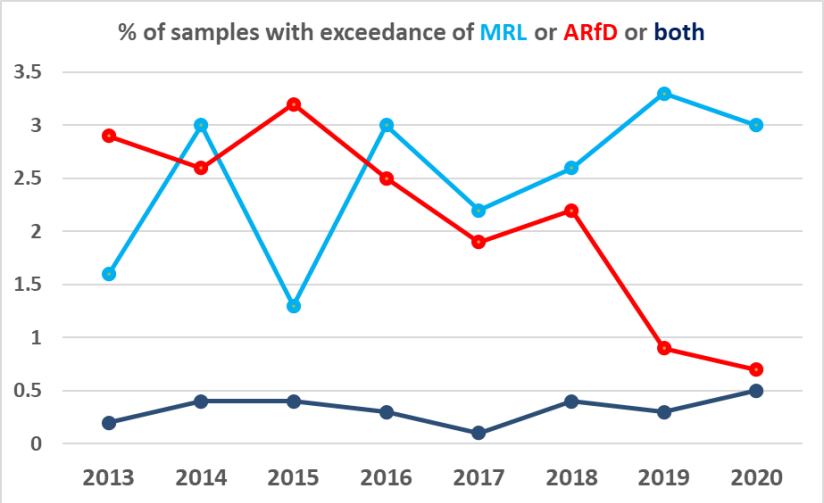


Figure 5. Time trends in frequency (sample percentage) of MRL and ARfD exceedances. ARfD exceedance based on single-substance point estimate calculations (IESTI in PRIMo 3.1). MRLs and ARfDs valid at the sampling date were used.

4.1.2 Cumulative risk assessments using MCRA

The main results from the cumulative risk assessments of Dutch children for the years 2013-2020 is shown in Table 10 and Figure 6. In the table all health effects are listed (if any) which might occur for at least 0.1% of the population. Two equivalent statistics are shown, the 99.9th percentile of the %ARfD distribution and the probability of critical exposure (POCE), which is the percentage of persondays with exceedance of the ARfD. In addition, the food-substance combinations that are responsible for such exceedances are listed. In the figure each year is represented by the health effect with the highest risk. Due to insufficient availability of amongst others processing factors, these results are provisional.

The cumulative assessments indicated that the probability of a critical acute exposure was estimated to be in the range 0.1- 0.4% during the period 2013-2019 (the results for 2020 were affected by an artificial low ARfD value and are therefore not useful to estimate real risk). Nevertheless, the main identified risk drivers were occurrences of chlorpyrifos and chlorpyrifos-methyl in some citrus fruit products such as juices for which no account of processing effects was included in the assessment due to lack of validated data.

Table 10. Provisional cumulative risk assessment for Dutch children. The ARfD values valid at the end of each year were used, including the artificially low values set by Food Compass for chloorpyrifos and chloorpyrifos-methyl in 2020.

Year	Assessment group(s) with potential risk[1]	Number of active substances / with exposure	P99.9 of exposure, as % of ARfD [95% conf. int.]	% of persondays exceeding ARfD [95% conf. int.]	food-substance responsible
2013	Developmental	109 / 54	131 [88; 173]	0.22 [0.07; 0.44]	Mandarins / chlorpyrifos 0.1% Table grapes / methiocarb 0.1%
	Nervous	54 / 29	126 [90; 173]	0.20 [0.06; 0.40]	Mandarins / chlorpyrifos 0.1% Oranges / chlorpyrifos 0.1% Table grapes / methiocarb 0.1%
	Eye	39 / 20	106 [69; 148]	0.12 [0.02; 0.24]	Mandarins / chlorpyrifos
	Liver	99 / 47	77 [54; 116]	0.05 [0; 0.16]	Table grapes / methiocarb
2014	Developmental	109 / 54	122 [89, 169]	0.19 [0.07; 0.37]	Mandarins / chlorpyrifos 0.2% Mandarins / lambda-cyhalothrin 0.1%
	Nervous	54 / 31	115 [82; 166]	0.16 [0.05; 0.33]	Mandarins / chlorpyrifos
	Eye	39 / 21	106 [77; 148]	0.13 [0.04; 0.27]	Mandarins / chlorpyrifos
2015	Developmental	109 / 55	159 [84; 290]	0.33 [0.05; 0.67]	Mandarins / chlorpyrifos 0.1% Apples / chlorpyrifos 0.1%,
	Nervous	54 / 30	158 [84; 290]	0.31 [0.04; 0.63]	Mandarins / chlorpyrifos 0.1% Apples / chlorpyrifos 0.1%,
	Eye	39 / 20	156 [77; 289]	0.28 [0.03; 0.62]	Mandarins / chlorpyrifos 0.1% Apples / chlorpyrifos 0.1%,
2016	Developmental	109 / 57	127 [72; 174]	0.18 [0.03; 0.39]	Mandarins / chlorpyrifos 0.2%, Apples/ chlorpyrifos 0.1%
	Nervous	54 / 34	122 [70; 169]	0.17 [0.02; 0.32]	Mandarins / chlorpyrifos 0.2%, Apples/ chlorpyrifos 0.1%
	Eye	39 / 22	118 [67; 167]	0.16 [0.02; 0.31]	Mandarins / chlorpyrifos 0.2%, Apples/ chlorpyrifos 0.1%
2017	Developmental	109 / 55	88 [55; 147]	0.07 [0; 0.21]	Mandarins / chlorpyrifos
	Nervous	54 /28	81 [44; 144]	0.06 [0; 0.20	Mandarins / chlorpyrifos
	Eye	39 / 22	72 [41; 129]	0.05 [0; 0.16]	Mandarins / chlorpyrifos
2018	Developmental	109 / 54	67 [49; 103]	0.03 [0; 0.11]	
2019	Developmental	109 /54	100 [59; 234]	0.11 [0.01; 0.39]	Mandarins / chlorpyrifos
	Nervous	54 / 30	93 [49; 227]	0.09 [0; 0.35]	Mandarins / chlorpyrifos
	Eye	39 / 22	83 [35; 198]	0.08 [0; 0.30]	Mandarins / chlorpyrifos
2020	Nervous	54 / 27	2370 [1100; 3700]	14 [9; 19]	Mandarins / chlorpyrifos 4.3% Oranges / chlorpyrifos 2.3% Apples / chlorpyrifos 2.2% Mandarins / chlorpyrifos-methyl 1.8% Oranges / chlorpyrifos-methyl 1.0% Grapefruits / chlorpyrifos 0.2% Grapefruits/ chlorpyrifos-methyl 0.1%
	Developmental	109 / 52	2350 [1080; 3670]	12 [7; 18]	Mandarins / chlorpyrifos 3.6% Oranges / chlorpyrifos 2.1% Mandarins / chlorpyrifos-methyl 1.8% Apples / chlorpyrifos 1.7% Oranges / chlorpyrifos-methyl 0.9% Grapefruits / chlorpyrifos 0.1% Grapefruits/ chlorpyrifos-methyl 0.1%
	Eye	39 / 18	2030 [940; 3320]	11 [6; 16]	Mandarins / chlorpyrifos 5.0% Apples / chlorpyrifos 2.9% Oranges / chlorpyrifos 2.7% Grapefruits / chlorpyrifos 0.3%
	Adrenal	10 / 8	1360 [395; 2630]	4.9 [3.2; 8.3]	Mandarins / chlorpyrifos-methyl 3.7% Oranges / chlorpyrifos-methyl 1.8% Grapefruits/ chlorpyrifos-methyl 0.3%

[1] Listed if uncertainty 97.5 % upper limit of cumulative exposure P99.9 is higher than ARfD.

[2] Median estimate, uncertainty not shown

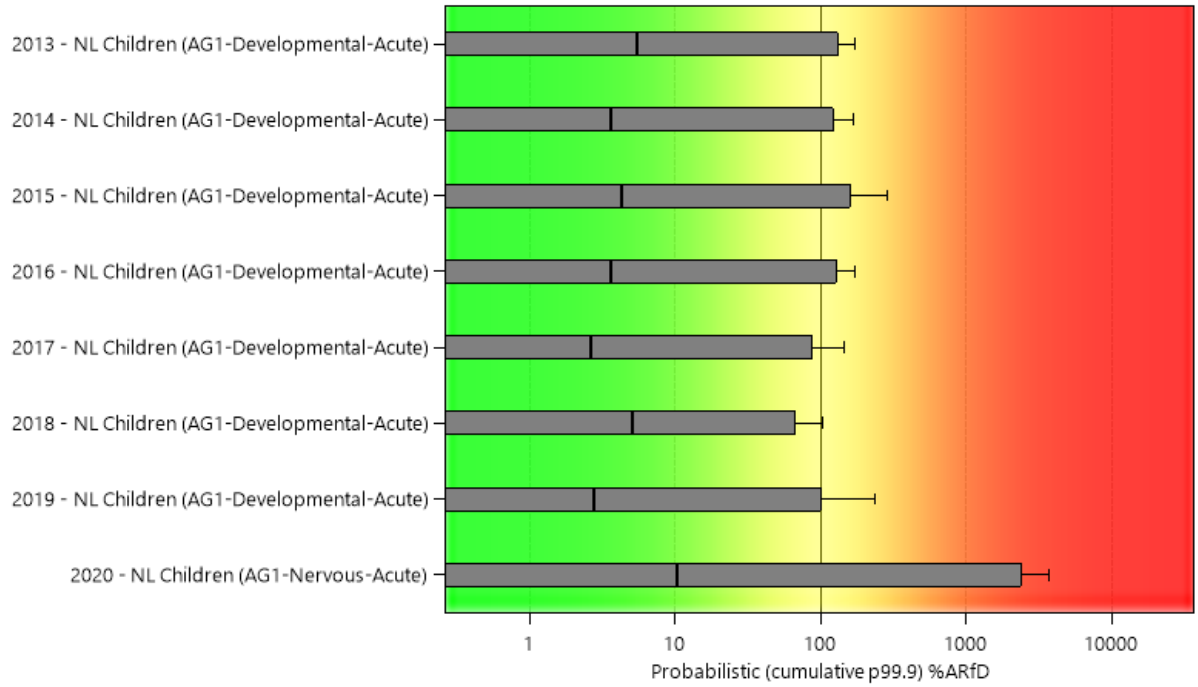


Figure 6. Batch comparison analysis in IPGF portal, showing the trend analysis of the index substance ARfD exceedance by the regulatory chosen 99.9th percentile of the cumulative exposure distribution. ARfDs valid at the end of each year were used, including the artificially low values set by Food Compass for chloorpyrifos and chloorpyrifos-methyl in 2020 which explains the artificial high %ARfD value in that year. Bars represent the P0.1-P99.9 variation in exposure on individual-days with the vertical line denoting the median exposure and the upper whisker showing the upper (97.5%) uncertainty bound on the 99.9th percentile.

Only few food-substance combinations were found that contribute to ARfD exceedance when using the probabilistic MCRA model. In order to have a better view on the food-substance combinations that lead to the highest %ARfD values in the simulations, Table 11 and Table 12 list the main contributing foods, substances and food-substance combinations for the upper 2.5% tail of the cumulative exposure distribution per year for the health effect with the highest %ARfD values. Figure 7, Figure 8 and Figure 9 show the trends in these main contributions graphically.

The main risk drivers over th ewhole period appeared to be chlorpyrifos in mandarins, apples and oranges. Other combinations that were found as occasional risk drivers with more than 10% contribution to the upper exposures were methiocarb in table grapes (in 2013), lambda-cyhalothrin in oranges (in 2019) and chlorpyrifos-methyl in mandarins (in 2020).

Table 11 Main foods (left) and substances (right) explaining at least 90% of the 2.5% upper tail of the cumulative exposure distribution of Dutch children for the health effect with the highest risk potential.

Year	Highest contrib. foods	% in tail		Year	Highest contrib. substances	% in tail
2013	Mandarins	53		**2013**	chlorpyrifos	66
	Table grapes	20			methiocarb	16
	Apples	11			ethephon	8
	Oranges	6			lambda-cyhalothrin	5
2014	Mandarins	79		**2014**	chlorpyrifos	85
	Table grapes	8			lambda-cyhalothrin	6
	Oranges	5				
2015	Apples	61		**2015**	chlorpyrifos	95
	Mandarins	32				
2016	Mandarins	57		**2016**	chlorpyrifos	88
	Apples	36			lambda-cyhalothrin	3
2017	Mandarins	78		**2017**	chlorpyrifos	73
	Apples	13			lambda-cyhalothrin	12
					imazalil	4
					captan	4
2018	Mandarins	67		**2018**	chlorpyrifos	66
	Oranges	19			lambda-cyhalothrin	12
	Apples	5			propiconazole	8
					ethephon	2
					chlorprofam	2
2019	Mandarins	72		**2019**	chlorpyrifos	69
	Oranges	24			lambda-cyhalothrin	19
					propiconazole	4
2020	Mandarins	39		**2020**	chlorpyrifos	72
	Oranges	31			chlorpyrifos-methyl	28
	Apples	29				

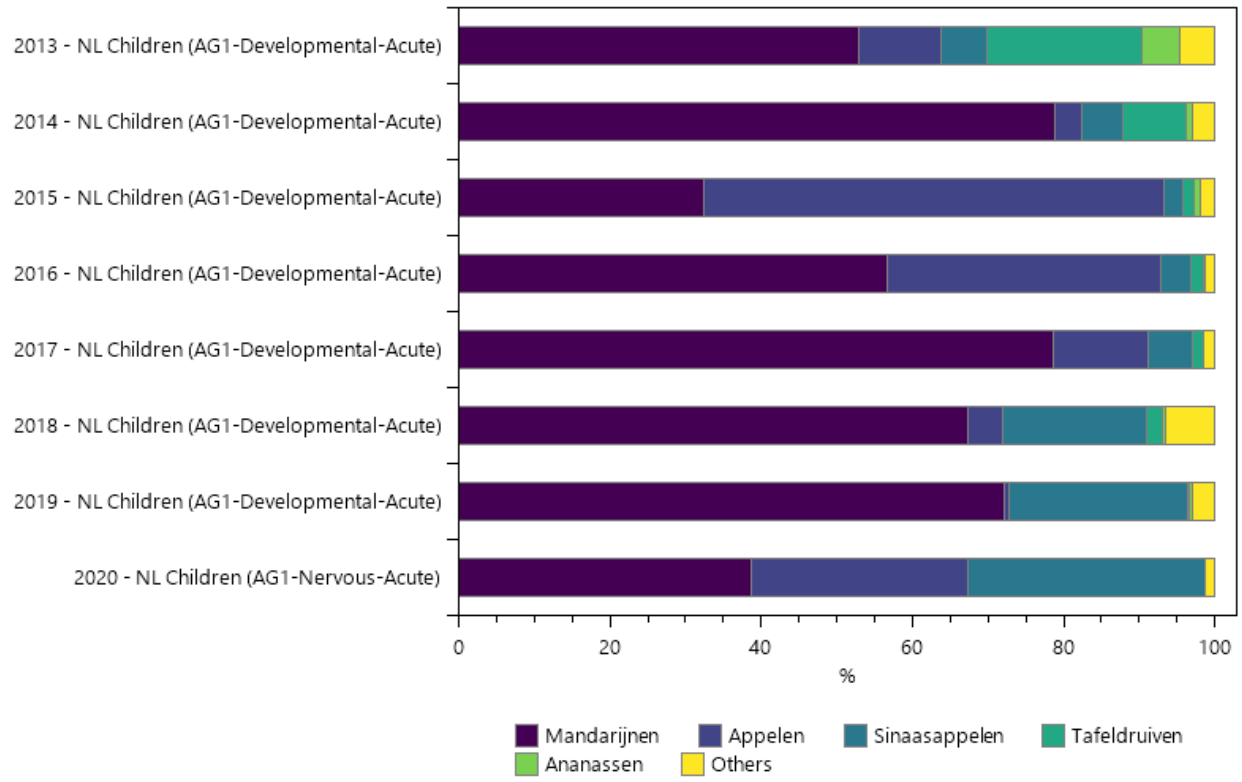


Figure 7. Trend analysis of the main contributing foods (as percentages) to the upper 2.5% tail of the cumulative exposure distribution. The 5 foods with the highest average contribution over years are shown.

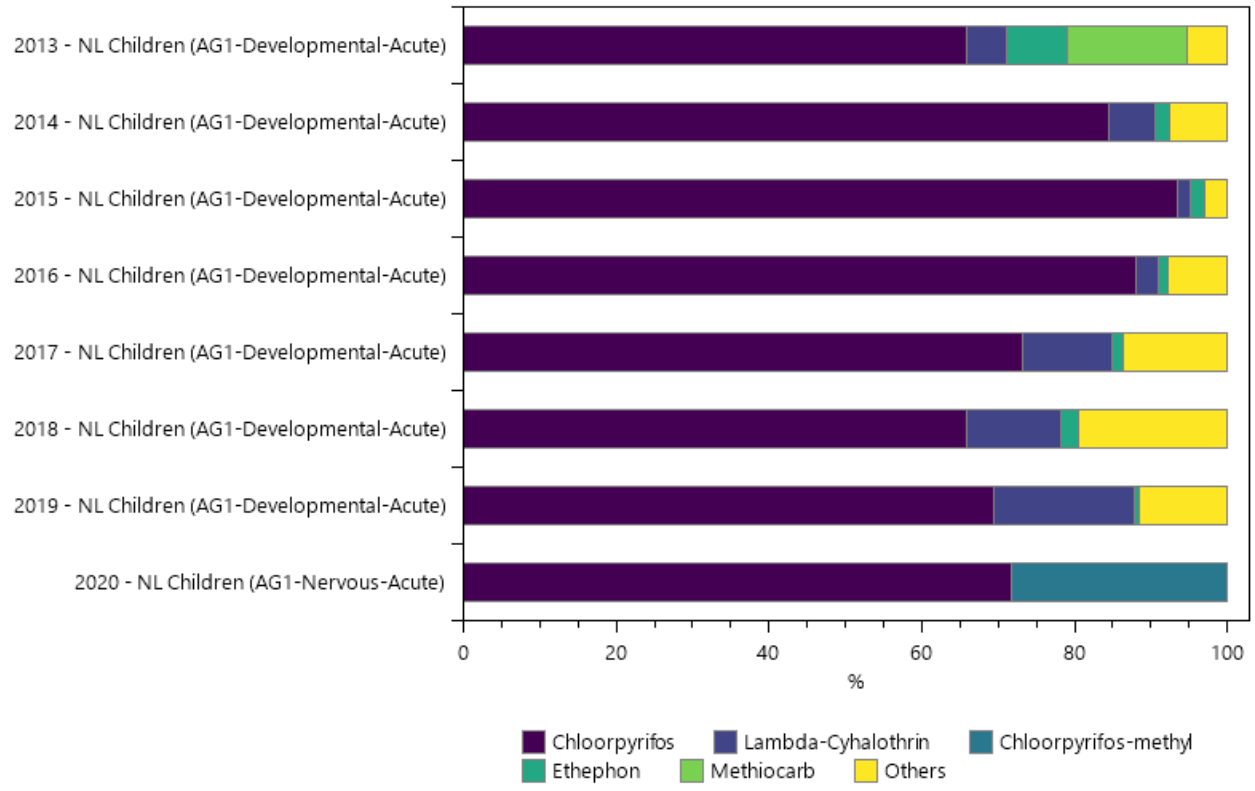


Figure 8. Trend analysis of the main contributing substances (as percentages) to the upper 2.5% tail of the cumulative exposure distribution. The 5 substances with the highest average contribution over years are shown.

Table 12 Main food-substance combinations explaining at least 90% of the 2.5% upper tail of the cumulative exposure distribution of Dutch children for the health effect with the highest risk potential.

Year	Highest contrib. food+subst	% in tail		Year	Highest contrib. food+subst	% in tail
2013	Mandarins / chlorpyrifos	50		2017	Mandarins / chlorpyrifos	68
	Table grapes / methiocarb	16			Mandarins / lambda-cyhalothrin	9
	Apples / chlorpyrifos	10			Apples / captan	4
	Pineapples / ethephon	5			Apples / imazalil	3
	Oranges / chlorpyrifos	4			Apples / chlorpyrifos	3
	Mandarins / lambda-cyhalothrin	2			Oranges / lambda-cyhalothrin	2
	Bananas / ethephon	2			Oranges - chlorpyrifos	2
	Oranges / lambda-cyhalothrin	2		**2018**	Mandarins / chlorpyrifos	54
	Table grapes / chlorpyrifos	2			Oranges / chlorpyrifos	9
2014	Mandarins / chlorpyrifos	74			Mandarins / propiconazole	8
	Table grapes / chlorpyrifos	4			Oranges / lambda-cyhalothrin	7
	Mandarins / lambda-cyhalothrin	4			Mandarins / lambda-cyhalothrin	4
	Oranges / chlorpyrifos	4			Potatoes / chlorprofam	2
	Apples / chlorpyrifos	3			Table grapes / ethephon	2
	Bananas / imazalil	2			Apples / pyraclostrobin	1
2015	Apples / chlorpyrifos	60			Apples / carbendazim	1
	Mandarins / chlorpyrifos	38			Apples / acetimiprid	1
2016	Mandarins / chlorpyrifos	53		**2019**	Mandarins / chlorpyrifos	66
	Apples / chlorpyrifos	33			Oranges / lambda-cyhalothrin	15
	Mandarins / lambda-cyhalothrin	2			Oranges / chlorpyrifos	3
	Oranges / chlorpyrifos	1			Mandarins / propiconazole	3
	Oranges / lambda-cyhalothrin	1			Mandarins / lambda-cyhalothrin	2
	Table grapes / pyraclostrobin	1			Oranges / dimethoate	2
				2020	Oranges / chlorpyrifos	31
					Apples / chlorpyrifos	29
					Mandarins / chlorpyrifos-methyl	27
					Mandarins / chlorpyrifos	12

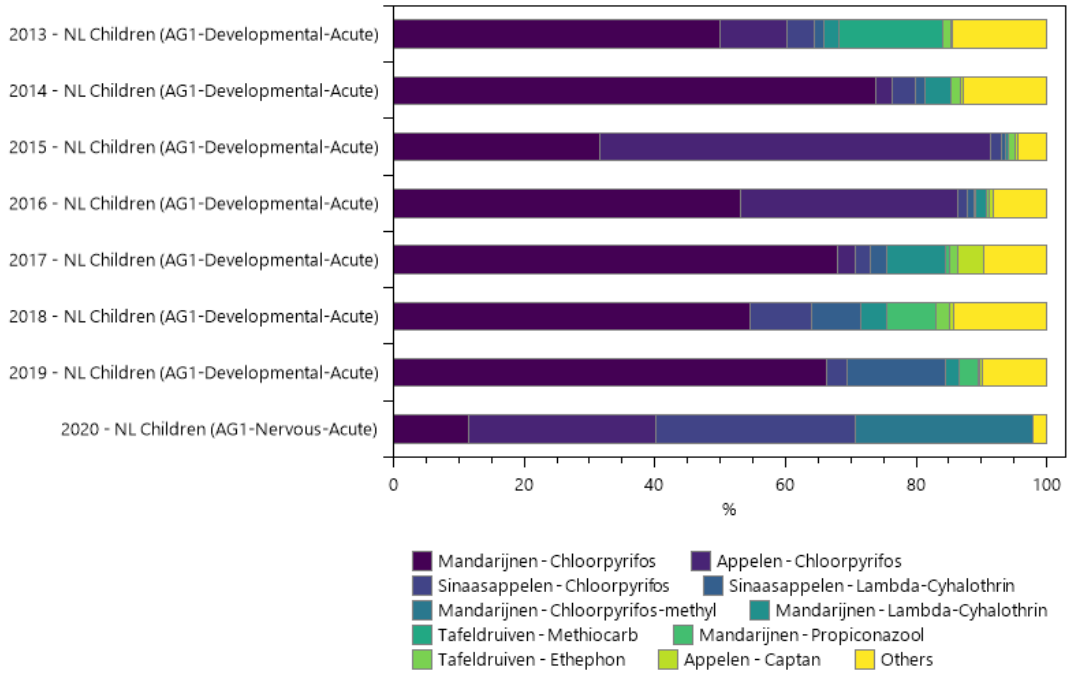


Figure 9. Trend analysis of the main contributions (as percentages) to the upper 2.5% tail of the cumulative exposure distribution. The 10 food/substance combinations with the highest average contribution over years are shown.

4.2 Example of detailed results (year 2015– Developmental effects)

In this section detailed results are shown for the batch analysis of the year 2015, which was the year with the highest observed risk index (excluding 2020, for which the high risk was due to an artifical low ARfD). These results and similar results for other years and health effects are available for users of the IPGF portal.

As in most years in the trend analysis, developmental effects were identified as the health effects of primary concern. The assessment group for developmental effects consists of 110 active substances, but one of these (fenoxaprop-P-ethyl) excluded from the assessment because of a missing ARfD value. For cumulative assessments, oxamyl was selected as the index substance, which means that all exposures are expressed as oxamyl equivalents based on ARfD ratios used as relative potency factors.

For 54 of the remaining 109 active substances no positive exposure from the diet was found. Therefore, the assessment group cumulated the risks from effectively 55 substances that were found in the diet of the Dutch children. In the simulations, at least one of these substances was present in the diet every day (100% exposure).

The cumulative exposure (in oxamyl equivalents) divided by the ARfD of oxamyl (which happens to be 1 µg/kg/day) specifies a hazard index (HI) distribution (**Figure 10**, Figure 11). EC, EFSA, RIVM and NVWA have agreed on using a 99.9% level of protection. Therefore, the cumulative exposure and HI distributions are evaluated at the 99.9th percent point (Table 13). Whereas the median estimate of HI is well below 1, the estimate of P99.9 is 1.6 with an uncertainty upper bound of 2.9. This means that for 0.1% of the children the cumulative exposure is estimated to be 1.6 times the ARfD and could be up to 2.9 times the ARfD. Another way to express these same results is to state that the probability of a critical exposure (POCE) is estimated as 0.33% with an uncertainty upper bound of 0.67%.

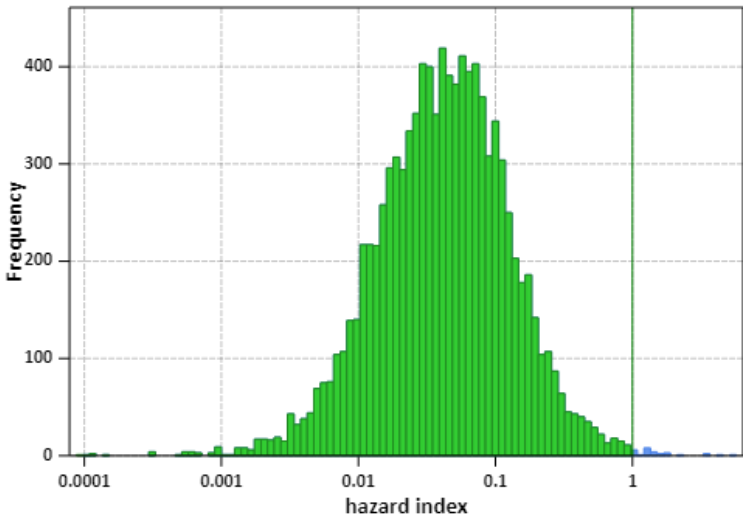


Figure 10. ***Hazard index distribution for Dutch children 2015, developmental effects, estimated from 10,000 Monte Carlo iterations.***

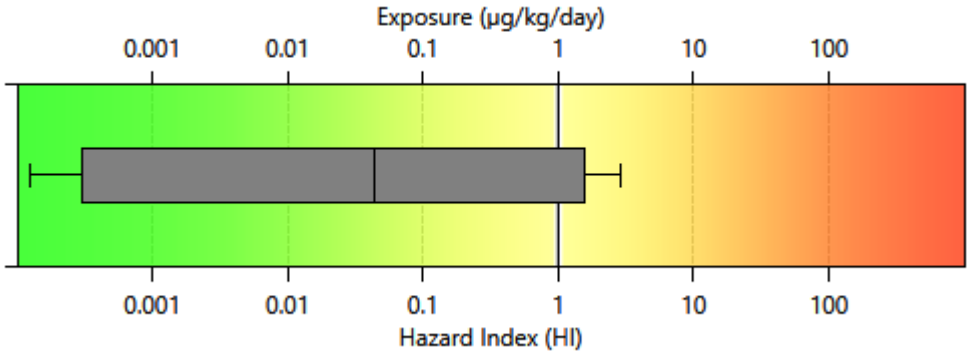


Figure 11. *Safety chart: bar shows variability of HI (range p0.1 - p99.9) in the population. The whiskers indicate a composed confidence interval, the left whisker is the lower 2.5% limit of p0.1, the right whisker is the upper 97.5% limit of p99.9.*

Table 13. Risks for Dutch children based on 2015 data (developmental effects). HI = Hazard Index. POCE = Probability of Critical Exposure. p = percentile. Unc = Uncertainty.

HI (p0.1)	HI (p50)	HI (p99.9)	HI (p99.9) - Unc (p97.5)	POCE (%)	POCE (%) lower bound (p2.5)	POCE (%) upper bound (p97.5)
0.0003	0.043	1.6	2.9	0.33	0.05	0.67

Zooming in on the individual substance contributions (Figure 12, Figure 13), by far the largest contribution to the cumulative risk is seen to come from Chlorpyrifos.

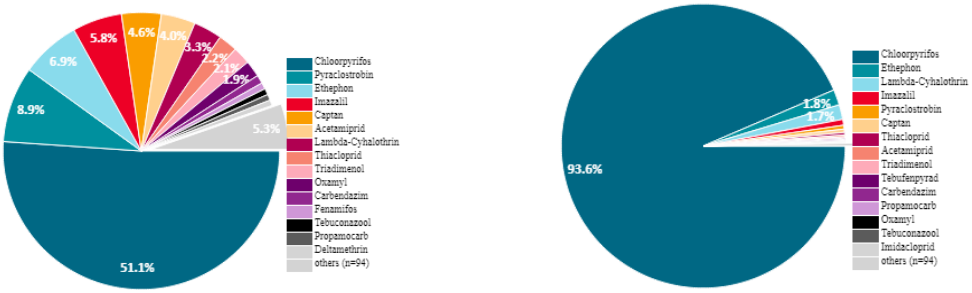


Figure 12. Contribution to total (left) and upper 0.1% tail (right) cumulative exposure from individual substances.

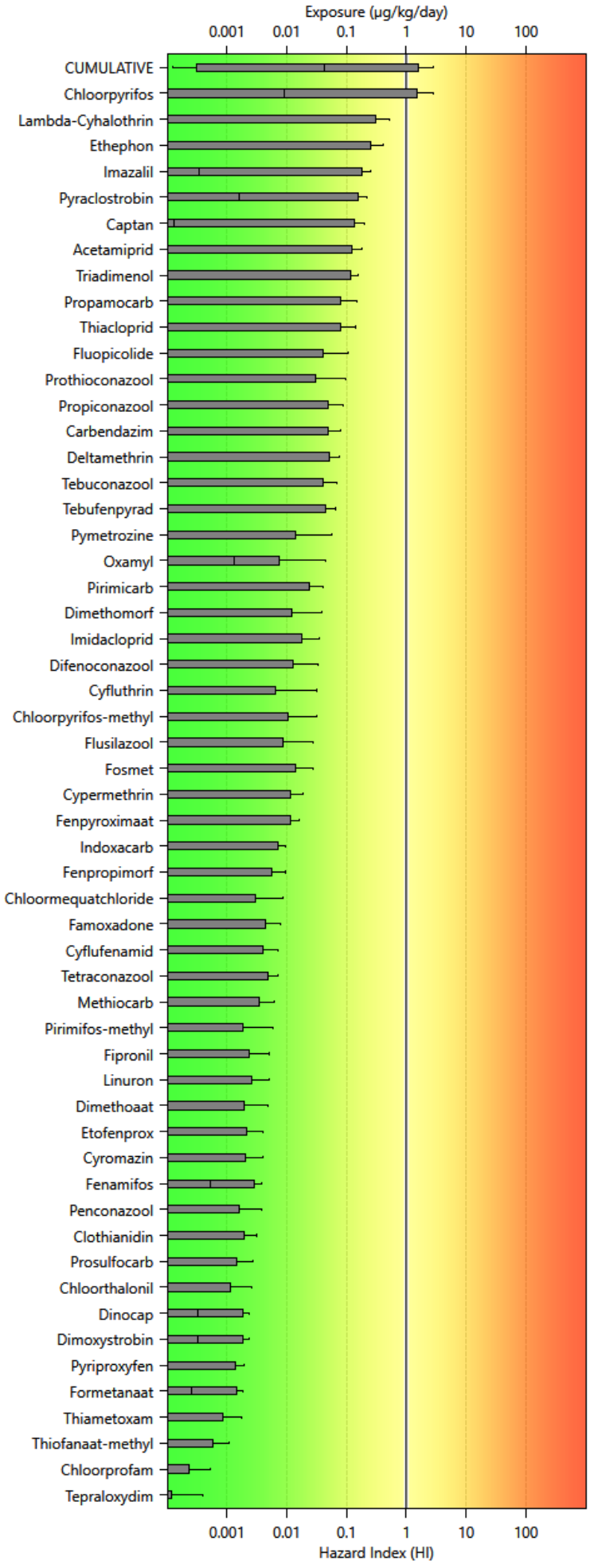


Figure 13. Hazard index (CUMULATIVE) and hazard quotients for contributing substances.

Zooming in on the individual vegetable and fruit contributions (Figure 14), the largest contributions to the cumulative risk is seen to come from Apples, Mandarins and Oranges. In terms of the consumed products, these are identified to be mainly the juiced products, i.e. apple juice, mandarin juice and orange juice.

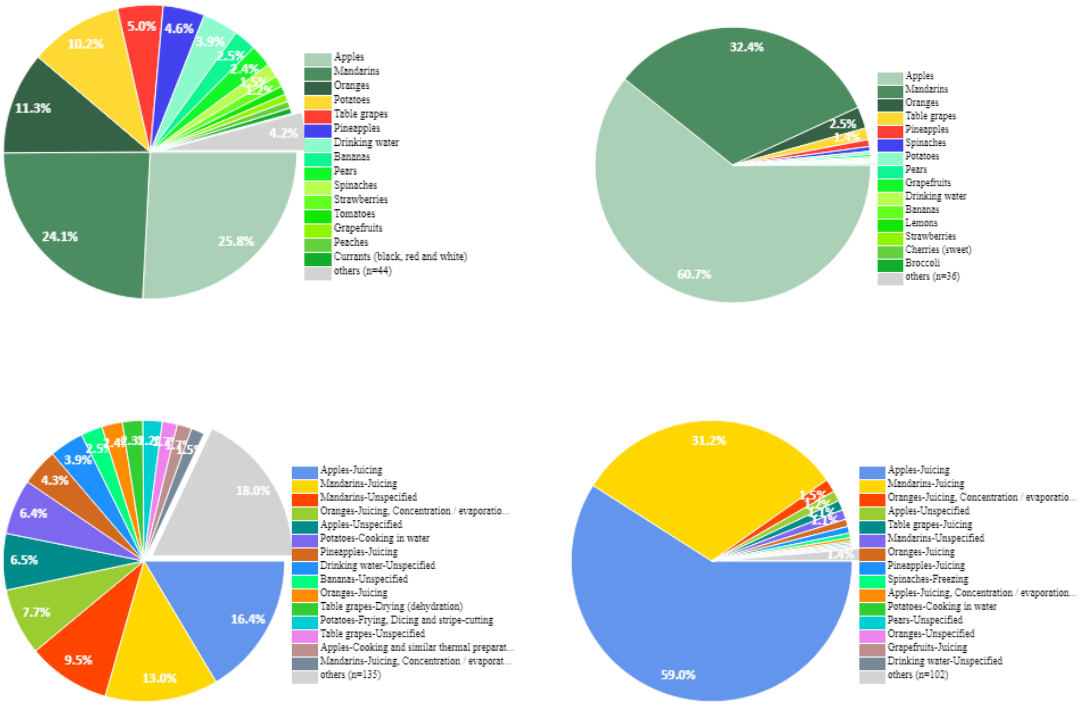


Figure 14. Contribution from individual vegetable and fruit products as measured to total (upper left) and upper 0.1% tail (upper right) cumulative exposure and contribution from vegetable and fruit products as consumed to total (lower left) and upper 0.1% tail (lower right) cumulative exposure.

If we consider the most detailed level, we see that indeed Chlorpyrifos in apple, mandarin and orange juices is primarily responsible for the higher exposures (Figure 15. Contribution from combinations of substance and vegetable and fruit product as consumed to total (left) and upper 0.1% tail (right) cumulative exposure.).

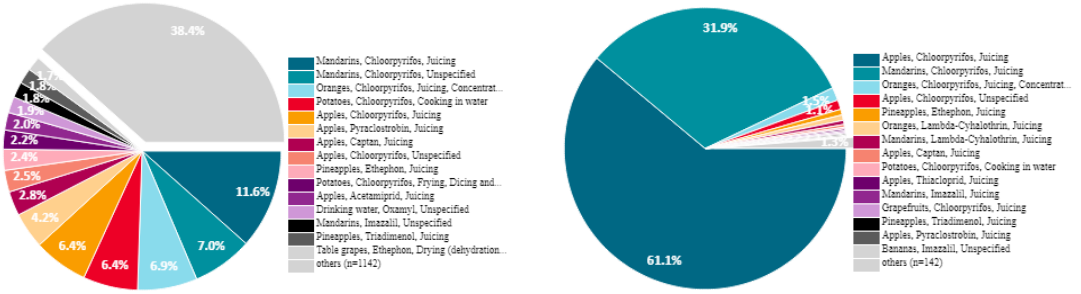


Figure 15. Contribution from combinations of substance and vegetable and fruit product as consumed to total (left) and upper 0.1% tail (right) cumulative exposure.

A further drill-down (Table 14) reveals that chlorpyrifos in orange juice has a processing factor of 0.025, i.e. the concentrations are assumed to be 40 times lower in orange juice as compared to the raw agricultural product oranges. However, it is also seen that no processing factors were used for apple juice, mandarin juice and for a different form of orange juice (Juicing, Concentration/evaporation). This suggests that exposure from these sources is over-estimated.

Table 14. Processing factors for risk drivers.

Substance name	Substance code	Food name	Food code	Processing type	Contribution (%) mean	Processing factor
chlorpyrifos	2921882	Apples	P0130010A	Juicing	58.31211028	1
chlorpyrifos	2921882	Apples	P0130010A	Unspecified	1.043602482	1
chlorpyrifos	2921882	Mandarins	P0110050A	Juicing	30.42689077	1
chlorpyrifos	2921882	Mandarins	P0110050A	Juicing, Concentration / evaporation	0.091850867	1
chlorpyrifos	2921882	Oranges	P0110020A	Juicing, Concentration / evaporation	1.428885321	1
chlorpyrifos	2921882	Oranges	P0110020A	Juicing	0.046311439	0.025

5 Discussion and conclusions

The IPGF portal has been made available for Food Compass as primary responsible stakeholder for food safety of vegetables and fruits in the Netherlands to perform cumulative acute risk assessments. Cumulative assessments, in contrast to IESTI single-substance assessments, address concerns of the EC and the general public about potential mixture effects. Probabilistic assessments are more realistic than simple conservative calculations (IESTI).

It was shown that cumulative assessment provides a useful addition for Food Compass or other private stakeholders to assess the combined risk of multiple chemicals. In this report, batch analyses per year were performed for investigating the trends in the period 2013-2020. The results presented in this report provide insight in the trends over the years and the high contributing food products and substances driving the (mixture) risk.

It is essential to note that the data are not perfect and there are many aspects where a lack of data (quality) is identified, which may lead to a potential bias in the calculations. For a part, this lack of data can be addressed by collecting more data and resolving the quality issues. For complex modelling this seems to be normal, and therefore we consider optimisation of data organisation as a form of a Retain & Refine (R&R) strategy (Kennedy et al. 2020). If a risk assessment with conservative elements due to imperfect data organisation shows no risk, it is not needed to improve the data and models (Retain). However, if potential risks are identified, refinement of the data and use of advanced models for analysis may be indicated (Refine).

The results of the current analysis highlight chlorpyrifos as the main risk driver. However, Chlorpyrifos (as well as chlorpyrifos-methyl) is now considered to be mutagenic genotoxic and is no longer allowed in the European Union. For these substances an ARfD is no longer available as it is considered mutagenic. This generates a problem for cumulative assessments which depend on estimation of the relative potencies. In this study we used ratios of ARfDs as relative potency factors. In this report, we therefore kept using ARfD values, in the form as were made available by GroentenFruit Huis. For Chlorpyrifos and Chlorpyrifos-methyl this led to an artificial high-risk estimate for the year 2020 because GroentenFruit Huis has set the corresponding ARfDs to artificial low values (0.0001 mg/kg bw/d) per 13-11-2020, just to generate alerts. As a consequence, the results of the current trend analysis show an increase in perceived risk in 2020 (note that the ARfD valid at 31-12-2020 was used for all exposures in the batch). It should be noted that this increase indicates a higher frequency of alerts only and *not* an increase in real risk (as someone might conclude from the 2020 results in chapter 4). For a more realistic comparison between years, it might be useful to perform calculations with the same ARfD values across the years.

Due to a missing ARfD value, fenoxaprop-P-ethyl was not included in the cumulative calculations. It could be considered to use the ARfD of fenoxaprop-P instead.

In this case study we grouped the pesticides in 15 CAGs corresponding with level 1 (organ level) CAGs as in Nielsen et al. (2012). In this way we covered a variety of potential health effects to illustrate the application of the proposed methodology. However, it should be remarked that these CAGs were not specifically derived for acute risk assessment, but rather for chronic risk assessment, i.e. following cumulative exposure over time. Specific CAGs for acute health risks have only been derived by EFSA for two specific neurological effects at level 2 (EFSA 2019c, van Klaveren et al. 2019a). The process to define more CAGs is ongoing.

Following the approach of te Biesebeek et al. (2021), the hazard characterisations used in the cumulative exposure assessments were ARfDs applying to the so-called critical effect. For some CAGs, the ARfD of a substance may not relate to the specific organ of the CAG, but to an adverse effect on another organ. The use of the ARfD may

therefore be seen as a conservative estimate of an organ-specific hazard dose and may lead to an overestimation of the risk.

For refinement of the calculations performed in this study we identify the following types of data that were not yet optimal:

1) Laboratory scopes did not always match with the reported substance measurements, and there is large number of samples and measurement reports with inconsistencies.
2) The set of processing factors was incomplete, as illustrated for example in Table 14. This can lead to an overestimation of the exposure, which was also observed in van Klaveren et al. (2019a).
3) In this report, we assumed that our collection of ARfD values represented the valid ARfD values during the period 2013-2020. However, it can be doubted if this collection is complete. The current GroentenFruit Huis web service only provides the most recent ARfD value. It should be discussed how the collection of historical ARfD values can be completed, and in fact, if this is considered a necessary approach.
4) Use of ARfD values to characterise hazard is a conservative approach because in a group of substances the ARfD is related to the the most critical health effect for each substance individually. If specific hazard characterisation data for each assessment group are available for all substaces in the group, these could be used (te Biesebeek et al. 2021).

The IPGF portal will be further developed in 2022, in line with developments in the methodology of mixture risk assessments by RIVM and EFSA. An update of the trend analysis in this report will be reported. Also, in this study we focused on cumulative risk assessments of year batches using the new IPGF portal and MCRA, in comparison to single-sample analyses for MRL and/or ARfD exceedances. In addition to the analyses described in this report, several other approaches are possible, some of them already implemented and other to be discussed:

- Instead of the Monte Carlo simulations, it would also be possible to perform probabilistic calculations for each single sample separately against a background of other samples, and then to summarise the sample results per year. In fact, this was originally the intention, but the computational load turned out to be very high. Further discussion might be needed if this would be a useful addition to the current approach.

- Here we have focused on trend analysis, i.e. a retrospective assessment. Another potential use of the IPGF portal would be a real-time use, where cumulative risk assessments for single samples representing product consignments could be used to decide on the acceptability of these consignments.

- In the ongoing discussions, retailers have set additional stringent criteria. In the IPGF portal we have already implemented tabular overviews of the performance of the analysed batches (e.g. per year) against these retail criteria. Based on the results of the cumulative risk assessments, retail requirements could be challenged.

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Supplementary material
Available at https://library.wur.nl/WebQuery/doi/562203

File	Description
Design and implementation of the IPGF Portal (v2.0.0-beta.1)	Document describing technical design and implementation of the IPGF portal.
EUProcessingFactorsDB_MCRA_FCCAS.1.0.3.zip	Processing factors dataset (in MCRA format) used in cumulative exposure assessments.
DTUCAG.1.2.0	Cumulative assessment groups dataset (in MCRA format) used in cumulative exposure assessments.
Substances.csv	Snapshot of substances catalogue (incl. PARAM mapping and hierarchy) at the time of calculating the results.
LabScopes.zip	Zip file containing three csv files describing the laboratory scopes user for import of the concentration data used in the calculations.
ARfDs.csv	Snapshot of the ARfDs catalogue as used in the calculations.

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