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Retrospective cumulative dietary risk assessment of craniofacial alterations by residues of pesticides

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Abstract

EFSA established cumulative assessment groups and conducted retrospective cumulative risk assessments for two types of craniofacial alterations (alterations due to abnormal skeletal development, head soft tissue alterations and brain neural tube defects) for 14 European populations of women in childbearing age. Cumulative acute exposure calculations were performed by probabilistic modelling using monitoring data collected by Member States in 2017, 2018 and 2019. A rigorous uncertainty analysis was performed using expert knowledge elicitation. Considering all sources of uncertainty, their dependencies and differences between populations, it was concluded with varying degrees of certainty that the MOET resulting from cumulative exposure is above 100 for the two types of craniofacial alterations. The threshold for regulatory consideration established by risk managers is therefore not exceeded. Considering the severity of the effects under consideration, it was also assessed whether the MOET is above 500. This was the case with varying levels of certainty for the head soft tissue alterations and brain neural tube defects. However, for the alterations due to abnormal skeletal development, it was found about as likely as not that the MOET is above 500 in most populations. For two populations, it was even found more likely that the MOET is below 500. These results were discussed in the light of the conservatism of the methodological approach.

Keywords: cumulative assessment groups, cumulative risk assessment, pesticide residues, probabilistic modelling, craniofacial alterations, expert knowledge elicitation, uncertainty analysis

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Summary

A retrospective cumulative risk assessment (CRA) of dietary exposure to pesticide residues in 2017, 2018 and 2019 was conducted for craniofacial alterations.

The first step of the process was the establishment of cumulative assessment groups (CAGs) of pesticides causing these effects. Two types of craniofacial alterations, resulting from distinct mechanisms and pathways and identifiable by specific indicators, were found to require separate assessments: alterations due to abnormal skeletal development and head soft tissue alterations and brain neural tube defects. These effects are acute, as they may be triggered by short-term exposure, or even by a single exposure event. Therefore, two CAGs were established: CAG-DAC for the alterations due to abnormal skeletal development, and CAG-DAH for the head soft tissue alterations and brain neural tube defects.

A list of 85 active substances and their metabolites to be scrutinised for these effects was established, based on monitoring data and toxicological profiles. After careful review of the respective toxicological dossiers, 39 and 41 active substances or metabolites were included in CAG-DAC and CAG-DAH, respectively. All were characterised by no observed adverse effect levels (NOAELs) for the craniofacial alterations under consideration, derived from the most sensitive indicator and using all available information across studies and species. Sources of uncertainty associated with the methods used to collect and assess toxicological data and resulting from the limitations in the available data and scientific knowledge were identified for appropriate consideration during the CRA.

In a second step, cumulative acute exposure calculations were performed using monitoring data collected by Member States under their official monitoring programmes in 2017, 2018 and 2019 in 36 raw primary commodities widely consumed within Europe, and two processed commodities (olive oil and wine). Individual consumption data from national surveys in 14 populations of women in childbearing age from different European countries were used for these calculations. The assessment also considered the possible intake of pesticide residues through drinking water. Exposure estimates from combined exposure to multiple pesticide residues were obtained with SAS® software, using a two-dimensional probabilistic method that is composed of an inner loop execution and an outer loop execution. Variability within the population was modelled through the inner loop execution and produced an exposure distribution. The outer loop execution was used to reflect the sampling uncertainty of occurrence and consumption data and to derive 95% confidence intervals around selected percentiles of the exposure distribution. The SAS programme had been validated beforehand against the Monte Carlo Risk Assessment (MCRA) software, version 8.3. As agreed by risk managers in the Standing Committee on Plants, Animals, Food and Feed (SCoPAFF), calculations were carried out according to a two-step tiered approach with well-defined assumptions and results were expressed as total margins of exposure (MOETs).

The focus of the assessment was on the MOET at the 99.9th percentile of the exposure distribution, in accordance with the threshold for regulatory consideration, which was set at 100 by the SCoPAFF. According to the Tier II scenario, median estimates of the MOET at the 99.9th percentile of cumulative exposure ranged from 73.5 to 298 for CAG-DAC in Ireland and Latvia, respectively, and from 534 to 1010 for CAG-DAH in Finland and Romania, respectively. The exposure estimates were predominantly driven by a few substance–commodity combinations (i.e. folpet in wine for CAG-DAC and folpet in wine, 2,4-D and thiabendazole in oranges for CAG-DAH).

To assess the impact of toxicological uncertainties and the limitations and assumptions affecting the exposure assessment, an uncertainty analysis was performed following the guidance of the EFSA Scientific Committee. Forty sources of uncertainty affecting the input data, model assumptions and the assessment methodology were identified. Their impact was assessed in a sequential approach using sensitivity analyses, expert knowledge elicitation (EKE) techniques and 1-D Monte Carlo simulations. First, the impact of each source of uncertainty on the MOETs at the 99.9th percentile of exposure was quantified for the German population, which was selected as the reference population. This step showed that the sources of uncertainty had variable effects on the MOET, e.g. tending to either overestimate (e.g. the metabolites were not considered in the assessment) or underestimate (e.g. limited availability of processing factors) the MOET. Subsequently, the combined impact of the sources of uncertainty was quantified for the German population. Finally, dependencies between sources of uncertainty and differences between populations were assessed.

As a result of this process, the MOETs at the 99.9th percentile and their confidence intervals, as derived from the cumulative exposure calculations, were adjusted to take account of the overall impact

of uncertainties and the probability of the MOET at the 99.9th percentile of the exposure distribution being above 100 was assessed for all 14 populations.

Taking account of all uncertainties identified by the experts, it was concluded that cumulative exposure results in an MOET above 100 for all population groups considered, with varying degrees of certainty. In the case of CAG-DAC, this certainty exceeded 90% for the Irish population, 93% for the German population, 97% for the Czech population and 99% for all other populations. In the case of CAG-DAH, this certainty is 100% for all populations.

Because craniofacial alterations are severe and irreversible effects, and by analogy with the risk assessment principles applied for this type of effects under the approval process of active substances under Regulation (EC) No 1107/2009 (e.g. use of an additional safety factor of 5), the probability of the MOET at the 99.9th percentile of the exposure distribution being above 500 was also assessed. In the case for CAG-DAH, this probability exceeded 66% for the German population, 90% for the Czech, Danish and Romanian populations and 95% for all other populations. In contrast, in the case of CAG-DAC, this probability was only between 33 and 66% in most countries. The probability was even lower in Germany (5–33%) and in Romania (10–50%). In Sweden, the probability was higher (50–80%).

The probabilities mentioned above need to be interpreted in the light of the extra risk (i.e. the incidence of fetuses affected minus the incidence in the control group divided by the non-affected fraction of the population) at the NOAELs set for craniofacial alterations in the context of this report. This extra risk was estimated to range between 0 and 1%, with a median value of 0.5%, i.e. lower than the usual extra risk at the NOAEL (5–10%) set for most toxicological effects. This indicates that the present assessment was conducted with a higher conservatism than the CRAs conducted earlier for the effects of pesticides on the thyroid and the nervous system.

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1. Introduction

Cumulative risk assessment (CRA) has been defined as the analysis, characterisation and possible quantification of the combined risks to health or the environment from multiple agents or stressors (U.S. EPA, 2003). It differs from most assessments which consider the effects of one agent or stressor solely.

In order to comply with provisions of Regulation (EC) No 396/2005 on maximum residue levels (MRLs) of pesticides in or on food and feed regarding cumulative and synergistic effects of pesticides, EFSA and the Panel on plant protection products and their residues (PPR panel) started in 2007 the development of the necessary methodologies to carry out CRA of pesticide residues. This methodological development included a tiered approach for the assessment of cumulative risks of pesticides residues (EFSA PPR Panel, 2008), a guidance on the use of probabilistic methodology for modelling dietary exposure to pesticide residues (EFSA PPR Panel, 2012) and a procedure to establish cumulative assessment groups (CAG) of pesticides on the basis of their toxicological profile (EFSA PPR Panel, 2013a).

In April 2020, EFSA completed a pilot project and issued the first two reports on retrospective CRAs of dietary exposure to pesticide residues (EFSA, 2020a,b). These reports concerned two acute effects on the nervous system and two chronic effects on the thyroid gland. In February 2021, EFSA completed another retrospective CRA regarding chronic acetyl cholinesterase inhibition (EFSA, 2021a).

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

The Plant Health & Pesticides Residues unit was requested by EFSA to prepare a scientific report on the CRA of craniofacial alterations by residues of pesticides. This request is motivated by the severity of such defects, the frequency of their occurrence in toxicological studies and the fact that they are among the most frequently recorded abnormalities in new-borns (Bartzela et al., 2017). Furthermore, there is a high plausibility for craniofacial alterations to result from a combined action of chemicals by triggering common molecular initiating events (MIE), and at least one adverse outcome pathway (AOP) has been described. In the forthcoming years, an exhaustive review of all effects pertaining to the developmental toxicity of pesticides will be conducted by EFSA. This review is expected to result in the identification of other specific effects relevant for CRA that will possibly trigger other specific assessments.

The legal background of this internal mandate is the article 32 of Regulation (EC) No 396/2005, which provides that EFSA draws up annual reports on pesticide residues taking account of the results of official control of pesticide residues in food commodities carried out by Member States and including an analysis of the risks to the health of consumers.

The precise assessment question addressed by the present report is defined as follows: *What was the cumulative risk of craniofacial alterations for European consumers resulting from dietary exposure to pesticide residues from 2017 to 2019?*

Non-dietary routes of exposure to pesticides and chemicals other than residues of pesticides are not considered in the assessment.

1.2. Input from risk managers and threshold for regulatory consideration

During the Standing Committee on Plants, Animals, Food and Feed (SCoPAFF) of 11–12 June 2015, Member States agreed on the use of the combined margin of exposure (MOET, also known as Total Margin of Exposure) concept as the mode of calculation and expression of cumulative risks.

Furthermore, during the SCoPAFF of 18–19 September 2018, Member States agreed on an MOET of 100 at 99.9th percentile of exposure at whole population level as a general threshold for regulatory consideration and as an indicative target of safety in consistency with the safety margin currently used for establishing toxicological reference values (i.e. assuming a factor 10 for interspecies variability and a factor of 10 for intraspecies variability). Additionally, in view of the severity of craniofacial alterations, and by analogy with the assessment practices during the approval process of active substances under Regulation (EC) No 1107/2009, it was decided to also evaluate whether an MOET of 500 would be met. Importantly, Member States also agreed on assumptions and parameters to be used in the calculation of cumulative exposure using monitoring data.[1]

[1] Available online: https://ec.europa.eu/food/plant/pesticides/max_residue_levels/cumulative_risk/technical-annex_en

1.3. Uncertainties

The uniform principles for evaluation and authorisation of plant protection products specify that in interpreting the results of evaluations, Member States shall take into consideration possible elements of uncertainty in order to ensure that the chances of failing to detect adverse effects or of underestimating their importance are reduced to a minimum. In addition, Article 1 of Regulation (EC) No 1107/2009 states that Member States shall not be prevented from applying the precautionary principle where there is scientific uncertainty. Estimates of cumulative risk from combined exposure to multiple pesticides are necessarily subject to a degree of scientific uncertainty, due to limitations in the data and to assumptions used to address those limitations. The present assessment therefore includes a rigorous analysis of the assumptions and uncertainties involved, leading to a quantitative assessment of the degree of certainty that the MOET at the 99.9th percentile of exposure is either above 100 or 500.

2. Data and methodologies

2.1. Cumulative assessment groups

The establishment of CAGs for craniofacial alterations followed a sequence of tasks comprising the identification and definition of the specific craniofacial alterations considered as relevant for CRA, the definition of the indicators of the specific craniofacial alterations, the establishment of CAGs and the characterisation of pesticides included in the CAG. Furthermore, in order to support the uncertainty analysis, the modalities of a weight of evidence assessment that an active substance, or a metabolite, included in the CAG actually causes craniofacial alterations as a primary effect, were defined.

2.1.1. Identification and definition of specific craniofacial alterations

The specific craniofacial alterations relevant for CRA were selected and defined based on the criteria established by the PPR Panel (2013a) and considering the hazard-driven criteria described by the EFSA Scientific Committee in its guidance document on scientific criteria for grouping chemicals into assessment groups for human risk assessment of combined exposure to multiple chemicals (EFSA Scientific Committee, 2021).

As a first step, a representative list of findings related to craniofacial alterations was prepared based on three data collections from toxicological studies on active substances performed by DTU (2012) and RIVM, ICPS and ANSES (2013, 2016). This list was complemented by the WHO global registry and database on craniofacial anomalies (WHO, 2001). Based on this list, the identification of the specific craniofacial alterations of relevance for CRA proceeded by expert judgement based on their documented relationship with primary toxicological events elicited by some chemicals during craniofacial morphogenesis.

The definition of indicators consisted in the elaboration of the list of findings, of macroscopic and/or histopathological nature, potentially observable in toxicological studies, which indicate that the exposure to the pesticide is causing the specific craniofacial alteration.

Account was taken of observations made in toxicological studies conducted following the requirements of the OECD Test Guidelines, eventual changes in nomenclature for craniofacial alterations over the years, and the scientific knowledge in this area.

2.1.2. Establishment of CAGs

2.1.2.1. Selection of the substances to be scrutinised

For reason of resources, it was not possible to review the toxicological properties of all active substances approved in EU and/or present as residues in food commodities. Therefore, a selection was conducted considering:

- The number of commodities covered by the EU-coordinated control programme (EUCP) for which acute intakes of the substance exceeded 20% of the acute reference dose (ARfD) during the 3-year monitoring cycle from 2017 to 2019 (EFSA, 2019a, 2020c, 2021b).
- Number of samples of the plant commodities selected for the assessment with quantifiable levels of the substance during the 3-year monitoring cycle 2016–2018 (EFSA, 2018a, 2019a, 2020c).

- Magnitude of the total chronic exposure to the substance in 2018 and 2019 as calculated according to the lower bound method in the latest two annual monitoring reports (EFSA, 2020c, 2021b).
- Reported craniofacial alterations in DTU (2012), EFSA conclusions for substances approved after 2009 and not covered by DTU (2012), or in RIVM, ICPS and ANSES (2016) for substances not approved in EU.
- Chemical structure (fungicides of the triazole group were selected preferentially, due to their well-described effects on craniofacial morphogenesis).
- Existence of an ARfD for the substance.

This resulted in the selection of 85 active substances which were:

2,4-D	Chlorpyrifos	Fenbuconazole	Iprodione	Prosulfocarb
Abamectin	Chlorpyrifos-methyl	Fenhexamid	Lambda-cyhalothrin	Prothioconazole
Acephate	Cyflufenamid	Fenpropidin	Mancozeb	Pyraclostrobin
Acetamiprid	Cyfluthrin	Fenpropimorph	Maneb	Spirotetramat
Acrinathrin	Cymoxanil	Fenpyrazamine	Metconazole	Spiroxamine
Alpha-cypermethrin	Cypermethrin	Fenpyroximate	Methiocarb	Tebuconazole
Azadirachtin	Cyproconazole	Flonicamid	Methomyl	Tebufenpyrad
Benomyl	Cyromazine	Fluazifop-P	Methoxyfenozide	Tetraconazole
Beta-cyfluthrin	Deltamethrin	Fluopyram	Myclobutanil	Thiabendazole
Beta-cypermethrin	Dieldrin	Flusilazole	Omethoate	Thiacloprid
Bitertanol	Difenoconazole	Flutriafol	Oxamyl	Thiophanate-methyl
Bromuconazole	Dimethoate	Folpet	Paclobutrazol	Thiram
Captan	Dithianon	Formetanate	Penconazole	Triadimefon
Carbendazim	Emamectin	Fosthiazate	Pirimiphos-methyl	Triadimenol
Carbofuran	Epoxiconazole	Haloxyfop-P	Propargite	Triclopyr
Chlormequat	Ethephon	Imazalil	Propiconazole	Ziram
Chlorpropham	Ethylene oxide	Imidacloprid	Propineb	Zeta-cypermethrin

In addition, during the evaluation of the active substances listed above, the toxicological information for the following metabolites was collected since they were considered relevant in the context of craniofacial alterations:

1,2,4-triazole (triazole derivative metabolite (TDM))	Prothioconazole-desthio[(a)]
3,5,6-trichloro-2-pyridinol (3,5,6-TCP, metabolite of chlorpyrifos, chlorpyrifos-methyl and triclopyr)	R154719 (metabolite of fluazifop-P)
Delta 8,9 isomer of avermectin B1a (metabolite of abamectin)	Triazole acetic acid (TDM)
Ethylene thiourea (ETU, common metabolite of maneb, mancozeb, and metiram and zineb)	Triazole alanine (TDM)
Propylene thiourea (PTU, metabolite of propineb)	Triazole lactic acid (TDM)
Prothioconazole-sulfonic acid[(b)]	

(a): 1-(2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl)-1H-1,2,4-triazol-5(4H)-one.
(b): 1-(2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl)-1H-pyrazole-5-sulfonic acid.

2.1.2.2. Collection of data

The sources scrutinised to retrieve toxicological information on the craniofacial alterations caused by the selected active substances were draft assessment reports (DAR), draft renewal assessment reports (DRARs) related to EFSA conclusions on the pesticide risk assessment in the context of Regulation (EC) No 1107/2009, Joint Meeting on Pesticide Residues (JMPR) evaluations, harmonised classification and labelling (CLH) reports submitted to the European Chemicals Agency and Committee for Risk Assessment (RAC) Opinions and other data in the context of the 'one-substance-one assessment' approach (e.g. Opinions by the Biocidal Products Committee (BPC) when the active substance has also been assessed as a biocide) finalised by 31 December 2020 at the latest.

According to the data requirements for active substances, as set in Regulation (EU) 283/2013, at least two species (i.e. rat and rabbit in the case of administration by the oral route) are required to

assess developmental toxicity. Information from other developmental studies in hamster and mice and reproduction studies was also collected when indicators of the specific craniofacial alterations were observed.

A spreadsheet was set up in Excel as template of a database to collect all the observations of interest from the available studies for the 85 selected active substances (Annex A – see front sheet for details on all recorded parameters about the study design and the observed effects). Standardised modalities, including a harmonised list of terminologies for the indicators of craniofacial alterations, to record the information were discussed and agreed to ensure the consistency of the data collection process.

Entries in the spreadsheet were created when indicators of the specific effects listed in Section 3.1.2 were observed in studies reported in the scrutinised sources either: (1) under a clear dose–response relationship[2] in the number of affected litters and/or fetuses; (2) at the highest dose only; (3) at the only tested dose; (4) in at least two dose levels without dose–response relationship due to being possibly masked by high maternal or fetal toxicity; or (5) at no dose-related incidence (i.e. when the indicator was observed with the same incidence at low and mid dose and higher incidence at the top dose, when the indicator was observed with the same incidence at mid and top dose or whenever the indicator was not showing a dose–response relationship but was observed with a relatively high incidence, unusual for this type of indicator and/or outside historical control data (HCD)).

In the assessment of the dose–response relationship, particular attention was dedicated to the incidence of alterations expressed as number of affected litters in the control and treated groups. Indeed, experimentally, the treated unit is the pregnant dam, and it is known that responses to treatment of fetuses or pups within a litter may be correlated, particularly in strains with low variability within pups (Hood, 2005). However, in the setting of no observed adverse effect levels (NOAELs) and lowest observed adverse effect levels (LOAELs), both litter and fetal incidences were considered.

In the case of substances for which observations as defined above were collected:

- One entry (corresponding to one individual line) was created per indicator of craniofacial alteration observed and per study. If more than one indicator of craniofacial alterations was observed in one study, these were recorded as distinct entries.
- One entry was created per each additional study available where no indicator of craniofacial alterations was observed. In these entries, only information about the study design was reported.

In the case of substances for which no observation as defined above was collected, one entry only was created with the name of the active substances indicated in strikethrough. To facilitate their identification, these entries were shaded in grey.

The data collection was performed by three independent experts, each one being assigned to about one-third of the 85 active substances.

Considering the size and the complexity of the information to be scrutinised, a quality check procedure was put in place to cross-check the data retrieved by every individual expert for each of the 85 active substances. Specific checkpoints (see Note 3 of Appendix F) were defined in advance and used to check the accuracy, clarity and consistency of the information reported. The quality check was done first by each individual expert for his/her own entries in the Excel database. Following this, the cross-check was repeated by the involved experts by randomly assigning the substances within the group. The comments were shared between the experts and inconsistencies were resolved. As a final step for an optimal harmonisation of the entries, a fourth expert not originally involved in the data collection checked the data entries for all the substances based on the agreed checkpoints.

The vast majority of the entries in the database were collected from studies assessed as 'acceptable' in the scrutinised sources of information. A fraction of the entries was also collected from studies assessed as 'supportive', 'supplementary', 'of limited reliability' or 'unacceptable' in the scrutinised sources. In this case, they were evaluated for their acceptability for the specific assessment of craniofacial alterations. They were taken into consideration for the elaboration of the CAGs and the characterisation of the substances as long as the limitations observed did not affect the validity of the observations relevant to craniofacial alterations. Studies considered unacceptable regarding the assessment of craniofacial alterations were disregarded.

[2] A clear dose–response relationship was considered demonstrated when the incidences of the indicators for the specific effect of interest were progressively increasing with the doses and the effect was considered biological relevant in at least two consecutive dose levels, including the highest dose and outside HCD.

RAC opinions were used whenever more detailed information on the effects of relevance was available for a specific substance (e.g. ethylene oxide). They were also consulted to check the classification status of the substances for developmental toxicity and if the craniofacial effect of interest was triggering such classification, this information was reported under the column 'Remarks' of the Excel template.

2.1.2.3. Establishment of CAGs

An active substance or metabolite was included in a CAG if one or more entries related to the respective indicators from a study considered as acceptable for the assessment of craniofacial alterations was present in the Excel template. The entries concerning indicators observed within the HCD and concluded as not related to treatment during the peer review of the substance by EFSA were disregarded.

This implies that a clear dose–response relationship was not a criterion for the inclusion of a substance in a CAG and that substances were included regardless of the presence of maternal toxicity.[3]

2.1.3. Toxicological characterisation of the substances included in the CAGs

Each substance included in the CAGs was characterised by the assignment of an NOAEL and an LOAEL for the respective specific craniofacial alteration.

Only studies considered as acceptable for the assessment of craniofacial alterations and where the test compound was administered by the oral route (gavage or dietary) were considered. Developmental toxicity studies and generational studies were considered of equal weight. Similarly, all indicators were considered of equal relevance and weight for the purpose of toxicological characterisation of substances included in the CAG.

In case a set of two or more studies of equivalent quality were available and testing different dose ranges, they were considered collectively to derive combined NOAEL and LOAEL for this set of studies. Studies were considered as being of equivalent quality and appropriate for a collective evaluation when

1) they were performed:
   - in the same species
   - in the same strain
   - by the same administration route
2) they were judged to have the same level of acceptability (i.e. 'acceptable' or 'of limited acceptability') for the assessment of craniofacial alterations (column AE of Annex A).

In case a study failed to identify an NOAEL and only provided an LOAEL for the indicators of interest, a default NOAEL was derived from this LOAEL by applying an extra uncertainty factor (UF). Although the EFSA guidance on default values to be used in the absence of measured data (EFSA Scientific Committee, 2012) recommends defining the size of such extra UF on a case-by-case basis, the concerned studies were not reassessed, and it was decided to apply a systematic approach and use an UF of 10.

The lowest of all observed LOAELs in studies (or sets of studies of equivalent quality) was adopted as the overall LOAEL of the substance in the respective CAG.

The overall NOAEL of the substance, to be used in the exposure calculations, was set at the highest tested dose in the same species and strain with no observed effect among all the fully acceptable studies (or at the default NOAEL mentioned above when it was above all the tested doses with no observed effects in other studies) that was below the overall LOAEL. Studies of limited acceptability were used when fully acceptable studies were not available, or in a few cases where fully acceptable studies did not provide an NAOEL or used a range of tested doses that was considered to be too low. To identify these cases, studies of limited acceptability used for the toxicological characterisation of substances are pinpointed in Appendices A1 or A2.

[3] This could result in the inclusion of a substance in a CAG although the observed effects have been disregarded in the setting of the ARfD of the substance during the peer review of the substance. The conservatism used to establish CAGs in the present assessment is, however, fully considered in the uncertainty analysis, which takes account of the probability that the substances included in the CAGs are actually causing the effect of concern.

Information on statistical significance of the observations concerning the indicators of craniofacial alterations were not taken into consideration for the allocation of a substance in a CAG or its characterisation but was rather discussed in the uncertainty analysis (Section 3.3).

The EFSA conclusions on the pesticide risk assessment in the context of Regulation (EC) No 1107/2009 finalised by the end of 2020 and dealing with the active substances included in the CAGs were considered to retrieve any element of expert judgement regarding the observations related to craniofacial alterations. Additionally, the NOAELs proposed for craniofacial effects were compared against the NOAELs taken into account for the derivation of the ARfD for the substances under consideration. For active substances not reviewed by EFSA, the ARfDs established by the body constituting the main source of the data collection (e.g. JMPR evaluations) were considered.

2.1.4. Procedure and quality check

Using the data collection as consolidated after the quality check (Section 2.1.2.2) and the criteria described in Section 2.1.3, two experts established CAG-DAC and CAG-DAH independently and assigned to each substance included an overall NOAEL and LOAEL for the respective effect. For this, they used a predefined template (Appendices A1 and A2). Then, they compared their individual entries and where appropriate cross-checked them against the information collected in the Excel database. After this was done, differences between the individual assessments by the two experts were discussed and the CAGs were agreed by consensus.

2.1.5. Weight of evidence assessment and elicitation of CAG-membership probabilities

The amount, reliability, relevance and consistency of evidence for causing craniofacial alterations vary among active substances. This makes it uncertain as to which substances should be included in a given CAG, with some substances being more likely to belong to a certain CAG than others. This can be quantified by assessing the probability that any substance actually causes the specific effect. In this report, this probability is referred to as CAG-membership probability.

The weight of evidence assessment was a stepwise process comprising the following sequence of tasks:

- Defining in precise terms the assessment question applicable to each substance included in the CAG.
- Identifying lines of evidence (LOE) that were important for assessing whether the substance causes the effect: LOEs typically include the indicators of the specific effect under consideration but are not necessarily restricted to these indicators. Depending on the specific effect, additional factors contributing to the evidence can be defined.
- Rating qualitatively the weight of each LOE: the LOEs are assessed with respect to their reliability and relevance to the assessment question. This assessment is conducted by expert discussion and results in rating each LOE for the strength of its contribution to the probability of the substance causing the effect.
- Reviewing the evidence available for individual substances included in the CAG.
- Listing the LOEs available for individual substances.
- Assessing for individual substances the CAG-membership probability using the 'approximate probability scale' from the EFSA's uncertainty guidance (EFSA Scientific Committee, 2018a).

The weight of evidence assessment was conducted by expert knowledge elicitation (EKE) (EFSA, 2014a). Two types of elicitation were performed: the elicitation of the weight of each LOE and the elicitation of the CAG-membership probability. In theory, the CAG-membership probability can be assessed for all the substances included in the CAG, as this was done when CAGs for the effects of pesticides on the nervous system and the thyroid were established (EFSA, 2019b,c). However, this process is time-consuming, and experience has shown that the outcome of a CRA is in most cases driven by a limited number of active substances. Therefore, it was decided to apply this procedure solely to the active substances emerging as risk drivers from the cumulative exposure assessment.

Five toxicology experts participated to the EKE processes (Anna Castoldi, Tamara Coja, Federica Crivellente, Kyriaki Machera and Elena Menegola).

The elicitation of the weight of each LOE was conducted in two steps. In the first step, the experts were requested to consider each LOE separately and to rate it as 'low', 'intermediate' or 'high' for its contribution to the certainty that a substance is actually causing the effect under consideration. The

experts made their judgement remotely and individually, and the answers provided by the experts were then collated. In the second step, differences in judgements were discussed during a Microsoft Teams meeting with a facilitator to develop a consensus judgement.

The elicitation of CAG-membership probabilities was conducted in a similar two-step process. The experts were first trained in the elicitation method to be used and the type of judgements required. The experts were then requested to evaluate the CAG-membership probability of each risk driver in each CAG. They made their judgement individually and remotely, being aware of the consensus judgement about the weight of each LOE. The answers provided by the experts were then collated, and in a second step, differences were discussed during a Microsoft Teams meeting with a facilitator to develop a consensus judgement.

2.2. Cumulative exposure assessments using SAS® software

2.2.1. General principles

The cumulative exposure to pesticide residues was assessed in accordance with the guidance on probabilistic modelling of dietary exposure to pesticide residues (EFSA PPR Panel, 2012). Acute exposure estimates were obtained using a two-dimensional method where variability is modelled by means of an inner loop execution, and uncertainty is modelled through an outer loop execution (see Figure 1).

The ***primary input data*** required for modelling cumulative exposure to pesticide residues are occurrence data (i.e. the amounts of pesticide residue that are present in foods) and food consumption data (i.e. the types and amounts of those food consumed in a person's diet). These data are stored in the EFSA Data Warehouse. When the exposure calculations are initiated, the data for the relevant food commodities, active substances and dietary surveys are extracted.

Within the ***inner loop execution***, occurrence data are subject to several simulations and imputations. These adjustments are intended to account for inaccuracies and missing information in the occurrence data set (e.g. unspecific measurements, measurements below the analytical limit of quantification (LOQ), etc.). The consumption data and adjusted occurrence data are then used to estimate acute dietary exposures using an empirical Monte Carlo simulation (i.e. with 100,000 iterations). This results in a distribution that represents the variability of acute exposures within the population.

The different simulations performed during the inner loop execution require the use of additional data, referred to as ***secondary input data***. This includes various types of data which can be used either for the adjustment of the occurrence data (e.g. authorised uses of active substances on specific crops) or for improvement of the exposure estimates (e.g. processing factors (PFs)).

To quantify the uncertainties, the model uses an ***outer loop execution*** where the inner loop execution is repeated several times. Prior to each execution, the original consumption and occurrence data sets are modified by means of bootstrapping, a random resampling technique for quantifying sampling uncertainty. By repeating the inner loop execution multiple times (i.e. 100), the model produces multiple distributions of exposure. The differences between those distributions reflect the sampling uncertainty around the true distribution of exposures.

During the ***output preparation***, summary statistics (i.e. percentiles of exposure) are generated for the multiple distributions, resulting in multiple estimates for each percentile of exposure. From these multiple estimates, confidence intervals around each percentile are produced. Subsequently, to identify risk drivers, details on the highly exposed consumers are extracted (i.e. consumers with exposure exceeding the 99th percentile) and average contributions per food commodity and active substance are calculated.

According to the risk management principles agreed among Member States (European Commission, online), the methodology described above is applied in a tiered approach. While the first-tier calculations (Tier I) use very conservative assumptions, the second-tier assessment (Tier II) includes assumptions that are more refined but still intended to be conservative. Furthermore, in order to better understand the impact related to some of the assumptions and uncertainties, several sensitivity analyses were carried out.

All extractions, simulations, imputations and calculations described in the subsequent sections were programmed with SAS® Studio 3.8 (Enterprise Edition).

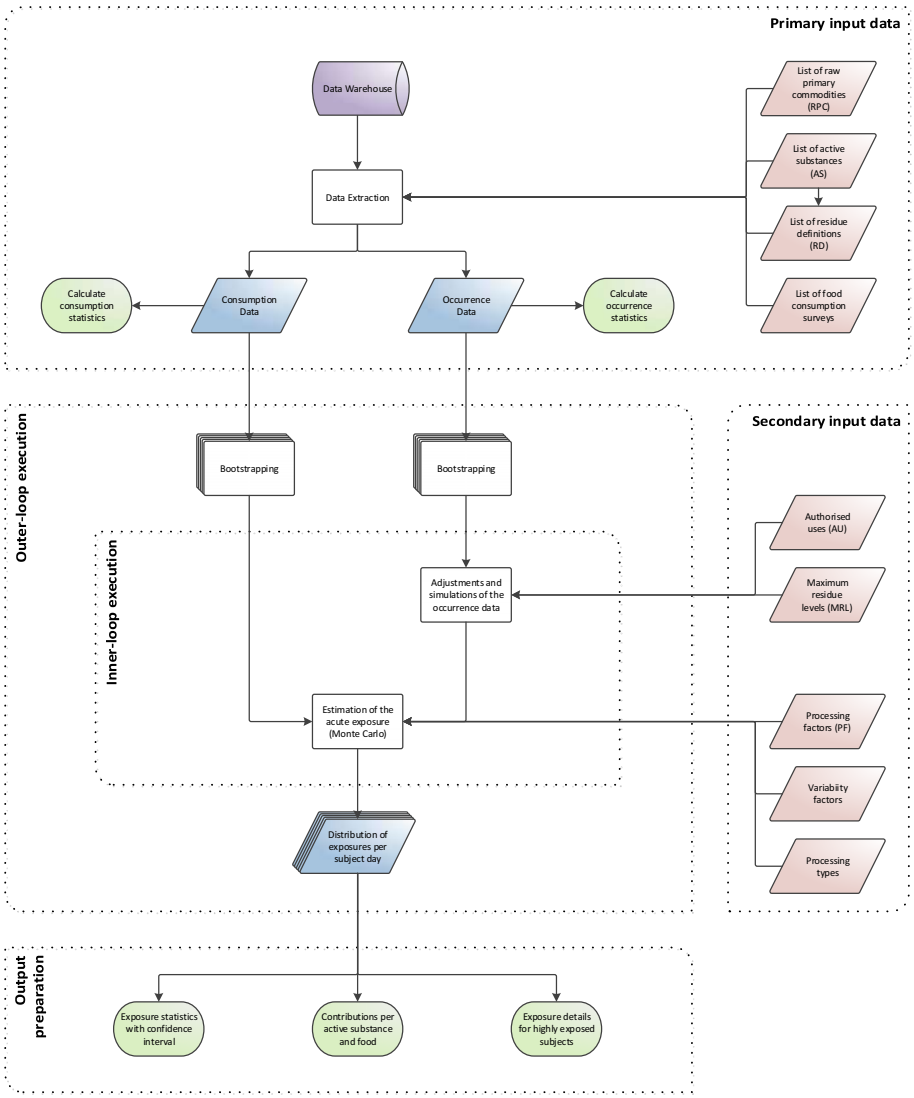


Figure 1: General process for calculating acute cumulative exposure to pesticides

2.2.2. Primary input data

2.2.2.1. Raw primary commodities

EFSA selected 36 raw primary commodities (RPCs) of plant origin that are widely consumed in Europe (EFSA, 2015a). In addition, water and foods specifically intended for infants and young children were integrated in the exposure assessment based on their importance in (certain) diets. The full list of the incorporated food commodities is provided in Annex B1, Table A.1.02 and Annex B2, Table A.2.02. The variables used to describe each food commodity are reported in Table 1.

Table 1: Description of the key variables used to describe the RPCs

Name	Label	Description
prodCode	RPC code	Code of the RPC as defined by EFSA's harmonised terminology for scientific research (MATRIX catalogue; EFSA, 2019d).
prodName	RPC name	Name of the RPC as defined by EFSA's harmonised terminology for scientific research (MATRIX catalogue; EFSA, 2019d).

For the dietary surveys used in this assessment (see Section 2.2.2.5), the average contribution of the 36 RPCs to the total consumption of plant commodities (excluding sugar plants) ranges from 75 to 89%.

2.2.2.2. Active substances

The active substances and metabolites considered for cumulative exposure assessment derived from the establishment of the CAGs (see Section 2.1.2). However, occurrence data were not available for all substances and metabolites.

The toxicity of the substances within each CAG is defined by means of the NOAEL. For one substance (ethylene oxide), the established NOAEL was however not appropriate for dietary risk assessment (Section 3.1.4).

The lists of active substances and metabolites considered for each CAG (incl. key input data) are presented in Annex B1, Table A.1.01 and Annex B2, Table A.2.01. The variables contained in the list of active substances are described in Table 2.

Table 2: Description of the variables contained in the list of active substances

Name	Label	Description
paramCode_AS	Substance code	Code of the active substance as defined by EFSA's harmonised terminology for scientific research (PARAM catalogue; EFSA, 2019d).
paramName_AS	Substance name	Name of the active substance as defined by EFSA's harmonised terminology for scientific research (PARAM catalogue; EFSA, 2019d).
Approval_status	Approval status	Approval status of the active substance, as defined under Regulation (EC) No 1107/2009.
NOAEL	NOAEL	NOAEL of the active substance (Appendices A1 and A2).
Mechanism	Mechanism of action	Short reference to the mechanism of action or to the mode of action (MoA), where available (Appendices A1 and A2).
Study_type	Study type	Type of regulatory toxicity study required by Regulation (EC) No 1107/2009 from which the NOAEL has been derived (Appendices A1 and A2).

2.2.2.3. Residue definitions

While the CAGs are defined at the level of the pesticide active substances, the occurrence data reported to EFSA refer to a residue definition for enforcement purposes (see Section 2.2.2.4). As the residue definitions, defined by Regulation (EC) No 396/2005, may change over time, single active substances may be associated with multiple residue definitions throughout the reference period. EFSA therefore collected all the residue definitions that were applicable to the selected food commodities and active substances during the reference period 2017–2019. The residue definitions collected for each CAG are presented in Annex B1, Table A.1.03 and Annex B2, Table A.2.03.

Depending on the metabolism and availability of analytical methods, residue definitions may either be equal to the active substance, include additional metabolites, or even incorporate multiple active substances. When the residue definition includes additional metabolites, which are specific to the active substance (i.e. a *complex* residue definition), the residue definition is assigned to the active substance assuming that the metabolite will have the same toxicological properties as the parent compound (e.g. sum of tebuconazole, hydroxy-tebuconazole and their conjugates, expressed as tebuconazole). When the residue definition includes or applies to multiple active substances, however, the active substances may have different toxicological properties (e.g. dithiocarbamates). The latter are referred to as *unspecific* residue definitions.

When active substances are associated with an unspecific residue definition (e.g. sum of carbendazim and thiophanate-methyl, expressed as carbendazim), further distinction is made between exclusive and non-exclusive associations:

- Supposing that carbendazim would be applied to the field, carbendazim cannot be metabolised into thiophanate-methyl and the measured residue would be attributed to carbendazim only. In this case, the association is considered exclusive.
- Supposing that thiophanate-methyl would be applied to the field, thiophanate-methyl would partially metabolise into carbendazim. In this case, only a proportion of the measured residue would be attributed to thiophanate-methyl and the remaining part would be attributed to carbendazim. Hence, the association is not exclusive.

Data on the proportions however were not readily available to EFSA. Therefore, a default proportion of 0.5 (≈ 50%) was assumed for all associations that are not exclusive.

To allow for the correct allocation of active substances to the measured residues (see Section 2.2.4.1.1), this information was integrated in the list of residue definitions. Table 3 provides an overview of all relevant variables.

Table 3: Description of the variables contained in the list of residue definitions

Name	Label	Description
paramCode_RD	Residue code	Code of the residue definition as defined by EFSA's harmonised terminology for scientific research (PARAM catalogue; EFSA, 2019d).
paramName_RD	Residue name	Name of the residue definition as defined by EFSA's harmonised terminology for scientific research (PARAM catalogue; EFSA, 2019d).
paramCode_AS	Substance code	Code of the associated active substance(s) as defined by EFSA's harmonised terminology for scientific research (PARAM catalogue; EFSA, 2019d).
paramName_AS	Substance name	Name of the associated active substance(s) as defined by EFSA's harmonised terminology for scientific research (PARAM catalogue; EFSA, 2019d).
MW_factor	MW conversion factor	Multiplication factor used to convert the amount of measured residue into active substance. This factor is derived from the molecular weights (MW) of both compounds.
Is_exclusive	Exclusive	Indicates whether the association between active substance and residue definition is exclusive.
Proportion	Proportion	Estimated proportion of the active substance within the associated residue definition, only applicable when the association is not exclusive.

2.2.2.4. Occurrence data

The occurrence data collected under Article 31 of Regulation (EC) No 396/2005 are the most appropriate data available to EFSA for performing a retrospective exposure assessment to pesticide residues. These data are obtained from the official control activities carried out in the EU Member States, Iceland and Norway. These data are reported to EFSA using the Standard Sample Description (SSD) (EFSA, 2010, 2013). Although the occurrence data are collected at the level of individual measurements, the SSD allows identification of measurements associated with a single food sample (e.g. samples analysed for multiple pesticide residues). After validation by EFSA, the collected data are integrated in the EFSA Data Warehouse.

All occurrence data referring to the relevant food commodities (see Section 2.2.2.1) and residue definitions (see Section 2.2.2.3) were extracted from the Data Warehouse. Only measurements validated under the 2017, 2018 and 2019 EU reports on pesticide residues in food were included (EFSA, 2019a, 2020c, 2021b).

According to the risk management principles agreed among Member States (European Commission, online), the following additional criteria were applied to the extracted data.

- Only samples resulting from the EUCP, national control programmes or a combination of those were selected (SSD codes K005A, K009A and K018A). Samples associated with increased control programmes on imported food (SSD code K019A) or any other type of programme were excluded as they were not considered to be representative of the market.
- Only samples obtained through selective or objective sampling were retained (SSD codes ST10A and ST20A). Samples obtained through suspect sampling (ST30A) or any other type of sampling were not considered to be representative of the market and therefore excluded.
- When the occurrence data were primarily reported for the RPC, samples for processed commodities were excluded and the assessment was based on the RPCs. However, when the occurrence data for the RPC were not available or fewer than for the processed derivatives (i.e. wine grapes, olives for oil production and foods for infants and young children), occurrence data for the processed foods were also retained.
- Only measurements reported as a numerical (i.e. quantifiable) value or as a non-quantified value were considered useful for the assessment (SSD codes VAL and LOQ). Other result types were not considered valid and therefore excluded.
- Only measurements reported for the enforcement residue definition that was applicable at the time of sampling, or for the most complete subset of the residue definition were used (SSD

codes P004A and P005A). Measurements referring to parts of the residue definition were excluded from the assessment.
- When the LOQ value for a measurement could not be reported by the Member States (i.e. for residue definitions composed of multiple components), the median LOQ of all measurements referring to the same combination of commodity and residue definition was assumed.
- When the LOQ value for a measurement was found to be more than 100 times higher compared to the median LOQ of all measurements referring to the same combination of commodity and residue definition, the measurement was no longer considered valid and excluded from the assessment.
- When several measurements with overlapping residue definitions were reported for the same sample, only the measurement referring to the most recent residue definition was retained for assessment.

Occurrence data from all EU Member States, Iceland and Norway were pooled into one single data set for each CAG.[4] The key variables retained in the occurrence data set are summarised in Table 4.

Considering the size of the occurrence data sets, only the summary statistics per residue definition and food commodity are reported (see Annex B1, Table A.1.09 and Annex B2, Table A.2.09). Occurrence data for water were not available to EFSA and were therefore imputed according to the assumptions elaborated in Section 2.2.4.1.4.

Table 4: Description of the variables contained in the occurrence data set

Name	Label	Description
labSampCode	Sample code	Alphanumeric code of the analysed sample.
prodCode	RPC code	Code of the RPC as defined by EFSA's harmonised terminology for scientific research (MATRIX catalogue; EFSA, 2019d).
prodName	RPC name	Name of the RPC as defined by EFSA's harmonised terminology for scientific research (MATRIX catalogue; EFSA, 2019d).
prodTreat	Treatment code	FoodEx2 facet code describing the treatment (or processing technique) that was applied to the analysed sample, including additional descriptors such as qualitative information or the nature of the food (EFSA, 2015b).
paramCode	Residue code	Code of the residue definition as defined by EFSA's harmonised terminology for scientific research (PARAM catalogue; EFSA, 2019d).
paramName	Residue name	Name of the residue definition as defined by EFSA's harmonised terminology for scientific research (PARAM catalogue; EFSA, 2019d).
resLOQ	Limit of quantification	The lowest quantifiable amount (in mg/kg) detectable by the laboratory's analytical system.
resVal	Result value	Concentration of the measured residue (in mg/kg) within the analysed sample.
resType	Result type	Indicates the type of result, whether it could be quantified/determined or not.

2.2.2.5. Consumption data

The EFSA Comprehensive European Food Consumption Database (Comprehensive Database) provides a compilation of existing national information on food consumption at individual level. It was first built in 2010 (EFSA, 2011; Huybrechts et al., 2011; Merten et al., 2011). Details on how the Comprehensive Database is used are published in the Guidance of EFSA (EFSA, 2011). Data reported in the Comprehensive Database may either refer to RPCs, RPC derivatives (i.e. single-component foods altered by processing) or composite foods (i.e. multicomponent). Consumption data for RPC derivatives and composite foods, however, cannot be used in exposure assessments when the occurrence data are reported for the RPCs.

To address the above issue, EFSA transformed the Comprehensive Database into a new RPC Consumption Database by means of the RPC model (EFSA, 2019e). This model converts the consumption data for composite foods or RPC derivatives into their equivalent quantities of RPCs. The

[4] Occurrence data included in the assessment were submitted to EFSA when the UK was a member of the EU, or in a period when, in accordance with the Agreement on the Withdrawal of the UK from the EU, and in particular with the established transition period, the EU requirements on data sampling also applied to the UK.

RPC model was applied to the Comprehensive Database as of 31 March 2018, when it contained results from 51 different dietary surveys carried out in 23 different Member States covering 94,523 individuals.

Considering that the effects considered for the establishment of the CAG occur during pregnancy and embryogenesis, and in the absence of food consumption surveys representative of women in the first months of pregnancy, the food consumption data extracted from the RPC Consumption Database were limited to women of childbearing age (i.e. adult women aged from 18 to 45 years old). Furthermore, in order to cover as many populations as possible without compromising the reliability of intake estimates at the 99.9th percentile of the distribution, only the dietary surveys with more than 300 survey subjects were retained, covering 14 different countries. An overview of the selected dietary surveys is provided in Annex B1, Table A.1.04 and Annex B2, Table A.2.04.

Using the extraction criteria described above, a single consumption data set was obtained for acute exposure assessment of both CAGs. The key variables retained in the food consumption data set are summarised in Table 5. Summary statistics on the quantities of RPC consumed per country, survey and population class are reported (see Annex B1, Table A.1.10 and Annex B2, Table A.2.10).

Table 5: Description of the variables contained in the food consumption data set

Name	Label	Description
Country	Country	Country where the dietary survey took place as defined by EFSA's harmonised terminology for scientific research (COUNTRY catalogue; EFSA, 2019d).
Survey	Survey	Acronym of the dietary survey.
PopClass	Population class	Participant's population class, based on age, as defined by EFSA's harmonised terminology for scientific research (AGECLS catalogue; EFSA, 2019d).
ORSUBID	Subject ID	A pseudonymised subject ID number generated by EFSA upon receipt of the data.
Weight	Body weight	Body weight of the subject (in kg).
ndays	Number of survey days	Number of days on which the participant's consumption was surveyed.
day	Survey day	Ordinal number of the day on which the participant's consumption was surveyed.
prodCode	RPC code	Code of the RPC as defined by EFSA's harmonised terminology for scientific research (MATRIX catalogue; EFSA, 2019d).
prodName	RPC name	Name of the RPC as defined by EFSA's harmonised terminology for scientific research (MATRIX catalogue; EFSA, 2019d).
FoodEx2_Facets	Processing code	FoodEx2 facet code describing the processing technique that was applied to the food consumed, including additional descriptors such as qualitative information, part consumed or the nature of the food (EFSA, 2015b).
RPCD_amount	RPCD amount	Amount of RPC derivative (in grams).
RPC_amount	RPC amount	Amount of RPC (in grams).

2.2.3. Secondary input data

2.2.3.1. Maximum residue levels

Certain assumptions on the authorised uses require information on the MRLs. An MRL is the upper legal level of a concentration for a pesticide residue in or on food or feed set in accordance with Regulation (EC) No 396/2005. This regulation also defines a procedure for the setting and modification of MRLs. MRLs may therefore have been modified throughout the 2017–2019 reference period. Hence, to obtain a single list of MRLs, EFSA decided to use the MRLs as of 31 December 2019 (i.e. the end of the reference period) and it was assumed that those MRLs were applicable during the entire reference period, regardless of whether the MRL or residue definition may have changed during that period.

MRLs for the relevant food commodities and residue definitions were extracted from the EU Pesticides Database and organised in a data format that can be used directly for exposure assessment (see Annex B1, Table A.1.05 and Annex B2, Table A.2.05). Table 6 describes the variables that were part of this data format.

Table 6: Description of the variables contained in the list of MRLs

Name	Label	Description
paramCode_RD	Residue code	Code of the residue definition as defined by EFSA's harmonised terminology for scientific research (PARAM catalogue; EFSA, 2019d).
paramName_RD	Residue name	Name of the residue definition as defined by EFSA's harmonised terminology for scientific research (PARAM catalogue; EFSA, 2019d).
prodCode	RPC code	Code of the RPC as defined by EFSA's harmonised terminology for scientific research (MATRIX catalogue; EFSA, 2019d).
prodName	RPC name	Name of the RPC as defined by EFSA's harmonised terminology for scientific research (MATRIX catalogue; EFSA, 2019d).
MRL	MRL (mg/kg)	Numerical value of the MRL as defined by Regulation (EC) No 396/2005, expressed in mg/kg.
atLOQ	MRL at LOQ	Indicates whether the MRL is set at the analytical LOQ. Under Regulation (EC) No 396/2005, such MRLs are marked with an asterisk (*).

2.2.3.2. Authorised uses

In some cases, the imputations and simulations performed on the occurrence data rely on the authorisations for use of plant protection products containing the active substance(s) (see Section 2.2.4.1). While the approval status of an active substance under Regulation (EC) No 1107/2009 is regulated at EU level, the authorisations for use on specific crops are delivered at national level within the EU Member States. A centralised database compiling these national authorisations is not yet available at EU level.

National authorisations can be reported to EFSA under Regulation (EC) No 396/2005, either for an MRL application under Article 10, or for an MRL review under Article 12. There is, however, no legal obligation to systematically report all national authorisations and the MRL review programme is still in progress. A comprehensive overview of all pesticide authorisation within the EU is therefore also not available to EFSA. Meanwhile, a tentative list of authorised uses was elaborated according to the following principles.

- When the MRL for a given combination of active substance and RPC was not set at the LOQ, the active substance was assumed to be authorised for use on that specific commodity. This assumption also accounts for uses authorised outside the EU and for which treated products may be placed on the EU market. Furthermore, this assumption concerns non-approved substances, including persistent organic pollutants, which are assumed to be authorised on crops for which MRLs are above the LOQ.
- When non-LOQ MRLs referred to unspecific residue definitions (i.e. including or applying to multiple active substances, see also Section 2.2.2.3), only the substances approved under Regulation 1107/2009 were assumed to be authorised for use on that crop. If none of the active substances was approved, it was assumed that any substance may be authorised for use outside the EU.
- When non-LOQ MRLs refer to an active substance that is phased out under Regulation 1107/2009 (e.g. carbendazim) but may still occur as a metabolite from another active substance (thiophanate-methyl), the MRL was not considered to represent an authorised use of the active substance that was phased out.
- For the group of dithiocarbamates, which comprises six substances, Regulation (EC) No 396/2005 provides specific information on the active substances that were considered for deriving the MRLs. Authorised uses for these active substances were identified accordingly.
- For the remaining combinations of active substance and RPC (i.e. where the MRL was set at LOQ), EFSA screened the relevant reasoned opinions issued under Regulation (EC) No 396/2005. Any authorised use reported in those reasoned opinions was recorded. Otherwise, it was assumed that the use was not authorised.

The authorised uses collected by EFSA were integrated in a data format that can be readily used for exposure assessment (see Annex B1, Table A.1.06 and Annex B2, Table A.2.06). Table 7 describes the variables of this data format.

Table 7: Description of the variables contained in the list of authorised uses

Name	Label	Description
paramCode_AS	Substance code	Code of the active substance as defined by EFSA's harmonised terminology for scientific research (PARAM catalogue; EFSA, 2019d).
paramName_AS	Substance name	Name of the active substance as defined by EFSA's harmonised terminology for scientific research (PARAM catalogue; EFSA, 2019d).
prodCode	RPC code	Code of the RPC as defined by EFSA's harmonised terminology for scientific research (MATRIX catalogue; EFSA, 2019d).
prodName	RPC name	Name of the RPC as defined by EFSA's harmonised terminology for scientific research (MATRIX catalogue; EFSA, 2019d).
Source	Source	Indicates the source of the information (i.e. MRL legislation, MRL review or MRL application).
Reference	Reference	EFSA Journal reference to the relevant reasoned opinion (i.e. when the information was retrieved from an MRL review or application).

2.2.3.3. Processing factors

Occurrence data for pesticide residues are primarily collected at the level of the RPC, whereas food consumption data may be collected at the level of RPC, RPC derivative or composite food. Hence, for the purpose of this assessment, all consumption data for composite foods and RPC derivatives were converted into their equivalent quantities of RPCs (see Section 2.2.2.5). Combining occurrence and consumption data at RPC level implies that all residues present in the RPC will reach the end consumer. This assumption is very conservative because the residues will most likely be altered through processing, such as peeling, washing, cooking, etc.

The effect of processing is usually addressed by means of processing factors (PFs). PFs are the ratios between the residue concentrations in the processed commodity and in the RPC, as determined according to the residue definition for enforcement. A PF is specific to each RPC, processing type and active substance, and it accounts for both the chemical alteration of the substance and weight change of the food. In studies on the effect of processing, PFs are quantified by dividing the residue concentration in the processed commodity by the residue concentration in the raw commodity.

The European database on PFs is the most recent and the most comprehensive compilation of PFs currently available at EU level (Scholz et al., 2018a). PFs for the active substances and RPCs under assessment were extracted from the database according to the following criteria.

- For each active substance, RPC and processing technique only the median PF was extracted.
- Only the PFs indicated as reliable or indicative were extracted. PFs indicated as unreliable were excluded from the assessment.

Processing techniques reported in the PF database were then compared to the processing techniques reported in the RPC consumption data set. The processing techniques from both databases were matched according to the following principles:

- When a generic processing technique was reported in the RPC consumption database (e.g. juice) while more specific processing techniques were reported in the PF database (e.g. pasteurised juice and unpasteurised juice), the specific processing technique with the highest PF was selected.
- When a specific processing technique was reported in the RPC consumption database (e.g. mashed potato) while a more generic processing technique was reported in the PF database (e.g. boiled potato), the generic PF was applied to the specific processing techniques.
- PFs were extrapolated between RPCs with similar properties (i.e. grapefruits, oranges and mandarins, apples and pears, table and wine grapes, wheat and rye grain).
- PFs for peeling were applied to the corresponding fruit with inedible peel, even when the processing technique was not specified in the RPC consumption database (i.e. grapefruits, oranges, mandarins, bananas and melons).

Although the European database on PFs is the most comprehensive compilation of PFs currently available at EU level, this compilation is limited to all PFs that have been evaluated by EFSA until 30 June 2016. Meanwhile, additional PFs were assessed by EFSA in the framework of Regulation (EC) No 396/2005 and Regulation (EC) No 1107/2009. Additional PFs evaluated by EFSA until 31 December 2020 were therefore sourced manually and integrated in the current assessment.

By following these principles, lists of PFs were obtained for the assessment of both CAGs (see Annex B1, Table A.1.07 and Annex B2, Table A.2.07, respectively). Table 8 describes the variables contained in the list of PFs.

Table 8: Description of the variables contained in the list of PFs

Name	Label	Description
paramCode_AS	Substance code	Code of the active substance as defined by EFSA's harmonised terminology for scientific research (PARAM catalogue; EFSA, 2019d).
paramName_AS	Substance name	Name of the active substance as defined by EFSA's harmonised terminology for scientific research (PARAM catalogue; EFSA, 2019d).
prodCode	RPC code	Code of the RPC as defined by EFSA's harmonised terminology for scientific research (MATRIX catalogue; EFSA, 2019d).
prodName	RPC name	Name of the RPC as defined by EFSA's harmonised terminology for scientific research (MATRIX catalogue; EFSA, 2019d).
facetCode	Processing code	FoodEx2 facet code describing the processing technique, including additional descriptors such as qualitative information, part consumed or the nature of the food (EFSA, 2015b).
facetDesc	Processing description	Description of the processing code.
procFac	Processing factor	Numerical value representing the expected residue concentration in the processed commodity divided by the residue concentration in the raw commodity.
Source	Source	Indicates the source of the information (i.e. type of report).
Reference	Reference	Journal reference to the relevant report.
Comment_PF	Comment	Indicates whether the PF relies on any type of assumption or extrapolation.

2.2.3.4. Variability factors

Acute exposure assessments for pesticide residues should account for variability among the single commodity units of the composite laboratory samples (see Section 2.2.4.2). To account for this variability, several parameters are required for each food commodity.

- Unit weight: estimated weight for a single commodity unit.
- Units per sample: estimated number of units within a composite laboratory sample.
- Variability factor (VF): expected variability among the single unit concentrations, which is defined as the ratio between the 97.5th percentile and mean of the distribution of unit concentrations.

Unit weights for each commodity were retrieved from the Pesticide Residues Intake Model (EFSA, 2018b). Commodities with a unit weight inferior to 25 g were not further considered because, in this case, the residue concentration in the composite laboratory sample is expected to reflect the residue concentration in the portion that would be consumed (FAO, 2003).

The number of units per sample was obtained from Commission Directive 2002/63/EEC, establishing community methods of sampling for the official control of pesticide residues in and on products of plant and animal origin. This directive defines a minimum weight and a minimum number of units for composite laboratory samples of each food category. Hence, the minimum number of units (as defined by Directive 2002/63/EEC) was used, unless the minimum sample weight divided by the corresponding unit weight was higher. In that case, the latter calculated value (rounded up to the next integer) was retained.

VFs were also retrieved from the Pesticide Residues Intake Model (EFSA, 2018b). According to the risk management principles agreed among Member States (European Commission, online), these factors were only used for the Tier I scenario. For the Tier II scenario, a more realistic VF of 3.6 applicable to market samples of food commodities (EFSA PPR Panel, 2005) was applied to all commodities having a unit weight above 25 g (see also Section 2.2.4.2).

As the above-mentioned parameters are defined by food commodity, the relevant variables were incorporated in the list of food commodities (see Annex B1, Table A.1.02 and Annex B2, Table A.2.02). Table 9 provides a complete overview of all the variables contained in the list of food commodities.

Table 9: Description of the variables contained in the list of RPCs

Name	Label	Description
prodCode	RPC code	Code of the RPC as defined by EFSA's harmonised terminology for scientific research (MATRIX catalogue; EFSA, 2019d).
prodName	RPC name	Name of the RPC as defined by EFSA's harmonised terminology for scientific research (MATRIX catalogue; EFSA, 2019d).
Cat_2002_63_EC	Category Directive 2002/63/EC	Commodity classification defined by Table 4 of the Annex to Commission Directive 2002/63/EC.
SampWeight	Minimum sample weight	Minimum size of each laboratory sample (expressed in kg) defined by Table 4 of the Annex to Commission Directive 2002/63/EC.
minUnits	Minimum units per sample	Minimum size of each laboratory sample (expressed in number of units) defined by Table 4 of the Annex to Commission Directive 2002/63/EC.
UnitWeight	Unit weight	Estimated weight (expressed in g) for a single commodity unit as reported in the Pesticide Residues Intake Model (EFSA, 2018b).
NrUnits	Units per sample	Estimated number of units required to obtain the minimum size of a laboratory sample, both in terms of weight and number of units.
VF	Variability factor	Default VF as reported in the Pesticide Residues Intake Model (EFSA, 2018b). This factor represents the variability among the single unit concentrations, which is defined as the ratio between the 97.5th percentile and mean of the distribution of unit concentrations.

2.2.3.5. Processing types

Variability among the single commodity units of the composite laboratory samples is not relevant when the food consumed is subject to processing techniques that involve bulking and blending.

EFSA therefore extracted all processing techniques reported in the RPC consumption data (see Section 2.2.2.5) and identified the processes that normally involve blending or bulking. Typically, these are processing techniques performed at industrial level (e.g. milling, oil production, etc.). Household processes, however, were assumed not to involve any bulking or blending (e.g. boiling, stewing, etc.). Although juicing may also be carried out at household level, EFSA assumed that most fruit juices are produced at industrial level.

The same list of processing types was used for the assessment of both CAGs (see Annex B1, Table A.1.08 and Annex B2, Table A.2.08). Table 10 describes the variables contained in the list of processing types.

Table 10: Description of the variables contained in the list of processing types

Name	Label	Description
Facets	Processing code	FoodEx2 facet code describing the processing technique, including additional descriptors such as qualitative information, part consumed or the nature of the food (EFSA, 2015b).
Facets_desc	Processing description	Description of the processing code.
Blending	Blending or bulking	Indicates whether the processing technique involves any type of blending or bulking.

2.2.4. Inner loop execution

2.2.4.1. Adjustments and simulations on the occurrence data

2.2.4.1.1. Allocation of active substances to occurrence data

While the CAGs are defined at the level of the pesticide active substances, the occurrence data reported to EFSA refer to residue definitions for enforcement purposes (see Section 2.2.2.3). Hence, the original occurrence data set obtained from the EFSA Data Warehouse is converted into a new intermediate data set where measurements are assigned to active substances instead of residue definitions.

Some of these residue definitions, however, referred to as unspecific residue definitions, may be associated with multiple active substances. Allocation of active substances to these unspecific residue definitions is performed in compliance with the risk management principles agreed among Member States (European Commission, online).

Under the Tier I assumptions, measurements for unspecific residue definitions are always assigned to the most potent active substance included in the CAG (i.e. the substance with the lowest NOAEL), regardless of its authorisation status in RPCs. This approach is expected to overestimate the exposure because a less potent active substance may have been used. This overestimation may be even more substantial when the most potent active substance is not authorised for use on the relevant commodity.

In Tier II calculations, each measurement is randomly assigned to one of the active substances authorised on that commodity, regardless of whether the active substance is part of the CAG or not. If none of the active substances associated with the unspecific residue definition is authorised for use on the commodity, any active substance is selected at random. Furthermore, special consideration is given to the active substances that may metabolise into another active substance, the non-exclusive substances. If the measurement is assigned to a non-exclusive substance (e.g. thiophanate-methyl), the model assumes that the measurement is partially composed of the assigned active substance while the remaining fraction is attributed to the active substance into which it metabolises (e.g. carbendazim), the exclusive substance.

A more detailed description of the methodologies used to allocate active substances to the occurrence data is provided in Appendix B.

Although the Tier II assumptions are expected to better reflect reality, some uncertainties related to this approach were still identified. Under ideal circumstances, the probability to select an active substance should be based on market share data for those active substances. Similarly, the proportion of the non-exclusive substance should be derived from the available metabolism data. Both market share data and metabolism data, however, were not readily available. In the absence of these data, assumptions on equal probability and equal proportion are applied instead. It should be noted that these assumptions may either underestimate or overestimate the exposure.

An additional uncertainty derives from the assumption that measurements for unspecific residue definitions result from the use of single active substances. This assumption implies that other active substances associated with that unspecific residue definition are not present (i.e. implicit zero measurements). Although it is unlikely that substances with similar pesticidal activity are used on the same crop, this possibility cannot be excluded.

2.2.4.1.2. Imputation of left-censored occurrence data

The imputation of left-censored occurrence data takes place after completion of the allocation of active substances to occurrence data.

Over 95% of the occurrence data used for the current exposure assessment are left-censored (see Section 2.2.2.4). Left-censored data are measurements reported below the LOQ and for which an accurate value is not available. Some of these results may be low positive residues while others will be true zeroes (no-residue situation).

To address the uncertainties resulting from the high proportion of left-censored data, measurements below the LOQ were imputed in compliance with the risk management principles agreed among Member States (European Commission, online).

Under Tier I assumptions, left-censored measurements were imputed with ½ LOQ when at least one positive result (i.e. above LOQ) was reported for a given substance–commodity combination. Measurements for all remaining combinations were imputed with a zero (i.e. assuming a no-residue situation).

For the Tier II assessment, use frequencies are estimated for each pesticide and each commodity, assuming that all samples were treated according to at least one agricultural use pattern (AUP). An AUP is one pesticide or a combination of several pesticides applied to a single commodity or crop. Information about the exact AUPs occurring in practice is not available. The AUPs and their frequencies are therefore subject to an assumption, which relies on the observed combination of pesticides from the CAG with measurable findings (i.e. above the LOQ) in the occurrence data set. The estimated use frequencies are then adjusted so that the total AUP frequency reaches 100% and the adjusted frequencies are used to calculate a proportion of true zeros and the corresponding number of left-censored measurements is selected at random from the data set. While the selected measurements

are imputed with zero, the remaining left-censored measurements are imputed with 1/2 LOQ. A more detailed description of the methodology is provided in Appendix C.

For authorised uses that result in pesticide residue concentrations below or close to the LOQ, the estimated use frequency will be 0% or close to 0% which is most likely an underestimation of the real use frequency. On the other hand, this scenario also assumes that the total AUP frequency is 100%, meaning that all commodities were treated according to at least one AUP, and consequently, tending to overestimate the exposure.

2.2.4.1.3. Imputation of missing occurrence data

The imputation of missing occurrence data takes place after completion of the imputation of left-censored occurrence data.

In acute cumulative exposure assessments, it is necessary to take account of any correlations that may exist between the concentrations of the different active substances within a given food sample (EFSA PPR Panel, 2012). Under the current assessment, the co-occurrence of chemicals within a single sample are accounted for because in the inner loop execution, the calculation model assigns to the amount of commodity consumed a random sample which includes measured concentrations for the different active substances (see Section 2.2.4.2). The samples, however, were not necessarily analysed for every substance of the CAG. Measurements within a sample may therefore be missing for some substances. The number of missing values for each substance–commodity combination can be retrieved from Annex B1, Table A.1.10 and Annex B2, Table A.2.10.

To avoid underestimation of the acute cumulative exposure, missing measurements are imputed according to the risk management principles agreed among Member States (European Commission, online).

For each substance–commodity combination, the number of missing values is counted, and the same number of measurements is randomly selected from the available data set. The missing values are then replaced with the selected measurements. The Tier I scenario uses a very conservative assumption where the missing value of the most contaminated sample is imputed with the highest possible imputation value. Under the Tier II scenario, a more realistic assumption is applied where imputation values are assigned at random. A more detailed description of the methodology is provided in Appendix D.

2.2.4.1.4. Imputation of occurrence data for water

Occurrence data for water are not available to EFSA (see Section 2.2.2.4). As required by the risk management principles agreed among Member States (European Commission, online), occurrence data for water are imputed for the five most potent active substances within the CAG.

Considering that non-approved substances are less likely to occur in drinking water, the five approved substances with the lowest NOAEL are extracted from the list of active substances (see Section 2.2.2.2) and a measurement in water is added to the occurrence data set for each of these substances. These measurements are associated with a single fictitious sample code. While under the Tier I assessment, a result value of 0.0001 mg/kg is assigned to each measurement, a result value of 0.00005 mg/kg is assigned under Tier II.

2.2.4.2. Acute exposure distribution

Acute dietary exposure is modelled at the level of individual consumption days by means of an empirical Monte Carlo simulation (EFSA PPR Panel, 2012). This means that individual days are selected at random from the consumption data set. For each food commodity consumed within the individual days, random samples of the occurrence data set are assigned. Using the individuals' body weights and the concentration of the different active substances measured in the different samples, the acute exposures resulting from each food commodity and active substance within each individual day are calculated.

The occurrence data used for the assessment however relate to the average concentrations in composite laboratory samples (see Section 2.2.2.4). Consumers on the other hand are exposed to individual units of the commodity. Residue concentrations may vary among the individual units, referred to as unit-to-unit variability. For RPCs that have a unit weight inferior to 25 g and for processed foods that were subject to blending or bulking, the unit-to-unit variability is not considered relevant (FAO, 2003). For the remaining food commodities, a fixed VF is usually applied for acute deterministic calculations.

For probabilistic exposure assessment, the use of a distribution of unit concentrations is considered more adequate than using a fixed VF. Therefore, unit-to-unit variability is modelled using a beta distribution, which can be bounded between 0 and an upper limit. Indeed, if the average concentration in a composite sample is 1, the concentration in a single unit can never be higher than the number of units within the composite sample (assuming all other units have a concentration of zero). Hence, for each RPC with a unit weight exceeding 25 g, the beta distribution was parameterised with the following restrictions.

- Lower bound = 0
- Mean = 1
- 97.5th percentile = VF
- Upper bound = number of units per sample

Stochastic VFs can then be drawn from the beta distribution and multiplied with the composite sample concentration to obtain a plausible estimate of the unit concentration. When the portion consumed by an individual is smaller than a single unit, the stochastic VF is directly applicable to the consumed portion. When the consumed portion is composed of multiple units however, multiple stochastic VFs will be drawn from the same beta distribution to estimate concentration in the whole portion consumed. Therefore, the concentration in the whole portion is estimated by multiplying the sample concentration with a weighted VF, which is calculated as follows.

$$WVF = SVF_n \qquad \text{if } n = 1$$

$$WVF = \frac{\left(\sum_{i=1}^{n-1} SVF_i\right) + SVF_n \cdot (n_0 - n + 1)}{n_0} \qquad \text{if } n > 1$$

where, WVF is the weighted VF;

SVF_i is the stochastic VF drawn for unit i;

n_0 is the estimated number of units within the consumed portion (unrounded), assuming the unit weights reported in Section 2.2.3.4;

n is the number of stochastic VFs to be drawn (i.e. ceiling of n_0).

Apart from the unit-to-unit variability, the exposure modelling also needs to account for the effect of processing prior to consumption. When occurrence data are reported for an RPC derivative, the effect of processing is already accounted for, and occurrence data can be directly combined with the consumed amount of processed food. Most of the occurrence data, however, are reported for the RPCs (see Section 2.2.2.4). Combining occurrence and consumption data at RPC level implies that all residues present in the RPC will reach the end consumer, while alteration of residues is expected to occur when the RPCs are processed prior to consumption. This uncertainty, which is generally expected to overestimate exposure, can be addressed by integrating PFs where available (see Section 2.2.3.3). When such PFs are available, occurrence values need to be combined with the consumed amount of processed food (i.e. RPC derivative) instead of the consumed amount of RPC because PFs account for both the chemical alteration of the substance and weight change of the food. Furthermore, as the consumed amounts are expressed in g and occurrence data are expressed in mg/kg, a correction factor of 1000 needs to be considered.

To combine ultimately the different substances in a total acute exposure estimate, the toxicological potency of each substance also needs to be accounted for. The use of relative potency factors (RPFs) has previously been suggested by EFSA (EFSA PPR Panel, 2012), but this method requires identification of an index compound for each CAG. Alternatively, the exposure estimates for the individual active substances are divided by the corresponding NOAEL. The potency-adjusted estimates can then be combined to obtain a reference point index (RPI)[5] for each individual day.

Based on the considerations above, the RPI is calculated for each individual day according to the equations reported below.

[5] In the previous reports on CRA of pesticides, the term 'total normalised exposure (NET)' was used instead.

$$RPI_{id} = \sum_{c}^{Commodities} \sum_{p}^{Processes} \sum_{s}^{Substances} \begin{cases} \dfrac{RPCD_{idcp} \cdot X_{idcps}}{BW_i \cdot NOAEL_s \cdot 10^3} & \text{if } X_{idcps} \text{ refers to the RPCD} \\ \dfrac{RPC_{idcp} \cdot X_{idcps} \cdot WVF_{idcps}}{BW_i \cdot NOAEL_s \cdot 10^3} & \text{if } X_{idcps} \text{ refers to the RPC and } PF_{cps} \text{ is not available} \\ \dfrac{RPCD_{idcp} \cdot X_{idcps} \cdot WVF_{idcps} \cdot PF_{cps}}{BW_i \cdot NOAEL_s \cdot 10^3} & \text{if } X_{idcps} \text{ refers to the RPC and } PF_{cps} \text{ is available} \end{cases}$$

where, RPI_{id} is the RPI of individual i on day d;

RPC_{idcp} is the amount of commodity c with processing type p consumed by individual i on day d, expressed in g of RPC;

$RPCD_{idcp}$ is the amount of commodity c with processing type p consumed by individual i on day d, expressed in g of RPC derivative;

BW_i is the body weight of individual i, expressed in kg;

X_{idcps} is the average concentration of substance s in the sample that was randomly assigned to individual i on day d for commodity c with processing type p, expressed in mg/kg;

WVF_{idcps} is the weighted VF that was randomly assigned to individual i on day d for substance s in commodity c with processing type p;

PF_{cps} is the PF for substance s in commodity c with processing type p;

$NOAEL_s$ is the NOAEL level for substance s, expressed in mg/kg body weight.

The Monte Carlo simulation described above is performed with 100,000 iterations. This means that, for each dietary survey, 100,000 individual days are randomly selected with replacement and RPIs are calculated for each individual day. This results in empirical distributions of RPIs, representing the variability of single day exposures within the different population groups.

The methodology used to derive the acute exposure distribution is generally the same for both scenarios (Tier I & II). The only difference lies in the beta distribution used to reflect unit-to-unit variability. While a very conservative VF of 5 or 7 is used for the Tier I scenario (see also Section 2.2.3.4), a fixed VF of 3.6 is applied under the Tier II scenario. A more detailed description of the methodology used to estimate acute dietary exposure is provided in Appendix E.

2.2.5. Outer loop execution

The consumption data used for this assessment are subject to sampling uncertainty and will not perfectly represent the true diets within the population. Likewise, the occurrence data will not perfectly reflect the true distribution of residue concentrations in food. These sampling uncertainties are addressed by repeating the inner loop execution multiple times, each time replacing the consumption and occurrence data sets with bootstrap data sets (EFSA PPR Panel, 2012). Bootstrap data sets are obtained by resampling, with replacement, the same number of observations from the original data sets. Each time the inner loop is executed with bootstrap data sets, a bootstrap distribution of RPIs will be obtained. This shows how the distribution of RPIs may have looked like if random sampling from the population would have generated different samples compared to the initial data set (Efron and Tibshirani, 1993).

It should be noted, however, that both the consumption and occurrence data incorporate several multivariate patterns (e.g. association of foods and individuals' characteristics, co-occurrence of residues, etc.). These patterns need to be preserved in the bootstrap data sets.

Consumption data are, therefore, resampled at the individual day level, i.e. selecting all consumption events of the resampled individual day. Hence, for each dietary survey, the bootstrap data sets contain the same number of individual days as the initial data set.

Occurrence data on the other hand are resampled at the level of the laboratory sample, i.e. selecting all measurements obtained in the resampled laboratory sample. Hence, the bootstrap data sets contain for each food commodity the same number of laboratory samples as the initial data set.

In the current exposure model, the inner loop execution is repeated 100 times. The first execution, also referred to as the nominal run, is performed with the original data sets. The remaining executions are performed with bootstrap data sets.

Although the outer loop execution is primarily intended to address the sampling uncertainty of the consumption and occurrence data, it also addresses uncertainty resulting from the probabilities applied in the model. This is particularly true for the Tier II scenarios where several simulations and imputations rely on the random selection of measurements (see Section 2.2.4.1).

2.2.6. Output preparation

Through the inner and outer loop executions, multiple RPI distributions are generated (i.e. 100 bootstrap distributions per dietary survey). To describe each bootstrap distribution, the following parameters are derived:

- mean of the RPI;
- standard deviation of the RPI;
- percentiles of the RPI (P2.5, P5, P10, P25, P50, P75, P90, P95, P97.5, P99, P99.9 and P99.99).

As required by the risk management principles agreed among Member States (European Commission, online), the parameters of the exposure distribution are expressed in MOET. The margin of exposure is normally calculated as the ratio of a toxicological reference dose (i.e. NOAEL) to the estimated exposure. Considering that the exposure is already normalised for toxicological potency (see Section 2.2.4.2), the MOET is in this case the reciprocal value of the RPI.

As a result, 100 MOET estimates are obtained for each parameter of the exposure distributions. These 100 estimates reflect the uncertainty distribution around the true value of those parameters. From these uncertainty distributions, a 95% confidence interval is calculated for each parameter. The median of the uncertainty distribution is selected as the central estimate for the confidence interval.

To better understand the factors that influence the lowest MOETs (or the highest RPIs), individual days with an MOET lower than the MOET calculated at the 99th percentile of the exposure distribution are extracted for the nominal run of each dietary survey. The relevant information associated with those individual days is also retrieved (i.e. amounts of foods consumed and concentrations of active substances). Based on the individual days' information, average contributions are calculated per dietary survey, active substance and food commodity.

Additional information is gathered throughout the calculation process to support the identification of missing occurrence data. For the Tier II scenario, the estimated use frequencies are also reported (see Section 2.2.4.1.2).

The above-reported percentiles were calculated using SAS® software, which provides five validated options for the definition of percentiles.[6] For the purpose of this assessment, the following percentile definition was selected. Let n be the number of non-missing values for a variable, let $x_1, x_2, \ldots, x_n$ represent the ordered values of the variable and set $p = t/100$. Then, the tth percentile is calculated as follows.

$$y = (1-g)x_j + gx_{j+1}$$

where, y is the tth percentile;
j is the integer part of np;
g is the fractional part of np.

The percentile definition is not expected to have a substantial impact for the acute exposure estimates because 100,000 individual days are simulated for each exposure distribution. With such a high number of observations, calculated percentiles are expected to be stable regardless of the percentile definition used.

[6] Available online: http://support.sas.com/documentation/cdl/en/procstat/66703/HTML/default/viewer.htm#procstat_univariate_details13.htm

2.2.7. Tiers and sensitivity analyses

As required by the risk management principles agreed among Member States (European Commission, online), the methodology described above is applied in a tiered approach:

1) The first-tier calculations (Tier I) use very conservative assumptions that are less resourceful regarding data and computational capacity. This allows for an efficient screening of the exposure with low risk for underestimation of the real exposure to pesticide residues.
2) The second-tier assessment (Tier II), which is more resourceful, includes more refined assumptions but it is still intended to be conservative.

Table 11 summarises the main assumptions and methodologies applied in the exposure model.

Table 11: Overview of the main assumptions and methodological approaches used for the acute exposure assessment

	Description	
Consumption data		
Number of surveys	14	
Population classes	Adult women, 18–45 years old	
Food commodities	36 RPCs (includes conversion from foods as eaten) + 4 categories of foods for infants and young children + drinking water	
Occurrence data (extraction)		
Reference period	2017–2019 (latest available 3-year cycle)	
Food commodities	36 RPCs (unprocessed or frozen) + 3 derivatives (red wine, white wine, and olive oil) + 4 categories of foods for infants and young children	
Residue definitions	All residue definitions associated with CAG-DAC and CAG-DAH during the reference period (excl. overlapping residue definitions at sample level)	
Sampling framework	EU-coordinated or national control programmes	
Sampling type	Objective or selective sampling only	
Occurrence data (simulations and imputations)		
Unspecific residue definitions	Tier I: Most potent active substance is allocated to each sample	Tier II: Random allocation of authorised active substances to each sample*
Left-censored data	Tier I: Imputed at 1/2 LOQ for food–substance combinations with quantifiable findings	Tier II: Imputed at 1/2 LOQ based on estimated use frequencies (assuming 100% crop treatment)
Missing measurements	Tier I: Highest values assigned to the most contaminated samples	Tier II: Random assignment of missing measurements to available samples
Drinking water	Tier I: Imputed at 0.1 µg/l for the 5 most potent, approved active substances	Tier II: Imputed at 0.05 µg/l for the 5 most potent, approved active substances
Exposure calculations		
Exposure model	Empirical Monte Carlo simulation (inner loop execution, n = 100000)	
Uncertainty model	Empirical bootstrapping (outer loop execution, n = 100)	
Processed foods	PFs obtained or extrapolated from the European database on PFs for pesticides in food (Scholz et al., 2018a), and additional PFs evaluated by EFSA between 30 June 2016 and 31 December 2020.	

	Description	
Unit-to-unit variability	Tier I: Unit concentration sampled from beta distribution with VFs defined by the Pesticide Residues Intake Model (PRIMo)	Tier II: Unit concentration sampled from beta distribution with a VF of 3.6

*: Accounts for substances that are not part of the CAG and for residue definitions that are not exclusive (see Section 2.2.4.1.1).

The key differences between Tier I and Tier II are also highlighted. Although the methods and assumptions applied in the model were selected with the view of minimising the uncertainties, resources may sometimes be insufficient to allow for a more accurate assessment (e.g. use frequencies and PFs). To assess how the data, methods and assumptions may impact on the exposure estimates, the following sensitivity analyses were also carried out (please refer to Section 3.2.3 for more description of each sensitivity analysis):

- Sensitivity analysis A assumes that left-censored data are imputed at 1/2 LOQ on commodities for which the use of the active substance is authorised.
- Sensitivity analysis B assumes that all left-censored data are imputed at zero.
- Sensitivity analysis C assumes that residues will not be present in any processed food.
- Sensitivity analysis D excludes all foods for infants and young children.
- Sensitivity analysis E excludes samples obtained through a selective sampling strategy.
- Sensitivity analysis F assumes that samples are not subject to unit-to-unit variability.
- Sensitivity analysis G excludes consumption of alcoholic beverages.
- Sensitivity analysis H excludes extreme consumers of orange juice concentrate (i.e. exceeding 200 g within a single day), wheat germ (i.e. exceeding 250 g within a single day) and wine (i.e. exceeding 1300 g within a single day).
- Sensitivity analysis I assumes that the use of propineb and thiram was still authorised during the reference period.
- Sensitivity analysis J assumes that dithiocarbamates are completely converted into ETU and PTU during food transformation processes that involve heating.
- Sensitivity analysis K assumes that the use of propineb and thiram was still authorised during the reference period and that dithiocarbamates are completely converted into ETU and PTU during food transformation processes that involve heating.

For these sensitivity analyses, only the impact on the 99.9th percentile of the exposure distribution (expressed in MOET) was assessed. Detailed results were not provided in this case.

2.3. Uncertainty analysis

There are several limitations in the available knowledge and data that affect the capacity of risk assessors to provide a precise answer to the assessment question mentioned in Section 1. Therefore, an uncertainty analysis was conducted in order to provide an answer to the following:

If all the uncertainties in the model,[7] exposure assessment, hazard identification and characterisation and their dependencies could be quantified and included in the calculation, what would be the probability that the MOET for the 99.9th percentile of exposure in 2017–2019 is below [100/500]? This question was considered separately for each of the 14 consumer populations addressed in the probabilistic modelling.

[7] Conceptual mathematical model on which probabilistic modelling is based.

The uncertainty analysis was conducted following the guidance of the EFSA Scientific Committee on uncertainty analysis in scientific assessments for case-specific assessments (EFSA Scientific Committee, 2018a).[8]

2.3.1. Model and process for characterising the overall uncertainty

The approach developed for characterising overall uncertainty in this assessment is summarised graphically in Figure 2. The whole approach is based upon taking the output of the probabilistic modelling – specifically the uncertainty distribution produced by the modelling for the MOET at the 99.9th percentile of exposure, represented diagrammatically at the top left of Figure 2 – as the starting point for the uncertainty analysis. The uncertainty analysis was carried out using a combination of EKE and probabilistic calculations.

A Steering Group comprising Maria Anastassiadou, Andy Hart and Luc Mohimont was established to manage the EKE: frame the questions, select the experts and decide on the elicitation method. The same three individuals also formed the Elicitation Group, training the experts and conducting and documenting the elicitation process. The following 12 experts were selected based on the EFSA procedures for establishing working groups to participate in the EKE:

Toxicology experts: Anna Federica Castoldi, Adeline Cavelier, Tamara Coja, Federica Crivellente, Kyriaky Machera, Francesca Metruccio.

Exposure experts: Chris Anagnostopoulos, Bruno Dujardin, Wim Hooghe, Samira Jarrah, Luc Mohimont and Christian Sieke.

In the first step of the analysis, the experts considered systematically each part of the cumulative assessment to identify sources of uncertainty that might influence the outcome. This was followed by five subsequent key steps as depicted on the right-hand side of Figure 2 and described below:

EKE Question 1 (EKE Q1): This was the first of three steps where the impact of uncertainties on the assessment was quantified by expert judgement. EKE Q1 required the toxicology or exposure experts to consider separately each source of uncertainty related to their respective area of expertise (i.e. toxicology or exposure) and quantify its impact on the assessment in terms of how much the median estimate of the MOET at the 99.9th percentile of exposure calculated by the probabilistic model for the German population[9] would change if that source of uncertainty was resolved (e.g. by obtaining perfect information on the input or assumption affected by the uncertainty). Focussing the assessment of EKE Q1 primarily on a single population avoided repeating this process 14 more times for each population, which would have been vulnerable to biases in judgement due to progressive expert fatigue. The experts expressed their judgements as multiplicative factors as follows: a factor of 1 would represent no change in the MOET at the 99.9th percentile of exposure, factors greater than 1 represent increases in the MOET, factors less than 1 represent decreases in the MOET. The scale and methods used for this step are described in Section 2.3.3. The experts were also asked at this point to record whether they expected the impact of each uncertainty to differ materially between populations, for use when considering the non-German populations in EKE Q3 (below). The results are reported in Section 3.3.2, Appendices G1 and G2.

EKE Question 2 (EKE Q2): For this question, the experts were asked to consider all the sources of uncertainty relating to exposure or toxicology (according to their expertise) and quantify their combined impact on the assessment in terms of how much the median estimate of the MOET at the 99.9th percentile of exposure calculated by the probabilistic model for the German population would change if all those sources of uncertainty were resolved. This focussed on German population for the same reason as EKE Q1 (see above) and the degree of change was again expressed as a multiplicative

[8] Case-specific assessments are needed in the following situations:

- there is no standardised procedure for the type of assessment in hand;
- there is a standardised procedure, but there are case-specific sources of uncertainty that are not included, or not adequately covered, by the standardised procedure;
- a standardised procedure has identified a potential concern, which is being addressed by a refined assessment involving data, methods or assumptions that are not covered by the standardised procedure;
- assessments where elements of a standardised procedure are being used, but other aspects are case-specific.

[9] The German population was selected as the focus of EKE Q1 and EKE Q2 because MOET estimates at the 99.9th percentile of the exposure distribution were among the most robust and the most critical (see more details in Section 3.3.2).

factor. When answering EKE Q2, the experts took account of their evaluations of the individual uncertainties, as assessed in EKE Q1, and combined them by expert judgement. The experts' uncertainty about the combined impact was elicited in the form of a distribution for the multiplicative factor. The methods used for this step are described in Section 2.3.4. The results are reported in Section 3.3.3, Appendices H and I.

Combination of distributions using Monte Carlo simulations: In this step, the distributions for the multiplicative factors quantifying the exposure and toxicology uncertainties, elicited in EKE Q2, were combined by multiplication with the uncertainty distribution for the MOET at the 99.9th percentile of exposure produced by the probabilistic model. Since each of the distributions from EKE Q2 is for a multiplicative adjustment to the MOET at the 99.9th percentile of exposure, multiplying the three distributions together results in a new distribution for the MOET at the 99.9th percentile of exposure which incorporates the experts' assessment of the impact of the exposure and toxicology uncertainties. This was repeated for each of the 14 modelled populations (see Section 2.3.5).

EKE Question 3 (EKE Q3): For reasons of practicality, the preceding steps involved two important simplifications. In EKE Q1 and Q2, the uncertainties were assessed with reference to only one of the 14 modelled populations (German population). Then, in the Monte Carlo simulations, the distributions elicited for the German population were applied to all 14 populations, and it was assumed that the model distributions and the distributions for exposure and toxicology uncertainties are independent of one another. These simplifications introduce additional uncertainties into the assessment. Therefore, EKE Q3 asked the experts to consider the calculated probability of the MOET at the 99.9th percentile of exposure being less than 100 (derived from the distribution produced by the Monte Carlo simulation for each population) and judge how that probability would change if it was adjusted for any dependencies between the exposure and toxicology uncertainties, for differences in uncertainty between the German population and each of the other populations, and for any other remaining uncertainties. In recognition of the difficulty of this judgement, the experts' response to this question was elicited as an approximate probability (range of probabilities) for each population. The method used for this step is described in Section 2.3.6. The results are reported in Section 3.3.4, Appendices J1 and J2.

Finally, the implication of the conclusions drawn for the 14 populations under consideration for all populations of consumers covered by the EFSA PRIMo model was discussed in Section 4.2.

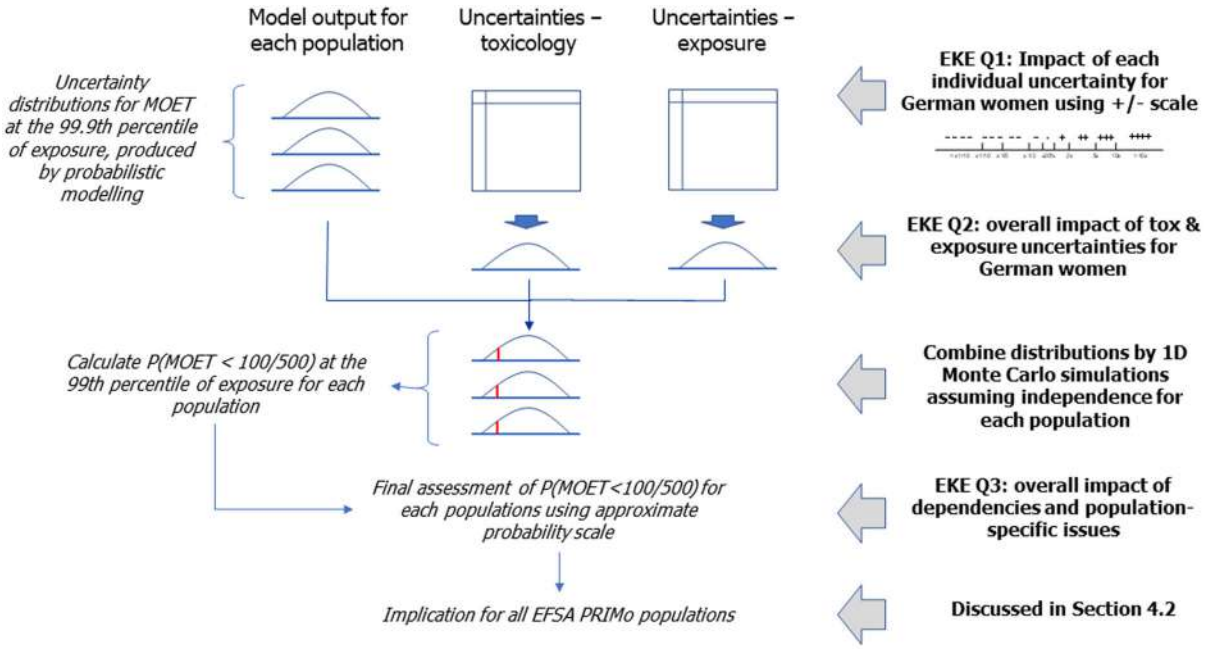


Figure 2: Overview of the approach to characterising overall uncertainty in the CRA

Note that different sources of uncertainty were combined by expert judgement in EKE Q2, whereas the two distributions resulting from that (one for exposure and the other for toxicology) were combined by Monte Carlo simulation. This combination of methods for combining uncertainties was

considered more practical than combining all the individual uncertainties by Monte Carlo simulation, which would have required eliciting distributions for each of them in EKE Q1 and specification of a suitable model to combine them. It was also considered more rigorous and reliable than combining all the uncertainties in a single expert judgement since that would have required simultaneous consideration of both the exposure and toxicology uncertainties while each expert was specialised in either exposure or toxicology.

2.3.2. Identification of sources of uncertainty affecting the assessment

Sources of uncertainty affecting the assessment were identified as recommended by EFSA Scientific Committee (2018a).

The sources of uncertainty were first identified by expert discussion using a systematic approach, reviewing each part of the assessment (e.g. establishment of CAGs, cumulative exposure assessment) for potential sources of uncertainty. Specifically, the experts examined each type of input data (e.g. occurrence data, PFs...) and each part of the assessment model (e.g. dose-addition model as mode of combined toxicity, acute exposure calculation model...) and considered whether it was affected by any of the types of uncertainty listed in Table 1 of the EFSA Scientific Committee (2018) (e.g. ambiguity, accuracy, sampling uncertainty, missing data, missing studies, assumptions, excluded factors, use of fixed values, etc.). All sources of uncertainty identified in previous CRAs on the nervous system and the thyroid (EFSA, 2020a,b, 2021a) were critically reviewed for their applicability to the present assessment.

Afterwards, the identified uncertainties were further discussed and precisely defined/described in such a way that they were unambiguously understood by the experts participating in the uncertainty analysis and overlapping with each other to the smallest possible extent. For instance, three sources of uncertainty were identified regarding the handling of left-censored measurements of residues, corresponding to three distinct assumptions: assumption of the authorisation status for pesticide/commodity combinations, assumption of the use frequency for authorised pesticide/commodity combinations and assumption of the residue level (1/2 LOQ) to be imputed to the commodity when it was treated.

All the identified sources of uncertainty were listed in Tables 22 and 23, which are presented in Section 3.3.1. The experts then collected and appraised further information that would be helpful to evaluate their impact. The results of these discussions and investigations were then summarised in a series of notes, which are included in Appendix F and cross-referenced to the list of uncertainties.

The identified sources of uncertainty were subsequently divided into two groups: those relating to exposure and those relating to toxicology. In subsequent steps of the uncertainty analysis (EKE Questions 1 and 2), the uncertainties relating to exposure were evaluated by the exposure experts of the Working Group and the uncertainties relating to toxicology were evaluated by the toxicology experts of the Working Group. Some sources of uncertainty were evaluated by the exposure and toxicology experts are they required both types of expertise for a proper evaluation.

2.3.3. Evaluation of individual sources of uncertainty (EKE Question 1)

EKE Question 1 comprised two subquestions, both of which were addressed for each of the sources of uncertainty identified by the experts. The subquestions were specified as follows:

EKE Q1A: *If this source of uncertainty was fully resolved (e.g. by obtaining perfect information on the issue involved) and addressed in the modelling, by what multiplicative factor would this change the median estimate of the MOET for [craniofacial alterations due to abnormal skeletal development/head soft tissues alterations and brain neural tube defects] at the 99.9th percentile of exposure in the German population at Tier II?*

EKE Q1B: *Is the impact of this source of uncertainty the same for the other populations that were assessed? If not, list those populations for which the impact would be smaller, and those for which it would be larger.*

The role of these questions in the uncertainty analysis and the detailed wording of the questions were explained to and discussed with the experts to ensure a common understanding. Examples were provided to illustrate the meaning of a source of uncertainty being 'fully resolved'. For instance, if the cause of a source of uncertainty was that there were very few data available for one of the model inputs, or that the data were biased or unreliable, then EKE Q1A would ask the experts to consider how the estimated MOET would change if the current data were to be replaced with a very large sample of perfectly reliable data, such that this source of uncertainty would be removed. It was also

explained that when assessing the impact of an uncertainty, the experts needed to consider the extent to which the active substances affected by it are risk drivers, as indicated by outputs from the Tier II calculations.

The meaning of 'multiplicative factor' was carefully explained to the experts, and they were asked to assess the factor using the scale as shown in Figure 3. They were asked to express their uncertainty by giving a range of factors that they judged has at least a 90% probability of containing the true factor (i.e. the change in estimated MOET that would actually occur if the uncertainty was really resolved). For example, '– – –/•' means at least a 90% chance the true factor is between ×1/10 and +20%; '++/++' means ≥ 90% chance between 2x and 5x, etc.

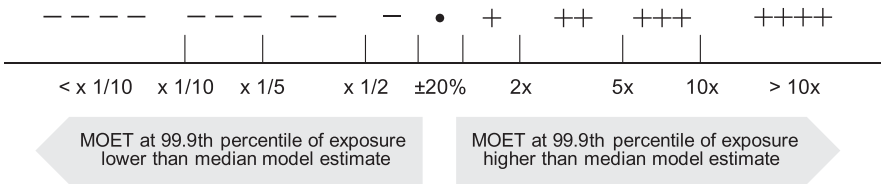


Figure 3: Scale used by the experts when assessing EKE Q1

It was explained to the experts that some sources of uncertainty were already quantified to some extent in the probabilistic modelling: specifically, sampling variability for occurrence and consumption data was quantified by bootstrapping. For these, the experts were asked to identify and assess any remaining uncertainty not addressed in the modelling.

When making their assessments, the experts were provided with the agreed description/definition of each of the uncertainties, the detailed notes summarising the information collected to support the assessment (Appendix F) and information on risk drivers (Sections 3.2.1 and 3.2.2, Annexes D1 and D2).

Twelve experts participated in answering EKE Q1: six exposure experts and six toxicology experts. The questions were first addressed separately by each expert, working individually and remotely. Each expert was asked to answer both questions (Q1A and Q1B) for each of the sources of uncertainty that related to their area of expertise (exposure or toxicology). The answers provided by the experts were then collated and differences among different experts were discussed in two Microsoft Teams meetings (one dedicated to exposure uncertainties and one dedicated to toxicology uncertainties) to arrive at a consensus judgement. The final judgements for EKE Q1A and Q1B for each source of uncertainty are reported in Section 3.3.2, Appendices G1 and G2.

2.3.4. Evaluation of combined impact of uncertainties relating to exposure and toxicology (EKE Question 2)

The EKE Q2 was specified as follows: *If all the identified sources of uncertainty relating to [exposure/hazard identification and characterisation] were fully resolved (e.g. by obtaining perfect information on the issues involved) and addressed in the modelling, by what multiplicative factor would this change the median estimate for the MOET at the 99.9th percentile of exposure for [abnormal skeletal development/head soft tissues alterations and brain neural tube defects] in the German population at Tier II?*

This question was addressed twice: once for the uncertainties relating to exposure and once for those relating to toxicology. As for EKE Q1, the experts' assessment of the impact of the uncertainties was elicited as a multiplicative factor relative to median estimate of the MOET at the 99.9th percentile of exposure for the German population.

Before answering the question, the meaning of 'perfect information' in the EKE question was discussed and defined as 'perfect information on actual consumption, occurrence, unit-to unit variability, processing methods and PFs, perfect fit of the exposure calculation model with the toxicokinetic and toxicodynamic processes, lowest BMDL05s (lower confidence bound of the benchmark dose (BMD) associated with a benchmark response (BMR) of 5%) for craniofacial

alterations from a perfect set of toxicity studies and perfect knowledge of CAG membership and how substances combine'.[10,11]

The elicitation was conducted in two stages. In the first stage, 12 experts (the same experts as for EKE Q1) worked separately to make individual judgements.

The experts' uncertainty about the multiplicative factor required by the question was elicited in the form of a probability distribution using the 'Sheffield' protocol described in EFSA's guidance document on EKE (EFSA, 2014a).[12] Application of this to EKE Q2 was guided and facilitated by a member of the Working Group who has extensive experience with the Sheffield protocol, who was not participating in making judgements on the question themselves. The facilitator also provided training to the experts in each step of the process, including how to make probability judgements and interpret fitted distributions, before they applied it to the present assessment.[13]

The individual judgements were elicited using the quartile method (EFSA, 2014a): experts were asked first for their lower and upper plausible bounds for the multiplicative factor, then for their median estimate and finally for their lower and upper quartile estimates. The individual judgements were elicited in this order to mitigate psychological biases known to affect expert judgement, especially anchoring and adjustment, and overconfidence (EFSA, 2014a). Since the individual judgements were made remotely by experts working on their own, they were asked to enter them in the MATCH software (Morris et al., 2014),[14] view the best-fitting distribution and feedback statistics (33rd and 66th percentiles) provided by MATCH, and adjust their judgements until they were satisfied that the final distribution appropriately represented their judgement.

The experts were asked to take account of the following evidence when making their judgements, together with any other relevant information they were aware of: the evaluations of the individual uncertainties from EKE Q1 (Section 3.3.2, Appendices G1 and G2) and detailed supporting notes on them (Appendix F); the results of the cumulative exposure assessments, information on risk drivers and sensitivity analyses (Sections 3.2.2 and 3.2.3); detailed graphics and tables on the model outputs and contributions of risk drivers (Figures C.03 in Annexes D1 and D2); tabulated data for the simulated individuals in the 99–100th percentile of total normalised exposure, showing the extent to which they were comprised of one or multiple substances and commodities (Tables C.03 in Annexes D1 and D2).

The experts were provided with a template document in which to record their judgements, reasoning and final distribution. These were then used by the facilitator to produce one graph in which the distributions provided by all the experts for the question on toxicology uncertainties were plotted together and a second graph, showing the distributions for the question on exposure uncertainties.

In the second stage, the experts met by two Microsoft Teams meetings (one dedicated to exposure uncertainties and one dedicated to toxicology uncertainties) and worked together to develop consensus judgements.

The consensus judgements were elicited following the guidance for facilitation of consensus judgements in the Sheffield protocol provided by EFSA (2014a) and in the SHELF framework.[15] The facilitator explained the form of consensus judgement required by the Sheffield method: not an average or compromise between the individual judgements, but the experts' collective assessment of what a rational impartial observer (RIO (concept)) would judge, having seen the evidence, the list of uncertainties and the individual judgements and having heard the experts' discussion (EFSA, 2014a; Oakley and O'Hagan, 2016).

[10] The BMDL is the benchmark dose's (BMD) lower confidence bound (usually with 95% confidence). This value, rather than the BMD estimated from the fitted dose–response curve, is normally used as reference point to derive an acceptable daily intake (ADI) or an ARfD. BMD modelling is a scientifically more advanced method compared to NOAEL-setting for deriving an RP, since it makes extended use of the dose–response data and it provides a quantification of the uncertainty in the estimated RP resulting from the statistical limitations in the dose–response data (EFSA Scientific Committee, 2017a).

[11] A critical benchmark response should normally be defined by risk managers because it relates to protection goals. However, this was not available, and therefore, a 5% extra risk was chosen by the Working Group. This differs from the 10% response level suggested by the guidance on the use of the benchmark dose approach in risk assessment (EFSA Scientific Committee, 2017a) for quantal data due to the severity of developmental toxicity and indications that BMDL05s are on average close to the NOAELs for this type of toxicity (Allen et al., 1994).

[12] The Sheffield method uses the Sheffield Elicitation Framework (SHELF) to structure the moderated group discussion during a face-to-face workshop to reach an appropriate expert consensus.

[13] The experts were invited to work through a practical example with a question on an unrelated quantity (proportion of daily smokers in the EU in 2022), to familiarise them with the process and software involved.

[14] Available online: http://optics.eee.nottingham.ac.uk/match/uncertainty.php

[15] Available online: http://www.tonyohagan.co.uk/shelf/

The consensus judgements were developed by facilitated discussion between the experts. First, the experts discussed the distributions fitted to their individual judgements and the evidence and reasoning that their judgements were based on. Next, the experts worked towards agreement on shared judgements, which they considered to be a consensus based on the RIO concept (see above). The experts were first asked for their consensus judgement for the plausible range for the multiplicative factor. Then, three further consensus judgements were elicited using the probability method, to reduce the tendency of experts to anchor on their individual judgements for medians and quartiles (Oakley and O'Hagan, 2016). In the probability method (described in EFSA (2014a) as the fixed interval method), the experts were asked to judge the probability that the quantity of interest lies above (or below) some specified value. For this purpose, the facilitator chose three values in different parts of the plausible range, favouring regions where differences between the individual distributions were most marked. The experts' consensus judgements for these three values, together with their consensus for the plausible range, were entered into the SHELF Shiny app for eliciting a single distribution and the best-fitting distribution provided by the app was displayed for review by the experts.[16]

A series of checks were then made and discussed with the experts: first, how closely the resulting distribution fitted the consensus judgements, then the values of the median, tertiles and 95% probability interval for that distribution. If any of these, or the visual shape of the distribution, were not judged by the experts as appropriate to represent their consensus, then alternative distributions fitted by the app were considered or, if necessary, the experts made adjustments to one or more of their judgements, until they were satisfied with the final distribution.

2.3.5. 1-D Monte Carlo simulation to combine distributions quantifying uncertainties related to exposure and toxicology

In this step, the two EKE Q2 distributions elicited to quantify uncertainties relating to exposure and toxicology, respectively, were combined by Monte Carlo simulation with the uncertainty distributions for the MOET at the 99.9th percentile of exposure generated by the model. The latter distributions comprised, for each modelled population, the 100 estimates of the MOET at the 99.9th percentile of exposure generated in the 100 outer loops (see Section 2.2.5). A computer programme to carry out these calculations was prepared in advance using the R software, assuming independence between the three distributions, and this programme was then run for each of the 14 consumer populations. This was done after the consensus EKE Q2 distributions became available, so that the results could be used as the starting point for EKE Q3.

Specifically, the following process was followed:

- Draw a sample of 10^5 values from the experts' exposure-factor distribution.
- Draw a sample of 10^5 values from the experts' toxicity-factor distribution.

Multiply corresponding pairs of exposure-factor and toxicity-factor values to produce a sample of 10^5 values for the combined toxicity and exposure factor.

For each population:

Multiply each of the 100 values for the estimates of the MOET at 99.9th percentile of exposure generated by the model by each of the 10^5 values from the previous bullet. This results in 10^7 values for the MOET at 99.9th percentile of exposure, adjusted for combined uncertainties (MOET adjusted for uncertainties).

From these 10^7 values, the MOETs at 2.5th, 25th, 50th, 75th and 97.5th percentiles of the exposure as well as the probability of the MOET at the 99.9th percentile of exposure being less than 100 were calculated for graphical presentation and tabulation (Figures 9 and 10, Tables 28 and 29).

The results of the Monte Carlo simulations were presented in two forms: first, boxplots showing the median, quartiles and 95% probability interval for the quantified uncertainty of the MOET at the 99.9th percentile of exposure for each of the 14 consumer populations in each CAG; and second, tables containing the numerical values used in the boxplots plus, for each CAG and population, the calculated probabilities of the MOET at the 99.9th percentile of exposure being less than 100 and less than 500, respectively. The latter probabilities were then used as the starting point for judgements on EKE Q3 (see below).

[16] https://jeremy-oakley.shinyapps.io/SHELF-single/

In addition, the Monte Carlo simulations described above were extended to explore the impact of different degrees of dependency between the uncertainties relating to exposure and toxicology (specifically, rank correlations (rho) of −1, −0.75, −0.5, −0.25, 0.25, 0.5, 0.75 and 1).

2.3.6. Accounting for dependencies, differences between populations and other uncertainties (EKE Question 3)

Two versions of EKE Q3 were defined, one for the German population and one for the other populations. This was necessary because the aim of EKE Q3 was to take account of all remaining uncertainties. For the German population, the focus of EKE Q3 was essentially the potential impact of dependencies between the distributions combined in the Monte Carlo simulations (described in the preceding section) while, for the other populations, EKE Q3 also assessed the additional uncertainty due to using the toxicology and exposure uncertainty distributions elicited for the German population also in the computations for the other 13 consumer populations.

For the German population, EKE Q3 was specified as follows: *If all the uncertainties in the model, exposure assessment, hazard identification and characterisation and their dependencies were fully resolved (e.g. by obtaining perfect information on the issues involved) and addressed in the modelling, what is your probability that this would result in the estimated MOET at 99.9th percentile of exposure for the German population in 2017–2019 being below [100/500]?*

For the other 13 consumer populations, EKE Q3 was specified as follows: *If all the uncertainties in the model, exposure assessment, hazard identification and characterisation and their dependencies, and differences in these between populations, were fully resolved (e.g. by obtaining perfect information on the issues involved) and addressed in the modelling, what is your probability that this would result in the estimated MOET at 99.9th percentile of exposure for [name of population] in 2017–2019 being below [100/500]?*

For both versions of the question, it was agreed that 'perfect information' had the same meaning as that defined for EKE Q2 (Section 2.3.4). These questions were addressed twice for each population: first for an MOET of 100, and then for a MOET of 500.

Before eliciting EKE Q3, the Working Group reviewed the issues to be considered. The facilitator explained that a dependency would exist between the toxicology and exposure uncertainty distributions if having perfect information on toxicology would alter the experts' assessment of the uncertainties on exposure, or vice versa. For instance, dependencies could be expected if resolving some uncertainties led to a change in the risk drivers, which might alter their assessment of the remaining uncertainties. The facilitator also explained that any additional uncertainties, which the experts considered had not been fully accounted for earlier, including any arising from the EKE process itself, should also be taken into account when making judgements for EKE Q3.

The facilitator asked the experts to consider, as their starting point for answering Q3 for each population, the calculated probability of the MOET at the 99.9th percentile of exposure being less than 100 or 500 provided by the Monte Carlo simulations in the preceding step. In addition, the experts were advised to consider the following:

- The information on the calculated MOET distribution for each population contained in the boxplots and tables reflecting the Monte Carlo simulations described in the preceding section;
- The results of the additional simulations exploring the impact of different degrees of dependency between the uncertainties relating to exposure and toxicology;
- Considerations about possible dependencies between the uncertainties relating to exposure and toxicology;
- Considerations identified in the group discussion of population differences for individual sources of uncertainty (outcome of the EKE Q1B in Section 3.3.2.2, Appendices G1 and G2);
- Their personal knowledge and reasoning about the issues involved.

Judgements for EKE Q3 were elicited using the Approximate Probability Scale, which is recommended in EFSA's guidance on uncertainty analysis for harmonised use in EFSA assessments (EFSA Scientific Committee, 2018a). The experts were advised to focus on the numeric probability ranges, not the verbal terms, and to consider which range (or, if appropriate, set of ranges) described their judgement on EKE Q3 for each population (Table 12).

Table 12: Approximate Probability Scale for harmonised use in EFSA

Probability term	Subjective probability range
Almost certain	99–100%
Extremely likely	95–99%
Very likely	90–95%
Likely	66–90%
About as likely as not	33–66%
Unlikely	10–33%
Very unlikely	5–10%
Extremely unlikely	1–5%
Almost impossible	0–1%

Elicitation for EKE Q3 was conducted in two stages.

In the first stage, the 12 experts (the same experts as for EKE Q1 and EKE Q2) worked remotely and separately to make individual judgements. They were asked to record their individual judgements in spreadsheet templates provided by the facilitator. The completed templates were collected, and the judgements were collated in a table, showing the number of experts who selected each probability range for each population.

To help the experts make judgements about this, new calculations were performed, showing how shifting the probability distribution for the MOET at the 99.9th percentile up or down (to reflect differences in uncertainty compared to the German population) would change the % probability that the MOET at the 99.9th percentile would be 100 for each population. These calculations assumed the whole of the distribution for the MOET at the 99.9th percentile is shifted up or down by the same amount and that the shape and width of the distribution are unchanged. Furthermore, this was repeated for different values of rho, to help the experts take account of dependency between the toxicology and exposure uncertainties. The results of these calculations were made available to the experts as additional information to support their assessment of EKE Q3.

In the second stage, the experts met by Microsoft Teams and the table compiling their judgements was displayed on screens for review by the group. The facilitator then led a discussion to develop consensus judgements (applying the RIO concept, see Section 2.3.4). This was done first for the German population, and subsequently for all other 13 populations. The agreed numeric probability ranges for each population and the associated rationale were displayed by the facilitator for review by the experts.

3. Assessment

3.1. Cumulative Assessment Groups

3.1.1. Identification of the specific craniofacial alterations

Based on expert judgement, two specific types of craniofacial alterations were considered as relevant for CRA:

- Craniofacial alterations due to abnormal skeletal development: leading to the establishment of CAG-DAC[17]
- Head soft tissue alterations and brain neural tube defects (NTDs), i.e. any abnormality due to abnormal morphogenesis of the central nervous system not due to abnormal skeletal development: leading to the establishment of CAG-DAH[18]

Since mechanistic information is, for the vast majority of substances, not available to identify MIEs and AOPs involved in these effects, no further mechanism-based effect was defined.

As craniofacial alterations are effects that are provoked after exposure to a substance during a very short but critical window of exposure, the derived NOAELs for the specific effects are relevant for short-term (acute) cumulative exposure/risk assessments.

[17] CAG-DAC stands for 'Cumulative Assessment Group – Developmental toxicity/Acute/Craniofacial alterations.
[18] CAG-DAH stands for 'Cumulative Assessment Group – Developmental toxicity/Acute/Head alterations.

3.1.1.1. Rationale of the selection of these two types of head alterations

3.1.1.1.1. Early morphogenesis of the head structures

The vertebrate head development is the result of a multistep processes that involves the reciprocal induction among different cell types mediated by multiple interconnected pathways. At the end of gastrulation, mesoderm induces the dorsal ectodermal cell to elongate forming, at the cephalic level, an enlarged neural plate folding and subsequently fusing to form a vesiculated neural tube beneath the overlying ectoderm. Subsequently, a series of swellings and constrictions defines the typical brain compartments. Neural tube closure requires complex molecular interactions and epigenetic regulations, and a number of factors (i.e. folate deficiencies) have been related to neural tube closure defects (at the cephalic level defined as anencephalia). Neural plate formation, folding and closure of the neural tube are defined as primary neurulation. Bone morphogenetic proteins (BMPs), fibroblast growth factors (FGFs) and members of the Wnt signalling family are critical for specifying neural plate induction. At the same time, head sensory organ primordia origins from brain (optic vesicles, giving rise to retina, tapetum nigrum, iris and ciliary body muscles) or cephalic placodes (olfactory, lentogen, otic and epibranchial placodes, giving rise to the olfactory mucosa, eye lens, internal ear membranous structures, gustative papillae, respectively). Abnormalities involving alterations in these morphogenetic processes were included in CAG-DAH list of indicators (see Section 3.1.2). Other head abnormalities (including skull defects) can be originated secondarily to brain/sensitive organ defects (i.e. skull vault cannot be formed in the case of anencephaly). This has been taken into account.

At the time of closure, cells at the fold margin trans-differentiate and detach from the fold epithelium, migrate and give rise to a vertebrate-specific pluripotent cell lineage named neural crest cells (NCCs). Differently to trunk-tail NCCs, cranial NCCs also contribute to the formation of head skeleton, giving rise to some elements of the cranial skull and to the entire facial skeleton. As far as cranial skeletal element development is concerned, in mammals, NCCs originating in the brain contribute to the frontonasal cartilages and give rise to the secondary palate, the jawbones, the middle ear ossicles as well as neck structures. NCC origin, specification, migration and differentiation is a multistep process requiring specific molecular pathways, described below. Among these, retinoic acid (RA)-related pathways play a master role. Abnormalities involving alteration in these morphogenetic processes were included in CAG-DAC list of indicators (see Section 3.1.2).

3.1.1.1.2. Molecular and cellular events involved in cranial NCC origin, specification and migration and craniofacial development

Origin of NCC

NCCs, in general, are a population of epithelial cells able to trans-differentiate in mesenchyme (the embryonic connective tissue), acquiring new cell properties (such as delamination–migration and multipotency).

NCCs origin from the neural plate border, the interface between the surface ectoderm (presumptive epidermis) and neuroepithelium. NCC induction requires contact-mediated interactions between the surface ectoderm and neuroepithelium and, importantly, each of these tissues contributes to the NCC lineage. Signals involved in neural tube formation (BMPs, FGFs, Wnt) are also involved in determining the boundary of neural and epidermal fate and play important roles in inducing and specifying the differentiation of NCCs. For this reason, neural tube failure is also secondarily related to multiple non-neural defects.

Cranial NCC specification

Differently from the trunk-tail ones, cranial NCCs are characterised by the acquisition of the differentiative commitment at the moment of their origin, when specific set of genes are switched on in order to define the antero-posterior patterning. The antero-posterior patterning is determined by FGF and RA gradients. The posterior pole of the embryo is characterised by FGF8 and RA production, while, near the anterior region, those signals drop off strongly because fgf8 mRNA is slowly degraded and RA catabolised. For RA gradient formation and maintenance, a number of enzymes are involved, including two steps metabolising enzymes transforming retinol (vitamin A) to retinaldehyde and then to RA and degrading enzymes oxidising RA. The site- and time-specific expression of these enzymes allows the formation of the axial RA gradient, regulating the expression of well-conserved genes involved in all animals in the anterior–posterior patterning and segmental identity attribution. Along the mammalian dorsal axis, the most anterior regions are independent of Hox (Homeobox) gene

expression while from the middle of hindbrain through the tail neural tube, NCCs, paraxial mesoderm and surface ectoderm express specific Hox genes in a combinatorial manner defined as Hox code. As far as the hindbrain is concerned, the switching on of specific Hox codes originates eight anatomical segmental units (named rhombomeres) in which cells are confined (cells within each rhombomere mix freely within it, but not with cells from adjacent rhombomeres) and specified for their fate.

Fate of NCCs contributing to the craniofacial morphogenesis

Rhombomeric migrating NCCs are directed to the pharyngeal region. They specifically origin from rhombomeres 1–2, 4 and 6–8 and, while at the level of rhombomeres 3 and 5 (usually named NCC-free zones) NCCs show restricted movements, quickly undergo apoptosis and are less produced. A specific relationship between site of specification and site of arrival after migration has been described: NCCs migrating from forebrain and midbrain colonise the frontonasal process and are involved in the formation of periocular ectomesenchyme (involved in development of different eye structure, including eyelid); those migrating from rhombomeres 1–2 reach the first pharyngeal arch (oral arch, devoted to jaw bone and incus and malleus morphogenesis); NCCs emerging from rhombomere 4 populate the second pharyngeal arch (hyoid arch, forming the hyoid cartilage and the stapes bone of the middle ear), those specified at the level of posterior rhombomeres (6–8) migrate to the posterior pharyngeal arches (3–6) to complete the hyoid morphogenesis and allow larynx cartilage formation. NCCs arising from the most caudal rhombomeres have also a role in the morphogenesis of neck glands (thyroid, parathyroid, thymus) and in the construction of the septum trunci (the structure dividing the aorta and pulmonary artery outflow). Hindbrain NCCs largely participate to the branchial arch innervation too.

The NCC migration streams are maintained separated by cell–environment interactions.

Once identified, streams of specified NCCs move along discrete migratory pathways without mixing. Once final colonisation by NCCs is concluded, the reciprocal induction between the mesenchyme derived by the paraxial mesoderm and the NCC-derived mesenchyme (named ectomesenchyme) is essential for the further differentiative steps. The absence of these inductive signals results in retarded tissue growth, defects in proper differentiation, apoptosis and finally in numerous craniofacial defects.

3.1.1.1.3. The head skeleton organisation

The vertebrate head skeleton is composed by neurocranium (skull vault and base, partially originated by NCCs) and splancnocranium (or viscerocranium, composed by jaw and neck skeletal elements, entirely originated by NCCs), both constituted by cartilaginous and osseous elements.

3.1.1.1.4. Adverse outcome pathways leading to craniofacial alterations

A linear AOP for skeletal craniofacial defects, supported by experimental data, has been described (Menegola et al., 2021). This AOP, which appears to be of relevance in humans, relies on the inhibition of CYP26, a RA metabolising enzyme, as the MIE. Intermediate key events (KEs) are RA disbalance, aberrant Hox gene expression, disrupted specification, migration and differentiation of NCCs (Figure 4). This AOP can lead to a range of defects which are listed as indicators for CAG-DAC (Section 3.1.2). These defects do not include alterations of the head skeletal structures, which are secondary to the disruption of other head morphogenetic processes (i.e. altered neurulation, see Section 3.1.1.1) through other not yet documented AOPs and leading to the alterations listed as indicators of CAG-DAH.

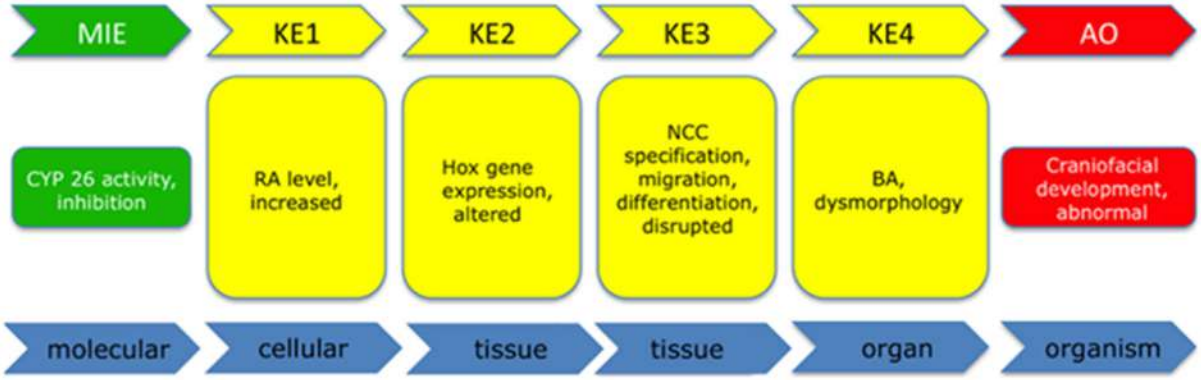


Figure 4: Schematic representation of the RA-related pathway involved in craniofacial development (Menegola et al., 2021)

3.1.1.1.5. Justification of the selection of the two effects

The head morphogenesis involves complex interconnected events but, in general, two different morphogenetic pathways are devoted, respectively, to skeleton and soft tissues head embryogenesis. Any alteration of molecular/cellular/tissue events in these two different pathways can directly affect the respective outcome, i.e. the craniofacial skeleton formation or the head soft tissue (including neural brain) development. Primary xenobiotic toxicity can affect just one or both head pathways, depending on mechanism(s) of action.

3.1.1.2. Vulnerability window during pregnancy

Embryogenesis, which in humans occurs between fertilisation and week 8 after conception, is the most vulnerable period to chemical-induced structural changes during pregnancy (at these stages, toxicants can act as teratogens). This, consequently, is also the most critical developmental time window for inducing head defects (craniofacial skeletal alterations and head soft tissue alterations and brain neural tube defects). In humans, neurulation (including neural fold formation/closure, forming the primordium of central nervous system, the neural tube) occurs from weeks 3 to 5 post-conception, concomitantly with the development of other organs/systems. After closure, the neural tube continues to develop, undergoing vesiculation at the cephalic region and ultimately producing the brain and spinal cord.

After week 8, with the completion of organ formation and the beginning of the fetal period, gross malformations are unlikely to result from exposure to toxicants, as opposed to delayed/enlarged growth and functional deficits. Time-dependent susceptibility to teratogens (e.g. retinoids, valproic acid, thalidomide) has been demonstrated in humans (Peters et al., 2015) and/or animal models.

Even during embryogenesis, an insult may differently affect organ morphogenesis depending on the specific developmental stage-related expression of potential molecular targets at the time of exposure. As an example, a stage-specific trend in the occurrence of craniofacial malformations has been demonstrated in mice at term after a single in utero dose of the fungicide triadimefon on embryonic (E) day E8, E9, E10, E11 or E12 (Di Renzo et al., 2011). Cleft palate peaked on E8 (associated with disruption of skull elements) and on E12 to a lower extent, while it was not induced at all on E9. Other cranial malformations (fusions abnormalities or agenesis of bones) were detected in E8–E10 group. Interestingly, the authors noted a good correlation between stage of migrating NCCs at the time of treatment and abnormal skeletal elements at term (Di Renzo et al., 2011).

3.1.2. Indicators of the specific craniofacial alterations

CAG-DAC/CAG-DAH endpoints were selected based on developmental biology knowledge and hypothetical teratogenic pathogenesis.

Head development is a complex process comprising different interconnecting pathways. The first visible event of head morphogenesis is neurulation, the process leading to neural tube formation. Neurulation starts with the mesodermal-mediated ectoderm induction. During neural tube closure groups of cells (NCCs) detach from neural epithelium, trans-differentiate and migrate in mesodermal territories constituting different embryonic derivatives, including ectomesenchyme. Ectomesenchyme derivatives include the whole facial skeleton and part of the cranial skeletal structures.

Head abnormalities include skeletal defects, neural tube defects (NTDs) and soft tissue (muscles, glands, lymphatic organs) abnormalities. Generally, in head NTDs include abnormalities resulting from teratological pathways directly affecting the encephalon morphogenesis (e.g. anencephaly) and brain abnormalities secondarily due to abnormal skull formation (e.g. exencephaly, secondarily produced by skull vault agenesis). A glossary of craniofacial alterations is given at the end of the document.

CAG-DAC endpoints include any abnormality directly correlated with abnormal head skeletogenesis (e.g. cleft palate, micrognathia, exencephaly) or, based on literature, considered as indicators of skeletal defects not easily detectable by routine procedures (e.g. open eye that is not a skeletal defect but can be considered a defect of an ectomesenchyme-derived structure).

CAG-DAH endpoints include any abnormality not directly correlated with abnormal head skeletogenesis but due to any other head dysmorphogenic pathway (e.g. anencephaly, related to the abnormal head neural tube morphogenesis).

The Excel database containing all recorded indicators of the two specific effects for the active substances in the scope of the data collection can be found in Annex A. For reason of harmonisation, these indicators were classified as follows:

CAG-DAC:

- Facial fissures: cleft lip (cheiloschisis, harelip).
- Facial fissures: cleft palate (palatoschisis, uranoschisis).
- Facial fissures: facial cleft (prosoposchisis, gnatoschisis).
- Facial fissures: cheilognathoschisis (syndromic, including upper and lower jaw clefting).
- Facial fissures: cheilognathopalatoschisis (syndromic, including upper and lower jaw and palate clefting).
- Facial fissures (not really a fissure, but a parameter of abnormal palatine fusion): oral cavity palatine ridge irregularity (palatal rugae abnormalities).
- Hyoid: any kind of hyoid defects (bent or accentuated curvature, fused, misshapen, short, supernumerary, crooked), with the exception of delayed/incomplete ossification in the context of a general delayed ossification.
- Jaw/Nasopharynx: any kind of shortening/enlarging/fusion of maxilla, mandible and nasopharynx.
- Skull defects include any abnormality (agenesis/absent, fused, misshapen, mispositioned) at alisphenoid, basioccipital, ethmoid, exoccipital, frontal, interparietal, parietal, squamosal, supraoccipital), with the exception of delayed/incomplete ossification in the context of a general delayed ossification.
- Skull vault agenesis: exencephaly/cranioschisis/acrania (note: acrania (skull not formed) sometimes is improperly used as synonym of acephaly (head not formed) or anencephaly (brain not formed), when only secondarily is inducing skull agenesis).
- Ear: any kind of abnormality described at skeletal evaluation (agenesis also named absent, fuse, misshapen, small, supernumerary).
- Eye: open eye/open eyelid/ablepharia.
- Extra ossification sites/accessory skull bones or cartilages.
- Abnormalities at the branchial apparatus level visible at embryo stages.
- Tongue: tongue protrusion (indicator of shortening of both mandibular and maxillary elements).

Any skull or hyoid defect reflecting delayed or incomplete ossification (e.g. incomplete ossification of the skull and wide cranial sutures, skull parietal partially ossified, increased incidence of hyoid incomplete ossification, hyoid unossified, etc.) requires careful evaluation as to whether it can be considered as being of primary nature. When the fetuses showed general condition of delayed ossification, affecting also other skeletal elements in the body than the skull and hyoid bones, the delayed ossification of the specific indicators was considered as secondary to the general toxicity. Therefore, these findings were not considered to be relevant to include the substance in CAG-DAC or to characterise it for craniofacial alterations due to delayed ossification and skeletal development.

CAG-DAH:

- Brain: anomalies of encephalon
- Brain: hydrocephalus (or cerebral ventricle dilation)
- Brain: meningocele (protrusion of meninges at the level of head or of the vertebral column))
- Brain: meningoencephalocele (protrusion of meninges and encephalon)
- Brain: microcephaly

- Brain: acephaly
- Brain: anencephaly
- Brain: craniorachischisis
- Brain: absent mesencephalon
- Brain: absent prosencephalon
- Brain: rudimentary cerebellum
- Brain: telencephalon hyperplasia
- Brain: cerebral oedema
- Ear: pinna malformation
- Eye: anophtalmia (eye agenesis)
- Eye: eye coloboma
- Eye: microphthalmia (reduced size of ocular orbit, small eyes)
- Eye: exophthalmia
- Eye: enlarged eyes
- Eye: eye bulge depression
- Eye: absent vitreous body in eye
- Eye: cyclopia
- Eye: Folded retina
- Haemorrhage: subcutaneous haemorrhage: nasal, cranial, jaw submandibular, brain
- Head: dome-shaped head
- Mouth: microstomia (reduced mouth opening)
- Mouth: absent mouth
- Tongue: macroglossia (enlarged tongue)
- Tongue: tongue protrusion (indicator of orofacial muscular imbalance or damage of the tongue muscles or hypoglossal nerve)

As indicated above, tongue protrusion represents an indicator of specific effect for both CAG-DAC and CAG-DAH. In fact, tongue protrusion may result from shortening of both mandibular and maxillary elements affecting the mouth which would result in tongue protrusion, but also as a consequence of orofacial muscular imbalance or the damage to muscles or hypoglossal nerve, forcing tongue to be protruded.

3.1.3. Establishment of CAGs

Table 13 lists the 85 selected active substances and 11 metabolites that were screened for craniofacial alterations. Each active substance or metabolite, for which at least one treatment-related indicator is reported in the database, has been included in the respective CAG. This resulted in 39 active substances and/or metabolites in CAG-DAC and 41 in CAG-DAH, with 29 active substances belonging to both CAGs (see blue-shaded cells).

Table 13: List of active substances and metabolites screened for toxicological properties and assigned to CAG-DAC and/or CAG-DAH

Chemical	CAG-DAC	CAG-DAH	Chemical	CAG-DAC	CAG-DAH
Active substances					
2,4-D	Yes	Yes	flusilazole	Yes	Yes
abamectin	Yes		flutriafol	Yes	Yes
acephate		Yes	folpet	Yes	Yes
acetamiprid		Yes	formetanate		
acrinathrin		Yes	fosthiazate		
alpha-cypermethrin			haloxyfop-P	Yes	Yes
azadirachtin		Yes	imazalil		
benomyl	Yes	Yes	imidacloprid		
beta-cyfluthrin			iprodione		
beta-cypermethrin			lambda-cyhalothrin		
bitertanol	Yes	Yes	mancozeb	Yes	Yes

Chemical	CAG-DAC	CAG-DAH	Chemical	CAG-DAC	CAG-DAH
bromuconazole	Yes	Yes	maneb		Yes
captan			metconazole	Yes	Yes
carbendazim	Yes	Yes	methiocarb		
carbofuran			methomyl		
chlormequat			methoxyfenozide		
chlorpropham			myclobutanil		Yes
chlorpyrifos	Yes	Yes	omethoate		
chlorpyrifos-methyl			oxamyl		
cyflufenamid			paclobutrazol	Yes	
cyfluthrin			penconazole		Yes
cymoxanil	Yes	Yes	pirimiphos-methyl		
cypermethrin			propargite	Yes	
cyproconazole	Yes	Yes	propiconazole	Yes	
cyromazine			propineb		Yes
deltamethrin	Yes	Yes	prosulfocarb	Yes	Yes
dieldrin	Yes		prothioconazole		Yes
difenoconazole			pyraclostrobin		
dimethoate			spirotetramat	Yes	Yes
dithianon			spiroxamine	Yes	Yes
emamectin	Yes	Yes	tebuconazole	Yes	Yes
epoxiconazole	Yes	Yes	tebufenpyrad	Yes	Yes
ethephon			tetraconazole		
ethylene oxide	Yes	Yes	thiabendazole	Yes	Yes
fenbuconazole			thiacloprid		Yes
fenhexamid			thiophanate-methyl		
fenpropidin		Yes	thiram		
fenpropimorph	Yes		triadimefon		
fenpyrazamine	Yes		triadimenol		
fenpyroximate			triclopyr		
flonicamid			ziram		
fluazifop-P	Yes	Yes	zeta-cypermethrin		
fluopyram					
Metabolites					
1,2,4-triazole	Yes	Yes	PTU		Yes
3,5,6-TCP	Yes	Yes	R154719 (metabolite of Fluazifop-P)		
delta 8,9 isomer of avermectin B1a	Yes		triazole acetic acid		
ETU	Yes	Yes	triazole alanine	Yes	
prothioconazole-desthio	Yes		triazole lactic acid		
prothioconazole-sulfonic acid	Yes	Yes			

It was discussed whether it was appropriate to include all active substances of the chemical class of triazoles in the CAGs, because an MoA (inhibition of CYP26 enzymes) has been proposed by literature with different experimental approaches in particular for this chemical class (Metruccio et al., 2020). Triazoles are supposed to cause developmental toxicity by inhibiting CYP26 (the RA inactivating enzyme) (Menegola et al., 2006), while the biological action of the triazole fungicides, making them effective against fungi, is to inhibit CYP51. However, not all triazoles are teratogenic: The molecular docking between the molecule and the enzyme is important and the pose of the triazole moiety binding to the enzyme is playing a crucial role (Menegola et al., 2016). Consequently, triazoles fungicides were not included by default in the CAGs for craniofacial abnormalities.

3.1.4. Characterisation of substances included in the CAGs

The active substances and metabolites included in the CAGs were characterised for the respective specific effect according to the principles explained in Section 2.1.3.

For 19 active substances and 2 metabolites in CAG-DAC, and for 15 active substances and 1 metabolite in CAG-DAH, a set of studies for collective evaluation (rather than one single study) was considered to derive the overall NOAELs and LOAELs. This concerned four of the six risk drivers in CAG-DAC (folpet, mancozeb, tebuconazole and thiabendazole) and three of the six risk drivers in CAG-DAH (deltamethrin, folpet and thiabendazole) (see Section 3.2.2 for full information about risk drivers). In 12 cases (including the risk driver thiabendazole and the metabolite ETU) in CAG-DAC and 9 cases in CAG-DAH (including the risk drivers deltamethrin and thiabendazole), the overall NOAELs and LOAELs were actually derived from different studies.

An NOAEL calculated by dividing the LOAEL by a default UF of 10 has been set for ethylene oxide, folpet (risk driver) and tebuconazole (risk driver) in CAG-DAC and for benomyl and cyproconazole (risk driver) in CAG-DAH.

For flutriafol, the partial ossification of frontal, parietal, interparietal and occipital bones (CAG-DAC) observed at the lowest tested dose (10 mg/kg bw per day) in [redacted] (1982) (line 310 of Annex A) was not considered for the characterisation of the substance because it was considered secondary to a general condition of delayed ossification as the partial ossification of sternebrae and the absence of ossification of calcaneum were also observed.

For some substances (i.e. the risk drivers 2,4-D, folpet, mancozeb and tebuconazole, as well as the other substances spirotetramat and paclobutrazol in CAG-DAC; the risk drivers 2,4-D, cyproconazole and folpet, as well as the other substances acephate, haloxyfop-P and spirotetramat in CAG-DAH), the NOAEL for the craniofacial alteration was below the NOAEL used to set the ARfD for the substance during the EU peer review process. The reasons for these divergences were considered carefully. For these substances, it was concluded during the peer review process that the effects were unlikely to be treatment related. The approach used in the present assessment as described in Section 2.1.3 was more conservative, but the impact of this conservatism was considered in the uncertainty analysis.

Regarding abamectin, in the rat developmental study ([redacted], 1982a), cleft palate was observed in one fetus together with anasarca, micrognathia, protruding tongue and ectromelia at 0.8 mg/kg bw per day (mid dose), suggesting the selection of this dose level as the LOAEL of the substance in CAG-DAC, and implying the setting of the NOAEL at 0.4 mg/kg bw per day (lowest dose). During the peer review experts' meeting (EFSA conclusions 2016), experts agreed that the cleft palate observed in this fetus was likely related to specific conditions of this single fetus and of doubtful relationship with treatment. Therefore, for consistency with EFSA conclusions on abamectin, the NOAEL was set at 0.8 mg/kg bw per day, based on the cleft palate observed at the top dose (1.6 mg/kg bw per day). The Working Group is, however, uncertain about this decision. Similarly, with respect to the delta 8,9 isomer of avermectin B1a (metabolite of abamectin), the EFSA Conclusions (2016, LoEP) reported that P-glycoprotein deficient animals (CF-1 mouse) are more sensitive to abamectin. Since non-functional p-glycoprotein has never been identified in humans and supplementary studies showed that only the CF-1 knockout mouse is more sensitive to abamectin toxicity, the studies with the unique polymorphic CF-1 mouse were considered as not relevant for human risk assessment and were therefore disregarded ([redacted], 1986d,g; [redacted], 1996a; [redacted], 1996a).

In both CAG-DAC and CAG-DAH, ethylene oxide was characterised based on a study intravenous administration. As these NOAELs are not appropriate for dietary risk assessment, it was decided not to include this substance in the cumulative exposure assessments.

Full details on the CAGs can be found in Appendices A1 and A2. For each substance included in the CAG, key details of the studies/sets of studies used for their characterisation are given, such as type of study, dose levels, exposure window, observed indicator(s), NOAEL and LOAEL, reference of the study (author, year), source in which the study was reported. For each substance, the overall NOAEL/LOAEL (derived from one single study or from a set of studies) is indicated in bold.

3.1.5. Lines of evidence and elicitation of CAG-membership probabilities

As explained in Section 2.1.5, the evidence that a substance is causing craniofacial alterations is variable. It cannot be excluded that some active substances included in the CAGs do not cause the respective craniofacial alteration as a primary effect. The assessment of the CAG-membership probability was conducted as described in Section 2.1.5.

The assessment questions applicable to each substance included in the CAG were formulated as follows:

- Substances included in CAG-DAC: 'What is the probability that this substance can cause, as a primary effect, any abnormality directly correlated with abnormal head skeletogenesis (e.g. micrognathia, exencephaly) or considered as indicator of skeletal defects (e.g. open eye)?'
- Substances included in CAG-DAH: 'What is the probability that this substance can cause, as a primary effect, any head soft tissue alteration or brain neural tube defect, not correlated with abnormal head skeletogenesis, but due to any other head dysmorphogenic pathway (e.g. anencephaly, related to the abnormal brain morphogenesis)?'

The associated LOEs and their respective weight (high, intermediate or low) were defined as follows:

- LOE 1: At least one indicator has been observed in toxicological studies
  Explanation: This is an obvious LOE, as the observation of any indicator relevant for CAG-DAC or CAG-DAH triggers the inclusion of the substance in the respective CAG. Because all the indicators listed in Section 3.1.2 do strongly, unambiguously and equally demonstrate the effect of the substance, their nature and their number do not matter.
  Weight: high (LOE rated as 'intermediate' by 1 expert and as 'high' by 4 experts). The indicators selected to trigger the inclusion of substances in the CAGs are in general very specific and unambiguous, and therefore strongly demonstrate the intrinsic capacity of a substance to cause the effect. It must however be kept in mind that they may be observed by chance and that their contribution to the evidence is to be duly mitigated by LOE 3.
- LOE 2: The substance belongs to a chemical class (triazoles, benzimidazoles and dithiocarbamates)
  Explanation: Substances from these chemical classes frequently exhibit a teratogenic activity targeting the embryonic structures involved in craniofacial formation. This suggests the existence for these compounds of a potential for craniofacial alterations based on a (common) morphogenetic pathway.
  Weight: low to intermediate (LOE rated as 'low' by two experts and as 'intermediate' by three experts). Compounds belonging to the three chemical classes listed frequently show craniofacial alterations, but not always. Their capability to interact with the molecular target and to trigger an MIE has been shown to vary significantly from one compound to the other, even between substances with a high degree of structural similarity. However, generally, for risk assessment purposes, the structural similarity is considered as a criterion to group chemicals (EFSA Scientific Committee, 2021).
- LOE 3: Degree of evidence of dose–response relationship (the five options given below are mutually exclusive):○
  - Option 1: The toxicological studies show a dose–response relationship (observable from progressive responses in at least two dose levels, including the highest dose) for the indicators of the specific effect.
    Weight: high (LOE rated as 'high' by (all) five experts). When demonstrated, a dose–response relationship establishes the causality link between the exposure to the chemical and the effect.
  - Option 2: The toxicological studies show indicators of the specific effect at the highest dose only.
    Weight: intermediate to high (LOE rated as 'intermediate' by two experts and as 'high' by three experts). The experts considered that the observation of indicators at the highest tested dose only is more likely due to the compound than to chance, considering their specific and unambiguous nature.
  - Option 3: The toxicological studies show indicators of the specific effect in at least two dose levels without dose–response relationship due to possible masking by high maternal or fetal toxicity.[19]

[19] Maternal or fetal toxicity were considered to be able to mask a dose–response relationship in the case of high maternal mortality, implantation losses or abortions (Carney, 2010).

Weight: high (LOE rated as 'intermediate' by one expert and as 'high' by four experts). Maternal and/or fetal toxicity can affect the observations of craniofacial alterations at the highest tested doses and hinder the establishment of a dose–response relationship. In such case, it is very unlikely that the observation of indicators at two dose levels is due to chance.

- Option 4: The toxicological studies show indicators of the specific effect at no dose related incidence (see explanation in Section 2.1.2.2).
  Weight: low (LOE rated as 'low' by four experts and as 'intermediate' by one expert). The observation of indicators in a non-dose-dependent manner and in the absence of maternal or fetal toxicity is likely to be due to chance.
- Option 5: The toxicological studies show indicators of the specific effect at the only dose tested.
  Weight: intermediate (LOE rated as 'low' by one expert, as 'intermediate' by three experts and as 'high' by one expert). The experts considered that the degree of evidence under this option is lower than under option 2 because the majority of the studies performed with one dose only have a peculiar design often involving a limited number of animals and aimed at investigating specific findings previously observed in other studies; in addition, in all cases but one (a study performed with epoxiconazole), the study has a limited acceptability or was not acceptable for the purpose of identifying craniofacial alterations.

Explanation: As basic principle in toxicological testing, the strongest indication of causality between exposure to a chemical and observed effect is a dose–response relationship. There are different degrees of evidence in dose–response relationship which need to be considered.

- LOE 4: Craniofacial alterations are observed in the absence of maternal toxicity (maternal LOAEL > LOAEL for craniofacial alteration).
  *Explanation: Chemicals can cause craniofacial alterations as secondary effects to maternal toxicity. In such case, the substance should not be included in the CAG because the dietary exposure to residues in food below the level causing maternal toxicity does not contribute to the effect. In practice, it is difficult to establish that the observed developmental toxicity is actually mediated by maternal toxicity, because the embryo development may be impaired by a direct action of the chemical at doses that also adversely affect the mother. In these circumstances, it is difficult to discriminate between a direct effect and an effect secondary to maternal toxicity (*Giavini and Menegola, 2012*)*.
  Weight: high (LOE rated as 'low' by one expert as 'high' by four experts). Considering the specificity and the unambiguousness of the effects under consideration, their observation in the absence of maternal toxicity strongly supports that they occur as a primary toxicity. It was noted that when this LOE is not present (i.e. when effects are observed in the presence of maternal toxicity), the CAG-membership probability is not necessarily affected. Indeed, even if it is known that in some cases craniofacial alterations result from maternal toxicity (e.g. folate deficiencies causing neural tube closure defects at the cephalic level defined as anencephalia, see also Section 3.1.1.1.1), it remains plausible that these effects, due to their specificity and unambiguousness, are still the result of a primary toxicity.
- LOE 5: At least one of the indicators has been observed in more than one study in the same species.
  Explanation: Repetition of observations in two independent studies in the same species contributes to the evidence that a substance is actually causing the effect.
  Weight: high (LOE rated as 'intermediate' by one expert and as 'high' by four experts). Repetition of observations in independent experimentations strongly supports the fact that they are not due to chance.
- LOE 6: Indicators of the specific effect have been observed across species.
  Explanation: Repetition of observations in two species contributes to the evidence that a substance is actually causing the effect.
  Weight: high (LOE rated as 'high' by all five experts). Repetition of observations in independent experimentations, especially in different species, strongly supports the fact that they are not due to chance.

It was considered whether computational toxicology and in vitro experimentation could be used as additional LOEs. However, it was found that the reliability of these tools is currently not sufficiently demonstrated (see Note 1 in Appendix F).

The experts agreed that these LOEs and their weights apply equally for CAG-DAC and CAG-DAH. They were referred to by the experts when eliciting the CAG-membership probability for each risk driver identified for CAG-DAC and CAG-DAH in the context of the assessment of the impact of U2 (uncertainty on whether the CAG contains only substances causing the effect). The CAG-membership probabilities of risk drivers were agreed in consensus as follows:

In CAG-DAC:

- 2,4-D: 33–90%
- Chlorpyrifos: 10–50%
- Folpet: 40–70%
- Mancozeb: 75–90%
- Tebuconazole: 90–99%
- Thiabendazole: 33–90%

In CAG-DAH:

- 2,4-D: 33–90%
- Chlorpyrifos: 10–66%
- Cyproconazole: 90–99%
- Deltamethrin: 10–70%
- Folpet: 75–90%
- Thiabendazole: 33–90%

More details on the rationale behind each CAG-membership probability can be found in Note 2 in Appendix F.

3.2. Cumulative exposure assessments using SAS® software

Section 3.2 summarises the acute exposure estimates obtained for CAG-DAC and CAG-DAH. Exposure estimates are presented for two different scenarios (Tier I and Tier II) and 14 different populations of women in childbearing age. Detailed information on input data and results (including graphs and charts) is provided in annexes.

- Annex B1 presents the input data for the cumulative exposure calculations to CAG-DAC
- Annex B2 presents the input data for the cumulative exposure calculations to CAG-DAH
- Annex C1 presents the results of the Tier I cumulative exposure calculations to CAG-DAC
- Annex C2 presents the results of the Tier I cumulative exposure calculations to CAG-DAH
- Annex D1 presents the results of the Tier II cumulative exposure calculations to CAG-DAC
- Annex D2 presents the results of the Tier II cumulative exposure calculations to CAG-DAH

All exposure estimates are expressed in MOET, which is the ratio of a toxicological reference dose (i.e. NOAEL) to the estimated exposure (see Section 2.2.6). Hence, an MOET below 1 implies that the estimated exposure exceeds the NOAEL. Likewise, an MOET of 100 means that the estimated exposure is 100 times lower than the NOAEL.

It should be emphasised that results presented are exposure estimates based on the methods and assumptions listed in Section 2 and do not account for all possible uncertainties. A complete analysis of all identified uncertainties is therefore performed in Section 3.3 as preliminary step to the overall risk characterisation (see Section 4).

3.2.1. Tier I

Table 14 presents MOET estimates for CAG-DAC under Tier I assumptions, ranging from 69.9 (Ireland) to 209 (Latvia) at the 99.9th percentile of the exposure distribution.

The main contributors were identified for the exposures exceeding the 99th percentile of the distribution (see Annex C1, Figure B.03 and Table B.02). Folpet made the greatest contribution (17–84%), followed by mancozeb (7–40%), tebuconazole (5–22%), 2,4-D (1–14%), chlorpyrifos (1–11%), thiabendazole (up to 9%). Most of the contribution of folpet came from wine grapes (up to 80%) and apples (up to 6%), whereas contribution of mancozeb mainly came from lettuces (up to 14%), peas

(without pods) (up to 12%), oranges (up to 9%), apples (up to 8%) and head cabbages (up to 7%). Other substances only played a minor role in the overall exposure (not more than 5% each).

MOET estimates for CAG-DAC were below 100 in two surveys, although Tier I calculations are by nature very conservative. A more refined calculation (Tier II) is presented in Section 3.2.2.

Table 14: Estimates of the MOET and their corresponding 95% confidence intervals in women of childbearing age at the 50th, 95th, 99th and 99.9th percentiles of the exposure distribution for the Tier I scenario of CAG-DAC

Country	50th Percentile	95th Percentile	99th Percentile	99.9th Percentile
BE - Belgium	4230 [4060–4400]	1130 [1070–1210]	475 [426–532]	160 [124–191]
CZ – Czechia	4390 [4240–4580]	1100 [1020–1180]	387 [327–457]	112 [85.8–137]
DE – Germany	3610 [3520–3680]	832 [780–890]	315 [272–366]	92.5 [72.5–116]
DK – Denmark	3410 [3340–3490]	970 [929–1020]	414 [368–460]	130 [104–158]
ES – Spain	3370 [3240–3520]	959 [899–1010]	435 [392–471]	146 [120–176]
FI – Finland	4300 [4100–4520]	1190 [1120–1290]	564 [517–636]	200 [161–237]
FR – France	4350 [4240–4490]	1050 [982–1130]	435 [370–484]	135 [104–160]
HU – Hungary	4180 [4020–4370]	1120 [1060–1180]	539 [499–581]	192 [150–222]
IE – Ireland	4610 [4480–4780]	1040 [948–1180]	294 [244–365]	69.9 [48.3–89.9]
IT – Italy	3520 [3430–3610]	1080 [1050–1140]	480 [442–523]	168 [135–197]
LV – Latvia	4840 [4500–5050]	1250 [1150–1350]	613 [551–672]	209 [170–253]
NL – Netherlands	4060 [3920–4230]	1100 [1030–1150]	485 [423–527]	150 [115–178]
RO – Romania	3700 [3600–3800]	1080 [1040–1120]	514 [477–547]	192 [166–213]
SE – Sweden	4020 [3860–4160]	1080 [1020–1140]	436 [371–501]	125 [87.7–152]

For CAG-DAH, MOET estimates obtained at the 99.9th percentile of the exposure distribution (see Table 15) were higher compared to CAG-DAC, ranging from 168 (Germany) to 238 (Denmark).

In this case (see Annex C2, Figure B.03 and Table B.02), main contributors to the exposures exceeding the 99th percentile of the distribution were propineb (24–51%) and cyproconazole (27–44%), followed by 2,4-D (1–12%), folpet (up to 9%), thiabendazole (1–7%) and chlorpyrifos (3–6%). Whereas the contribution of propineb is mainly driven by its occurrence in lettuces (up to 20%), peas (without pods) (up to 17%), apples (up to 12%), oranges (up to 11%), head cabbages (up to 8%) and broccoli (up to 5%), the contribution of cyproconazole is driven by its occurrence in apples (up to 29%), oranges (up to 21%), wheat (up to 18%), tomatoes (up to 7%) and mandarins (up to 5%). Contribution of folpet was lower compared to that measured for CAG-DAC, possibly due to the higher NOAEL assigned to the active substance in CAG-DAH. Other substances contributed less than 5% each.

For CAG-DAH, the margins of exposure were above 100 in all countries. It should be noted that also for CAG-DAH, MOET estimates obtained for Tier I are conservative by nature. This is clearly evidenced by the contributions of propineb, while the use of this substance is not authorised (see Annex C2, Table B.03). As for cyproconazole, the contribution is mainly driven by left-censored measurements. The authorisation status and imputation of left-censored data are better accounted for under the Tier II assumptions.

Table 15: Estimates of the MOET and their corresponding 95% confidence intervals in women of childbearing age at the 50th, 95th, 99th and 99.9th percentiles of the exposure distribution for the Tier I scenario of CAG-DAH

Country	50th Percentile	95th Percentile	99th Percentile	99.9th Percentile
BE - Belgium	2870 [2750–3020]	825 [780–872]	466 [429–508]	209 [181–239]
CZ – Czechia	3060 [2950–3240]	851 [799–911]	454 [402–505]	211 [175–243]
DE – Germany	2450 [2400–2510]	703 [682–720]	401 [381–419]	168 [138–192]
DK – Denmark	2280 [2240–2330]	751 [729–769]	457 [443–472]	238 [221–255]
ES – Spain	2460 [2380–2560]	776 [750–803]	431 [409–452]	192 [169–218]
FI – Finland	2770 [2630–2930]	799 [736–861]	408 [363–473]	174 [145–210]
FR – France	3120 [3050–3170]	872 [847–894]	478 [459–499]	214 [195–234]

Country	50th Percentile	95th Percentile	99th Percentile	99.9th Percentile
HU – Hungary	2860 [2780–2970]	826 [796–866]	444 [414–480]	215 [191–239]
IE – Ireland	3400 [3320–3530]	917 [866–972]	424 [364–471]	171 [148–234]
IT – Italy	2390 [2330–2430]	790 [762–819]	446 [422–468]	213 [189–235]
LV – Latvia	3470 [3230–3640]	959 [911–1020]	534 [493–578]	232 [202–267]
NL – Netherlands	2860 [2740–2980]	829 [789–874]	460 [429–487]	210 [188–234]
RO – Romania	2820 [2760–2890]	853 [826–876]	452 [429–478]	217 [197–234]
SE – Sweden	2770 [2680–2860]	861 [827–895]	491 [466–511]	228 [206–259]

3.2.2. Tier II

Table 16 presents MOET estimates in Tier II scenario for CAG-DAC, at the 99.9th percentile of the exposure distribution, ranging from 73.5 (Ireland) to 298 (Latvia). This corresponds with a 1- to 1.5-fold increase compared to the Tier I scenario. The MOET estimate was below 100 in the Irish population only. In Czechia, Germany, Denmark and Sweden, although the MOET estimates were above 100, the lower limits of their confidence interval were below 100.

The confidence intervals of the exposure distributions for CAG-DAC in Tier II generally show regular shapes (see Figure 12), suggesting an overall stability of the calculations.

Table 16: Estimates of the MOET and their corresponding 95% confidence intervals in women of childbearing age at the 50th, 95th, 99th and 99.9th percentiles of the exposure distribution for the Tier II scenario of CAG-DAC

Country	50th Percentile	95th Percentile	99th Percentile	99.9th Percentile
BE – Belgium	23500 [21600–25400]	2340 [2080–2660]	694 [566–832]	179 [133–240]
CZ – Czechia	24900 [23100–27200]	2440 [2100–2780]	540 [405–741]	119 [90–180]
DE – Germany	19900 [18700–21500]	1700 [1480–1930]	438 [342–563]	107 [84.5–151]
DK – Denmark	17100 [16300–18000]	2280 [2080–2530]	645 [516–781]	146 [98.4–194]
ES – Spain	18900 [17600–20300]	2060 [1890–2310]	673 [583–800]	194 [144–255]
FI – Finland	23600 [22000–25400]	2800 [2510–3110]	999 [859–1160]	294 [242–392]
FR – France	22500 [21100–23900]	2030 [1740–2400]	595 [496–740]	148 [117–197]
HU – Hungary	27800 [26000–30000]	2990 [2710–3280]	958 [837–1080]	267 [187–335]
IE – Ireland	26000 [24200–27900]	2410 [2010–2790]	393 [284–570]	73.5 [50.9–106]
IT – Italy	18600 [17700–19800]	2420 [2090–2740]	740 [607–871]	203 [162–266]
LV – Latvia	35500 [32600–38700]	3630 [3220–4020]	1130 [961–1340]	298 [237–359]
NL – Netherlands	21700 [20200–23100]	2400 [2090–2660]	722 [598–872]	173 [130–236]
RO – Romania	25500 [24000–26700]	3220 [2990–3520]	1000 [837–1120]	288 [242–343]
SE – Sweden	22800 [21600–23900]	2440 [2140–2770]	646 [515–849]	134 [98.7–186]

The main contributors to exposures exceeding the 99th percentile of the distribution for CAG-DAC in Tier II are presented in Table 17, for further details, see also Annex D1, Figure C.03 and Table C.02. The contribution of folpet, mostly through wine grapes, exceeded 50% in 11 of 14 populations and 25% in the other ones.

Lower, but still important, contributors were mancozeb (head cabbages, lettuce and oranges), tebuconazole (peaches and apples), 2,4-D (oranges), chlorpyrifos (potatoes) and thiabendazole (oranges).

For the Irish population, folpet was the main contributor to the exposure, through the consumption of processed wine grapes: white wine, red wine and distillates, contributing 45%, 11% and 38% of the cumulative exposure exceeding the 99th percentile of the distribution, respectively (see Annex D1, Figure C.03, Table C.02).

Table 17: CAG-DAC: Pesticide/commodity combinations contributing, in Tier II, at least 5% of the cumulative exposures exceeding the 99th percentile estimate in the assessed populations

Pesticide	Commodity	Contribution to exposures above 99th percentile of distribution													
		BE	CZ	DE	DK	ES	FI	FR	HU	IE	IT	LV	NL	RO	SE
Folpet	Wine grapes	77	86	83	83	62	28	80	41	94	65	46	73	26	82
Mancozeb	Head cabbage	< 5	< 5	< 5	< 5	< 5	< 5	< 5	6	< 5	< 5	< 5	< 5	10	< 5
Tebuconazole	Peaches	< 5	< 5	< 5	< 5	5	< 5	< 5	< 5	< 5	< 5	< 5	< 5	15	< 5
Mancozeb	Lettuce	< 5	< 5	< 5	< 5	10	6	< 5	< 5	< 5	6	6	< 5	< 5	< 5
2,4-D	Oranges	< 5	< 5	< 5	< 5	< 5	13	< 5	< 5	< 5	< 5	5	< 5	< 5	< 5
Mancozeb	Oranges	< 5	< 5	< 5	< 5	< 5	9	< 5	< 5	< 5	< 5	6	< 5	< 5	< 5
Chlorpyrifos	Potatoes	< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5	9	< 5
Folpet	Apples	< 5	< 5	< 5	< 5	< 5	< 5	< 5	5	< 5	< 5	< 5	< 5	< 5	< 5
Tebuconazole	Apples	< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5	5	< 5	< 5	< 5
Thiabendazole	Oranges	< 5	< 5	< 5	< 5	< 5	9	< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5

MOET estimates obtained in Tier II scenario for CAG-DAH are presented in Table 18, ranging from 534 (Finland) to 1010 (Romania) at the 99.9th percentile of the exposure distribution. Also, the lower bounds of their confidence intervals are well above 100 in all populations. These results correspond to a 2.7- to 4.7-fold increase compared to the Tier I scenario and are higher than those obtained for the Tier II scenario of CAG-DAC.

Table 18: Estimates of the MOET and their corresponding 95% confidence intervals in women of childbearing age at the 50th, 95th, 99th and 99.9th percentiles of the exposure distribution for the Tier II scenario of CAG-DAH

Country	50th Percentile	95th Percentile	99th Percentile	99.9th Percentile
BE – Belgium	51900 [49300–54600]	5470 [4870–6100]	1810 [1580–2010]	597 [488–716]
CZ – Czechia	53500 [51300–56400]	7160 [6390–8030]	2030 [1710–2390]	573 [446–723]
DE – Germany	44400 [42900–45900]	5490 [5000–6050]	1740 [1550–1940]	553 [474–653]
DK – Denmark	38600 [36700–39900]	5990 [5430–6400]	2150 [1880–2380]	751 [622–898]
ES – Spain	49800 [47500–52800]	5580 [5210–6010]	1970 [1750–2200]	674 [584–820]
FI – Finland	47300 [45400–49700]	5610 [5050–6320]	1810 [1490–2170]	534 [386–754]
FR – France	53700 [51800–55700]	5950 [5450–6440]	2020 [1800–2240]	659 [544–789]
HU – Hungary	78900 [73800–84200]	9090 [8300–10100]	2830 [2460–3230]	775 [615–950]
IE – Ireland	57100 [54200–60100]	6950 [6250–7870]	1980 [1700–2320]	562 [399–717]
IT – Italy	50700 [48700–53100]	6850 [6070–7490]	2320 [1940–2590]	714 [579–930]
LV – Latvia	84100 [79000–89700]	10100 [8870–11300]	3020 [2550–3540]	812 [606–1020]
NL – Netherlands	45800 [43600–48200]	5600 [5060–6220]	1880 [1670–2170]	601 [499–737]
RO – Romania	72600 [69600–76800]	12100 [11200–13000]	4280 [3730–4740]	1010 [739–1300]
SE – Sweden	51700 [49000–54400]	6440 [5860–7040]	2090 [1880–2340]	684 [577–839]

Table 19 presents the main contributors in Tier II scenario for CAG-DAH, for further details, see also Annex D2, Figure C.03 and Table C.02.

The main contributors to exposures exceeding the 99th percentile of the distribution in Tier II scenario for CAG-DAH were folpet (1–51%), 2,4-D (5–49%), chlorpyrifos (10–35%), thiabendazole (5–30%), deltamethrin (2–13%) and cyproconazole (2–11%). Some contributors are common with CAG-DAC. In Tier II, the contribution of propineb is nil due to the Tier II assumptions about the authorisation status on RPCs (see Note 26 in Appendix F). In 12 populations, the substance/commodity combination contributing the most to the exposure was 2,4-D in orange, essentially through the consumption of orange juice, which contributed between 22% in Italy and 38% in Belgium and the Netherlands (see Annex D2, Figure C.03, Table C.02). In Ireland, the main combination driving the MOET estimates was folpet in wine grapes. In Romania, the pesticide/commodity combinations with the highest contribution were deltamethrin in wheat (refined wheat flour) and chlorpyrifos on potatoes.

Table 19: CAG-DAH: Pesticide/commodity combinations contributing, in Tier II, at least 5% of the cumulative exposures exceeding the 99th percentile estimate in the assessed populations

Pesticide	Commodity	Contribution to exposures above 99th percentile of distribution													
		BE	CZ	DE	DK	ES	FI	FR	HU	IE	IT	LV	NL	RO	SE
Folpet	Wine grapes	8	21	20	24	9	< 5	19	6	51	9	6	9	7	19
2,4-D	Oranges	40	29	32	32	29	42	34	34	14	34	32	40	< 5	29
Thiabendazole	Oranges	24	21	21	18	16	23	19	17	9	13	27	23	< 5	16
Chlorpyrifos	Potatoes	10	14	< 5	< 5	6	5	8	9	9	6	9	6	15	19
Deltamethrin	Wheat	< 5	< 5	< 5	< 5	< 5	< 5	< 5	10	< 5	11	< 5	< 5	12	< 5
2,4-D	Mandarins	< 5	< 5	< 5	< 5	< 5	7	< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5
Chlorpyrifos	Tomatoes	< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5	7	< 5
Thiabendazole	Mandarins	< 5	< 5	< 5	< 5	< 5	7	< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5

Note that no cyproconazole/commodity combination contributed to at least 5% of the cumulative exposure in any population.

3.2.3. Sensitivity analyses

Although Tier II calculations are expected to reflect a more realistic exposure, this scenario is still subject to uncertainties. Some of these uncertainties were addressed through sensitivity analyses. A comparison between the MOETs obtained at the 99.9th percentile from the Tier II calculations and their corresponding sensitivity analyses is made in Table 20 for CAG-DAC and Table 21 for CAG-DAH.

Sensitivity analyses A and B tested the uncertainty of imputing left-censored data with 1/2 LOQ based on use frequencies. Sensitivity analysis A imputes all left-censored data with 1/2 LOQ based on authorisation rather than use frequency. This is over-conservative, as the commodities are not expected to be treated with all authorised substances at the same time. On the other hand, sensitivity analysis B imputes all left-censored data with zero. This is under-conservative, as not all left-censored data would be true zeros. In sensitivity analysis A, the MOETs dropped by 1.0–1.2 times for CAG-DAC and by 1.3–2.5 times for CAG-DAH. In sensitivity analysis B, the MOETs increased by a factor 1.0–1.1 for both CAG-DAC and CAG-DAH. These findings indicate that left-censored measurements have a negligible impact on the cumulative exposure estimates for CAG-DAC at the 99.9th percentile of the distribution. For CAG-DAH, the impact is more important for certain populations but overall, remains limited. This observation is in line with the results of previous acute exposure assessments (EFSA, 2020a).

Sensitivity analysis C investigated the effect that missing information on PFs and/or monitoring data in processed foods might have on the margins of exposure. When, in the absence of this information, it was assumed that no residues were transferred to processed foods, the MOETs increased by a factor 1.6–5.0 for CAG-DAH. For a large part, this is explained by the fact that PFs and monitoring data were missing for most of the major contributors to exposure (see Annex B2, Table A.07). The generation of PFs for pesticide/commodity combinations driving the risk, or monitoring data in the respective processed foods, could therefore substantially increase the MOET, although not to the extent suggested by the sensitivity analysis. For CAG-DAC, however, the MOET only increased by a factor 1.0–1.5. This can be attributed to the fact that the risk in this case was mainly driven by the contribution of folpet in wine grapes, where the available occurrence values are already obtained from monitoring data in wine. Therefore, additional PFs or additional information on the occurrence of residues in processed foods would have limited impact on the outcome of the exposure assessment for CAG-DAC.

Sensitivity analysis D investigated the effect of excluding foods for infants and young children. There were no substantial changes in the margins of exposure when this assumption was made. Considering that the current assessment was limited to women of childbearing age, findings are consistent with the expectation that persons of this age category do no consume foods for infants and young children.

Sensitivity analysis E investigated the effect of excluding samples obtained through a selective sampling strategy (corresponding to the sampling strategy code ST20A). Selective sampling implies the selection of a random sample from a subpopulation that may be defined on a risk basis. Selective sampling may therefore induce a slight bias towards an increased frequency of higher residue concentrations, and lower MOET estimates. However, excluding those samples from the calculations, MOET estimates remained within the same confidence intervals, with no substantial change at 99.9th

percentile (changes by a factor of 0.9–1.2 for CAG-DAC and a factor of 0.9–1.1 for CAG-DAH). Therefore, the potential bias introduced by selective sampling is not pertinent for this assessment.

Sensitivity analysis F investigated the effect of unit-to-unit variability. Unit-to-unit variability was accounted for in the Tier II scenario (see Section 2.2.4.2). However, to better understand the impact on the exposure estimates and the associated uncertainties, sensitivity analysis F was carried out, eliminating the effect of unit-to-unit variability. Results obtained for this sensitivity analysis were very similar to those obtained for the Tier II scenario (of both CAGs). This is consistent with the substance–commodity contributions reported in Annex D1, Table C.02 and Annex D2, Table C.02. Highest contributions to the Tier II scenario were reported for blended processed food commodities, where unit-to-unit is anyhow not applicable. Hence, the impact of unit-to-unit variability and associated uncertainties is expected to be small.

Sensitivity analysis G looked into the importance of alcoholic beverages. The Tier II scenario for CAG-DAC revealed an important contribution of folpet in wine and distillates. To better understand the overall importance of alcoholic beverages in the exposure estimates, sensitivity analysis G was executed, excluding the consumption of these commodities. For CAG-DAC, an increase of the MOET estimates at the 99.9th percentile in all populations was observed, with values 1.2–7.8 times higher than in Tier II, consistent with the contribution of folpet in these beverages to the exposure. In Germany, where a large percentage of exposure (up to 39%) is related to folpet in wine grapes with the facet 'PROCESS=Unspecified' (therefore not considered as an alcoholic beverage in this sensitivity analysis), the MOET was increased by a factor of 1.4 only, and the lower limit of the confidence interval remained below 100. Further clarifications on this observation are discussed in Section 3.3.2.1.1. The MOET estimates for CAG-DAH remained (almost) unaffected with the exception of Ireland, where the MOET showed a 1.7-fold increase. This can be explained by the fact that the exposure to folpet in alcoholic beverages was still important for this population.

Sensitivity analysis H investigated the impact of some extreme consumers on the MOET estimates and confidence intervals at the 99.9th percentile of the exposure distribution. Indeed, the drill-drown information for both CAG-DAC and CAG-DAH (see Annex D1, Table C.03 and Annex D2, Table C.03, respectively) revealed the presence of some extreme consumers of orange juice concentrate (i.e. exceeding 200 g within a single day), wheat germ (i.e. exceeding 250 g within a single day) and wine (i.e. exceeding 1300 g within a single day). This refers to the following surveys:

- Czechia: One extreme consumer of wine
- Denmark: Two extreme consumers of wine
- Germany: Five extreme consumers of orange juice concentrate, one extreme consumer of wheat germ and one extreme consumer or wine
- Finland: One extreme consumer of orange juice concentrate
- Ireland: Three extreme consumers of wine

To assess the impact of those consumers, sensitivity analysis H was performed, excluding the subjects listed above. The change in exposure estimates for the above-mentioned populations was limited for both CAGs, with a slight increase of the MOET by a factor of approximately 1.0–1.1. The results of the analysis remained within their corresponding 95% confidence intervals of Tier II, indicating that these extreme consumers have a minor impact on the results. Furthermore, visual inspection of the violin plots reported in Note 17 of Appendix F did not reveal any tendency to multimodality for the concerned populations.

Sensitivity analyses I, J and K explored a combination of uncertainties related to the group of dithiocarbamate active substances. Tier II relied on the assumption that propineb and thiram were no longer authorised for use during the reference period, while for at least a part of it the use of those substances was still authorised. Furthermore, the Tier II scenario did not account for the possible transformation of dithiocarbamates into ETU (resulting from the presence of maneb, mancozeb and metiram) or PTU (resulting from the presence of propineb), as such transformation may occur when food are processed under heat treatment. Therefore, several sensitivity analyses were executed to simulate the authorisation of thiram and propineb throughout the whole reference period (sensitivity analysis I), simulate transformation of dithiocarbamates to ETU and PTU (sensitivity analysis J) and simulate a combination of both assumptions (sensitivity analysis K). For CAG-DAC, the impact of authorisations of thiram and propineb (sensitivity analysis I) were negligible, whereas the assumptions made for analysis J led to a decrease of the MOETs by a factor of 1.0–2.3. The largest decrease was observed for Romania which is consistent with the observation that mancozeb was the substance with the highest contribution in this population (up to 32%) (see Annex D1, Table C.02). Also, for CAG-DAH

the MOETs dropped by 1.1–1.6 times in analysis J and a very slight decrease was also seen in analysis I (1.0–1.2 times). When assumptions regarding both the authorisation of thiram and propineb and the degradation of dithiocarbamates (sensitivity analyses H) were combined, the MOET estimates were reduced by a factor ranging from 1.1 to 2.1 for CAG-DAC and 1.2 to 1.8 for CAG-DAH. These sensitivity analyses indicated that accounting for uncertainties affecting the approval/authorisation status of dithiocarbamates and their potential degradation into ETU and PTU had a significant impact.

Table 20: Estimates of the MOET from the sensitivity analyses and their corresponding ratio to the Tier II results in women of childbearing age at the 99.9th percentiles of the exposure distribution for CAG-DAC. Tier II results are reported as median values with their 95% confidence intervals

Country	Tier II	Sensitivity analysis A[a]	Sensitivity analysis B[b]	Sensitivity analysis C[c]	Sensitivity analysis D[d]	Sensitivity analysis E[e]	Sensitivity analysis F[f]	Sensitivity analysis G[g]	Sensitivity analysis H[h]	Sensitivity analysis I[i]	Sensitivity analysis J[j]	Sensitivity analysis K[k]
BE – Belgium	179 [133–240]	173 [1.0]	181 [1.0]	199 [1.1]	185 [1.0]	184 [1.0]	186 [1.0]	402 [2.2]	187 [1.0]	185 [1.0]	135 [0.8]	135 [0.8]
CZ – Czechia	119 [90–180]	113 [0.9]	124 [1.0]	123 [1.0]	121 [1.0]	119 [1.0]	118 [1.0]	397 [3.3]	131 [1.1]	123 [1.0]	107 [0.9]	109 [0.9]
DE – Germany	107 [84.5–151]	104 [1.0]	111 [1.0]	109 [1.0]	110 [1.0]	125 [1.2]	111 [1.0]	140 [1.3]	111 [1.0]	112 [1.0]	92.4 [0.9]	96.4 [0.9]
DK – Denmark	146 [98.4–194]	136 [0.9]	148 [1.0]	145 [1.0]	147 [1.0]	138 [0.9]	145 [1.0]	472 [3.2]	148 [1.0]	143 [1.0]	129 [0.9]	133 [0.9]
ES – Spain	194 [144–255]	180 [0.9]	195 [1.0]	232 [1.2]	193 [1.0]	219 [1.1]	208 [1.1]	328 [1.7]	199 [1.0]	200 [1.0]	124 [0.6]	132 [0.7]
FI – Finland	294 [242–392]	237 [0.8]	300 [1.0]	433 [1.5]	303 [1.0]	307 [1.0]	315 [1.1]	368 [1.3]	325 [1.1]	309 [1.1]	170 [0.6]	174 [0.6]
FR – France	148 [117–197]	143 [1.0]	157 [1.1]	171 [1.2]	152 [1.0]	153 [1.0]	155 [1.0]	373 [2.5]	156 [1.1]	155 [1.0]	116 [0.8]	119 [0.8]
HU – Hungary	267 [187–335]	233 [0.9]	271 [1.0]	288 [1.1]	265 [1.0]	264 [1.0]	281 [1.1]	385 [1.4]	269 [1.0]	270 [1.0]	142 [0.5]	148 [0.6]
IE – Ireland	73.5 [50.9–106]	73.4 [1.0]	74.1 [1.0]	107 [1.5]	74.3 [1.0]	87.2 [1.2]	75.9 [1.0]	576 [7.8]	78.5 [1.1]	74.9 [1.0]	70.1 [1.0]	68.4 [0.9]
IT – Italy	203 [162–266]	186 [0.9]	213 [1.0]	216 [1.1]	205 [1.0]	206 [1.0]	216 [1.1]	405 [2.0]	209 [1.0]	205 [1.0]	157 [0.8]	159 [0.8]
LV – Latvia	298 [237–359]	263 [0.9]	299 [1.0]	378 [1.3]	297 [1.0]	304 [1.0]	316 [1.1]	390 [1.3]	301 [1.0]	304 [1.0]	207 [0.7]	217 [0.7]
NL – Netherlands	173 [130–236]	162 [0.9]	177 [1.0]	215 [1.2]	175 [1.0]	186 [1.1]	177 [1.0]	390 [2.3]	174 [1.0]	177 [1.0]	121 [0.7]	121 [0.7]
RO – Romania	288 [242–343]	249 [0.9]	294 [1.0]	316 [1.1]	287 [1.0]	288 [1.0]	319 [1.1]	341 [1.2]	287 [1.0]	296 [1.0]	128 [0.4]	134 [0.5]
SE – Sweden	134 [98.7–186]	129 [1.0]	133 [1.0]	156 [1.2]	139 [1.0]	141 [1.1]	135 [1.0]	435 [3.2]	138 [1.0]	136 [1.0]	116 [0.9]	119 [0.9]

(a): Sensitivity analysis assuming that left-censored data are at 1/2 LOQ on commodities for which the use of the active substance is authorised.
(b): Sensitivity analysis assuming that all left-censored data are at zero.
(c): Sensitivity analysis assuming that residues will not be present in any processed food.
(d): Sensitivity analysis excluding foods for infants and young children.
(e): Sensitivity analysis excluding samples obtained through a selective sampling strategy.
(f): Sensitivity analysis assuming that samples are not subject to unit-to-unit variability.
(g): Sensitivity analysis excluding consumption of alcoholic beverages.
(h): Sensitivity analysis excluding extreme consumers of orange juice concentrate (i.e. exceeding 200 g within a single day), wheat germ (i.e. exceeding 250 g within a single day) and wine (i.e. exceeding 1300 g within a single day).
(i): Sensitivity analysis assuming that uses of propineb and thiram were still authorised during the reference period.
(j): Sensitivity analysis assuming that dithiocarbamates are completely converted into ETU and PTU during food transformation processes that involve heating.
(k): Sensitivity analysis assuming that uses of propineb and thiram were still authorised during the reference period and dithiocarbamates are completely converted into ETU and PTU during food transformation processes that involve heating.

Table 21: Estimates of the MOET from the sensitivity analyses and their corresponding ratio to the Tier II results in women of childbearing age at the 99.9th percentiles of the exposure distribution for CAG-DAH. Tier II results are reported as median values with their 95% confidence intervals

Country	Tier II	Sensitivity analysis A[(a)]	Sensitivity analysis B[(b)]	Sensitivity analysis C[(c)]	Sensitivity analysis D[(d)]	Sensitivity analysis E[(e)]	Sensitivity analysis F[(f)]	Sensitivity analysis G[(g)]	Sensitivity analysis H[(h)]	Sensitivity analysis I[(i)]	Sensitivity analysis J[(j)]	Sensitivity analysis K[(k)]
BE – Belgium	597 [488–716]	435 [0.7]	610 [1.0]	1660 [2.8]	603 [1.0]	535 [0.9]	609 [1.0]	607 [1.0]	588 [1.0]	590 [1.0]	505 [0.8]	487 [0.8]
CZ – Czechia	573 [446–723]	361 [0.6]	581 [1.0]	1120 [2.0]	582 [1.0]	523 [0.9]	575 [1.0]	628 [1.1]	575 [1.0]	562 [1.0]	503 [0.9]	485 [0.8]
DE – Germany	553 [474–653]	306 [0.6]	563 [1.0]	1000 [1.8]	551 [1.0]	516 [0.9]	560 [1.0]	572 [1.0]	566 [1.0]	538 [1.0]	445 [0.8]	381 [0.7]
DK – Denmark	751 [622–898]	419 [0.6]	769 [1.0]	1200 [1.6]	749 [1.0]	693 [0.9]	774 [1.0]	835 [1.1]	755 [1.0]	706 [0.9]	662 [0.9]	602 [0.8]
ES – Spain	674 [584–820]	489 [0.7]	704 [1.0]	1470 [2.2]	683 [1.0]	637 [0.9]	720 [1.1]	713 [1.1]	678 [1.0]	640 [0.9]	555 [0.8]	535 [0.8]
FI – Finland	534 [386–754]	409 [0.8]	547 [1.0]	2690 [5.0]	535 [1.0]	479 [0.9]	557 [1.0]	530 [1.0]	585 [1.1]	526 [1.0]	457 [0.9]	436 [0.8]
FR – France	659 [544–789]	427 [0.6]	670 [1.0]	1440 [2.2]	652 [1.0]	628 [1.0]	679 [1.0]	713 [1.1]	661 [1.0]	640 [1.0]	527 [0.8]	519 [0.8]
HU – Hungary	775 [615–950]	397 [0.5]	820 [1.1]	2020 [2.6]	760 [1.0]	716 [0.9]	815 [1.1]	800 [1.0]	774 [1.0]	706 [0.9]	597 [0.8]	565 [0.7]
IE – Ireland	562 [399–717]	227 [0.4]	573 [1.0]	999 [1.8]	554 [1.0]	597 [1.1]	548 [1.0]	933 [1.7]	575 [1.0]	534 [1.0]	480 [0.9]	458 [0.8]

Country	Tier II	Sensitivity analysis A[(a)]	Sensitivity analysis B[(b)]	Sensitivity analysis C[(c)]	Sensitivity analysis D[(d)]	Sensitivity analysis E[(e)]	Sensitivity analysis F[(f)]	Sensitivity analysis G[(g)]	Sensitivity analysis H[(h)]	Sensitivity analysis I[(i)]	Sensitivity analysis J[(j)]	Sensitivity analysis K[(k)]
IT – Italy	714 [579–930]	412 [0.6]	745 [1.0]	1560 [2.2]	712 [1.0]	669 [0.9]	785 [1.1]	729 [1.0]	723 [1.0]	689 [1.0]	618 [0.9]	574 [0.8]
LV – Latvia	812 [606–1020]	500 [0.6]	837 [1.0]	2440 [3.0]	822 [1.0]	755 [0.9]	837 [1.0]	794 [1.0]	813 [1.0]	779 [1.0]	683 [0.8]	603 [0.7]
NL – Netherlands	601 [499–737]	443 [0.7]	612 [1.0]	1710 [2.8]	596 [1.0]	552 [0.9]	608 [1.0]	626 [1.0]	592 [1.0]	596 [1.0]	499 [0.8]	471 [0.8]
RO – Romania	1010 [739–1300]	475 [0.5]	1080 [1.1]	1570 [1.6]	1050 [1.0]	978 [1.0]	1110 [1.1]	1090 [1.1]	1070 [1.1]	854 [0.8]	623 [0.6]	567 [0.6]
SE– Sweden	684 [577–839]	420 [0.6]	702 [1.0]	1330 [1.9]	686 [1.0]	657 [1.0]	712 [1.0]	761 [1.1]	691 [1.0]	663 [1.0]	584 [0.9]	552 [0.8]

(a): Sensitivity analysis assuming that left-censored data are at 1/2 LOQ on commodities for which the use of the active substance is authorised.
(b): Sensitivity analysis assuming that all left-censored data are at zero.
(c): Sensitivity analysis assuming that residues will not be present in any processed food.
(d): Sensitivity analysis excluding foods for infants and young children.
(e): Sensitivity analysis excluding samples obtained through a selective sampling strategy.
(f): Sensitivity analysis assuming that samples are not subject to unit-to-unit variability.
(g): Sensitivity analysis excluding consumption of alcoholic beverages.
(h): Sensitivity analysis excluding extreme consumers of orange juice concentrate (i.e. exceeding 200 g within a single day), wheat germ (i.e. exceeding 250 g within a single day) and wine (i.e. exceeding 1300 g within a single day).
(i): Sensitivity analysis assuming that uses of propineb and thiram were still authorised during the reference period.
(j): Sensitivity analysis assuming that dithiocarbamates are completely converted into ETU and PTU during food transformation processes that involve heating.
(k): Sensitivity analysis assuming that uses of propineb and thiram were still authorised during the reference period and dithiocarbamates are completely converted into ETU and PTU during food transformation processes that involve heating.

3.2.4. Selection of the reference population for the uncertainty analysis

The German population was chosen as the reference population to focus on in the EKE Q1 and Q2 for CAG-DAC and CAG-DAH for the following reasons:

- The German population shows one of the lowest median estimates of the MOET at the 99.9th percentile of exposure, and therefore is one of the critical populations in terms of risk.
- The German population is the largest one, consequently with a relative low sensitivity to subjects with extreme consumption pattern, compared to other populations, as confirmed by the relatively small size of the confidence interval of the median estimate of the MOET at the 99.9th percentile of exposure, especially in the case of CAG-DAH.
- The sensitivity to the various model assumptions or input data of the German population is in the range of the observations for all populations.
- The risks drivers for this population are well representative of the overall pattern of risk drivers in all populations when referring to the active substance and the RPC for both CAGs. A difference is however noted in the case of CAG-DAC when considering the contribution of commodities as consumed (RPCD) (i.e. a major contribution of unprocessed wine grapes is noted for the German population only).
- The contribution of active substances other than risk drivers is low for the German population (less than 1% for CAG-DAC and less than 5% for CAG-DAH – see figures C.03 in Annexes D1 and D2).

3.3. Uncertainty analysis

3.3.1. Sources of uncertainty

Thirty-six sources of uncertainty related to the input data were identified as affecting the CRA (Table 22).

Table 22: Sources of uncertainty concerning the input data and affecting the CRA of craniofacial alterations (CAG-DAC and CAG-DAH)

Input data and type of uncertainty	Uncertainty number	Description	Information note	Area of expertise
NOAEL (adequacy of the CAG)	U1	It is uncertain whether the CAGs contain all active substances causing the respective craniofacial alterations	Note 1	Toxicology
NOAEL (adequacy of the CAG)	U2	It is uncertain whether the CAG contains only active substances causing the respective effect as a primary toxicity	Note 2	Toxicology
NOAEL (accuracy)	U3	The accuracy of the NOAEL setting is affected by the data collection methodology (e.g. interpretation of raw data by the assessors (human factor), transfer of information from original studies to source documents (DARs, DRARs, JMPR evaluations, etc.), and from source documents to working documents (Excel database in Annex A).	Note 3	Toxicology
NOAEL (accuracy)	U4	The accuracy of the NOAEL setting is affected by the assessment methodology and principles (i.e. how the available information was assessed to derive NOAELs for craniofacial alterations)	Note 4	Toxicology
NOAEL (accuracy)	U5	The accuracy of the NOAEL setting is affected by the study design of the critical study (e.g. study duration, route/ mode of administration (gavage, diet), staining method in case of CAG-DAC…).	Note 5	Toxicology

Input data and type of uncertainty	Uncertainty number	Description	Information note	Area of expertise
NOAEL (accuracy)	U6	The accuracy of the NOAEL setting is affected by the original key study(ies) quality (e.g. study conducted under Good Laboratory Practice (GLP), use of test guidelines, statistical analysis performed, availability of HCD, steadiness of the administered dose demonstrated, overall quality of reporting)	Note 6	Toxicology
Consumption data (excluded data)	U7	Consumption data of animal commodities and plant commodities not in the list of the 36 selected RPCs and their processed derivatives have not been included in the exposure calculations	Notes 7–9	Exposure
Consumption data (ambiguity)	U8	The consumption data do not always discriminate between different commodities of a same group as defined in part B of annex I to Regulation (EC) No 396/2005 (e.g. tomatoes and cherry tomatoes are considered as tomatoes).	Note 10	Exposure
Consumption data (accuracy)	U9	The accuracy of the reported amount of food consumed in surveys may be affected by methodological limitations (e.g. survey method, number of days in the survey, number of days between non-consecutive days, interview administration, portion size estimation, dietary software and related databases, additional food information (brand, household processing, packaging)) or by psychological factors (under- and over-reporting).	Notes 11, 12	Exposure
Consumption data (representativeness - sampling bias)	U10	Selection bias of consumers sampling design (sampling method, sampling frame), sample stratification variables (age, geographical areas, day of the week and season, other variables (education level, urban vs rural residence, ethnicity)), excluded groups (e.g. institutionalised persons, pregnant or breastfeeding women) and subjects' long-term dietary pattern (e.g. vegetarian, health related or slimming) in food consumption surveys affects the representativeness of consumption data of the respective populations. The age of the survey is also part of this sources of uncertainty	Note 13	Exposure
Consumption data (exclusion of consumers in period of fertility)	U11	The populations used in the exposure calculations do not include women below the age of 18 and above the age of 45, who may have different dietary practices	Note 14	Toxicology and exposure

Input data and type of uncertainty	Uncertainty number	Description	Information note	Area of expertise
Consumption data (representativeness of pregnancy diet)	U12	Exposure calculations use the consumption data of women irrespective of the pregnancy status. Therefore, these data may not be fully representative of the actual food consumption of pregnant women during the period of vulnerability to craniofacial alterations.	Note 15	Toxicology and exposure
Consumption data (representativeness of alcohol consumption during pregnancy)	U13	Exposure calculations use the consumption data of women irrespective of the pregnancy status. These data may therefore overestimate the consumption of alcohol, as this consumption might be reduced during the vulnerability period of pregnancy to craniofacial alterations.	Note 16	Toxicology and exposure
Consumption (sampling uncertainty)	U14	The reliability of risk estimates at the 99.9th percentile of exposure is affected by the sample size (number of consumers) of the respective surveys. Note: This source of uncertainty does not include the sampling variability which is quantified by the confidence interval of estimates at the 99.9th percentile of exposure.	Note 17	Exposure
Consumption data (use of fixed values)	U15	In the RPC model, one invariable recipe and conversion factor are used to convert the amount of food consumed into the respective amount of RPC.	Note 18	Exposure
Occurrence data (missing data)	U16	The contribution of active substance/ commodity combinations, for which occurrence data are missing was not accounted in the exposure calculations.	Note 19	Exposure
Occurrence data (excluded data)	U17	The contribution to the risk of metabolites and degradation products in the selected commodities and drinking water which are relevant for the risk but not included in the residue definition for monitoring has not been considered.	Note 20	Exposure
Occurrence data (ambiguity)	U18	The occurrence data do not always discriminate between different commodities of a same group as defined in part B of annex I to Regulation (EC) No 396/2005 (e.g. tomatoes and cherry tomatoes are considered as tomatoes).	Note 10	Exposure
Occurrence data (accuracy)	U19	The accuracy of the quantification of residue levels above the LOQ is affected by the laboratory analytical uncertainty.	Note 21	Exposure
Occurrence data (sampling bias)	U20	Selection bias of lots of commodities to be controlled in official monitoring programmes affects the representativeness of occurrence data.	Note 22	Exposure
Occurrence data (sampling uncertainty)	U21	The reliability of risk estimates at the 99.9th percentile of exposure is affected by the sample size (number of occurrence data) for each pesticide/ commodity combination.	Note 17	Exposure

Input data and type of uncertainty	Uncertainty number	Description	Information note	Area of expertise
		Note: This source of uncertainty does not include the sampling variability which is quantified by the confidence interval of estimates at the 99.9th percentile of exposure		
Occurrence data (country to country extrapolation)	U22	It is uncertain whether the use of pooled occurrence data from all EU Member states is representative of the actual residue levels to which the 14 populations under consideration are actually exposed to.	Note 23	Exposure
Occurrence data (imputation)	U23	Uncertainty of the imputation of a pesticide residue level to food samples in which the pesticide residues were not measured.	Note 24	Exposure
Occurrence data (assumption)	U24	The assumption used to assign occurrence data to active substances in case of unspecific residue definition for monitoring is subject to uncertainty.	Note 25	Exposure
Occurrence data (assumption)	U25	In the handling of left-censored data, the assumption about the authorisation status of the pesticide/commodity combinations under consideration is subject to uncertainty.	Note 26	Exposure
Occurrence data (assumption)	U26	In the handling of left-censored data, the assumption about the use frequency for authorised pesticide/commodity combinations is subject to uncertainty.	Note 27	Exposure
Occurrence data (assumption)	U27	In the handling of left-censored data, the assumption about the residue level (1/2 LOQ as imputed value) when an active substance is used is subject to uncertainty.	Note 27	Exposure
Occurrence data (assumption)	U28	The assumption about the occurrence of residues in drinking water is subject to uncertainty.	Note 28	Exposure
VF (use of fixed values)	U29	Uncertainty about the VF of 3.6 applied to all commodities having a unit weight above 25 g.	Note 29	Exposure
Individual unit sizes (use of fixed values)	U30	Uncertainty about the unit weights for each commodity as retrieved from the Pesticide Residues Intake Model (EFSA, 2018b)	Note 30	Exposure
PFs (missing data, assumptions)	U31	The assumption that, when PFs are not available, pesticide residues are transferred without any loss to processed commodities is subject to uncertainty.	Note 31	Exposure
PFs (ambiguity)	U32	The assignment of PFs, derived from standardised studies to food items of the EFSA food classification and description system (FoodEx) resulting from multiple and variable processing techniques of the EFSA RPC model, is subject to uncertainty.	Note 32	Exposure

Input data and type of uncertainty	Uncertainty number	Description	Information note	Area of expertise
PFs (accuracy)	U33	In processing studies, the accuracy of the quantification of residue levels above the LOQ in raw and processed commodities is affected by the laboratory analytical uncertainty.	–	Exposure
PFs (accuracy)	U34	PFs are overestimated when residue levels in the processed commodity are below the LOQ.	Note 33	Exposure
PFs (use of fixed values)	U35	The value of PFs used in the calculations is the median value of a limited number of independent trials.	Note 34	Exposure
PFs (excluded data)	U36	Some PFs are not considered in the assessment (e.g. peeling of commodities with edible peel and washing of commodities eaten raw).	Note 35	Exposure

Five additional sources of uncertainty were found to be associated with the assessment methodology and are listed in Table 23.

Table 23: Sources of uncertainty concerning the model/assessment methodology and affecting the CRA of craniofacial alterations (CAG-DAC and CAG-DAH)

Element of the assessment methodology	Uncertainty number	Description	Information note	Area of expertise
Mode of characterisation of the active substances	U37	It is uncertain how well NOAELs represent true BMDL05s	Note 36	Toxicology
Dose-addition model	U38	It is uncertain how well dose-addition represents the actual mode of combined toxicity	Note 37	Toxicology
Exposure calculation model	U39	It is uncertainty how well the acute exposure calculation model fits to human toxicokinetic and toxicodynamic processes involved in the craniofacial alterations.	Note 38	Toxicology and exposure
Combination of occurrence and consumption data	U40	It is uncertain how well the way occurrence and consumption data are combined is representative of real life.	Note 39	Exposure
UF for inter- and intraspecies variability	U41	It is uncertain if the default UF for inter- and intraspecies variability covers the sensitivity to craniofacial alterations in the full population of women of childbearing age.	Note 40	Toxicology

U41 will not be included in the uncertainty analysis because any element questioning the validity of the default for inter- and intraspecies variability cannot be properly captured by a multiplicative factor for adjusting the MOET estimates. Instead, any issue identified with respect to the inter- and intraspecies variability concerning craniofacial alterations will be analysed in Note 40 of Appendix F and in Section 4.3.2 for its impact on the level of protection offered by MOETs of 100 or 500.

3.3.2. Impact of individual sources of uncertainty

The elicitation questions to be addressed here for each source of uncertainty were expressed as follows:

EKE Q1A: *If this source of uncertainty was fully resolved (e.g. by obtaining perfect information on the issue involved) and addressed in the modelling, by what multiplicative factor would this change the median estimate of the MOET for [craniofacial alterations due to abnormal skeletal development/head*

soft tissues alterations and brain neural tube defects] at the 99.9th percentile of exposure in the German population of women of childbearing age at Tier II?

EKE Q1B: *Is the impact of this source of uncertainty the same for the other populations that were assessed? If not, list those populations for which the impact would be smaller, and those for which it would be larger*.

The 40 sources of uncertainty retained for the elicitation process were divided into two groups according to the area of expertise they are related to (exposure and/or toxicology) as indicated in Tables 22 and 23. The sources of uncertainty of each group were evaluated by six experts (see Section 2.3.1).

EKE Q1A was addressed using the Information Notes compiled in Appendix F.

The outcome of the expert discussions (ranges of multiplicative factors applicable to the MOET at 99.9th percentile of exposure distribution at Tier II) are reported in detail in Appendix G1 (CAG-DAC) and Appendix G2 (CAG-DAH). Experts reached a consensus for 28/39 sources of uncertainty in the case of CAG-DAC and for 22/39 sources of uncertainty in the case of CAG-DAH. In the cases where a consensus was not reached, the range of opinions at the end of the discussion is reported. By lack of time, the individual assessments of some sources of uncertainty were not discussed but, in most cases, these individual assessments were identical.

The experts were unable to quantify the impact of U37 (uncertainty on how well NOAELs represent true BMDL05s) by multiplicative factors. As explained in Note 36 of Appendix F, the attempts to derive BMDL05s for the risk drivers in both CAG-DAC and CAG-DAH failed. For this reason, the impact of this source of uncertainty could not be accounted in the following steps (EKE Q2 and EKE Q3) of the uncertainty analysis process. The consequence of this on how the outcome of the risk characterisation process needs to be interpreted is discussed in Section 4.

U2 was considered, but it was noted that unlike the other sources of uncertainty, CAG-membership probabilities do not affect the magnitude of an input parameter of the exposure calculations (in this case the NOAEL) but reflect 2 possibilities for a binary event for each substance: The substance belongs to the CAG or not, or in other words, contributes to the cumulative risk or not. This has important implications. In the case of CAG-DAC, folpet is a major risk driver (contributing about 85% of the risk above the 99th percentile) and is more likely causing the effect than not causing it (CAG-membership probability 40–70%). Therefore, repeating the exposure calculations a large number of times, with or without this substance in proportion to the CAG-membership probability (as shown in Figure 11 in Appendix F) will result in a bimodal distribution of MOETs with 40–70% of the estimates drawn from the distribution with folpet included, and the remainder of the estimates at higher MOETs, drawn from the distribution with folpet excluded. The consequence of this is that the quantification of the impact of U2 by the means of multiplicative factors to be applied to the median MOET ignores the impact on the shape and width of the MOET distribution. The same issue applies also to folpet in CAG-DAH and to substances other than folpet in both CAGs, although to a lesser extent because they do not dominate the exposure as much as folpet in CAG-DAC.

For these reasons, the impact of U2 was not quantified under EKE Q1 and not accounted under EKE Q2, but a specific approach was defined in order to consider it under EKE Q3 (see Information Note 2 in Appendix F).

3.3.2.1. German population

3.3.2.1.1. CAG-DAC

For CAG-DAC, U13 (alcohol consumption during pregnancy) was found to be the source of uncertainty with the highest impact. Some experts considered that perfect information could increase the MOET by more than a factor 2. There was, however, no consensus about the potential magnitude of this impact.

A consensus for multiplicative factors potentially above 1.2 was however reached concerning U4 (uncertainty deriving from the NOAEL-setting principles) and potentially below 0.8 for U7 (commodities not included in the assessment) and for the combination of U14 and U21 (sampling uncertainty of consumption and occurrence data).

In addition, some experts assigned multiplicative factors potentially above 1.2 to U5 (uncertainty resulting from the study design of the critical studies), U20 (representativeness of occurrence data) and U36 (effect of peeling/washing of commodities with edible peel, effect of washing of commodities eaten raw). Similarly, some experts assigned multiplicative factors potentially below 0.8 to U1 (substances not included in the CAG, but causing the effect), U9 (accuracy of consumption data) and U16 (pesticide/commodity combinations without occurrence data).

Rather large ranges of multiplicative factors, extending potentially below 0.8 and above 1.2, were assigned by some experts to uncertainties with undirected impact (i.e. with impact tending to either increase or decrease the MOET): U6 (uncertainties related to the quality of the original studies), U19 (analytical uncertainty affecting occurrence data), U23 (imputation of residue levels in case of missing measurements) and U39 (adequacy of the exposure calculation model).

The impact of all other sources of uncertainty was agreed to be minor.

It was pointed out that a large part (39%) of the exposure of the German population for subjects with exposures exceeding the 99th percentile was resulting from the consumption of wine grapes with the facet '*PROCESS=Unspecified*' (See table C.02 of Annex D1). As wine grapes are normally grown for wine production, it was unclear which type of commodity was exactly meant. Possibly this could be table grapes, reported as wine grape due to erroneous translation of the German word 'Weintraube'. In such case, combining table grape consumption with residues present in wine grapes would have resulted in an overestimation of the exposure because the MRLs and residue levels in table grapes and wine grapes are very different. This could also relate to the consumption of alcoholic beverages not reported as wine. In this case, sensitivity analysis C would have underestimated the potential impact of processing in the particular case of the German population. As this source of uncertainty could not be correctly covered under the sources of uncertainty addressed EKE Q1A, the experts considered it under EKE Q2.

3.3.2.1.2. CAG-DAH

A consensus for multiplicative factors potentially above 1.2 was reached concerning U31 (missing PFs) and potentially below 0.8 for U7 (commodities not included in the assessment), for the combination of U14 and U21 (sampling uncertainty of consumption and occurrence data) and for U17 (unaccounted metabolites).

In addition, some experts assigned multiplicative factors potentially above 1.2 to U5 (uncertainty resulting from the study design of the critical studies), U20 (representativeness of occurrence data) and U36 (effect of peeling/washing of commodities with edible peel, effect of washing of commodities eaten raw). Similarly, some experts assigned multiplicative factors potentially below 0.8 to U1 (substances not included in the CAG, but causing the effect), U4 (uncertainty deriving from the NOAEL-setting principles), U9 (accuracy of consumption data) and U16 (pesticide/commodity combinations without occurrence data).

Rather large ranges of multiplicative factors, extending potentially below 0.8 and above 1.2, were assigned by some experts to uncertainties with undirected impact: U6 (uncertainties related to the quality of the original studies), U19 (analytical uncertainty affecting occurrence data), U23 (imputation of residue levels in case of missing measurements), U29 (use of fixed values for the VF), U35 (use of fixed values for PFs), U38 (applicability of the dose-addition model) and U39 (adequacy of the exposure calculation model).

The impact of all other sources of uncertainty was agreed to be minor.

3.3.2.2. Other populations

3.3.2.2.1. CAG-DAC

For 14 sources of uncertainties, differences with Germany in the impact of uncertainties are expected. The magnitude of the differences is variable from one uncertainty to the other and from one country to the other. The uncertainties for which differences with Germany are expected to be the largest are U13 (alcohol consumption during pregnancy) and U17 (metabolites not accounted).

3.3.2.2.2. CAG-DAH

For 11 sources of uncertainties, differences with Germany in the impact of uncertainties are expected. The magnitude of the differences is variable from one uncertainty to the other, and from one country to the other. The uncertainty for which differences with Germany are expected to be the largest is U31 (missing PFs).

3.3.3. Combined impact of uncertainties relating to toxicology and exposure in the German population

The combined impact of individual uncertainties was evaluated as described in Section 2.3.4, addressing the following elicitation question:

EKE Q2: *If all the identified sources of uncertainty relating to [exposure/hazard identification and characterisation] were fully resolved (e.g. by obtaining perfect information on the issues involved) and addressed in the modelling, by what multiplicative factor would this change the median estimate for the MOET at the 99.9th percentile of exposure for [abnormal skeletal development/head soft tissues alterations and brain neural tube defects] in the German population of women in childbearing age at Tier II?*

In view of the fact that U2 and U37 were excluded from the elicitation of the combined impact of uncertainties related to toxicology, the meaning of 'perfect information' given in Section 2.3.4 was updated as follows: 'perfect information on actual consumption, occurrence, unit-to unit variability, processing methods, and PFs, perfect fit of the exposure calculation model with the toxicokinetic and toxicodynamic processes, and the overall NOAEL (highest tested dose below the lowest LOAEL), for craniofacial alterations from a perfect set of toxicity studies'.

The elicitation took place in February (exposure uncertainties) and March 2022 (toxicology uncertainties) by Microsoft Teams meetings. It was mainly based on the outcome of the elicitation process on EKE Q1a. Records can be found in Appendix H and in Appendix I. Only a summary is provided in Sections 3.3.3.1 and 3.3.3.2.

3.3.3.1. Combined impact of uncertainties related to toxicology

3.3.3.1.1. CAG-DAC

Following discussion, the experts identified the major contributors to the combined uncertainty related to toxicology as follows[20]:

- U1: Active substances not included in the CAG, but causing the effect (−)
- U4: Uncertainty resulting from the methodology and principles used for NOAEL-setting (+)
- U5: Uncertainty associated with the study design of critical studies (+)

To a lesser extent, U6 (uncertainty related to the quality of key studies (+)) was also found to contribute to the combined impact of toxicology uncertainties.

Minor dependencies between uncertainties affecting the NOAEL (U3, U4, U5 and U6) were postulated.

To some degree, the impact of sources of uncertainty tend to cancel each other out. Overall, the experts agreed that resolving all uncertainties affecting toxicology would however most likely increase the MOET at the 99.9th percentile of exposure in the German population. The median value of the consensus distribution of multiplicative factors is 1.31. The distribution is shown in Figure 5 and the key parameters are given in Table 24.

Table 24: Parameters of the consensus distribution shown in Figure 5

Consensus distribution	Experts' toxicology multiplicative factor (*f*)
Lower plausible bound	$f = 0.7$ (experts judged there to be < 1% probability that f would be < 0.7)
Upper plausible bound	$f = 2.5$ (experts judged there to be < 1% probability that f would be > 2.5)
Probability 1	P ($f < 1$) = 17% (experts' probability that f would be less than 1)
Probability 2	P ($f > 1.5$) = 31% (experts' probability that f would be more than 1.5)
Probability 3	P ($f < 1.25$) = 43% (experts' probability that f would be less than 1.25)
Type	Scaled Beta (alpha = 2.03; beta = 3.66; median and 90% PI: 1.31, 0.86–1.94)

[20] Symbols indicate if the modelled estimate of the MOET at 99.9th percentile of exposure for the German population would tend to increase (+) or decrease (−) if the uncertainty would be resolved (i.e. by obtaining perfect information).

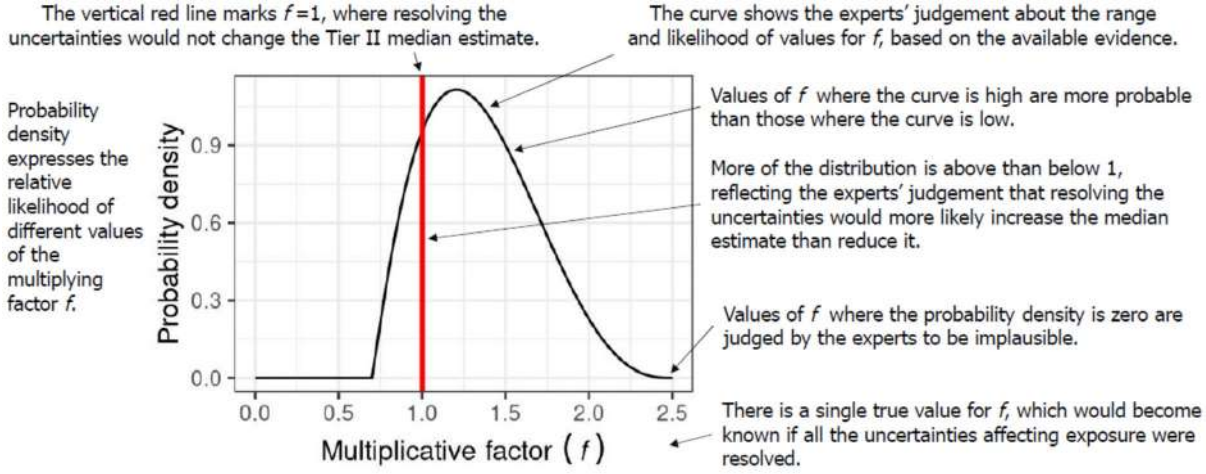


Figure 5: CAG-DAC: Consensus distribution of the experts for the combined impact of the quantified uncertainties affecting toxicology (if resolved) on the MOET at the 99.9th percentile of exposure for the German population, expressed as a multiplicative factor *f* to be applied to the Tier II median estimate shown in Table 16. The probability distribution is shown by the curve, which represents the probability density (relative likelihood) for different values of the multiplicative factor *f*. Distribution parameters are shown in Table 24.

3.3.3.1.2. CAG-DAH

Following discussion, the experts identified the major contributors to the combined uncertainty related to toxicology as follows:

- U1: Active substances not included in the CAG, but causing the effect (−)
- U4: Uncertainty resulting from the methodology and principles used for NOAEL-setting (−)
- U6: uncertainty related to the quality of key studies (+)

Minor dependencies between uncertainties affecting the NOAEL (U3, U4, U5 and U6) were postulated.

To a large extent, the impact of sources of uncertainty tend to cancel each other out. Overall, the experts agreed that resolving all uncertainties affecting toxicology would be a little more likely to increase the MOET at the 99.9th percentile of exposure in the German population. The median value of the consensus distribution of multiplicative factors is 1.03. The distribution is shown in Figure 6 and the key parameters are given in Table 25.

Table 25: Parameters of the consensus distribution shown in Figure 6

Consensus distribution	Experts' toxicology multiplicative factor (*f*)
Lower plausible bound	f = 0.5
Upper plausible bound	f = 1.5
Probability 1	P (f < 0.8) = 20%
Probability 2	P (f > 1.2) = 25%
Probability 3	P (f < 1) = 45%
Type	Scaled Beta (alpha = 1.98; beta = 1.80; median and 90% PI: 1.03, 0.64–1.39)

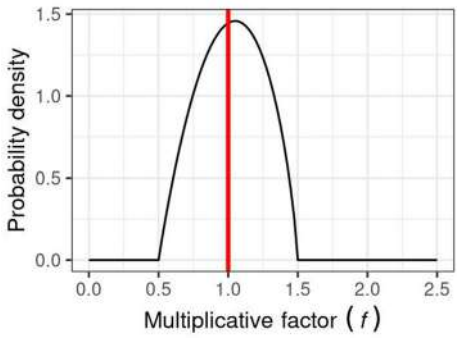


Figure 6: CAG-DAH: consensus distribution of values of the multiplicative factor representing the combined effect of toxicology uncertainties

3.3.3.2. Combined impact of uncertainties related to exposure

3.3.3.2.1. CAG-DAC

Following discussion, the experts identified the major contributors to the combined uncertainty related to exposure as follows:

- U7: Uncertainty due to the exclusion of food commodities from the calculations (−)
- U13: Uncertainty related to the reduction of alcohol consumption during pregnancy (+ to ++)
- U14/U21: Sampling uncertainty of consumption and occurrence data, especially sampling bias affecting skewed distributions (−)
- The possible misclassification of consumption events of wine grapes with the facet '*PROCESS=Unspecified*' (+)

To a lesser extent, U9 (accuracy of consumption data, possibly affected by under-reporting of alcohol consumption (−)) was also found to contribute to the combined impact of exposure uncertainties.

A positive dependency was identified between U14 and U21.

To some degree, the impact of sources of uncertainty tend to cancel each other out. Overall, the experts agreed that resolving all uncertainties affecting exposure would however most likely increase the MOET at the 99.9th percentile of exposure in the German population. The median value of the consensus distribution of multiplicative factors is 1.5. The distribution is shown in Figure 7 and the key parameters are given in Table 26.

Table 26: Parameters of the consensus distribution shown in Figure 7

Consensus distribution	Experts' exposure multiplicative factor (*f*)
Lower plausible bound	$f = 0.4$
Upper plausible bound	$f = 3.5$
Probability 1	P ($f < 1$) = 12%
Probability 2	P ($f > 2$) = 15%
Probability 3	P ($f < 1.5$) = 50%
Type	Scaled Beta (alpha = 3.78; beta = 6.63; median and 90% PI: 1.50, 0.85–2.30)

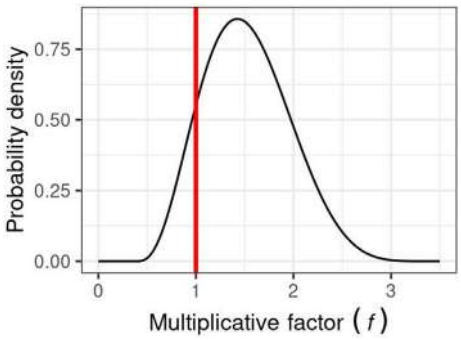


Figure 7: CAG-DAC: consensus distribution of values of the multiplicative factor representing the combined effect of exposure uncertainties

3.3.3.2.2. CAG-DAH

Following discussion, the experts identified the major contributors to the combined uncertainty related to exposure as follows:

- U7: Uncertainty due to the exclusion of food commodities from the calculations (−)
- U14/U21: Sampling uncertainty of consumption and occurrence data, especially the sampling bias affecting skewed distributions (−)
- U31: Missing PFs (+)

To a lesser extent, U9 (accuracy of consumption data, possibly affected by under-reporting of alcohol consumption (−)) and U17 (contribution of metabolites not considered (−)) were also found to contribute to the combined impact of exposure uncertainties.

A positive dependency was identified between U14 and U21.

To some degree, the impact of sources of uncertainty tend to cancel each other out. Overall, the experts agreed that resolving all uncertainties affecting exposure would however most likely increase the MOET at the 99.9th percentile of exposure in the German population. The median value of the consensus distribution of multiplicative factors is 1.2. The distribution is shown in Figure 8 and the key parameters are given in Table 27.

Table 27: Parameters of the consensus distribution shown in Figure 8

Consensus distribution	Experts' exposure multiplicative factor (*f*)
Lower plausible bound	$f = 0.3$
Upper plausible bound	$f = 2$
Probability 1	P ($f < 1$) = 30%
Probability 2	P ($f > 1.5$) = 20%
Probability 3	P ($f < 1.25$) = 55%
Type	Scaled Beta (alpha = 2.89; beta = 2.61; median and 90% PI: 1.20, 0.64–1.73)

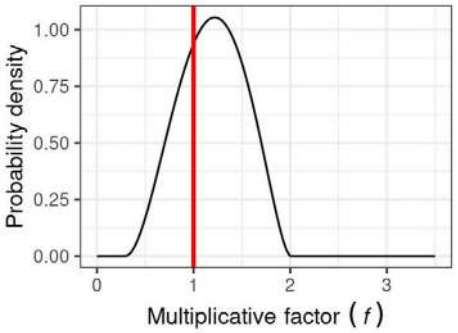
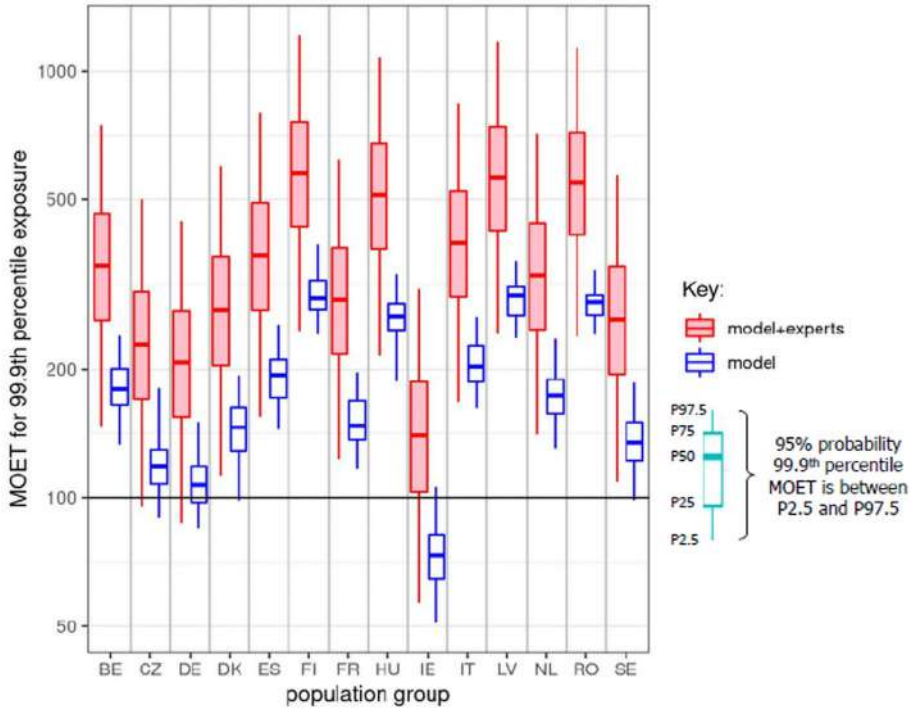


Figure 8: CAG-DAH: consensus distribution of values of the multiplicative factor representing the combined effect of exposure uncertainties

3.3.3.3. Combined impact of uncertainties related to exposure and toxicology

The elicited distributions of multiplicative factors for the uncertainties related to toxicology and exposure regarding the German population were combined with the output of the Tier II model for the MOET at the 99.9th percentile of exposure in each consumer population, using the Monte Carlo calculation described in Section 2.3.5. These calculations were conducted assuming perfect independence between the elicited distributions for uncertainties affecting exposure and toxicology. The results are shown in Figure 9 (CAG-DAC) and Figure 10 (CAG-DAH). In these figures, the 'Model' boxplots show the MOET estimates and their confidence intervals at the 99.9th percentile of exposure in each consumer population, as calculated by the Tier II model. The 'Model+experts' boxplots show the result the combination of these estimates with the elicited distributions of multiplicative factors quantifying the impact of sources of uncertainty related to toxicology and exposure, assuming perfect independence between them. Note that the vertical axis is plotted on a logarithmic scale.



Keys: 'Model' boxplots show the output of the Tier II model for the MOET at the 99.9th percentile of exposure in each consumer population. 'Model+experts' boxplots show the result of combining the output of the Tier II model with the distributions of multiplicative factors quantifying additional sources of uncertainty related to toxicology and exposure, as elicited for the German population, assuming perfect independence between them. Note that the vertical axis is plotted on a logarithmic scale; the values plotted for 'model+experts' are shown numerically in Table 28. The lower and upper edges of each boxplot represent the quartiles (P25 and P75) of the uncertainty distribution for each estimate, the horizontal line in the middle of the box represents the median (P50) and the 'whiskers' above and below the box show the 95% probability interval (P2.5 and P97.5).

Figure 9: CAG-DAC: Combination of MOET estimates and confidence intervals at the 99.9th percentile of exposure in each consumer population, with the elicited distributions of multiplicative factors quantifying the impact of uncertainties related to toxicology and exposure

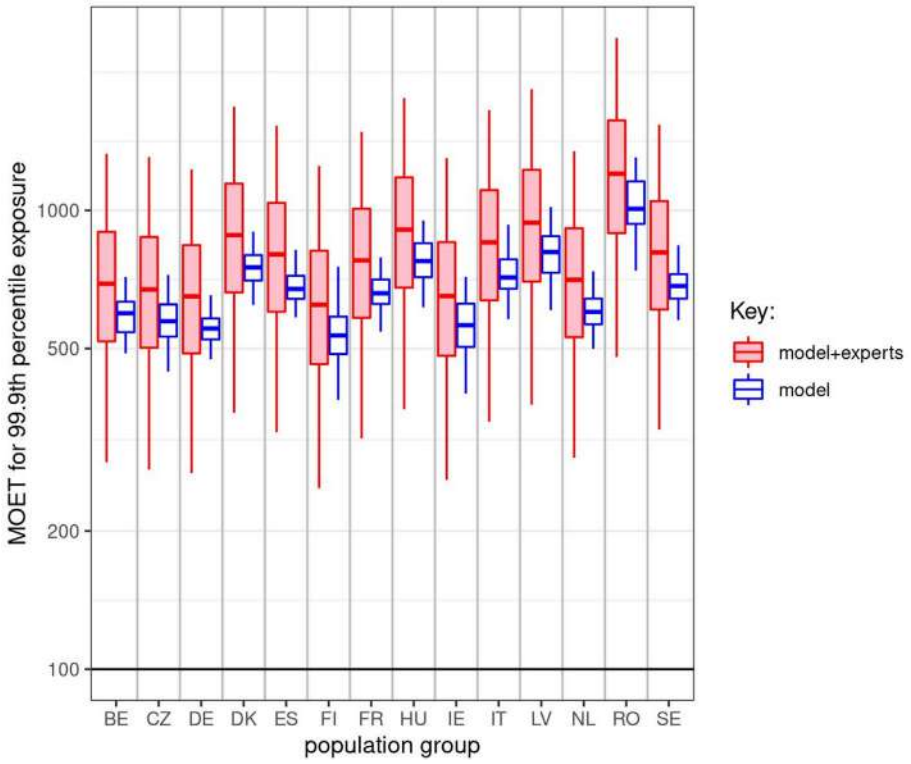


Figure 10: CAG-DAH: Combination of MOET estimates and confidence intervals at the 99.9th percentile of exposure in each consumer population, with the elicited distributions of multiplicative factors quantifying the impact of uncertainties related to toxicology and exposure. Graph content is explained in Figure 9

It can be seen in Figure 9 that, in the case of CAG-DAC, the median estimates for 'model+experts' are markedly higher than those for 'model'. This indicates that the Tier II calculations were conservative, as expected, because the uncertainties quantified in the expert elicitation include the impact of assumptions that make the calculations intentionally conservative (overestimating exposure and hence underestimating MOETs). In contrast, Figure 10 shows that, in the case of CAG-DAH, the median estimates for 'model+experts' are only slightly higher than those for 'model'. This reflects the fact that the consensus distributions of multiplicative factors elicited under EKE Q2, for both toxicology and exposure uncertainties, had median values close to 1.

For both CAGs, the boxplots for 'model+experts' and 'whiskers' are much wider than those for 'model', indicating that the contribution of sampling uncertainty for consumption and occurrence data, which are quantified in the calculation model, represent a fraction only of the overall uncertainty.

The values plotted for 'model+experts' in each population group, as well as calculated probabilities for the MOET at the 99.9th percentile of exposure being below 100 and 500, are shown numerically in Tables 28 and 29. They suggest that the risk associated with CAG-DAC is larger than the risk associated with CAG-DAH. Note that statistics shown in Tables 28 and 29 do not take account of U2, dependencies and population differences, which are addressed in EKE Q3 (see below).

Table 28: CAG-DAC: Statistics of the 'model+experts' boxplots in Figure 9

Country	Statistics of the distribution of MOET estimates in 'model+expert' boxplots shown in Figure 9					Probability of MOET at 99.9th percentile of exposure being	
	P2.5	P25	P50	P75	P97.5	< 100	< 500
BE – Belgium	749	464	351	262	147	0.2	81
CZ – Czechia	500	304	229	170	95	3.2	97
DE –Germany	446	275	208	155	88	4.8	99
DK –Denmark	599	368	276	204	113	1.3	93
ES – Spain	799	491	370	276	155	0.1	76
FI – Finland	1216	761	578	433	247	0.0	37
FR – France	621	385	291	218	123	0.7	91
HU – Hungary	1075	675	512	383	216	0.0	48
IE – Ireland	308	187	140	103	57	23	100
IT – Italy	838	522	395	296	168	0.1	71
LV – Latvia	1177	742	565	424	242	0.0	39
NL – Netherlands	715	441	333	249	140	0.3	84
RO – Romania	1130	720	550	415	239	0.0	41
SE – Sweden	572	349	263	195	109	1.6	94

Table 29: CAG-DAH: Statistics of the 'model+experts' boxplots in Figure 10

Country	Statistics of the distribution of MOET estimates in 'model+expert' boxplots shown in Figure 10					Probability of MOET at 99.9th percentile of exposure being	
	P2.5	P25	P50	P75	P97.5	< 100	< 500
BE – Belgium	1329	898	692	518	282	0.0	23
CZ – Czechia	1307	875	672	502	272	0.0	25
DE –Germany	1228	840	650	488	267	0.0	27
DK – Denmark	1682	1144	883	662	362	0.0	10
ES – Spain	1528	1038	802	601	329	0.0	14
FI – Finland	1249	817	623	462	248	0.0	31
FR – France	1483	1008	778	583	318	0.0	16
HU – Hungary	1756	1180	908	678	369	0.0	9.2
IE – Ireland	1299	853	651	482	259	0.0	28
IT – Italy	1654	1107	851	636	346	0.0	12
LV – Latvia	1838	1226	940	700	377	0.0	8.3
NL – Netherlands	1345	914	706	529	289	0.0	21
RO – Romania	2376	1571	1201	892	479	0.0	3.0
SE – Sweden	1537	1048	810	608	333	0.0	14

3.3.4. Accounting for dependencies, population differences and additional uncertainties

EKE was used to evaluate how much the calculated probabilities for the MOETs at the 99.9th percentile of exposure to be below 100/500 should be adjusted to take account of (a) sources of uncertainty not accounted for under EKE Q1 and EKE Q2, (b) dependencies between the elicited distributions for exposure and toxicology and the uncertainties quantified in the model (which were assumed in the calculation to be independent), (c) differences between the uncertainties affecting exposure and toxicology for the German population (which were quantified by the elicited distributions of multiplicative factors) and the uncertainties for other population groups (which were assumed in the 'model+experts' calculation to be the same as for the German population).

This was addressed by the following elicitation question (EKE Q3) for each of the 2 CAGs:

For the German population: '*If all the uncertainties in the model, exposure assessment, hazard identification and characterisation and their dependencies were fully resolved (e.g. by obtaining perfect*

information on the issues involved) and addressed in the modelling, what is your probability that this would result in the MOET for the 99.9th percentile of exposure for the German population in 2017–2019 being below [100/500]?'

For each of the other 13 modelled populations: '*If all the uncertainties in the model, exposure assessment, hazard identification and characterisation and their dependencies, and differences in these between populations, were fully resolved (e.g. by obtaining perfect information on the issues involved) and addressed in the modelling, what is your probability that this would result in the MOET for the 99.9th percentile of exposure for the [name of the population] in 2017–2019 being below [100/500]?*'

3.3.4.1. Initial considerations

(a) One source of uncertainty (U2 – substances not causing the effect included in the CAG) could not be accounted for under EKE Q1 and EKE Q2 for the reasons explained in Section 3.3.2. CAG-membership probabilities were elicited for the risk drivers identified in the two CAGs (see Note 2 in Appendix F). Appendices J1 and J2 explain how they contributed to the experts' judgements on EKE Q3 probabilities for CAG-DAC and CAG-DAH, respectively.

(b) As indicated in Section 2.3.5, the assessment of dependencies between uncertainties in the exposure and hazard assessments was facilitated by additional simulations exploring the impact of different degrees of dependency between them. This quantified the possible effects resulting from different degrees of positive or negative dependency on the probability for the MOET being below 100 or 500. This information is available in Appendices J1 and J2 for CAG-DAC and CAG-DAH, respectively.

(c) Differences between populations were noted under EKE Q1b for multiple sources of uncertainty and reported in Appendices G1 and G2 for CAG-DAC and CAG-DAH, respectively. In case of sources of uncertainty documented by a sensitivity analysis, information is available to help quantifying differences of the impacts between populations. Sensitivity analyses suggesting the largest differences between populations were sensitivity analysis C (assuming no transfer to processed commodities when PFs are not available – U31), sensitivity analysis G (assuming total alcohol abstinence during pregnancy – U13) and sensitivity analysis K (assuming that propineb and thiram were authorised during the reference period and that dithiocarbamates were completely converted into ETU and PTU during food transformation processes that involve heating – U24 and part of U17).

(d) An uncertainty about the exact nature of the commodity reported as wine grapes with the facet 'PROCESS=Unspecified' is specific to the German population. It affects largely the calculations concerning CAG-DAC (see Section 3.3.2.1.1).

EKE Q3 was addressed by the 12 experts listed in Section 2.3.1. As 56 distinct probabilities (2 CAGs/2 threshold/14 countries) had to be elicited, it was decided to perform the elicitation following the modalities described in Section 2.3.6 for seven of them only, corresponding to the following combinations:

- CAG-DAC/MOET<100/Germany
- CAG-DAC/MOET<100/Czechia
- CAG-DAC/MOET<100/Ireland

because Germany, Czechia and Ireland have the largest probabilities for the MOET<100 after combination of the model output with the distributions of multiplicative factors for toxicology and exposure uncertainties;

- CAG-DAC/MOET<500/Finland

because Finland has the smallest probabilities for the MOET<500 after combination of the model output with the distributions of multiplicative factors for toxicology and exposure uncertainties;

- CAG-DAH/MOET<500/Germany
- CAG-DAH/MOET<500/Finland
- CAG-DAH/MOET<500/Romania

because Germany was the reference population for EKE Q1, while Finland and Romania have the largest and smallest probabilities, respectively, for the MOETs<500 after combination of the model output with the distributions of multiplicative factors for toxicology and exposure uncertainties.

The consensus discussion of the probabilities for the selected combinations took place on 31 March and 01 April.

For the other 49 non-selected combinations, one expert made an assessment using the same criteria and reasoning supporting the consensus judgement of the seven selected combinations. This

assessment was shared with the other 11 experts for comments and a final assessment was achieved based on their comments.

Full records of the EKE Q3 elicitation can be found in Appendices J1 and J2 for CAG-DAC and CAG-DAH, respectively.

3.3.4.2. Outcome of the elicitation process

Perfect information on U2 can only increase the MOET at the 99.9th percentile of the cumulative exposure distribution. The ranges of CAG-membership probabilities elicited for the six risk drivers in CAG-DAC and in CAG-DAH are similar, suggesting that the overall level of certainty that the included substances are actually causing the effect as a primary mode of toxicity is similar between the two CAGs. It is however extremely difficult to quantify the impact of U2 for each CAG/population combination individually, due to the specific nature of U2.

Dependencies were postulated between U2, uncertainties relating to toxicology and uncertainties relating to exposure. If factual, these dependencies would generally be of negative nature. The postulated dependencies would apply equally to all CAG/population combinations.

In the elicitation of EKE Q3, the experts considered mainly the following sources of uncertainty to quantify differences with the German population: U4 (uncertainty related to the NOAEL-setting process), U12 (representativeness of consumption data for pregnancy diet), U13 (uncertainty about the alcohol abstinence in early pregnancy), U17 (uncertainty about the contribution of metabolites, especially of ETU and PTU), U31 (missing PFs) and U36 (effect of peeling and/or washing of commodities with edible peel and/or consumed raw). In addition, the uncertainty about the actual nature of the food commodity reported as wine grape with the facet '*PROCESS=Unspecified*' in the German food consumption survey only, and creating a difference with all the other populations, was also considered.

The results are given in Table 30 (CAG-DAC) and Table 31 (CAG-DAH).

Table 30: CAG-DAC: Probabilities of the MOET at the 99.9th percentile of the exposure distribution being below 100 and 500 in the assessed populations

Country	Probability (%) of 99.9%ile MOET<100, before EKE Q3 elicitation[(a)]	Probability (%) of 99.9%ile MOET<100, after EKE Q3 elicitation[(b)]	Probability (%) of 99.9%ile MOET<500, before EKE Q3 elicitation[(a)]	Probability (%) of 99.9%ile MOET<500, after EKE Q3 elicitation[(b)]
BE – Belgium	0.2	0–1	81	33–66
CZ – Czechia	3.2	0–3	97	33–66
DE –Germany	4.8	0–7	99	66–95
DK – Denmark	1.3	0–1	93	33–66
ES – Spain	0.1	0–1	76	33–66
FI – Finland	0.0	0–1	37	33–66
FR – France	0.7	0–1	91	33–66
HU – Hungary	0.0	0–1	48	33–66
IE – Ireland	23	0–10	100	33–66
IT – Italy	0.1	0–1	71	20–66
LV – Latvia	0.0	0–1	39	10–66
NL – Netherlands	0.3	0–1	84	33–66
RO – Romania	0.0	0–1	41	50–90
SE – Sweden	1.6	0–1	94	20–50

(a): i.e. assuming 100% CAG-membership probability no difference between populations and full independence between exposure and toxicology uncertainties.
(b): i.e. taking account of U2, dependencies and additional differences in uncertainties compared to the German population.

In CAG-DAC, the probability of the MOET being below 100 at 99.9th percentile of the cumulative exposure distribution is low in all populations. The probability range including the largest probability was found for the Irish population (0–10%).

The probability of the MOET being below 500 is however substantial. The probability range including the highest probabilities was found for the German population (66–95%). For the majority of populations, the consensus probability range was concluded to be 33–66%, for pragmatic reasons of

communication, although the experts' opinions were actually ranging more widely (e.g. from 10 to 90%). The large width of the elicited probability ranges results mainly from the impact of CAG-membership, which is difficult to quantify, and from the uncertainty about the extent of alcohol abstinence/binge drinking during early pregnancy.

Table 31: CAG-DAH: Probabilities of the MOET at the 99.9th percentile of the exposure distribution being below 100 and 500 in the assessed populations

Country	Probability (%) of 99.9%ile MOET<100, before EKE Q3 elicitation[(a)]	Probability (%) of 99.9%ile MOET<100, after EKE Q3 elicitation[(b)]	Probability (%) of 99.9%ile MOET<500, before EKE Q3 elicitation[(a)]	Probability (%) of 99.9%ile MOET<500, after EKE Q3 elicitation[(b)]
BE – Belgium	0.0	0.0	23	0–5
CZ – Czechia	0.0	0.0	25	1–10
DE – Germany	0.0	0.0	27	5–33
DK – Denmark	0.0	0.0	10	0–10
ES – Spain	0.0	0.0	14	0–5
FI – Finland	0.0	0.0	31	0–5
FR – France	0.0	0.0	16	0–5
HU – Hungary	0.0	0.0	9.2	0–5
IE – Ireland	0.0	0.0	28	0–5
IT – Italy	0.0	0.0	12	0–5
LV – Latvia	0.0	0.0	8.3	0–5
NL – Netherlands	0.0	0.0	21	0–5
RO – Romania	0.0	0.0	3.0	0–10
SE – Sweden	0.0	0.0	14	0–5

(a): i.e. assuming 100% CAG-membership probability no difference between populations and full independence between exposure and toxicology uncertainties.
(b): i.e. taking account of U2, dependencies and additional differences in uncertainties compared to the German population.

In CAG-DAH, the probability of the MOET being below 100 at 99.9th percentile of the cumulative exposure distribution is virtually nil in all populations.

The probability of the MOET being below 500 is generally low for CAG-DAH. The probability range including the highest probabilities was found for the German population (5–33%).

4. Risk characterisation

4.1. Risks for the assessed populations

The results of the assessment are summarised in Table 32, and, contrary to Section 3.3.3, are expressed in terms of the probability that the MOET at the 99.9th percentile of cumulative exposure in 2017–2019 is equal or greater than the thresholds of 100 and 500 for each population. Also shown in the table are verbal probability terms associated with the assessed range of percent certainty, based on the approximate probability scale recommended for harmonised use in EFSA assessments (EFSA Scientific Committee, 2018a).

EFSA's guidance on communicating uncertainty (EFSA, 2019f) recommends that for the purpose of communication, probabilities quantifying uncertainty should be expressed as 'percentage certainty' of the more probable outcome. In the present assessment, the more probable outcome in nearly all cases is that the MOET at the 99.9th percentile of cumulative exposure in 2017–2019 is equal or greater than 100/500, rather than less: for this reason, the probabilities in Table 32 are communicated as % certainty for that outcome. However, for Germany and Romania, it is more probable that the MOET at the 99.9th percentile for CAG-DAC is below 500 than above, so for these populations, the result should rather be expressed as % certainty of that outcome: i.e. 67–95% certainty that the MOET at the 99.9th percentile is less than 500 for Germany, and 50–90% certainty for Romania.

Table 32: CAG-DAC and CAG-DAH: Outcome of the CRA for craniofacial alterations resulting from dietary exposure to pesticides residues in 2017–2019

Country	Probability for the MOET at 99.9th percentile of cumulative exposure distribution to be above 100	Probability for the MOET at 99.9th percentile of cumulative exposure distribution to be above 500
CAG-DAC		
BE – Belgium	99–100% (almost certain)	33–66% (about as likely as not)
CZ – Czechia	97–100% (extremely likely to almost certain)	33–66% (about as likely as not)
DE – Germany	93–100% (very likely to almost certain)	5–33% (very unlikely to unlikely)
DK – Denmark	99–100% (almost certain)	33–66% (about as likely as not)
ES – Spain	99–100% (almost certain)	33–66% (about as likely as not)
FI – Finland	99–100% (almost certain)	33–66% (about as likely as not)
FR – France	99–100% (almost certain)	33–66% (about as likely as not)
HU – Hungary	99–100% (almost certain)	33–66% (about as likely as not)
IE – Ireland	90–100% (very likely to almost certain)	33–66% (about as likely as not)
IT – Italy	99–100% (almost certain)	33–80% (about as likely as not to likely)
LV – Latvia	99–100% (almost certain)	33–90% (about as likely as not to likely)
NL – Netherlands	99–100% (almost certain)	33–66% (about as likely as not)
RO – Romania	99–100% (almost certain)	10–50% (unlikely to about as likely as not)
SE – Sweden	99–100% (almost certain)	50–80 (about as likely as not to likely)
CAG-DAH		
BE – Belgium	100%	95–100% (extremely likely to almost certain)
CZ – Czechia	100%	90–99% (very likely to extremely likely)
DE – Germany	100%	66–95% (likely to very likely)
DK – Denmark	100%	90–100% (very likely to almost certain)
ES – Spain	100%	95–100% (extremely likely to almost certain)
FI – Finland	100%	95–100% (extremely likely to almost certain)
FR – France	100%	95–100% (extremely likely to almost certain)
HU – Hungary	100%	95–100% (extremely likely to almost certain)
IE – Ireland	100%	95–100% (extremely likely to almost certain)
IT – Italy	100%	95–100% (extremely likely to almost certain)
LV – Latvia	100%	95–100% (extremely likely to almost certain)
NL – Netherlands	100%	95–100% (extremely likely to almost certain)
RO – Romania	100%	90–100% (very likely to almost certain)
SE – Sweden	100%	95–100% (extremely likely to almost certain)

4.2. Risks for the other PRIMo populations

During the Standing Committee on Plants, Animals, Food and Feed of 18–19 September 2018 (European Commission, online), Member States recommended considering, in CRA, all population subgroups of consumers included in the EFSA PRIMo model (EFSA, 2018).

For reasons of resources, calculations were restricted to a representative set of 14 population groups of women in childbearing age in Northern, Central and South EU countries, providing however a reasonable insight into the level of risk of craniofacial alterations in European Union.

4.3. Other points to be considered

This section deals with specific issues that were encountered during this assessment and/or were not addressed before.

4.3.1. Overall estimation of the average extra risk at the NOAELs established for craniofacial alterations in the present assessment

As explained in Section 1.2, Member States agreed on an MOET of 100 at the 99.9th percentile of exposure as a general threshold for regulatory consideration. For a correct understanding of the concept of a margin of exposure and the level of protection that it offers, the level of risk against which the margin of exposure is expressed needs to be unambiguous.

For this reason, in previous CRAs for the effects of pesticides on the nervous system and the thyroid, the MOET at 99.9th percentile of cumulative exposure distribution were ultimately assessed with respect to BMDLs of various response levels, and not with respect to NOAELs. Following the recommendations of the EFSA Scientific Committee for effects measured by quantal data, BMDL10s (corresponding to a level of extra risk of 10%) were for instance selected as reference for the MOET estimations regarding cumulative risks of hypothyroidism and functional alterations of the motor division. In the assessment of the risks of inhibition of acetylcholinesterase, an effect measured by continuous data, BMDL20s were selected as reference for the MOET estimations (corresponding to a reduction of the enzymatic activity of 20% compared to non-exposed populations).

In the present assessment, it was initially intended to estimate the probabilities of the MOET at the 99.9th percentile being below 100/500 with respect to a level of extra risk of 5% considering the severity of the effect under consideration (and not of 10% as recommended by the EFSA Scientific Committee for quantal data). This required assessing how well NOAELs, as set in this report, represent true BMDL05s (U37). However, for the reasons explained in Section 3.3.2 and in Note 36 of Appendix F, this has not been possible.

Therefore, in order to provide risk managers with the information about the level of risk against which the MOETs were assessed, the experts were asked to estimate the average extra risk of craniofacial alterations (incidence of fetuses affected minus the incidence in the control group divided by the non-affected fraction of the population) at the NOAELs for the substances included in the CAGs, as established according to the hazard characterisation principles described in Section 2.1.3. In first instance, the experts made their own judgement individually, mainly based on the following:

- The principles used for the derivation of NOAELs as described in Section 2.1.3.
- The information contained in the tables reported in Appendices A1 and A2 about the key studies used for the establishment of NOAELs and LOAELs.
- The data collection (Excel spreadsheet) in Annex A.
- The Note 36 in Appendix F, as well as the individual data retrieved from the original study reports that were used for the attempt of BMD modelling reported in this Note.

A collective assessment was later completed by written procedure. At the end of the process, it was collectively agreed that the average extra risk of craniofacial alterations ranges from 0 to 1%, with a median value of 0.5% at the NOAEL of the substances included in CAG-DAC and CAG-DAH. This low level of response can be explained by the high number of pups that can be examined in developmental toxicity studies and the fact that the statistical significance of the observations was not taken into account in the setting of the NOAEL, considering the high toxicological specificity and relevance of these observations.

4.3.2. Validity of the 10x10 UF to take inter- and intraspecies variability into account

As indicated in Section 3.3.1, the eventual uncertainty related to the default 10x10 UF for inter- and intraspecies variability in the sensitivity to toxicological effects has not been considered in the uncertainty analysis. Indeed, in setting an MOET of 100 as threshold for regulatory consideration, risk managers indicated that they considered this UF applicable by default to the assessment of cumulative risks.

Nevertheless, the Working Group considered whether it was in possession of any information questioning the soundness of this default UF. This was not the case, and therefore, in the absence of empirical evidence supporting a different approach for the assessment of risks of craniofacial alterations, the use of the default 10X10 UF is appropriate. This also meets the recommendation of the EFSA Scientific Committee (2012) to use a default UF of 100 (10x10) for inter- and intraspecies extrapolation.

4.3.3. Co-exposure to alcohol and pesticides

In the case of CAG-DAC, a major part of the cumulative exposure results from the consumption of wine. Alcohol, as explained below in this section, is by itself capable of causing craniofacial alterations. The issue of co-exposure to folpet and alcohol, the nature of their combined toxic action and the impact of this on the risk of craniofacial malformations were out of the scope of this report (see recommendation for additional consideration in Section 6).

In short, Chernoff (1977) has simulated the condition of human chronic alcoholism in female mice and observed a pattern of malformations similar to those observed in children with the fetal alcohol syndrome (FAS). The term 'fetal alcohol syndrome' is used to describe a specific pattern of anomalies in offspring of women with chronic alcoholism, including developmental and psychomotor delay, behavioural disorders, pre- and postnatal growth deficiency, growth deformities, impaired intellectual development and performance and craniofacial, cardiac and joint defects.

In humans, as reported by the Dutch Expert Committee on Occupational Standards (2006), 'the most critical non-carcinogenic effects appear to be liver cirrhosis and effects on the development of offspring and fertility. Epidemiological studies suggest that consumption levels below 10–12 g of ethanol per day, will probably not cause liver cirrhosis. However, the Committee on Alcohol consumption and reproduction concluded that at these consumption levels effects on fertility and development have been reported. Even long-term oral exposure to levels of 1–12 g ethanol per day might result in effects on the development (like increased incidence of spontaneous abortion, fetal death, pre-term delivery and decreased length of gestation) and fertility, according to the Committee on Alcohol consumption and reproduction.'

The American College of Obstetricians and Gynaecologists describes FAS as the most severe 'Fetal Alcohol Spectrum Disorder' (FASD).[21] It is noted that FAS can cause problems with brain development, lower-than-average height and weight, smaller-than-normal head size, abnormal facial features.

For every child born with FAS, many more are born with other FASDs. These children may have problems with coordination, behaviour, attention, learning and understanding consequences without any of the physical signs of FAS.

Drinking any alcohol quantity during pregnancy is associated with about 1.5% risk of giving birth to a child with FAS. Drinking large quantities, defined as 2 standard drinks a day, or 6 standard drinks in a short time, carries a 50% risk of an FAS birth (Popova et al., 2017).

5. Conclusions

EFSA established CAGs and conducted CRAs for two types of craniofacial alterations (alterations due to abnormal skeletal development and head soft tissue alterations and brain neural tube defects) for 14 European populations of women of childbearing age. To this end, cumulative exposure calculations were performed by probabilistic modelling using monitoring data collected by Member States in 2017, 2018 and 2019. Based on a rigorous uncertainty analysis, considering all sources of uncertainty, their dependencies and differences between populations, it was concluded with varying degrees of certainty that the MOET resulting from cumulative exposure exceeds 100 and even 500 for head soft tissue alterations and brain neural tube defects. It was also concluded with varying degrees of certainty that, for alterations due to abnormal skeletal development, the MOET resulting from cumulative exposure exceeds 100, but generally not 500. These results need to be considered in the light of the conservative methodological approach used for the toxicological characterisation of the substances included in the CAGs.

6. Recommendations

Despite the considerable amount of data used, these CRAs are subject to important uncertainties. To reduce their impact or to facilitate the assessment of their impact, it is recommended to:

- Investigate the combined toxicity of pesticide residues and alcohol and the impact of co-exposure (see Section 4.3.3);
- Consolidate the list of validated PFs available for CRAs;
- Include CAG-membership probabilities in Tier II calculations;
- Progress the inclusion of monitoring data in processed commodities in cumulative exposure calculations (e.g. fruit juice);

[21] https://www.acog.org/womens-health/faqs/alcohol-and-women

- Collect information on (a) national authorisations; (b) use statistics of plant protection products; (c) pesticide residues in drinking water, from the respective competent organisations on risk-based criteria;
- Clarify the actual nature of the commodities corresponding to wine grapes with the facet '*PROCESS=unspecified*' in the German food consumption survey;
- Assess the contribution of metabolites to the effects under consideration, through the application of the guidance of the PPR Panel on the establishment of the residue definition for dietary risk assessment (EFSA PPR Panel, 2016);
- Develop further guidance for a consistent use of the code ST20A (Selective sampling) in the context of Regulation (EC) No 396/2005 by data providers.

References

Note to the reader:

The following references cited in the Scientific Report and its Appendixes are not included in the reference list:

- Laboratory toxicological studies: References to these studies are borrowed from different source documents (DARs, JMPR evaluations) which can be found elsewhere (see below). Moreover, the names of the authors of these studies are blacked out because article 63 of Regulation (EC) No 1107/2009 requires a confidential treatment of the names of persons involved in testing on vertebrate animals.
- DARs, DRARs and their addenda can be found in OpenEFSA at https://open.efsa.europa.eu/questions.
- JMPR evaluations: Inventories of evaluations performed by the JMPR are available online at https://apps.who.int/pesticide-residues-jmpr-database/ (toxicological evaluations), https://inchem.org/#/ (toxicological evaluations) and https://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/lpe/en/ (Residue evaluations).
- EFSA conclusions, reasoned opinions and statements can be found on the EFSA website at https://www.efsa.europa.eu/en/publications.
- EC review reports can be found in the EU pesticide database of the European Commission at https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/active-substances/?event=search.as.
- CLH Report and RAC Opinions can be found at the following link of the European Chemicals Agency: https://echa.europa.eu/registry-of-clh-intentions-until-outcome.

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Abbreviations

ADI	Acceptable daily intake
AOP	Adverse outcome pathway
ARfD	Acute reference dose
AUC	Area under the concentration-time curve
AUP	Agricultural use pattern
BMD	Benchmark dose
BMDL	Lower confidence bound of the benchmark dose
BMP	Bone morphogenic protein
BMR	Benchmark response
BPC	Biocidal Products Committee (of ECHA)
CAG	Cumulative assessment group
CAG-DAC	Cumulative Assessment Group – Developmental toxicity/Acute/Craniofacial (skeletal) alterations
CAG-DAH	Cumulative Assessment Group – Developmental toxicity/Acute/Head (soft tissues) alterations
CAG-NAM	Cumulative Assessment Group – Nervous system/Acute/Motor division effects
CAG-NAN	Cumulative Assessment Group – Nervous system/Acute/Neurochemical effects
CAG-TCP	Cumulative Assessment Groups – Thyroid/Chronic/Parafollicular cells
CLH	Harmonised classification and labelling
C-max	Maximum/peak concentration
CRA	Cumulative risk assessment
DAR	Draft assessment report
DART	Developmental and reproductive toxicology
DMBU	Upper confidence bound of the benchmark dose
DRAR	Draft renewal assessment report
ECCO	European Community Co-ordination[(a)]
EKE	Expert knowledge elicitation
EPCO	EFSA Peer Review Co-ordination[(a)]
ETU	Ethylene thiourea
EUCP	EU-coordinated control programme
FAS	Fetal alcohol syndrome

FASD	Fetal alcohol spectrum disorder
FGF	Fibroblast growth factor
GAG-TCF	Cumulative Assessment Groups - Thyroid/Chronic/Follicular cells
GLP	Good laboratory practice
HCD	Historical control data
Hox	Homeobox
HQ	Hazard quotient
JMPR	Joint meeting on pesticide residues
KE	Key event
LOAEL	Lowest observed adverse effect level
LOE	Line of evidence
LOQ	Limit of quantification
MIE	Molecular initiating event
MoA	Mechanism/mode of action
MOET	Combined (total) margin of exposure
MRL	Maximum residue level
NCC	Neural crest cell
NE	Normalised exposure
NOAEL	No observed adverse effect level
PF	Processing factor
PoD	Point of departure
PTDI	Provisional tolerable daily intake
PTU	Propylene thiourea
RA	Retinoic acid
RAC	Committee for risk assessment (ECHA)
RIO	Rationale impartial observer (concept)
RMS	Rapporteur member state
RPC	Raw primary commodity
RPCD	Raw primary commodity derivative
RPF	Relative potency factor
RPI	Reference point index
SCoFCAH	Standing Committee on the Food Chain and Animal Health
SCoPAFF	Standing Committee on Plants, Animals, Food and Feed
SSD	Standard sample description
TDI	Tolerable daily intake
TDM	Triazole derivative metabolite
TG	Test guideline
UF	Uncertainty factor
VF	Variability factor
WEC	Whole embryo culture

(a): The programme for evaluating existing active substances under Directive 91/414/EEC has been initially co-ordinated by the European Commission (ECCO, European Community Co-ordination), with the assistance of an ECCO Team since 1996. The ECCO-Team consisted of two groups; one situated at the Pesticides Safety Directorate (United Kingdom) and the other at the Bundesamt für Verbraucherschutz und Lebensmittelsicherheit – BVL (Federal Office for Consumer Protection and Food Safety) (Germany). They provided technical and administrative support to the programme for the evaluation of active substances on behalf of the European Commission and were responsible for the ECCO Peer Review programme. In November 2003, the European Food Safety Authority (EFSA) has taken over the responsibility for the scientific peer review of the evaluations prepared by Member States, supported during a few years by the ECCO-Team (EPCO, EFSA Peer Review Co-ordination).

Appendix A1 – CAG-DAC (Craniofacial alterations due to abnormal skeletal development)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[a] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c. = post coitum)	Source
1,2,4-triazole	Facial fissures: cleft palate	100	**200**	[redacted] (1988b), Developmental toxicity, WISW rat (SPF Cph), oral gavage[b]	0, 100, 200 days 6–15 p.c.	Addendum to the draft assessment reports on various triazole containing pesticides (2018) EFSA conclusions (Peer review of the pesticide risk assessment for the triazole derivative metabolites in light of confirmatory data submitted, 2018); DAR difenoconazole (2006)
	No indicators	**100**	–	[redacted] (1988a), Developmental toxicity, WISW rat (SPF Cph), oral gavage	0, 10, 30, **100** days 6–15 p.c.	Addendum to the draft assessment reports on various triazole containing pesticides (2018) EFSA conclusions (Peer review of the pesticide risk assessment for the triazole derivative metabolites in light of confirmatory data submitted, 2018)
2,4-D	Skull vault agenesis: exencephaly Jaw/Nasopharynx: agnathia	**5**	**20**	[redacted] (1984), Two-generational, Fischer 344 rat, oral diet	F0: 0, 5, 20, 80; F1: 0, 5, 20 from 105 days prior to first mating and throughout all subsequent phases until termination	DAR (2013), EFSA Conclusion (2014)
3,5,6-TCP (metabolite of chlorpyrifos, chlorpyrifos-methyl and triclopyr)	Skull defects: misshapen skull Jaw/Nasopharynx: agnathia	**100**	**150**	[redacted] (1987a), Developmental toxicity, Fischer 344 rat, oral gavage	0, 50, 100, 150 days 6–15 p.c.	DAR (2017) (chlorpyrifos), EFSA Conclusion (2014) (chlorpyrifos), Statement (2019) (chlorpyrifos)
	Hyoid: crooked hyoid	100	250	[redacted] (1987b), Developmental toxicity, Fischer 344 rat, oral gavage	0, 25, 100, 250 days 7–18 p.c.	DAR (2017), EFSA Conclusion, (2014); Statement 2019

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[a] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c. = post coitum)	Source
Abamectin	Facial fissures: cleft palate Skull vault agenesis: exencephaly	**0.8**	**1.6**	[redacted] (1982a), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 0.4, 0.8, 1.6 days 6–17 p.c.	DAR (2005) and Addendum (2016), EFSA Conclusion (2016)
Benomyl	Jaw/Nasopharynx: micrognathia	62.5 **(10)**	125	[redacted] (1980), Developmental toxicity, Sprague Dawley rat, oral gavage[b],[c]	0, 3, **10**, 30, 62.5, 125 days 7–16 p.c.	DAR (1998), LoEP European Community Co-ordination (ECCO) 61
	Facial fissures: cleft lip	< 31.2	**31.2**	[redacted] (1986), Developmental toxicity, Sprague Dawley rat, oral gavage[b]	0, 31.2 days 7–16 and 7–21 p.c.	DAR (1998), LoEP ECCO 61
	Skull vault agenesis: anencephaly Facial fissures: cleft palate	< 31.2	**31.2**	[redacted] (1987), Developmental toxicity, Sprague Dawley rat, oral gavage[b]	0, 31.2, 62.5, 125 days 7–21 p.c.	DAR (1998), LoEP ECCO 61
	Skull defects: enlarged frontal and occipital fontanels	<62.5	62.5	[redacted] (1979), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 62.5, 125, 250, 500 days 6–15 p.c.	DAR (1998), LoEP ECCO 61
Bitertanol	Facial fissures: facial cleft	**30**	**100**	[redacted] (1977), Developmental toxicity, Long Evans rat, oral gavage	0, 10, 30, 100 days 6–15 p.c.	DAR (2005) and Addendum (2009), EFSA Conclusion (2010)
	Facial fissures: cleft palate	**30**	**100**	[redacted] (1983), Developmental toxicity, Himalayan (=Chbb: HM15) rabbit, oral gavage	0, 10, 30, 100 days 6–18 p.c.	DAR (2005) and Addendum (2009), EFSA Conclusion (2010)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[(a)] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c. = post coitum)	Source
Bromuconazole	Hyoid: hyoid cornua bent outwards Skull defects: irregular ossification of frontal suture	**12.5**	**50**	[redacted] (1990), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 12.5, 50, 200 days 6–19 p.c.	DAR (2009), EFSA Conclusion (2010)
Carbendazim	Skull vault agenesis: exencephaly Skull defects: fused skull, domed frontal area	20	90	[redacted] (1987), Developmental toxicity, Sprague Dawley rat, oral gavage	0,5,10,20,90 days 7–16 p.c.	DAR (2009), EFSA Conclusion (2010)
	Skull vault agenesis: exencephaly Jaw/Nasopharynx: micrognathia	**30**	**60**	[redacted] (1987a), Developmental toxicity, Sprague Dawley rat, oral gavage	0,10,30,60,100, 300, 1000, 3000 days 6–15 p.c.	DAR (2009), EFSA Conclusion (2010)
	No indicators	30 **(30)**	–	[redacted] (1987b), Developmental toxicity Sprague Dawley rat, oral gavage	0, 10, **30** days 6–15 p.c.	DAR (2009), EFSA Conclusion (2010)
Chlorpyrifos	Facial fissures: cleft palate	**3**	**15**	[redacted] (1983), Developmental toxicity, Fischer 344 rat, oral gavage	0, 0.1, 3, 15 days 6–15 p.c.	DAR (2017), EFSA Conclusion (2014)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[a] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c. = post coitum)	Source
Cymoxanil	Facial fissures: cleft palate	8	**32**	[redacted] (1982), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 1, 4, 8, 32 days 6–18 p.c.	DAR (2007), EFSA Conclusion (2008)
	No indicators	32	–	[redacted] (1981), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 8, 16, 32 Day 6–18 p.c.	DAR (2007), EFSA Conclusion (2008)
	No indicators	25 **(25)**	–	[redacted] (1999), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 5, 15, **25** Day 6–18 p.c.	DAR (2007), EFSA Conclusion (2008)
Cyproconazole	Facial fissures: cleft palate	7.5	30	[redacted] (1985a), Developmental toxicity, Wistar rat, oral gavage[b]	0, 7.5, 30, 75, 120 days 7–19 p.c.	DAR (2006) and Addendum (2010), EFSA Conclusion (2010)
	Facial fissures: cleft palate	24 **(12)**	48	[redacted] (1985b), Developmental toxicity, Wistar rat, oral gavage	0, 6, **12**, 24, 48 days 6–15 p.c.	DAR (2006) and Addendum (2010). EFSA Conclusion (2010)
	Facial fissures: cleft palate	< 20	**20**	[redacted] (1995), Developmental toxicity, Wistar rat, oral gavage[b]	0, 20, 50, 75 days 6–16 p.c.	DAR (2006) and Addendum (2010), EFSA Conclusion (2010)
Delta 8,9 isomer of avermectin B1a (metabolite of abamectin) folpet	Facial fissures: cleft palate	**1.5**	**3**	[redacted] (1996b), Developmental toxicity, CD1 mouse, oral gavage	0, 0.75, 1.5, 3.0 days 6–15 p.c.	DAR (2005) (abamectin) and Addendum (2016), EFSA Conclusion (2016)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[a] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c. = post coitum)	Source
Deltamethrin	Skull vault agenesis: exencephaly	4	**16**	[redacted] (1977c), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 1, 4, 16 days 6–19 p.c	DAR (1998), Addendum (2002), (DRAR 2018), EC Review report (2002)
	No indicators	32 **(10)**	–	[redacted] (2001), Developmental toxicity, New Zealand White rabbit oral gavage	0, 3, **10**, 32 days 6–28 p.c	DAR (1998), Addendum (2002), (DRAR 2018), EC Review report (2002)
Dieldrin	Facial fissures: cleft palate	< 15	**15**	[redacted] (1974), Developmental toxicity, CD1 mouse, oral gavage[b]	0, 15 single oral dose on day 9	JMPR (1994), EFSA PPR Panel (2007); JMPR (1989)
	No indicators	6 **(6)**	–	[redacted] (1975), Developmental toxicity CD1 mouse, oral gavage[b]	0, 1.5, 3, **6** days 7–16 p.c.	JMPR (1994), EFSA PPR Panel (2007); JMPR (1989)
Emamectin	Facial fissures: cleft palate	**4**	**8**	[redacted] (1992c), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 2, 4, 8 days 6–19 p.c.	DAR (2011), EFSA Conclusion (2012)
	No indicators	2.5		[redacted] (1993), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 0.1, 0.6, 3.6/2.5 days 6–20 p.c.	DAR (2011), EFSA Conclusion (2012)
Epoxiconazole	Facial fissures: cleft palate	**60**	**180**	[redacted] (1989), Developmental toxicity, Wistar rat, oral gavage[b]	0, 20, 60, 180 days 6–15 p.c.	DAR (2005), EFSA Conclusion (2008)
	No indicators	45		[redacted] (1990b), Developmental toxicity, Wistar rat, oral gavage	0, 5, 15, 45 days 6–15 p.c.	DAR (2005), EFSA Conclusion (2008)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[a] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c. = post coitum)	Source
Ethylene oxide	Facial fissures: cleft palate	< 75 **(7.5)**	**75**	[redacted] (1980), Developmental toxicity, CD-1 mouse, intravenous[b]	0, 75, 150 I: days 4–6 p.c. II: days 6–8 p.c. III: days 8–10 p.c. IV: days 10–12 p.c.	EFSA Conclusion ethylene (2012); CLH report (2016), RAC Opinion (2017)
ETU (metabolite of ethylene-bis-dithiocarbamates)	Skull defects: 'skull anomaly' Hyoid: hyoid unossified	15	**30**	[redacted] (2015d), Developmental toxicity Sprague Dawley rat, oral gavage	0, 2.5, 5, 15, 30 day 6–15 p.c	DAR (2019) (mancozeb), EFSA Conclusion (2020) (mancozeb)
	Facial fissures: cleft palate Jaw/Nasopharynx: micrognathia	40	80	[redacted] (1979), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 5, 10, 20, 30, 40, 80 day 7–15 p.c.	DAR (2019) (mancozeb), EFSA Conclusion (2020) (mancozeb)
	Facial fissures: cleft palate, cleft lip Jaw/Nasopharynx: micrognathia Eye: ablepharia	20	40	[redacted] (1978), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 20, 40 day 7–15 p.c	DAR (2019) (mancozeb), EFSA Conclusion (2020) (mancozeb)
	No indicators	35 **(25)**	–	[redacted] (1991), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 15, **25**, 35 day 6–20 p.c.	DAR (2019) (mancozeb), EFSA Conclusion (2020) (mancozeb)
Fenpropimorph	Facial fissures: cleft palate Skull vault agenesis: exencephaly, cranioschisis Eye: open eye	**15**	**30**	[redacted] 1993a, Developmental toxicity, Russian Chbb:HM rabbit, oral gavage	0, 7.5, 15, 30 days 7–19 p.c.	DAR (2005), EFSA Conclusion (2008)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[a] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c. = post coitum)	Source
Fenpyrazamine	Jaw/Nasopharynx: zygomatic arch fusion	125	**500**	[redacted] (2009), Developmental toxicity, Wistar rat, oral gavage	0, 30, 125, 500 days 6–15 p.c	DAR (2011), EFSA Conclusion (2012)
	No indicators	500 **(300)**	-	[redacted] (2006), Developmental toxicity, Wistar rat, oral gavage	0, 150, **300**, 500 days 6–15 p.c.	DAR (2011), EFSA Conclusion (2012)
Fluazifop-P	Facial fissures: cleft palate Skull vault agenesis: acephaly	**10**	**50**	[redacted] (1993), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 2, 10, 50 days 8–20 p.c.	DAR (2010) and Addendum (2011), EFSA Conclusion (2012)
Flusilazole	Facial fissures: cleft palate	50	250	[redacted] (1984), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 0.4, 2, 10, 50, 250 days 7–16 p.c.	DAR (2009), Addendum (1999, 2004), EC Review report (2007)
	Jaw/Nasopharynx: naris atresia	**10**	**50**	[redacted] (2000), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 0.5, 2, 10, 50 days 6–20 (group 1) and days 6–15 (group 2) p.c.	DAR (2009), Addendum (1999, 2004), EC Review report (2007)
Flutriafol	Skull defects: delayed ossification in frontal, interparietal and occipital	**7.5**	**15**	[redacted] (1982), Developmental toxicity, Dutch rabbit, oral capsules	0, 2.5, 7.5, 15 days 6–18 p.c.	DAR (2006), EFSA Conclusion (2010)
Folpet	Hyoid: hyoid alae angulated	< 10 **(1)**	**10**	[redacted] (1984), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 10, 20, 60 days 7–28 p.c.	DAR (2019), EFSA Conclusion (2009)
	No indicators	160	–	[redacted] (1985c), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 10, 40, 160 days 7–19 p.c.	DAR (2019), EFSA Conclusion (2009)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[(a)] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c. = post coitum)	Source
Haloxyfop-P	Hyoid: hyoid crocked Skull vault agenesis: exencephaly	7.5	**20**	[redacted] (1983a), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 1, 7.5, 20 days 6–18 p.c.	DAR (2004) and Additional DAR (2009), EFSA Conclusion (2009)
	No indicators	15 **(15)**	–	[redacted] (1984), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 3, 7.5, **15** days 6–18 p.c.	DAR (2004) and Additional DAR (2009), EFSA Conclusion (2009)
Mancozeb	Jaw/Nasopharynx: agnathia Skull vault agenesis: exencephaly Skull defects: incomplete ossification of the skull and wide cranial suture Facial fissures: cleft palate, cleft lip Eye: ablepharia	128	512	[redacted] (1980), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 2, 8, 32, 128, 512 days 6–15 p.c.	DAR (2019), EFSA Conclusion (2020)
	Skull defects: large anterior fontanel	60	360	[redacted] (1988), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 10, 60, 360 days 6–15 p.c.	DAR (2019), EFSA Conclusion (2020)
	Hyoid: hyoid unossified	**10**	**40**	[redacted] (2015c), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 10, 40, 160 days 6–19 p.c.	DAR (2019), EFSA Conclusion (2020)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[a] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c. = post coitum)	Source
Metconazole	Jaw/Nasopharynx: brachygnathia	30 **(12)**	75	[redacted] (1991b), Developmental toxicity, Sprague Dawley rat, oral gavage	0, **12**, 30, 75 days 6–15 p.c.	DAR, (2004), EFSA Conclusion (2006)
	Skull defects: large anterior fontanel	6	**24**	[redacted] (1992a), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 6, 24, 60 days 6–15 p.c.	DAR, (2004), EFSA Conclusion (2006)
Paclobutrazol	Jaw/Nasopharynx: dental malocclusion and/ or twisted snout	50 ppm (corresponding to **3.3** mg/kg bw per day)	250 ppm (corresponding to **16.5** mg/kg bw per day)	[redacted] (1987), Two-generational Alderley Park: AP rat, oral diet.	0, 50, 250, 1250 (corresponding to 0, 3.3, 16.5, 82.5 mg/kg bw per day) 2 weeks prior to mating, during mating, gestation and lactation for 2 consecutive generations	DAR (2006) and Additional Report (2010), EFSA Conclusion (2010)
Propargite	Skull defects: fused skull bones	**6**	**8**	[redacted] (1989), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 2, 4, 6, 8, 10 days 6–15 p.c.	DAR (2007), EFSA Conclusion (2011), EFSA reasoned opinion (2018)
Propiconazole	Facial fissures: cleft palate	**30**	**90**	[redacted] (1987), Developmental toxicity, COBS rat, oral gavage	0, 30, 90, 360/300 days 7–16 p.c.	DAR (2016), EFSA Conclusion (2017)
Prosulfocarb	Jaw/Nasopharynx: agnathia	**50**	**250**	[redacted] (1986), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 10, 50, 250 days 6–20 p.c.	DAR (2006), EFSA Conclusion (2007)
Prothioconazole-desthio	Facial fissures: cleft palate	**2**	**10**	[redacted] (1992), Developmental toxicity, Chinchilla rabbit, oral gavage[b]	0, 2, 10, 50 days 6–18 p.c.	DAR (2004) (prothioconazole), Addendum, B.6′ (Toxicology and metabolism of prothioconazole-desthio), EFSA Conclusion (2007) (prothioconazole)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[(a)] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c. = post coitum)	Source
Prothioconazole-sulfonic acid	Jaw/Nasopharynx: agnathia	**150**	**750**	[redacted] (2001), Developmental toxicity, Wistar rat, oral gavage	0, 30, 150, 750 days 6–20 p.c.	DAR 2004 (prothioconazole), EFSA Conclusion (2007) (prothioconazole)
Spirotetramat	Facial fissures: cleft palate	**40**	**160**	[redacted] (2004c), Developmental toxicity, Russian Himalayan (=Chbb:HM15) rabbit, oral gavage	0, 10, 40, 160 days 6–28 p.c.	DAR (2008), EFSA Conclusion (2013)
Spiroxamine	Facial fissures: cleft palate	**30**	**100**	[redacted] (1992), Developmental toxicity, Wistar rat, oral gavage	0, 10, 30, 100 days 6–15 p.c.	DAR (2009), EFSA Conclusion (2010)
Tebuconazole	Facial fissures: cleft palate Skull vault agenesis: exencephaly, partial acrania Eye: open eye	< 10 **(1)**	**10**	[redacted] (1995c), developmental toxicity Mouse NMRI, oral, gavage	0, 10, 30, 100 days 6–15 p.c.	DAR (2006) and Addendum (2012), EFSA Conclusion (2014)
	Skull vault agenesis: Rudimentary skull ossification centres	10	30	[redacted] (1988b), developmental toxicity oral, gavage Mouse NMRI	0, 10, 30, 100 days 6–15 p.c.	DAR (2006) and Addendum (2012), EFSA Conclusion (2014)
Tebufenpyrad	Facial fissures: cleft palate	50	**150**	[redacted] (1992a), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 15, 50, 150 days 6–15 p.c.	DAR (2007), EFSA Conclusion (2008)
	No indicators	90 **(90)**	–	[redacted] (1992b, Developmental toxicity, Sprague Dawley rat, oral gavage	0, 15, 50, **90** days 6–15 p.c.	DAR (2007), EFSA Conclusion (2008)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[(a)] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c. = post coitum)	Source
Thiabendazole	Skull defects: enlarged anterior and posterior fontanels	24	**120**	[redacted] (1989), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 24, 120, 600 days 6–18 p.c.	DAR (2013), EFSA Conclusion (2014)
	No indicators	600 **(50)**		[redacted] (1992), Developmental toxicity, New Zealand White rabbit, oral gavage	0, **50**, 150, 600 days 6–15 p.c.	DAR (2013), EFSA Conclusion (2014)
Triazole alanine	Hyoid: hyoid angulated alae	**30**	**100**	[redacted] (2010b), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 30, 100, 250 days 6–29 p.c.	Addendum to the draft assessment reports on various triazole containing pesticides (2018) EFSA conclusions (Peer review of the pesticide risk assessment for the triazole derivative metabolites in light of confirmatory data submitted, 2018)

*: NOAEL and LOAEL of the specific indicator for craniofacial alteration. Values indicated in bold characters represent the overall NOAEL and LOAEL of the substance, after eventual collective evaluation of sets of studies of equivalent quality. Numbers in parenthesis represent the overall NOAEL when derived from the combination of different studies or when derived from a LOAEL divided by 10.
(a): Reference as given in the respective DAR/DRAR and other source documents mentioned in the 'source and comment' column.
(b): NOAEL derived from studies considered of limited acceptability (column AE of Annex N).
(c): The dose of 30 mg/kg bw per day, although not causing any effect, was not taken as NOAEL of benomyl because it was too close to the LOAEL of 31.5 in [redacted] (1986) and [redacted] (1987).

Appendix A2 – CAG-DAH (head soft tissues alterations and brain neural tube defects not due to abnormal skeletal development)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[a] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c.=post coitum)	Source and comment
1,2,4-triazole	Eye: anophthalmia Eye: microphthalmia	**30**	**100**	[redacted] (1988a), Developmental toxicity, WISW (SPF Cph) rat, oral gavage	0, 10, 30, 100 days 6–15 p.c.	Addendum to the draft assessment reports on various triazole containing pesticides (2018) EFSA conclusions (Peer review of the pesticide risk assessment for the triazole derivative metabolites in light of confirmatory data submitted, 2018)
2,4-D	Eye: microphthalmia	**5**	**20**	[redacted] (1984), Two generational toxicity, Fischer 344 rat, oral diet	F0: 0, 5, 20, 80 F1: 0, 5, 20 from 105 days prior to first mating and throughout all subsequent phases until termination	DAR (2013), EFSA Conclusion (2014)
3,5,6-TCP	Brain: hydrocephalus	**25**	**100**	[redacted] (1987b), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 25, 100, 250 days 7–19 p.c.	DAR (2017) (chlorpyrifos), EFSA Conclusion, (2014) (chlorpyrifos), Statement (2019) (chlorpyrifos)
Acephate	Head: dome-shaped head	**3**	**10**	[redacted] (1980), Developmental toxicity, Dutch rabbit, oral gavage	0, 1, 3, 10 days 6–27 p.c.	JMPR (2002), DAR (1999) JMPR (2005)
Acetamiprid	Eye: microphthalmia	**15**	**30**	[redacted] (1997b), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 7.5, 15, 30 days 6–18 p.c.	DRAR (revised, 2016), EFSA Conclusion (2016)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[a] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c.=post coitum)	Source and comment
Acrinathrin	Eye: microphthalmia Brain: hydrocephalus	**6**	**18**	[redacted] (1988b), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 2, 6, 18 days 6–15 p.c.	DAR (2010), EFSA Conclusion (2013)
Azadirachtin	Subcutaneous haemorrhage: nasal, cranial, jaw, submandibular, brain	**300**	**1000**	[redacted] (1997), Developmental toxicity, CD BR VAF/Plus rat, oral gavage	0, 100, 300, 1000 days 6–19 p.c.	DAR (2009), EFSA Conclusion (2018)
Benomyl	Eye: anophthalmia Eye: microphthalmia	3	**10**	[redacted] (1980), Developmental toxicity, Sprague Dawley rat, oral gavage[b]	0, 3, 10, 30, 62.5, 125 days 7–16 p.c.	DAR (1998), LoEP ECCO 61
	Mouth: microstomia	< 62.5 **(6.25)**	62.5	[redacted] (1979), Developmental toxicity, Sprague Dawley rat, oral gavage	0, **62.5**, 125, 250, 500 days 6–15 p.c.	DAR (1998), LoEP ECCO 61
	Brain: hydrocephalus Eye: anophthalmia Eye: microphthalmia	< 31.2	31.2	[redacted] (1986), Sprague Dawley rat, oral gavage[b]	0, 31.2 days 7–16 and 7–21 p.c.	DAR (1998), LoEP ECCO 61
	Brain: hydrocephalus, meningoencephalocele and anencephaly Eye: anophthalmia Eye: microphthalmia	< 31.2	31.2	[redacted] (1987), Sprague Dawley rat, oral gavage[b]	0, 31.2, 62.5, 125 days 7–21 p.c.	DAR (1998), LoEP ECCO 61
Bitertanol	Brain: hydrocephalus	**10**	**30**	[redacted] (1977), Developmental toxicity, Long Evans rat, oral gavage	0, 10, 30, 100 days 6–15 p.c.	DAR (2005) and Addendum (2009), EFSA Conclusion (2010)
Bromuconazole	Eye: microphthalmia	**10**	**70**	[redacted] (1990), Developmental toxicity, *rat strain not specified*, oral gavage	0, 10, 70, 500 days 6–15 p.c.	DAR (2009), EFSA Conclusion (2010)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[a] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c.=post coitum)	Source and comment
Carbendazim	Eye: microphthalmia	**10**	**20**	[redacted] (1987), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 5, 10, 20, 90 days 6–16 p.c.	DAR (2009), EFSA Conclusion (2010)
	Brain: meningocele	10	30	[redacted] (1987a), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 10, 30, 60, 100, 300, 1000, 3000 days 6–15 p.c.	DAR (2009), EFSA Conclusion (2010)
	Brain: hydrocephalus	10	30	[redacted] (1987a), Developmental toxicity, Sprague Dawley rat, oral gavage and [redacted] (1987b), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 10, 30, 60, 100, 300, 1000, 3000 days 6–15 p.c. 0, 10, 30 days 6–15 p.c.	DAR (2009), EFSA Conclusion (2010)
Chlorpyrifos	Eye: microphthalmia	**3**	**15**	[redacted] (1983), Developmental toxicity, Fischer 344 rat, oral gavage	0, 0.1, 3, 15 days 6–15 p.c.	DAR (2017), EFSA Conclusion (2014)
Cymoxanil	Brain: anomalies of encephalon	8	**16**	[redacted] (1980), Developmental toxicity, New Zealand White rabbit, oral gavage[b]	0, 4, 8, 16 days 6–18 p.c.	DAR (2007), EFSA Conclusion (2008)
	Brain: hydrocephalus	**8**	32	[redacted] (1982), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 1, 4, 8, 32 days 6–18 p.c.	DAR (2007), EFSA Conclusion (2008)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[a] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c.=post coitum)	Source and comment
	No indicators	32	–	[redacted] (1981), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 8, 16, 32 days 6–18 p.c.	DAR (2007), EFSA Conclusion (2008)
	No indicators	25	–	[redacted] (1999), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 5, 15, 25 days 6–18 p.c.	DAR (2007), EFSA Conclusion (2008)
Cyproconazole	Brain: hydrocephalus	< 2 **(0.2)**	**2**	[redacted] (1986), Developmental toxicity, Chinchilla rabbit, oral gavage	0, 2, 10, 50 days 6–18 p.c.	DAR (2006) and Addendum (2010), EFSA Conclusion (2010)
Deltamethrin	Brain: hydrocephalus	4	**16**	[redacted] (1977c), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 1, 4, 16 days 6–19 p.c.	DAR (1998), Addendum (2002), (DRAR, 2018), EC Review report (2002)
	No indicators	32 **(10)**	–	[redacted] (2001), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 3, **10**, 32 days 6–28 p.c.	DAR (1998), Addendum (2002), (DRAR, 2018), EC Review report (2002)
Emamectin	Brain: hydrocephalus	**3**	**6**	[redacted] (1992d), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 1.5, 3, 6 days 6–18 p.c.	DAR (2011), EFSA Conclusion (2012)
Epoxiconazole	Head: dome-shaped head Tongue: macroglossia	< 180	**180**	[redacted] (2002), Developmental toxicity, Wistar rat, oral gavage	0, 180 days 6–19 p.c.	DAR (2005), EFSA Conclusion (2008)
	No indicators	45 **(45)**	–	[redacted] (1990b), Developmental toxicity, Wistar rat, oral gavage	0, 5, 15, **45** Days 6–15 p.c.	DAR (2005), EFSA Conclusion (2008)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[a] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c.=post coitum)	Source and comment
	No indicators	180	–	[redacted] (1989), Developmental toxicity, Wistar rat, oral gavage[b]	0, 20, 60, 180 days 6–15 p.c.	DAR (2005), EFSA Conclusion (2008)
Ethylene oxide	Eye: eye coloboma	**75**	**150**	[redacted] (1980), Developmental toxicity, CD1 mouse, intravenous exposure on either p.c. days 4–6, 6–8 or 8–10[b]	0, 75, 150 I = days 4–6 p.c. II = days 6–8 p.c.	CLH report (2016), RAC Opinion (2017), EFSA Conclusion ethylene (2012)
ETU	Brain: hydrocephalus	**5**	**15**	[redacted] (2015d), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 2.5, 5, 15, 30 days 6–15 p.c.	DAR (2019) (mancozeb), EFSA Conclusion (2020) (mancozeb)
	Brain: microcephaly Eye: anophthalmia Eye: microphthalmia	20	40	[redacted] (1978), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 20, 40 days 7–20 p.c.	DAR (2019) (mancozeb), EFSA Conclusion (2020) (mancozeb)
	Brain: hydrocephalus	10	20	[redacted] (1979), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 5, 10, 20, 30, 40, 80 days 7–15 p.c.	DAR (2019) (mancozeb), EFSA Conclusion (2020) (mancozeb)
	Brain: meningoencephalocele Brain: hydrocephalus	25	35	[redacted] (1991), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 15, 25, 35 days 6–20 p.c.	DAR (2019) (mancozeb), EFSA Conclusion (2020) (mancozeb)
Fenpropidin	Brain: hydrocephalus	**47.5**	**87.8**	[redacted] (1981), Developmental toxicity, Sprague Dawley rat, oral diet[b]	0, 19.5, 47.5, 87.8 days 7–16 p.c.	DAR (2005), EFSA Conclusion (2007)
Fluazifop-p	Brain: anomalies of encephalon Eye: microphthalmia	**10**	**50**	[redacted] (1993), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 20, 10, 50 days 8–20 p.c.	DAR (2010) and Addendum (2011), EFSA Conclusion (2012)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[a] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c.=post coitum)	Source and comment
Flusilazole	Brain: hydrocephalus	**2**	**5**	[redacted] (1984), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 2, 5, 12 days 7–19 p.c.	DAR (2009), Addendum (1999, 2004)
Flutriafol	Head: dome-shaped head	50	**150**	[redacted] (2008d), Developmental toxicity, Wistar rat, oral gavage[b]	0, 5, 10, 50, 150 days 6–20 p.c.	Addendum to DAR (2010), EFSA Conclusion (2010)
	No indicators	100 **(100)**	–	[redacted] (2008c), Developmental toxicity, Wistar rat, oral gavage[b]	0, 2, 5, **100** days 6–20 p.c.	Addendum to DAR (2010), EFSA Conclusion (2010)
	No indicators	75	–	[redacted] (2008b), Developmental toxicity, Wistar rat, oral gavage	0, 2, 5, 10, 75 days 6–20 p.c.	Addendum to DAR (2010), EFSA Conclusion (2010)
Folpet	Brain: hydrocephalus	**10**	**20**	[redacted] (1984), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 10, 20, 60 days 7–28 p.c.	DAR (2019), EFSA Conclusion (2009)
		160	–	[redacted] (1985c), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 10, 40, 160 days 7–19 p.c.	DAR (2019), EFSA Conclusion (2009)
Haloxyfop-p	Eye: microphthalmia	1	**7.5**	[redacted] (1983a), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 1, 7.5, 15 days 6–18 p.c.	DAR (2004) and Additional DAR (2009), EFSA Conclusion (2009)
	Brain: hydrocephalus	7.5 **(3)**	15	[redacted] (1984), Developmental toxicity, New Zealand White rabbit, oral gavage	0, **3**, 7.5, 15 days 6–18 p.c	DAR (2004) and Additional DAR (2009), EFSA Conclusion (2009)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[(a)] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c.=post coitum)	Source and comment
Mancozeb	Brain: hydrocephalus	60	**360**	[redacted] (1988), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 10, 60, 360 days 6–15 p.c.	DAR (2019), EFSA Conclusion (2020)
	Brain: meningoencephalocele Brain: hydrocephalus	128	512	[redacted] (1980), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 2, 8, 32, **128**, 512 days 6–15 p.c.	DAR (2019), EFSA Conclusion (2020)
	No indicators	160 **(160)**	–	[redacted] (2015b), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 80, 120, **160** days 7–19 p.c.	DAR (2019), EFSA Conclusion (2020)
	No indicators	160 **(160)**	–	[redacted] (2015c), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 10, 40, **160** days 6–19 p.c.	DAR (2019), EFSA Conclusion (2020)
Maneb	Brain: meningocele Tongue: macroglossia	**100**	**500**	[redacted] (1991), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 20, 100, 500 days 6–15 p.c.	JMPR (1993), EC Review Report (2005)
	No indicators	500	–	[redacted] (1992), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 20, 100, 500 days 6–15 p.c.	JMPR (1993), EC Review Report (2005)
Metconazole	Brain: hydrocephalus	4	**10**	[redacted] (1992), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 2, 4, 10, 40 days 7–19 p.c.	DAR (2004), EFSA Conclusion (2006)
	Brain: hydrocephalus	10	25	[redacted] (1991a), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 4, 10, 25, 62.5 days 6–19 p.c.	DAR (2004), EFSA Conclusion (2006)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[a] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c.=post coitum)	Source and comment
	Brain: hydrocephalus	10	40	[redacted] (1992b), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 0.5, 1, 2, 10, 40 days 7–19 p.c.	DAR (2004), EFSA Conclusion (2006)
	No indicators	40 **(5)**	–	[redacted] (1997), Developmental toxicity, New Zealand White rabbit, oral gavage	0, **5**, 10, 20, 40 days 6–28 p.c.	DAR (2004), EFSA Conclusion (2006)
Myclobutanil	Brain: hydrocephalus, craniorachischisis	**312.6**	**468.9**	[redacted] (1984a), [redacted] (2005), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 31.3, 93.8, 312.6, 468.9 days 6–15 p.c.	DAR (2009), EFSA Conclusion (2009)
Penconazole	Brain: hydrocephalus Eye: microphthalmia	**75**	**150**	[redacted] (1982), Developmental toxicity, Chinchilla rabbit, oral gavage	0, 25, 75, 150 days 6–18 p.c.	DAR (2007), EFSA Conclusion (2008)
Propineb	Eye: microphthalmia	**10**	**30**	[redacted] (1974), Developmental toxicity, FB30 rat, oral gavage[b]	0, 3, 10, 30, 100 days 6–15 p.c.	DAR (2016), EFSA Conclusion (2016)
Prosulfocarb	Eye: microphthalmia	**50**	**250**	[redacted] (1985), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 10, 50, 250 days 7–19 p.c.	DAR (2006), EFSA Conclusion (2007)
Prothioconazole	Brain: anomalies of encephalon	< 80	**80**	[redacted] (1997), developmental toxicity, Chinchilla rabbit, oral gavage[b]	0, 80, 100, 300, 480 days 6–27 p.c	DAR (2004), EFSA Conclusion (2007)
	No indicators	350 **(30)**	–	[redacted] (1998), developmental toxicity, Rabbit, Chinchilla, oral, gavage	0, 10, **30**, 80, 350 days 6–27 p.c.	DAR (2004), EFSA Conclusion (2007)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[(a)] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c.=post coitum)	Source and comment
Prothioconazole (sulfonic acid)	Eye: microphthalmia Mouth: microstomia	**150**	**750**	[redacted] (2001), Developmental toxicity, Wistar rats, oral gavage	0, 30, 150, 750 days 6–20 p.c.	DAR (2004) (prothioconazole), EFSA Conclusion (2007) (prothioconazole)
PTU	Head: dome-shaped head Brain: hydrocephalus	**2.029**	**17.89**	[redacted] (2004), Two-generational toxicity study, Wistar rat, oral drinking water	0.202, 2.029 and 17.89 administered to parental animals prior and during mating, during pregnancy and up to weaning of F1 and F2	DAR (2016) (propineb), EFSA Conclusion (2016) (propineb)
Spirotetramat	Head: dome-shaped head Eye: microphthalmia	**40**	**160**	[redacted] (2004c), Developmental toxicity, Himalayan rabbit, oral gavage	0, 10, 40, 160 days 6–28 p.c.	DAR (2008), EFSA Conclusion (2013)
Spiroxamine	Brain: hydrocephalus	**20**	**80**	[redacted] (1995), Developmental toxicity, Himalayan rabbit, oral gavage	0, 5, 20, 80 days 6–18 p.c.	DAR (2009), EFSA Conclusion (2010)
Tebuconazole	Eye: anophthalmia	**10**	**30**	[redacted] (1985a), Developmental toxicity, Wistar rat, oral gavage	0, 10, 30, 100 days 6–15 p.c.	DAR (2006) and Addendum (2012), EFSA Conclusion (2014)
	Mouth: microstomia Eye: anophthalmia	60	120	[redacted] (1988a), Developmental toxicity, Wistar rat, oral gavage	0, 30, 60, 120 days 6–15 p.c.	DAR (2006) and Addendum (2012), EFSA Conclusion (2014)
Tebufenpyrad	Eye: microphthalmia	**15**	**50**	[redacted] (1992a), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 15, 50, 150 days 6–15 p.c.	DAR (2007), EFSA Conclusion (2008)
	No indicators	90	–	[redacted] (1992b), Developmental toxicity, Sprague Dawley rat, oral gavage	0, 15, 50, 90 days 6–15 p.c.	DAR (2007), EFSA Conclusion (2008)

Active substance	Type of indicator	NOAEL mg/kg bw per day*	LOAEL mg/kg bw per day*	Reference[(a)] and study type	Dose levels mg/kg bw per day and exposure window (days; p.c.=post coitum)	Source and comment
Thiabendazole	Head: dome-shaped head Brain: hydrocephalus	24	**120**	[redacted] (1989), Developmental toxicity, New Zealand White rabbit, oral gavage	0, 24, 120, 600 days 6–18 p.c.	DAR (2013), EFSA Conclusion (2014)
	No indicators	600 **(50)**	–	[redacted] (1992), Developmental toxicity, New Zealand White rabbit, oral gavage	0, **50**, 150, 600 days 6–18 p.c.	DAR (2013), EFSA Conclusion (2014)
Thiacloprid	Eye: anophthalmia, microphthalmia	**10**	**50**	[redacted] (1997), Developmental toxicity, Wistar rat, oral gavage	0, 2, 10, 50 days 6–19 p.c.	DAR (2018), EFSA Conclusion (2019)

*: NOAEL and LOAEL of the specific indicator for craniofacial alteration. Values indicated in bold characters represent the overall NOAEL and LOAEL of the substance, after eventual collective evaluation of sets of studies of equivalent quality. Numbers in parenthesis represent the overall NOAEL when derived from the combination of different studies or when derived from a LOAEL divided by 10.
(a): Reference as given in the respective DAR/DRAR and other source documents mentioned in the 'source and comment' column.
(b): NOAEL derived from studies considered of limited acceptability (column AE of Annex N).

Appendix B – Procedure for the allocation of active substances to measurements

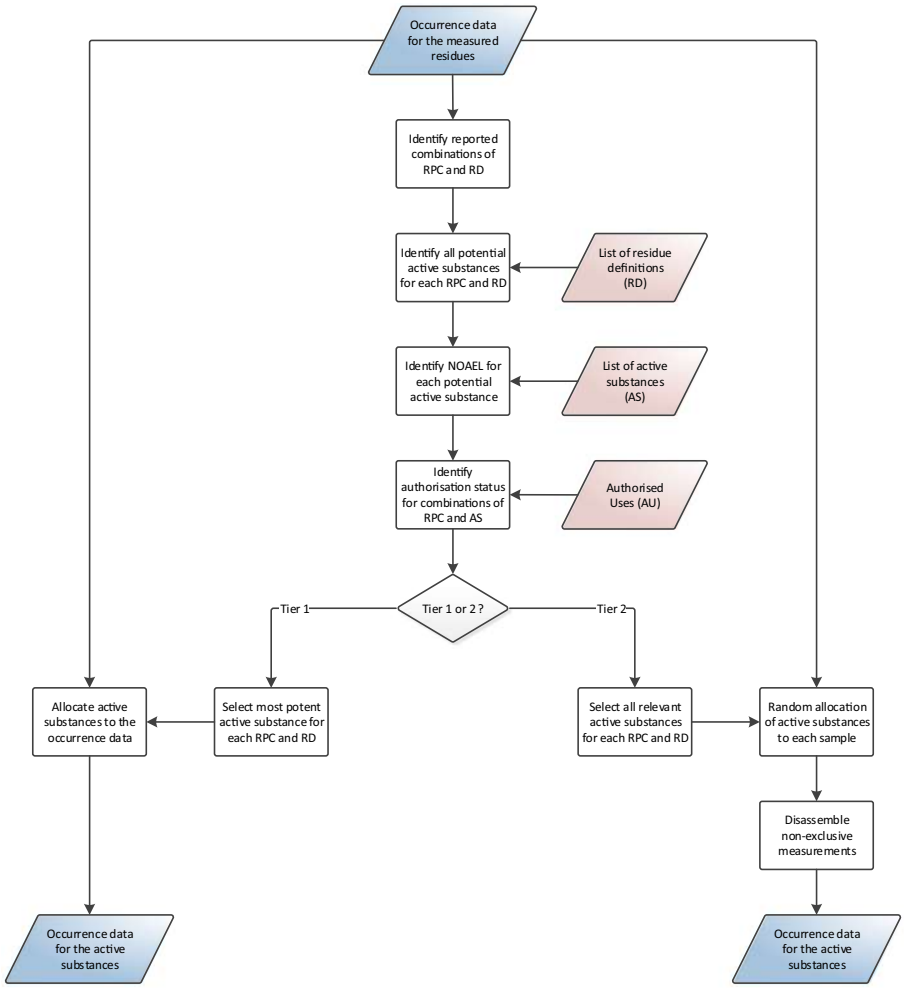
1) Select distinct combinations of RPC and residue definition reported in the occurrence data set.
2) Identify the possible combinations of RPC, residue definition and active substance (by joining the information of the residue definitions table). Retain information on the MW conversion factor, on whether this combination is exclusive or not, and on the proportion for the non-exclusive combinations.
3) Add the relevant NOAEL to each combination (join information from the active substance table using the active substance as the key).
4) Identify the authorisation status for each combination (join information from the authorisations table using the RPC and active substance as the keys).

Tier I

5) There may now be combinations of RPC, residue definition and active substance (AS) which refer to the same RPC and residue definition. Data are sorted by RPC, residue definition and NOAEL (ascending) and for each combination of RPC and residue definition, the first combination of RPC, residue definition and AS is retained, i.e. the one with the lowest NOAEL (most toxic AS).
6) For each measurement in the occurrence data set, the AS is assigned on the basis of the combinations derived at step 5 (using the RPC and the residue definition as keys).

Tier II

5) There may now be combinations of RPC, residue definition and active substance (AS) which refer to the same RPC and residue definition. For each RPC and residue definition, only the combinations with authorised uses are retained. If none are authorised, all combinations are retained.
6) For each measurement in the occurrence data set, the AS is assigned on the basis of the combinations derived at step 5 (using the RPC and the residue definition as keys). If for a given measurement more than one AS could be assigned, only one AS is selected randomly using equal probability (regardless of whether the AS is part of the CAG).
7) For each measurement, it is verified whether the combination RPC, residue definition and AS assigned is exclusive or not. If it is not exclusive:
    a) The residue value and the LOQ value are multiplied by the proportion specified in the residue definition table.
    b) The exclusive active substance of that residue definition is identified (from the residue definitions table)
    c) A new measurement is generated for the same sample but for the exclusive active substance identified above. The residue value and the LOQ value are also multiplied by a factor equal to (1 – proportion of the non-exclusive substance).



Flowchart for the allocation of active substances to the measurements

Appendix C – Procedure for the imputation of left-censored measurements

Tier I

1) Retrieve from the occurrence data set all records which refer to a quantifiable result and identify distinct combinations of RPC, product treatment (PT) and active substance (AS). This results in a list of RPC/PT/active substance combinations where the non-quantifiable results will be assumed to be at 1/2 LOQ.
2) Identify in the occurrence data set all left-censored records that refer to any of the combinations listed at step 1 (using RPC, PT and AS as keys). Assign 1/2 LOQ as a result for those records.
3) Assign zero to all remaining left-censored records in the occurrence data set.

Tier II

1) Define the list of AUPs observed in the data set. An AUP is the combination of active substances (AS) quantified for an RPC with a given product treatment (PT). The list is derived as follows:

   a) Retrieve from the occurrence data set all samples which have at least one quantifiable result.
   b) Identify for each of the previous samples the AUP by concatenating the active substances quantified in each sample.
   c) Select all the distinct AUPs and assign an identifier to each AUP.

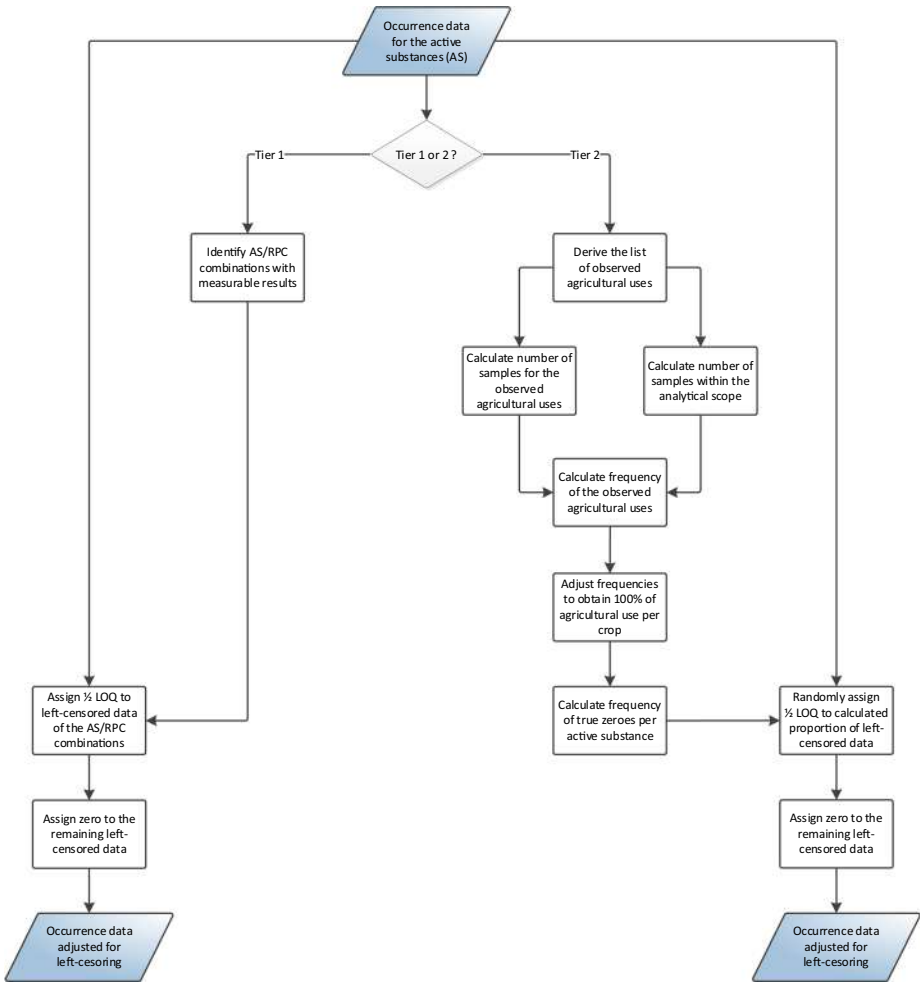
   Example: Among all unprocessed apple samples, substances X, Y and Z were measured, and the following combinations were quantified within single samples: (X), (X-Y-Z), (Y), (X-Y) and (Y-Z). These combinations are now identified as AUP1, AUP2, AUP3, AUP4 and AUP5, respectively.
2) Count the number of samples for each AUP, i.e. the number of times that the AUP appears in the data set.
   Example: Number of unprocessed apple samples where AUP1 was observed is 200; number of unprocessed apple samples where AUP2 was observed is 23, etc.
3) Identify the analytical scope of each sample and, for each AUP, identify the number of samples where the AUP is covered by the analytical scope:

   a) From the occurrence data set, identify for each sample the analytical scope by concatenating the active substances measured in each sample.
      Example: Samples were measured either for substance Y only (Scope1), for substances X and Y (Scope2), for substances X, Y and Z (Scope3) or for substances Y and Z (Scope4).
   b) Count the number of samples for each analytical scope.
      Example: Number of samples where Scope1 was measured is 500; number of samples where Scope2 was measured is 250; number of samples where Scope3 was measured is 1250; Number of samples where Scope4 was measured is 2000.
   c) For each AUP, identify the analytical scopes that include all active substances of that AUP.
      Example: AUP1 is covered by Scope2 and Scope3 only.
   d) For each AUP, sum the number of samples for all analytical scopes identified at step 3c.
      Example: The number of samples where Scope2 and Scope3 were measured is 250 and 1250. Hence, the total number of samples where AUP1 is covered by the analytical scope is 1500.

4) Calculate frequency for each AUP (N samples AUP / N samples analytical scope).
   Example: Number of unprocessed apple samples where AUP1 was observed is 200 (calculated at step 2). Number of unprocessed apple samples where AUP1 is covered by the analytical scope is 1500 (calculated at step 3). Hence, the frequency of AUP1 in unprocessed apples is 13.3%.
5) Adjust frequencies for authorised AUPs (i.e. when all substances in the AUP are authorised) to obtain a total AUP frequency of 100% per RPC and PT. This assumes that each sample in the occurrence data set was treated according to one AUP.

Example: Five AUPs were observed in unprocessed apples and frequencies for each AUP were calculated: AUP1 (13.3%), AUP2 (2.3%), AUP3 (9.8%), AUP4 (1.2%) and AUP5 (0.2%). However, only AUP1, AUP3 and AUP4 include substances that are all authorised. Therefore, only these AUPs are adjusted to obtain a total number AUP frequency of 100%. Frequencies of AUP2 and AUP5 remain unchanged, and the following adjusted frequencies are obtained: AUP1 (53.4%), AUP2 (2.3%), AUP3 (39.3%), AUP4 (4.8%) and AUP5 (0.2%).

6) Calculate use frequency for each combination of RPC, PT and AS and identify the corresponding number of measurements that should be set to 1/2 LOQ:
   a) For each combination of RPC, PT and AS, calculate the use frequency by summing the AUP frequencies of all AUPs that contain the AS.
      Example: Five AUPs were observed in unprocessed apples and the following adjusted frequencies are obtained: AUP1 (53.4%), AUP2 (2.3%), AUP3 (39.3%), AUP4 (4.8%) and AUP5 (0.2%). Only AUP1, AUP2 and AUP4 include the use of substance X. Therefore, the estimated use frequency of substance X in unprocessed apples is 60.5%.
   b) For each combination of RPC, PT and AS, calculate the percentage of true zeros (i.e. 100 – use frequency calculated at step 6.a)
      Example: If the estimated use frequency of is 60.5%, the expected percentage of true zeros is 39.5%.
   c) For each combination of RPC, PT and AS, calculate the number of true zeros by multiplying the percentage of true zeros (calculated at step 6.b) with number of measurements for that active substance and RPC and divide by 100.
      Example: For substance X in unprocessed apples, if the expected percentage of true zeros is 39.5% and the total number of measurements is 3562, the estimated number of true zero measurements is 1407.
   d) For each combination of AS, RPC and PT, count the total number of measurements. Subtract from this value the number of samples that already have a measured value and the number of true zeroes calculated at step 6c. This is the number of samples that should be set to 1/2 LOQ. If a negative number is obtained, set to 0.
      Example: For substance X in unprocessed apples, if the total number of measurements is 3562, the number of quantifiable measurements is 126 and the estimated number of true zero measurements is 1407, the number of measurements to be imputed at 1/2 LOQ is 2029.
7) From the left-censored data reported in the occurrence data set, randomly select for each RPC, PT and AS the number of samples (as calculated above). Assign a residue value of 1/2 LOQ.
8) Assign zero to all remaining left-censored records in the occurrence data set.



Flowchart for the imputation of left-censored measurements

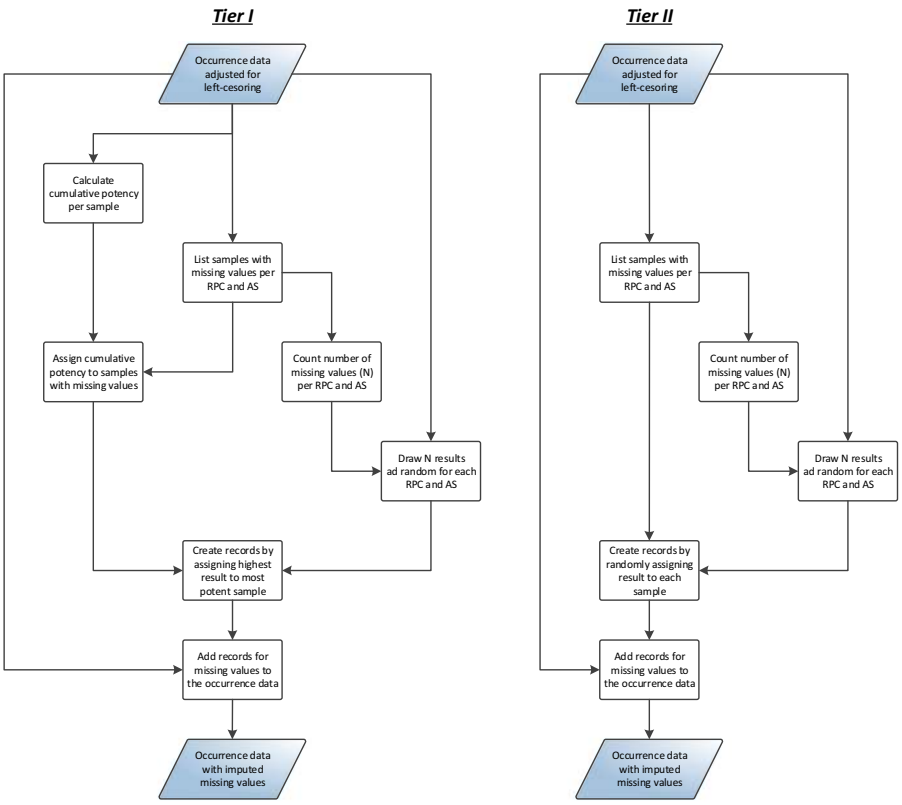
Appendix D – Procedure for the imputation of missing measurements

Tier I

1) From the occurrence data set calculate the cumulative potency (sum of concentrations of active substances divided by the respective NOAEL) for each sample.
2) From the occurrence data set derive the list of samples with missing measurements for each combination of RPC, product treatment (PT) and active substance (AS). This implies that no imputation will be done if there are no measurements at all for a certain combination of RPC, PT and AS.
3) Assign cumulative potency to samples with missing measurements created at step 2 by joining the information created at step 1 and order all measurements from high to low according to their cumulative potency for each RPC, PT and AS.
4) Count number of missing measurements (N) for each RPC, PT and AS.
5) Drawn N measurements at random from existing samples for each RPC, PT and AS and order the generated measurements from high to low for each RPC, PT and AS.
6) Create N new records by joining measurements generated at step 5 to samples identified at step 3. This implies that the highest extracted measurements will be assigned to the most potent samples.
7) Add records for missing measurements to the occurrence data set.

Tier II

1) From the occurrence data set derive the list of samples with missing measurements for each combination of RPC, product treatment (PT) and active substance (AS):
    a) Create records for implicit zero measurements of active substances associated with unspecific residue definitions that were considered not present in a sample and add these records to the occurrence data set.
    b) From the occurrence data set created at step 1a derive the list of samples with missing measurements for each combination of RPC, PT and AS. This implies that no imputation will be done if there are no measurements at all for a certain combination of RPC, PT and AS.
2) Count number of missing measurements (N) for each RPC, PT and active substance.
3) Drawn N measurements at random from existing samples for each RPC, PT and active substance.
4) Create N new records by randomly assigning the measurements extracted in step 3 to each sample identified at step 1b and add records for missing measurements to the occurrence data set.



Flowchart for the imputation of missing measurements

Appendix E – Procedure for deriving the acute exposure distribution

1) From the consumption data set randomly select (with replacement) 100000 subject days for each dietary survey. For each resampled subject day all consumption events within the day are retained.
2) For each combination of RPC and foodEx2 facet, identify the matching product treatment (PT) in the occurrence data set. If no matching PT is identified, assign the PT 'Unprocessed'.
3) For each combination of RPC and FoodEx2 facet consumed within the individual subject days, assign random samples extracted from the occurrence data set (with replacement, using the RPC and the PT assigned at step 2 as keys).
4) Assign PF to the relevant records of the data set created at step 3 by joining information from the PFs table (using the RPC, active substance and foodEx2 facet as the keys). If no PF is available for a specific combination, then a missing value is assigned to the PF.
5) Incorporate VF to the relevant records of the data set created at step 4:

   a) Calculate the two parameters *a* and *b* of a beta distribution defined over the interval $(0, \text{nUnits})$, where nUnits is the number of units per sample as defined in Section 2.2.1. An iterative method is applied to find *a* such that the cumulative probability $P[\text{Beta}(a, b)] = 0.975$ for $b = a(\text{nUnits} - 1)$.

      Tier I

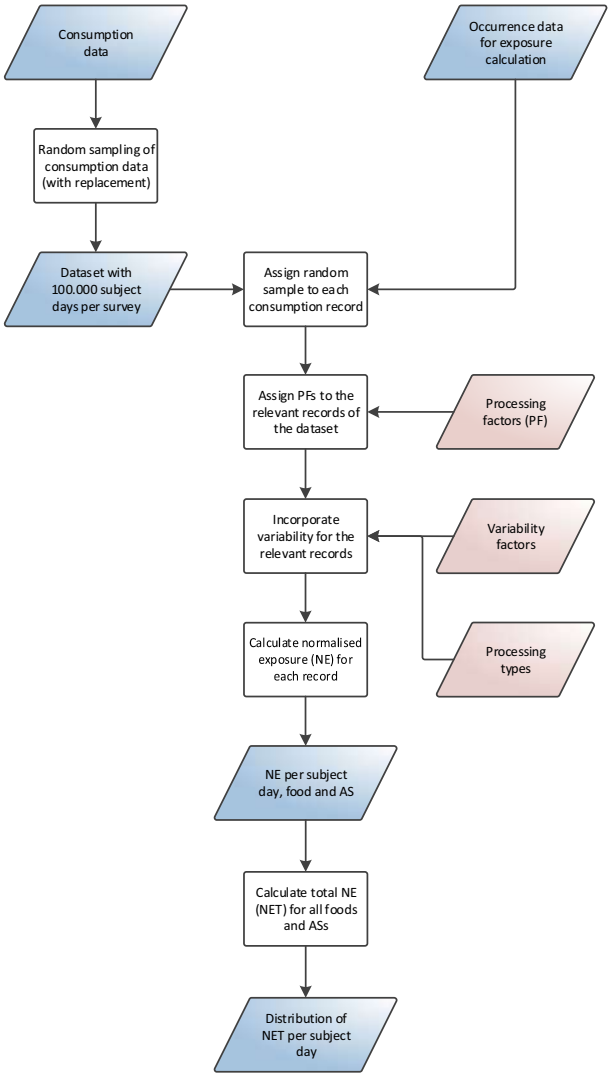
      A VF of 5 or 7 is used to derive the beta distribution.

      Tier II

      A VF of 3.6 is used to derive the beta distribution.

   b) Join information from the processing types table (using foodEx2 facet as the key), the RPC table (using RPC as the key) and the parameters *a* and *b* derived at step 5a to the data set created at step 4.
   c) For each active substance (AS) measured in the sample assigned to the consumption event randomly derive a stochastic VF from the beta distribution defined at step 4a. When the consumed portion is composed of multiple units, multiple stochastic VFs are drawn from the same beta distribution in order to calculate a weighted VF as described in Section 2.2.4.2.
   d) An adjusted concentration is calculated by multiplying the concentration measured in the sample with the weighted VF (or stochastic VF) calculated at step 5c. If no VF is available for a certain RPC or if the processing type involves bulking/blending, then the adjusted concentration is equal to the concentration measured in the sample.

6) Calculate normalised exposure (NE) for each record using formula described in Section 2.2.4.2 to obtain NE per subject day, RPC, foodEx2 facet and AS.
7) Sum all normalised exposures of RPCs and AS per subject day to obtain a RPI for each subject day.



Flowchart for the calculation of acute exposure

Appendix F – Information notes supporting the assessment of the impact of uncertainties

Note 1 (Active substances missing from the CAGs) – U1

If the CAG does not contain active substances contributing to the risk, the outcome of the risk assessment might be underestimated. A substance with the potential to cause craniofacial alterations may be missing from CAGs for 3 reasons: the substance has not been considered, the substance has been considered but did not cause craniofacial alterations in the toxicological studies or the substance has been considered and caused craniofacial alterations in toxicological studies that were dismissed/ disregarded during the establishment of the CAGs.

Non-considered substances

For the present assessment, only 85 active substances have been evaluated for craniofacial alterations. Although these substances were selected based on pragmatic criteria listed in Section 2.1.2.1, it is expected that other substances can also cause craniofacial alterations and contribute to the risk.

In a recent project aiming at streamlining future CRAs, EFSA developed a systematic risk-based screening method aiming at identifying pesticides which should be considered in CRA. The method is based on the determination of the exposure level to each pesticide present in food at the 99.9th percentile of the short- and long-term exposure distribution over 3-year monitoring cycles in all populations of the PRIMo model by probabilistic modelling. Pesticides for which this exposure exceeds 10% of the ADI and/or ARfD, equivalent to a hazard quotient (HQ) of 0.1, in at least one population are included in a priority list for being considered in the context of the establishment of any CAG. It must be noted that these calculations were conducted under conservative conditions regarding the handling of left censored data (i.e. according to the Tier I conditions described in Table 11). Moreover, for several substances, the ADI was used as surrogate ARfD. It was shown that if this screening method would have been used for the establishment of the CAGs for the acute effects on the nervous system and the chronic effects on the thyroid, the number of substances included in the CAGs would have been reduced by 50% in the case of the nervous system effects and by 70% in the case of the thyroid effects (te Biesebeek et al., 2021). When the CRAs conducted in 2020 (EFSA, 2020a,b) were repeated with prioritised substances only, moderate increases of the MOET were observed in case of CAG-NAN (average 3%, maximum 8%), CAG-NAM (average 4%, maximum 6%) and CAG-TCF (average 5%, maximum 10%). Surprisingly, for CAG-TCP, decreases of the MOET were observed (average −11%, maximum -20%). This was explained by the overall very low level of risks which is therefore very sensitive to the imputation of left-censored data.

This method was implemented the first time in 2021, based on the monitoring data collected in 2017, 2018 and 2019 (EFSA, 2022, not published yet), i.e. after the selection of the 85 substances evaluated for craniofacial alterations. The priority list deriving from the short-term calculations included 99 active substances, of which 53 were not in the list of the 85 evaluated substances. These 53 active substances are: amitraz, amitrole, azinphos-methyl, azocyclotin, benfuracarb, benzalkonium chloride, carbaryl, carbosulfan, chlorates, chlordane, chlorfenapyr, chlorfenvinphos, chlorothalonil, clopyralid, cyhexatin, diafenthiuron, dichlorvos, dicrotrophos, dimoxystrobin, diniconazole-M, diquat, dodine, endosulfan, endrin, fenamiphos, fenthion, fipronil, furathiocarb, gamma-cyhalothrin, glufosinate-ammonium, glyphosate, heptachlor, hexachlorobenzene, hexachlorocyclohexane (HCH) beta-isomer, indoxacarb, lindane (gamma-isomer of hexachlorocyclohexane (HCH)), mecarbam, methamidophos, methidathion, metribuzin, mevinphos, monocrotophos, nicotine, oxydemeton-methyl, parathion, permethrin, phenthoate, phorate, phosmet, phospamidon, prochloraz, propoxur, prothiophos, quinalphos, tefluthrin, terbufos and triazophos.

As these active substances were not included in the scope of the present assessment, information on their capacity to cause craniofacial alterations was collected and summarised in Table F.1. This information was retrieved from EFSA conclusions, 3 external scientific reports (DTU, 2012; RIVM, ICPS and ANSES, 2013, 2016) and from toxicological evaluations performed by various international or national bodies. Table F.1 also includes information about the estimated acute exposure level in adult populations at the 99.9th percentile of the distribution, and the basis (ARfD) of the estimation. This information, considered together with the level at which craniofacial alterations are eventually observed, helps quantifying the magnitude of the risk underestimation resulting from the omission of these substances.

Table F.1: Observations of craniofacial alterations for prioritised substances not considered for the establishment of CAGs

Active substance	Median HQ at 99.9th percentile of acute exposure in adult populations	Observation of indicators of craniofacial alterations				Comments*
		DTU, 2012	RIVM, ICPS and ANSES, 2013	RIVM, ICPS, ANSES, 2016	EFSA conclusions (evaluation and LoEP)	
Amitraz	0.03	Not covered	Not covered	No	Not available	ARfD: 0.01 mg/kg bw (EC Review report, 2003) JMPR (1998) did not report any craniofacial alteration
Amitrole	0.14	Yes	Yes	Not covered	Yes	ARfD: 0.015 mg/kg bw (EFSA conclusion, 2014) DRAR (2013, FR): • Rabbit (Study on maternotoxicity in the pregnant female rabbit): doses 0, 3, 15, 75 mg/kg bw per day, days 6–18 of gestation: At 75 mg/kg bw per day, 3/66 fetuses in 2 different litters displayed a domed head, probably related to dilatation of cerebral ventricles/hydrocephaly. A relationship to treatment could not be ruled out. ([redacted], 2000) • Rabbits: doses of 0, 4, 40 and 400 mg/kg bw per day: Increased incidences of irreversible structural changes were found at 40 and 400 mg/kg bw per day, which involved mainly the head and limbs at 40 and 400 mg/kg bw per day ([redacted], 1986b)
Azinphos-methyl	0.04	Not covered	Not covered	No	Not available	HQ based on tentative ARfD of 0.01 mg/kg bw (EC Review report, 2006) JMPR, 2007: • Rats: doses of 0, 0.4, 1.2, or 3.6 mg/kg bw per day, days 6–15 of gestation: delayed ossification (pubic, hyoid, and supraoccipital bones) in fetuses at 3.6 mg/kg bw per day [redacted], 1988)
Azocyclotin	0.05	Not covered	Not covered	Not covered	Not available	HQ based on tentative ARfD of 0.02 mg/kg bw (JMPR, 2005) JMPR (2005) did not report any craniofacial alteration
Benfuracarb	0.03	Not covered	Not covered	No	No	ARfD: 0.02 mg/kg bw (EFSA conclusions, 2009)

Active substance	Median HQ at 99.9th percentile of acute exposure in adult populations	Observation of indicators of craniofacial alterations				Comments*
		DTU, 2012	RIVM, ICPS and ANSES, 2013	RIVM, ICPS, ANSES, 2016	EFSA conclusions (evaluation and LoEP)	
Benzalkonium chloride	0.03	Not covered	Not covered	No	Not available	HQ based on tentative ARfD of 0.1 mg/kg bw (BfR, 2002: https://www.bfr.bund.de/cm/349/health-assessment-of-benzalkonium-chloride-residues-in-food.pdf) Memorandum 'Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision Document on Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC)' August 06, 2006 (US EPA): No evidence for developmental toxicity.
Carbaryl	0.01	Not covered	Not covered	No	No	ARfD: 0.01 mg/kg bw (EFSA conclusions, 2006)
Carbosulfan	0.12	Not covered	Not covered	Yes	Yes	ARfD: 0.005 mg/kg bw (EFSA conclusions, 2009) DAR (2004, BE): • Rats: doses 0, 2, 10 and 20 mg/kg bw per day, days 6–19 of gestation: significant increase in the occurrence of incomplete ossification of various skeletal structures such as sternebrae 4 and/or 6 and hyoid body ([redacted], 1980a)
Chlorates	0.18	Not covered	Not covered	Not covered	Not available	ARfD: 0.036 mg/kg bw (EFSA CONTAM Panel, 2015) EFSA CONTAM Panel (2015) did not report any craniofacial alteration in developmental toxicity studies in rats and rabbits up to 780 and 371 mg chlorate/kg bw per day, respectively
Chlordane	0.06	Not covered	Not covered	No	Not available	HQ based on tentative ARfD of 0.0005 mg/kg bw (provisional tolerable daily intake (PTDI) established by the JMPR (1994) used as surrogate for ARfD) https://inchem.org/documents/ehc/ehc/ehc34.htm#SectionNumber:6.3: No evidence of teratogenicity
Chlorfenapyr	0.03	Not covered	Not covered	No	Not available	HQ based on tentative ARfD of 0.015 mg/kg bw (outcome of the European Community Co-ordination (ECCO, 1999))

Active substance	Median HQ at 99.9th percentile of acute exposure in adult populations	Observation of indicators of craniofacial alterations				Comments*
		DTU, 2012	RIVM, ICPS and ANSES, 2013	RIVM, ICPS, ANSES, 2016	EFSA conclusions (evaluation and LoEP)	
						JMPR (2012) did not report any craniofacial alteration
Chlorfenvinphos	0.29	Not covered	Not covered	No	Not available	HQ based on tentative ARfD of 0.0005 mg/kg bw (ADI established by JMPR (1994) used as surrogate for ARfD) JMPR (1994) did not report any craniofacial alteration
Chlorothalonil	0.03	No	No	Not covered	No	ARfD: 0.05 mg/kg bw (EFSA conclusions, 2018)
Clopyralid	0.03	Yes	Yes	Not covered	Yes	ARfD: 0.17 mg/kg bw (EFSA conclusions, 2018) DRAR (2018, FI): • Rabbits: doses of 0, 50, 110 or 250 mg/kg bw per day, days 7–19 of gestation: hydrocephaly in 8 fetuses from 3 litters at 250 mg/kg bw per day ([redacted] 1990)
Cyhexatin	0.04	Not covered	Not covered	Not covered	Not available	HQ based on tentative ARfD of 0.02 mg/kg bw (JMPR, 2005) JMPR (2005) did not report any craniofacial alteration
Diafenthiuron	0.11	Not covered	Not covered	Not covered	Not available	HQ based on tentative ARfD of 0.003 (ADI set by set by the Australian Pesticides and Veterinary Medicines Authority used as surrogate ARfD - https://apvma.gov.au/node/26581) Detailed evaluation not found.
Dichlorvos	0.04	Not covered	Not covered	No	No	HQ based on tentative ARfD of 0.002 mg/kg bw (EFSA Peer Review Co-ordination (EPCO)) EFSA conclusions (2006): The developmental toxicity studies available in the DAR for the evaluation of dichlorvos do not meet the most recent guidelines for developmental toxicity

Active substance	Median HQ at 99.9th percentile of acute exposure in adult populations	Observation of indicators of craniofacial alterations				Comments*
		DTU, 2012	RIVM, ICPS and ANSES, 2013	RIVM, ICPS, ANSES, 2016	EFSA conclusions (evaluation and LoEP)	
Dicrotrophos	0.09	Not covered	Not covered	No	Not available	HQ based on tentative ARfD of 0.0003 mg/kg bw per day (US EPA - https://www.regulations.gov/document/EPA-HQ-OPP-2008-0440-0024) Detailed evaluation not found.
Dimoxystrobin	0.05	No	No	Not covered	No	ARfD: 0.004 mg/kg bw (EFSA conclusions, 2005)
Diniconazole-M	0.01	Not covered	Not covered	Not covered	Not available	HQ based on tentative ARfD of 0.02 mg/kg bw per day (DAR FR, 2007) DAR (2007, FR): • Rats: doses of 0, 1, 5, 20, 80 and 300 mg/kg bw per day, days 6–17 of gestation: cleft palate, minor microcephaly, eyelids open, Maxillo-mandibular synostosis and slightly dilated lateral ventricles of brain at 300 mg/kg bw per day ([redacted], 1986) • Rabbit: doses of 0, 5, 15, 50 and 70 mg/kg per day, days 7–19 of gestation: domed head, cleft, not/incompletely ossified palate at 70 mg/kg per day; complex of at least 3 variations in skull ossification (fontanels, tympanic rings, hyoid alae or any skull bone shape, structure or suture) and irregular suture of nasal/frontal bones at 50 and 70 mg/kg per day ([redacted], 1990)
Diquat	0.05	No	No	Not covered	No	ARfD: 0.01 mg/kg bw per day (EFSA conclusions, 2015)
Dodine	0.01	No	No	Not covered	No	ARfD: 0.1 mg/kg bw per day (EFSA conclusions, 2010)
Endosulfan	0.04	Not covered	Not covered	No	Not available	HQ based on tentative ARfD of 0.015 mg/kg bw (outcome of ECCO, 2001) JMPR (1998) did not report any craniofacial alteration
Endrin	0.15	Not covered	Not covered	Yes	Not available	HQ based on tentative ARfD of 0.0002 mg/kg bw (PTDI established by JMPR (1994) used as surrogate)

Active substance	Median HQ at 99.9th percentile of acute exposure in adult populations	Observation of indicators of craniofacial alterations				Comments*
		DTU, 2012	RIVM, ICPS and ANSES, 2013	RIVM, ICPS, ANSES, 2016	EFSA conclusions (evaluation and LoEP)	
						https://inchem.org/documents/ehc/ehc/ehc130.htm: • Mouse: One single dose tested (2,5 mg/kg bw per day – days 9 or 10 of gestation): incidence of total anomalies was increased over that in controls: 2/ 117 fetuses had cleft palates, three had open eye, and two had other anomalies ([redacted], 1974) • Hamster: One single dose of 5 mg/kg bw per day on day 7, 8, and 9 of gestation in 3 groups of 7, 24 and 8 animals, respectively: after treatment on day 8, congenital abnormalities were seen in 28% of fetuses, with open eye in 22%, webbed foot in 16%, cleft palate in 5%, and fused ribs in 8% [redacted], 1974) • Hamster: Doses of 0, 0.5, 1.5, 5, 7.5, or 10 mg/kg bw per day on day 8 of pregnancy: increased incidences of meningoencephaloceles were observed at 5 mg/kg bw per day and above, with no dose–response relationship ([redacted] 1979)
Fenamiphos	0.09	Yes	Yes	Not covered	Yes	ARfD: 0.0025 mg/kg bw (EFSA conclusions, 2019) DRAR (2017, GR): • Rats: doses of 0, 0.25, 0.85 and 3 mg/kg bw per day, days 6–15 of gestation: variations of the hyoid body or arch at 3 mg/kg bw per day ([redacted], 1989)
Fenthion	0.04	Not covered	Not covered	No	Not available	HQ based on tentative ARfD of 0.01 mg/kg bw (JMPR, 1997) JMPR (1995) did not report any craniofacial alteration
Fipronil	0.03	No	No	Not covered	No	ARfD: 0.009 mg/kg bw (EFSA conclusions, 2006)

Active substance	Median HQ at 99.9th percentile of acute exposure in adult populations	Observation of indicators of craniofacial alterations				Comments*
		DTU, 2012	RIVM, ICPS and ANSES, 2013	RIVM, ICPS, ANSES, 2016	EFSA conclusions (evaluation and LoEP)	
Furathiocarb	0.10	Not covered	Not covered	Not covered	Not available	HQ based on tentative ARfD of 0.006 mg/kg bw (rapporteur Member State (RMS) evaluation, 1999) Detailed evaluation not found.
Gamma-cyhalothrin	0.28	Not covered	Not covered	Not covered	No	ARfD: 0.0025 mg/kg bw (EFSA conclusions, 2014)
Glufosinate-ammonium	0.07	No	No	Not covered	No	ARfD: 0.021 mg/kg bw (EFSA conclusions, 2005)
Glyphosate	0.01	No	No	Not covered	No	ARfD: 0.5 mg/kg bw (EFSA conclusions, 2015)
Heptachlor	0.34	Not covered	Not covered	No	Not available	HQ based on tentative ARfD of 0.0001 mg/kg bw (PTDI established by JMPR (1994) used as surrogate) https://www.atsdr.cdc.gov/toxprofiles/tp12.pdf: No craniofacial alteration reported in available studies.
Hexachlorobenzene	0.50	Not covered	Not covered	Yes	Not available	HQ based on tentative ARfD of 0.00016 mg/kg bw (ADI of WHO – International programme on chemical safety (1997) used as surrogate for ARfD) https://inchem.org/documents/ehc/ehc/ehc195.htm#SectionNumber:7.5: Limited data on developmental toxicity • Mouse: one dose tested only (100mg/kg bw per day), GD 7–16: some cleft palates in one litter ([redacted] 1976)
Hexachlorocyclohexane (HCH) beta-isomer	3.46	Not covered	Not covered	Not covered	Not available	HQ based on tentative ARfD of 0.00002 mg/kg bw (TDI in RIVM report 711701 025, 2000 (https://www.rivm.nl/bibliotheek/rapporten/711701025.pdf) used as surrogate ARfD). https://inchem.org/documents/ehc/ehc/ehc123.htm#SectionNumber:7.5: No compound-related increase in teratogenic effects was found in fetuses from F2c litters of a 2-generation study ([redacted], 1986). No developmental toxicity study is however reported.
Indoxacarb	0.18	No	No	Not covered	No	ARfD: 0.005 mg/kg bw (EFSA conclusions, 2018)

Active substance	Median HQ at 99.9th percentile of acute exposure in adult populations	Observation of indicators of craniofacial alterations				Comments*
		DTU, 2012	RIVM, ICPS and ANSES, 2013	RIVM, ICPS, ANSES, 2016	EFSA conclusions (evaluation and LoEP)	
Lindane (gamma-isomer of hexachlorocyclohexane (HCH))	0.01	Not covered	Not covered	Yes	Not available	HQ based on tentative ARfD of 0.01 mg/kg bw (outcome of ECCO, 1999) DAR (1998, FR): • Mice: doses of 0, 12, 30 or 60 mg/kg bw per day, days 6–15 of gestation: cleft palate and cheilognathoschisis at 30 mg/kg bw per day. Number of live fetuses considerably reduced at top dose ([redacted] 1972).
Mecarbam	0.02	Not covered	Not covered	Not covered	Not available	HQ based on tentative ARfD of 0.002 mg/kg bw, (ADI established by JMPR (1986) used as surrogate for ARfD) JMPR (1983) (https://inchem.org/documents/jmpr/jmpmono/v83pr30.htm): • Rats: Doses 0, 1 and 3 mg/kg bw per day, days 6–19 of gestation: Multiple defects characterised by for example facio-cranial schisis, ablepharia and domed palate observed in 4/17 fetuses from 1/24 litters at 3 mg/kg bw. The fact that all four of the malformed fetuses were from a single litter tends to indicate that these abnormal findings are unlikely to be compound-related ([redacted] 1983).
Methamidophos	0.03	Not covered	Not covered	Yes	Not available	ARfD: 0.003 mg/kg bw (EC review report 2006) (JMPR, 2002): Anencephaly was reported at a dose below 1 mg/kg bw per day in a published study of the developmental toxicity in rats. However, in adequately conducted studies of developmental toxicity in rats and rabbits, no evidence of malformations was found at doses up to 3 and 2.5 mg/kg bw per day, respectively. The Meeting concluded that metahamidophos is not teratogenic.

Active substance	Median HQ at 99.9th percentile of acute exposure in adult populations	Observation of indicators of craniofacial alterations				Comments*
		DTU, 2012	RIVM, ICPS and ANSES, 2013	RIVM, ICPS, ANSES, 2016	EFSA conclusions (evaluation and LoEP)	
Methidathion	0.03	Not covered	Not covered	No	Not available	HQ based on tentative ARfD of 0.01 mg/kg bw (JMPR, 1997) JMPR (1992) did not report any craniofacial alteration
Metribuzin	0.02	Yes	Yes	Not covered	Yes	ARfD: 0.02 mg/kg bw (EFSA conclusions, 2006) Observed indicators: delayed ossification of skull bones in a context of general delayed ossification
Mevinphos	0.01	Not covered	Not covered	Not covered	Not available	HQ based on tentative ARfD of 0.003 mg/kg bw (JMPR, 1996) JMPR, 1996 did not report any craniofacial alteration
Monocrotophos	0.03	Not covered	Not covered	No	Not available	HQ based on tentative ARfD of 0.002 mg/kg bw (JMPR, 1995) JMPR, 1995 did not report any craniofacial alteration
Nicotine	1.40	Not covered	Not covered	No	No	ARfD: 0.0008 mg/kg bw (EFSA statement, 2009) Detailed information was not found.
Oxydemeton-methyl	0.01	Not covered	Not covered	Yes	No	ARfD: 0.0016 mg/kg bw (EFSA conclusions, 2006) DAR (2004, FR): • Rats: doses of 0, 0.3, 1 and 3 mg/kg bw per day, days 6–15 of gestation: At 3 mg/kg bw per day, incidence of hypoplasia of telencephalon was slightly increased (2/242, 8/257, 2/237 and 17/243, respectively, at 0, 0.3, 1 and 3 mg/kg bw per day). The observed effects were not reproduced in an independent assay (hypoplasia telencephalon: 0/288 and 3/257, respectively, at 0 and 3 mg/kg bw per day) and all did not occur in a dose dependent manner ([redacted] 1979)
Parathion	0.02	Not covered	Not covered	No	Not available	HQ based on tentative ARfD of 0.005 mg/kg bw (outcome of ECCO, 2000) DAR (1998, IT) did not report any craniofacial alteration

Active substance	Median HQ at 99.9th percentile of acute exposure in adult populations	Observation of indicators of craniofacial alterations				Comments*
		DTU, 2012	RIVM, ICPS and ANSES, 2013	RIVM, ICPS, ANSES, 2016	EFSA conclusions (evaluation and LoEP)	
Permethrin	0.05	Not covered	Not covered	No	Not available	HQ based on tentative ARfD of 0.01 mg/kg bw (ADI established by the Committee for Veterinary Medical Products of EMEA (2002) (https://www.ema.europa.eu/en/documents/mrl-report/permethrin-summary-report-3-committee-veterinary-medicinal-products_en.pdf) used as surrogate for ARfD) JMPR (1999) did not report any craniofacial alteration
Phenthoate	0.05	Not covered	Not covered	No	Not available	HQ based on tentative ARfD of 0.003 mg/kg bw (ADI established by the JMPR (1984) used as surrogate for ARfD) JMPR (1980) did not report any craniofacial alteration
Phorate	0.08	Not covered	Not covered	Not covered	Not available	HQ based on tentative ARfD of 0.003 mg/kg bw (JMPR, 2004) JMPR (2004): • Rabbits: doses of 0, 0.15, 0.5, 0.9 or 1.2 mg/kg bw per day, days 6–18 of gestation: at the top dose, open eye in all three fetuses from a single litter, considered to be due to considerable toxicity (evidenced a marked body-weight loss) by the evaluators ([redacted] 1986).
Phosmet	0.87	No	Yes	Not covered	No	ARfD: 0.001 mg/kg bw (EFSA conclusions, 2020) DAR (2004, ES): • Rabbit: doses of 0, 2, 5 and 15 mg/kg bw per day, days 7–19 of gestation: anencephaly, exencephaly and cleft palate at 5 mg/kg bw per day; internal hydrocephaly, open eye and microphthalmia at 15 mg/kg bw per day ([redacted] 1991)
Phosphamidon	0.03	Not covered	Not covered	Not covered	Not available	HQ based on tentative ARfD of 0.0005 mg/kg bw (ADI established by the JMPR (1986) used as surrogate for ARfD)

Active substance	Median HQ at 99.9th percentile of acute exposure in adult populations	Observation of indicators of craniofacial alterations				Comments*
		DTU, 2012	RIVM, ICPS and ANSES, 2013	RIVM, ICPS, ANSES, 2016	EFSA conclusions (evaluation and LoEP)	
						JMPR (1986) (https://inchem.org/documents/jmpr/jmpmono/v86pr15.htm): • Rats: doses of 0, 1, 2, or 4 mg/kg bw per day, days 6–15 of gestation: Hydrocephalus was observed in 2, 2 and 3 fetuses of the 1, 2 and 4 mg/kg bw per day groups, respectively. Although the incidences were not statistically-significantly increased and no external observations of dome-shaped head were noted in any of the fetuses with suspected hydrocephalus, the finding of hydrocephalus was considered to be equivocal ([redacted] 1985b).
Prochloraz	0.10	Not covered	No	Not covered	No	ARfD: 0.025 mg/kg bw (EFSA conclusions, 2011)
Propoxur	0.31	Not covered	Not covered	Not covered	Not available	HQ based on tentative ARfD of 0.0005 mg/kg bw (Health Canada, 2014 - https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/decisions-updates/reevaluation-decision/2014/document-propoxur-rvd2014-01.html) JMPR (1989) did not report any craniofacial alteration
Prothiophos	1.43	Not covered	Not covered	Not covered	Not available	HQ based on tentative ARfD of 0.0001 mg/kg bw (ADI of the Australian Pesticides and Veterinary Medicines Authority (1993) used as surrogate for ARfD - https://apvma.gov.au/node/26581). No detailed evaluation found.
Quinalphos	0.08	Not covered	Not covered	Not covered	Not available	HQ based on tentative ARfD of 0.0005 mg/kg bw (ADI of the EPA (1987) used as surrogate for ARfD: https://iris.epa.gov/ChemicalLanding/&substance_nmbr=189). No detailed evaluation available.
Tefluthrin	0.05	Not covered	No	Not covered	No	ARfD: 0.005 mg/kg bw (EFSA conclusions, 2010)

Active substance	Median HQ at 99.9th percentile of acute exposure in adult populations	Observation of indicators of craniofacial alterations				Comments*
		DTU, 2012	RIVM, ICPS and ANSES, 2013	RIVM, ICPS, ANSES, 2016	EFSA conclusions (evaluation and LoEP)	
Terbufos	0.02	Not covered	Not covered	Not covered	Not available	HQ based on tentative ARfD of 0.002 mg/kg bw (JMPR, 2003) JMPR (2003) did not report any craniofacial alteration
Triazophos	0.04	Not covered	Not covered	No	Not available	HQ based on tentative ARfD of 0.001 mg/kg bw (JMPR, 2001) JMPR (2002) did not report any craniofacial alteration

*: Includes references as given in the respective source.

Substances considered but not showing craniofacial alterations in toxicological studies or showing craniofacial alterations in toxicological studies that were dismissed/disregarded during the establishment of the CAGs

Following regulation (EC) No 283/2013 setting out the data requirements for active substances, developmental toxicity studies are required for rat and rabbit by the oral route. Although available for two species, studies may in theory fail to detect craniofacial effects in the following circumstances:

- The highest tested dose was not high enough (no maternal toxicity observed, i.e. clinical signs or a 10–20% decrease in body weight gain without mortality and/or any other severe symptoms). In such case, however, supposing that the substance is causing craniofacial effects, the NOAEL would be rather high (equal or above the highest tested dose although observations at dose levels close to the maximum tolerated dose would need to be interpreted with caution).
- The effects/indicators are not identified by the author of the study because of the subjective nature of morphological examination which rely upon the judgement and experience of the pathologist in the absence of standardised and strict criteria for identifying them and the advanced level of specialised training required for the effective utilisation of these endpoints.
- Studies conducted before the adoption of the second version of the OECD test guideline (TG) 414 in 2001 may suffer from a lack of robustness.[22] This is the case for the vast majority of the studies conducted with the 85 substances that were reviewed. Details about the year of completion of the studies can be found in Annex A. The substances for which tests were performed after 2001 on at least one species are: 1,2,4-triazole, acetamiprid, epoxiconazole, ETU, fenpyrazamine, flutriafol, folpet, mancozeb, metabolite R154719 of Fluazifop-P, propineb, prothioconazole, prothioconazole-sulfonic acid PTU, spirotetramat and triazole Alanine.

Therefore, the selected active substances for which the toxicological data did not show indicators of craniofacial effects (42 in total) were investigated with the OECD QSAR Toolbox 4.4 for developmental and reproductive toxicology (DART) properties. For 21 of them (Alpha-cypermethrin, Beta-cyfluthrin, Beta-cypermethrin, Carbofuran, Chlorpropham, Cypermethrin, Difenoconazole, Fenbuconazole, Fenhexamid, Imazalil, Iprodione, Methiocarb, Methomyl, Methoxyfenozide, Oxamyl, Tetraconazole, Thiophanate-methyl, Thiram, Triadimenol, Triclopyr and Zeta-cypermethrin), DART alerts were flagged, suggesting that toxicological studies might not have been sensitive enough to detect the capacity to cause craniofacial effects. This was also the case for the metabolite triazole lactic acid. No information on direction for a DART alert could be retrieved for Chlorpyrifos-methyl, Dimethoate, Omethoate and Pirimiphos-methyl, since their chemical structures are not covered by the current version of the decision tree in OECD QSAR Toolbox 4.4. The positive DART alerts in OECD QSAR Toolbox 4.4 are very general alerts ('known precedent reproductive and developmental toxic potential') and it is not known if the DART alert is eventually related to e.g. RA pathway or in general to craniofacial development. In order to further explore the information from OECD QSAR Toolbox for DART alerts, US EPA CompTox Chemical Dashboard has been investigated for potentially relevant *in vitro* assays related to RA pathway. 13 assays with corresponding genes were proposed as relevant (ATG_RARa_TRANS_up, ATG_RARb_TRANS_up, ATG_RARg_TRANS_up, ATG_RXRa_TRANS_up, ATG_RXRb_TRANS_up, NVS_ENZ_hHDAC3, NVS_ENZ_hHDAC3_Activator, NVS_ENZ_hHDAC6, NVS_ENZ_hHDAC6_Activator, TOX21_RAR_LUC_Agonist, TOX21_RXR_BLA_Agonist_ratio, TOX21_RAR_LUC_Antagonist, ATG_DR5_CIS_up) and two were of unclear relevance (NVS_NR_hRAR_Antagonist, NVS_NR_hRAR_Agonist).

[22] In 2001, the second version of the OECD 414 TG included new requirements improving the stringency of conditions and the reliability of the study results:
- Minimum requirements for housing conditions are defined.
- A minimum number of animals with implantation sites (16) is required and a maximum tolerable maternal mortality rate (10%) is defined.
- Precise requirements regarding the examination of foetuses (number of foetuses per litter, methodology, type of observation) are set.
- Gravid uterine weight was required.
- Detailed requirements for reporting (presentation of results, modality of statistical analyses, dose response relationship, categorisation of fetal external, soft tissue and skeletal alterations, maternal toxic dose) are defined.
- In the absence of effects, the bioavailability of test substance has to be demonstrated.

Investigation of 39 substances allocated to CAG-DAC, 41 allocated to CAG-DAH and 25 substances excluded from CAGs but with either positive or unclear DART alerts from OECD QSAR Toolbox 4.4. could not show that substances allocated to CAGs were more frequently or continuously positive in the selected assays, compared to the substances excluded from the CAGs.

Note 2 (Active substances wrongly included in the CAGs) – U2

If an active substance, or a metabolite, is included in a CAG, but does not actually cause the respective effect, the cumulative exposure and risk will be overestimated. The generic principles used to include a substance in a CAG are described in Section 2.1.2.

The LOEs, and their respective relative weight, supporting that an active substance is actually causing craniofacial effects are described in Section 3.1.5. All risk drivers were reviewed to establish whether they met each of the LOEs. As the assaessment of some LOEs was complex, the following was agreed:

- For the implementation of LOE 3 (dose–response relationship), the assessment was based on the incidence of the effects in fetuses/litters observed at different doses of the studies reported in tables in Appendices A1 and A2. For this, all indicators in each CAG were assumed to be originating from the same pathway or mechanism and were considered equally valid. If in one fetus, several indicators of the same CAG (e.g. facial cleft, hyoid defects and skull vault agenesis) were observed, this incremented the fetal incidence in the litter by one. If indicators of the same CAG were observed in a second and third fetuses of the same litter, the total fetal incidence in the corresponding litter was three. This approach required the use of raw data. When they were not available to EFSA, the assessment of the dose–response relationship was based on the information collected in Annex A.
- For the implementation of LOE 4 (absence of maternal toxicity): a 'Yes' was in principle assigned when the LOAEL for maternal toxicity was above the LOAEL for craniofacial alterations in the study from which the overall LOAEL of the substance for the effect was derived, as indicated in tables in Appendices A1 and A2. However, the other studies reported in the same tables, when providing usable information, were also considered and the final assessment was based on expert judgement, taking account of all pieces of information.
- For the implementation of LOE 5 (effect observed in more than one study in the same species), the Yes/No assessment was conducted separately for rats and rabbits. Furthermore, when one study only was available in a species, the case was be reported as 'n.a.' (not available).

The compilation of the LOEs observed for all risk drivers can be found in Tables F.2 and F.3.

Table F.2: LOEs supporting the inclusion of risk drivers in CAG-DAC

LOE (weight)	2,4-D	Chlorpyrifos	Folpet	Mancozeb	Tebuconazole	Thiabendazole
LOE 1 (high)	Yes	Yes	Yes	Yes	Yes	Yes
LOE 2 (low-intermediate)	No	No	No	Yes	Yes	Yes
LOE 3, option 1 (high)				Yes	Yes	Yes
LOE 3, option 2 (intermediate/high)	Yes	Yes				
LOE 3, option 3 (high)						
LOE 3, option 4 (low)			Yes			
LOE 3, option 5 (intermediate)						
LOE 4 (high)	No	No	Yes	Yes	Yes	No
LOE 5, rats (high)	No	No	No	Yes	Yes	n.a.
LOE 5, rabbits (high)	n.a.	n.a.	No	No	Yes	No
LOE 6 (high)	Yes	No	Yes	No	Yes	No
Elicited CAG-membership probability (%)	33–90	10–50	40–70	75–90	90–99	33–90

Table F.3: LOEs supporting the inclusion of risk drivers in CAG-DAH

Risk drivers	2,4-D	Chlorpyrifos	Cyproconazole	Deltamethrin	Folpet	Thiabendazole
LOE 1 (high)	Yes	Yes	Yes	Yes	Yes	Yes
LOE 2 (low-intermediate)	No	No	Yes	No	No	Yes
LOE 3, option 1 (high)			Yes		Yes	Yes
LOE 3, option 2 (intermediate/high)	Yes	Yes		Yes		
LOE 3, option 3 (high)						
LOE 3, option 4 (low)						
LOE 3, option 5 (intermediate)						
LOE 4 (high)	No	No	Yes	Yes	No	No
LOE 5, rats (high)	No	No	Yes	No	No	n.a.
LOE 5, rabbits (high)	n.a.	n.a.	No	No	Yes	No
LOE 6 (high)	Yes	No	Yes	No	Yes	No
Elicited CAG-membership probability (%)	33–90	10–66	90–99	10–70	75–90	33–90

The CAG-membership probabilities of risk drivers were agreed in consensus as follows:

In CAG-DAC:

- 2,4-D: 33–90%
  Explanation: In addition to the LOEs collected in Table F.2, the experts took in account additional elements either supporting the CAG-membership probability (unambiguousness of the observed indicator in rabbits (cleft palate)) or lowering this probability (in rabbits, only one fetus was affected; the indicators in rats (exencephaly and agnathia) were observed in a same fetus in [redacted] (1984 – generational study) and were not repeated in [redacted] (2010 – extended one generation reproductive toxicity) or in [redacted] (1983 – developmental toxicity study))
- Chlorpyrifos: 10–50%
  Explanation: In addition to the LOEs collected in Table F.2, the experts took in account additional elements either supporting the CAG-membership probability (unambiguousness of the observed indicator (cleft palate)) or lowering this probability (from all available studies, only one fetus was affected; studies are available in 3 species (rats, rabbits and mouse), but effects were observed in rats only)
- Folpet: 40–70%
  Explanation: In addition to the LOEs collected in Table F.2, the experts took in account additional elements either supporting the CAG-membership probability (there is uncertainty in the assignment of the dose–response relationship to option 4, because the number of affected fetuses in rabbits is low and in rats, a dose–response relationship was observed) or lowering this probability (the indicator observed in rats (anterior fontanelle large) is not very specific, was also found with high incidence in the control group and in a context of general delayed ossification)
- Mancozeb: 75–90%
  Explanation: In addition to the LOEs collected in Table F.2, the experts took in account additional elements supporting the CAG-membership probability (the substance produces ETU in mammalian metabolism, a metabolite for which strong evidence shows that it causes the effects; unambiguousness of the indicators (e.g. cleft palate))
- Tebuconazole: 90–99%
  Explanation: In addition to the LOEs collected in Table F.2, the experts took in account additional elements either supporting the CAG-membership probability (observation of effects in 3 species (rats, rabbit and mouse), observation of effects after dermal exposure) or lowering this probability (one study in rabbits was negative despite the fact that dose levels were comparable to positive studies; dose–response relationship was observed in 2 studies in mouse but not in studies in other species)
- Thiabendazole: 33–90%
  Explanation: In addition to the LOEs collected in Table F.2, the experts took in account additional elements lowering the CAG-membership probability (only one indicator was observed (enlarged anterior and posterior fontanelles); studies are available in 3 species (rats, rabbits and mouse) but effects were observed in one species only (rabbit) – although only 1 study is available for rats and mouse and the tested doses in rats could have not been high enough)

In CAG-DAH:

- 2,4-D: 33–90%
  Explanation: In addition to the LOEs collected in Table F.3, the experts took in account additional elements either supporting the CAG-membership probability (unambiguousness of the observed indicator in rats (microphthalmia)) or lowering this probability (In rats, only one fetus was affected; In rats, the effect observed in [redacted] (1984 – generational study) was not repeated in [redacted] (2010 – extended one generation reproductive toxicity) or in [redacted] (1983 – developmental toxicity study); in rabbits, only one litter (but 3 fetuses) was affected)
- Chlorpyrifos: 10–66%
  Explanation: In addition to the LOEs collected in Table F.3, the experts took in account additional elements either supporting the CAG-membership probability (unambiguousness of the observed indicator (microphthalmia), the difficulty to observe this indicator and the fact that its incidence may be underestimated) or lowering this probability (from all available studies, only 2 fetuses were affected; studies are available in 3 species (rats, rabbits and mouse), but effects were observed in rats only)

- Cyproconazole: 90–99%
  Explanation: The CAG-membership probability was not assigned through a formal elicitation but by analogy to tebuconazole in CAG-DAC because the LOEs were similar
- Deltamethrin: 10–70%
  Explanation: In addition to the LOEs collected in Table F.3, the experts took in account additional elements either supporting the CAG-membership probability (the high neurotoxicity of the compounds prevented the use of high doses in developmental toxicity studies, reducing therefore the capacity of the tests to detect indicators) or lowering this probability (studies are available in 3 species (rats, rabbits and mouse) but effects were observed in one species only (rabbit); in rabbits, only one fetus was affected)
- Folpet: 75–90%
  Explanation: In addition to the LOEs collected in Table F.3, the experts took in account additional elements supporting the CAG-membership probability (the negative studies in rats were conducted at lower doses than the positive study, therefore the assessment of LOE 5 for rats is uncertain; in rabbits, the same indicator was observed in 2 studies)
- Thiabendazole: 33–90%
  Explanation: In addition to the LOEs collected in Table F.3, the experts took in account additional elements lowering the CAG-membership probability (only 2 interrelated indicators were observed (hydrocephalus and dome-shaped head); studies are available in 3 species (rats, rabbits and mouse) but effects were observed in one species only (rabbit) – although only 1 study is available for rats and mouse and the tested doses in rats could have not been high enough)

The large range assigned in many cases to the CAG-membership probabilities reflects the impact of opposite influence of available or not available evidence as well as the range of individual opinions of the experts.

It was recognised that, for the reasons explained in Section 3.3.2, it was not appropriate to assess the impact of U2 using multiplicative factors applied to the median estimate of the MOET from Tier II. Ideally, CAG-membership probabilities would be included in the Tier I and II exposure models, including or excluding each substance or risk driver in each bootstrap iteration in proportion to its membership probability. Doing that was not feasible for the present assessment so, instead, separate calculations were performed to explore the impact of the CAG-membership probabilities for two risk drivers considered separately: folpet in both CAGs and 2,4-D in CAG DAH. These calculations required the execution of 2 additional sensitivity analyses (sensitivity analyses L and M) reported in Table F.4.

Table F.4: Additional sensitivity analyses supporting the assessment of the impact of CAG-membership probabilities for folpet in CAG-DAC and CAG-DAH and for 2,4-D in CAG-DAH

Country	CAG-DAC Tier II	CAG-DAC Sensitivity analysis L[(a)]	CAG-DAH Tier II	CAG-DAH Sensitivity analysis L[(a)]	CAG-DAH Sensitivity analysis M[(b)]
BE – Belgium	179 [133–240]	422 [369–495]	597 [488–716]	601 [492–731]	827 [699–962]
CZ – Czechia	119 [90–180]	426 [342–497]	573 [446–723]	629 [504–877]	753 [593–971]
DE – Germany	107 [84.5–151]	322 [276–379]	553 [474–653]	603 [523–716]	696 [587–830]
DK – Denmark	146 [98.4–194]	507 [445–564]	751 [622–898]	820 [700–986]	928 [748–1120]
ES – Spain	194 [144–255]	349 [281–413]	674 [584–820]	721 [594–862]	898 [726–1100]
FI – Finland	294 [242–392]	368 [270–486]	534 [386–754]	543 [399–716]	840 [576–1080]
FR – France	148 [117–197]	426 [349–488]	659 [544–789]	710 [608–827]	863 [702–1030]
HU – Hungary	267 [187–335]	421 [358–478]	775 [615–950]	792 [626–1030]	1060 [773–1330]
IE – Ireland	73.5 [50.9–106]	488 [403–596]	562 [399–717]	854 [713–1020]	589 [436–767]
IT – Italy	203 [162–266]	417 [343–472]	714 [579–930]	737 [601–913]	937 [698–1160]
LV – Latvia	298 [237–359]	469 [366–560]	812 [606–1020]	821 [626–1080]	1110 [804–1360]
NL – Netherlands	173 [130–236]	418 [372–487]	601 [499–737]	620 [505–777]	818 [655–982]
RO – Romania	288 [242–343]	358 [318–413]	1010 [739–1300]	1110 [799–1410]	1110 [807–1450]
SE – Sweden	134 [98.7–186]	470 [400–547]	684 [577–839]	775 [626–908]	900 [722–1060]

(a): Sensitivity analysis L assumes that folpet is not included in the CAG.
(b): Sensitivity analysis M assumes that 2,4-D is not included in the CAG.

The method used for these calculations was as follows. For each combination of population, CAG and excluded substance (population/CAG-DAC/folpet, population/CAG-DAH/folpet and population/CAG-DAH/2,4-D):

1) The 100 bootstrap estimates of the 99.9th percentile MOET were extracted from the Tier II outputs (including all CAG members), and from sensitivity analysis L (excluding folpet) or M (excluding 2,4-D).
2) Each set of 100 bootstrap estimates was resampled with replacement to produce a larger set of 10,000 values.
3) 10,000 random numbers between 0 and 1 were generated.
4) Each random number in turn (n = 1–10,000) was used to select either the n-th estimate including the substance or the n-th estimate excluding the substance, in proportion to its probability of CAG-membership. As the membership probabilities were assessed as ranges, this operation was repeated twice, once with the lower bound probability and once with the upper bound probability (e.g. 40% and 70% for folpet in CAG-DAC). This resulted in two sets of 10,000 MOET estimates: one set for the lower membership probability and one for the higher probability.
5) Four histograms were produced, showing the distribution of 10,000 MOET estimates (a) with the substance always included, (b) with the substance included in proportion to the upper bound probability, (c) with the substance included in proportion to the lower bound probability, (d) with the substance always excluded. For each distribution, the median, quartiles, 95% probability interval and probabilities of MOET< 100 and < 500 were derived.

The results from these calculations were provided to the experts to assist them in taking account of uncertainty U2 in EKE Q3.

An example of the histograms produced for CAG-DAC (folpet in, out, high probability, low probability) for the German population is shown in Figure F.1, and all the results of the calculations for the German populations are presented in Table F.5 (impact of CAG-membership probability of folpet on Tier II calculations for CAG-DAC), Table F.6 (impact of CAG-membership probability of 2,4-D on Tier II calculations for CAG-DAH) and Table F.7 (impact of CAG-membership probability of folpet on Tier II calculations for CAG-DAH). It is important to keep in mind that these results are based on the Tier II calculations, and do not include adjustment for the exposure and toxicology uncertainties assessed in EKE Q2.

Note that within upper and lower bounds defined by the Tier II calculations and sensitivity analyses L and M, the probabilities for the MOET being below 100 (or 500) decrease approximately in proportion to the CAG membership probability.

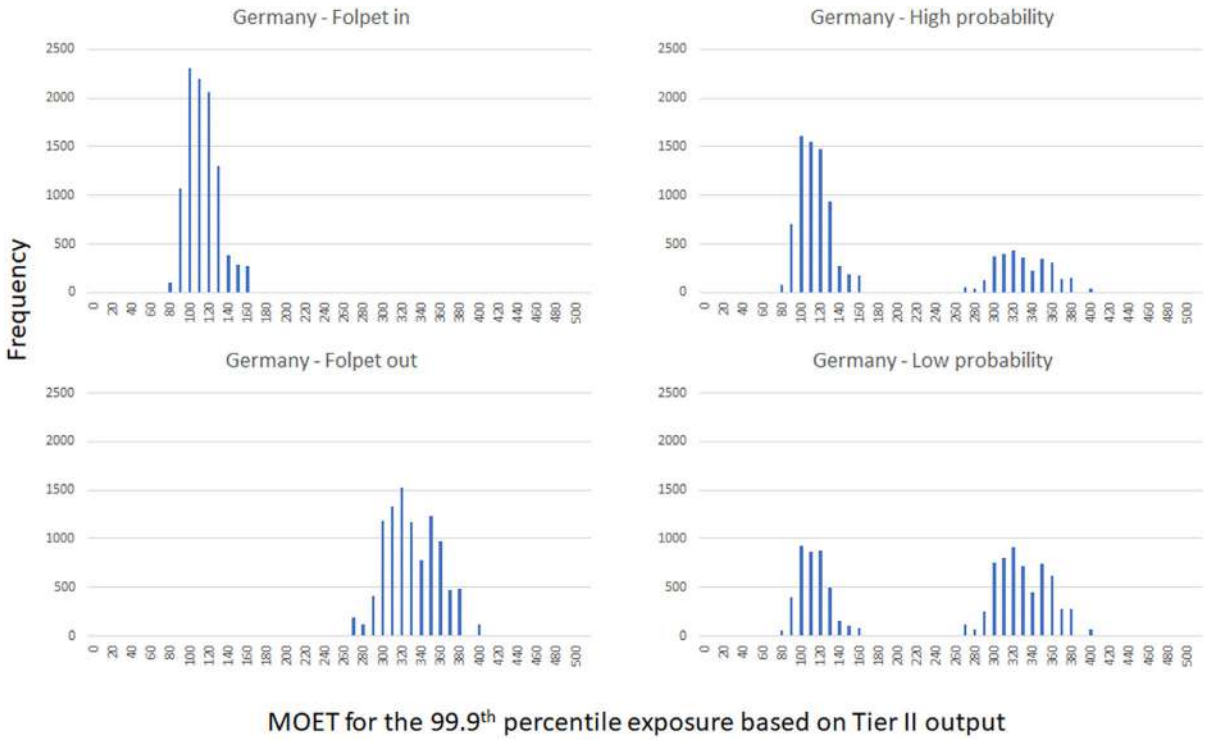


Figure F.1: Distributions quantifying uncertainty of the MOET for the 99.9th percentile exposure based on Tier II output for CAG-DAC, with folpet included, folpet excluded, and folpet included in the CAG with higher probability (70%) or lower probability (40%) bounds

Table F.5: Statistics quantifying uncertainty of the MOET for the 99.9th percentile exposure based on Tier II output for CAG-DAC, with folpet included, folpet excluded, and folpet included in the CAG with higher probability (70%) or lower probability (40%)

MOET at 99.9th percentile exposure (DE)	Folpet included	Folpet included with high probability (70%)	Folpet included with low probability (40%)	Folpet excluded
P2.5	85	85	88	278
P25	98	101	112	306
Median	107	118	298	322
P75	119	298	327	343
P97.5	149	368	372	378
P(MOET< 100)	35.0%	24.0%	13.7%	0.0%
P(MOET< 500)	100%	100%	100%	100%

Table F.6: Statistics quantifying uncertainty of the MOET for the 99.9th percentile exposure based on Tier II output for CAG-DAH, with 2,4-D included, 2,4-D excluded, and 2,4-D included in the CAG with higher probability (90%) or lower probability (33%).

MOET at 99.9th percentile exposure (DE)	2,4-D included	2,4-D included with high probability (90%)	2,4-D included with low probability (33%)	2,4-D excluded
P2.5	475	474	495	588
P25	523	527	576	667
Median	553	557	669	696
P75	581	599	714	728
P97.5	652	725	828	829

MOET at 99.9th percentile exposure (DE)	2,4-D included	2,4-D included with high probability (90%)	2,4-D included with low probability (33%)	2,4-D excluded
P(MOET< 100)	0.0%	0.0%	0.0%	0.0%
P(MOET< 500)	13.0%	12.0%	4.1%	0.0%

Table F.7: Statistics quantifying uncertainty of the MOET for the 99.9th percentile exposure based on Tier II output for CAG-DAH, with folpet included, folpet excluded, and folpet included in the CAG with higher probability (90%) or lower probability (75%)

MOET at 99.9th percentile exposure (DE)	Folpet included	Folpet included with high probability (90%)	Folpet included with low probability (75%)	Folpet excluded
P2.5	475	474	476	524
P25	523	528	532	565
Median	553	556	566	603
P75	581	590	601	640
P97.5	652	672	681	705
P(MOET< 100)	0.0%	0.0%	0.0%	0.0%
P(MOET< 500)	13.0%	11.3%	9.6%	1.0%

Note 3 (Impact of the data collection methodology on the accuracy of NOAELs) – U3

The robustness of the hazard characterisation process and, in particular, the accuracy of the NOAELs reflecting craniofacial alterations, depend on multiple factors, which, for the sake of the uncertainty analysis, have been grouped under 4 themes: data collection methodology, principles used to assess the data, design of the key study and quality of the key study. The present note deals with the first factor, the data collection methodology.

The first-hand information concerning craniofacial alterations lies in the outcome of the original toxicological studies. The setting of NOAELs for these effects requested the identification and collection of information through the following steps:

- Step 1 - Analysis of raw data by the authors of the studies and reporting of the results in study reports.
- Step 2 - Assessment of the study reports by the regulatory assessors/bodies and reporting of relevant observations in assessment reports (DARs, JMPR evaluations).
- Step 3 - Transfer of information from the assessment reports to the Excel database in Annex A by the authors of the present scientific report.

In each step, information can in theory be lost or altered considering the huge amount and complexity of data, with possible impact on the accuracy of the NOAELs.

The step 1 suffers from the same difficulties related to the subjectivity of human judgement as described in Note 1, although, here, these difficulties may impact the choice of the dose which will be considered as the NOAEL for the indicator under consideration. However, reproductive and developmental toxicity studies are conducted by trained and specialised personal and macroscopic evaluation is unlikely to be subject to misinterpretation.

The risk of mistakes in step 2 is mitigated by procedures prevailing in the EU approval process of substances (e.g. circulation of the dossier to all Member States, peer-review procedure). Despite this, careful review of original study reports to extract data for BMD analysis (see Note 36) showed that observations are sometimes overlooked by regulatory assessors. In the case of deltamethrin, for instance, cleft palate observed in [redacted] (2001) at highest dose (32 mg/kg bw per day) were not reported in the DAR, and consequently not included in the data collection.

With respect to step 3, the existing EFSA conclusions or JMPR evaluations were considered to capture any element of expert judgement which might have been relevant for the present assessment, as explained in Section 2.1.3. In addition, a specific quality check process was implemented independently by 2 experts to consolidate the correctness of the information collected in the database (see Annex A). Specific check points were defined to verify the consistency of the content of:

- Column M ('observed effects related to CAG-DAC or CAG-DAH') and column N ('craniofacial alterations due to abnormal skeletal development (CAG DAC) OR head soft tissue alterations and brain neural tube defects (CAG DAH)'), based on the list of indicators defined for CAG-DAC and CAG-DAH in Section 3.1.2.
- Column M ('observed effects related to CAG-DAC or CAG-DAH) and column T ('Details on the indicators and dose-related incidence'), based on the possible variants of some indicators (e.g. skull vault agenesis and skull defects) described in Section 3.1.2.
- Column K ('Doses tested') and columns O ('effect NOAEL'), P ('effect LOAEL') and T ('Details on the indicators and dose-related incidence'), with respect to the reported doses
- Column U ('Kind of dose response') and column T ('Details on the indicators and dose-related incidence'), with respect to the respective doses
- Column AE ('Study acceptability for identification of craniofacial alterations') and column AH ('Remarks'). The validity of a study for purpose of identification of craniofacial effects was evaluated by expert judgement. The handled criteria were less strict/exhaustive than the general criteria for considering the full study as valid. This is because in several cases, reporting bias on e.g. maternal toxicity could invalidate the results of the study for maternal findings but if the craniofacial alterations are reported in sufficient detail the finding should not be neglected.
- Column AD ('Study reference') with column K ('Doses tested'). In column AD several studies of the same authors could be listed, distinguishable by the same subscripts (a, b, c..) as used in the respective DAR/DRAR/Addenda. In such case, these different studies should correspond to different doses regimens.
- Column N ('craniofacial alterations due to abnormal skeletal development (CAG DAC) OR head soft tissue alterations and brain neural tube defects (CAG DAH)') and columns O, P, R, S, T, U and X, which should be left empty when 'none' has been selected in column N.

Note 4 (Impact of the hazard characterisation principles on the accuracy of the NOAELs) – U4

The second factor impacting the accuracy of the NOAELs lies in the hazard characterisation principles that were adhered to and the associated expert judgements. These are described in Section 2.1.3.

A particular point of the hazard characterisation methodology was the use of sets of studies for collective evaluation when at least two studies of similar quality were available in a same strain of a species. If the combination of studies implies, per se, the use of more information, it is important to ensure that the combined studies are of similar quality and reliability, so that the uncertainty of the NOAEL-setting process is actually reduced. The precise conditions to be met for combining studies are also described in Section 2.1.3.

Section 3.1.4 gives key information on how the hazard characterisation principles were applied, in particular regarding risk drivers.

Note 5 (Impact of the design of the critical study on the accuracy of the NOAELs and LOAELs) – U5

The third factor affecting the hazard characterisation process concerns the experimental protocol of the study from which the NOAEL and LOAEL were derived.

The most relevant elements of the study design for the setting of robust NOAELs/LOAELs for craniofacial alterations were identified as being the study type (developmental toxicity study or other study), the exposure period to the substance (adequacy for the vulnerability period to craniofacial effects), the route and mode of administration (adequacy for dietary risk assessment) as well as any other aspect of technical nature which affect the accuracy of the NOAEL and LOAEL or need to be taken into consideration in their interpretation, e.g. the type of staining (single or double, for the appropriate interpretation of observations related to specific indicators of CAG-DAC). Tables F.8 and F.9 provide information on these key points for the studies that were used to establish the NOAELs of the risk drivers in CAG-DAC and CAG-DAH.

Table F.8: Components of the design of the study used to establish the NOAELs and LOAELs of risk drivers in CAG-DAC

Active substance	Study type and reference[a]	Exposure period (p.c.=post coitum)	Mode of administration	Critical indicators	Staining method
2,4-D	Rat generational ([redacted] 1984)[b]	Not clear from the report	Diet	Exencephaly Agnathia	Not relevant for the critical indicators
Chlorpyrifos	Rat developmental ([redacted] 1983)	Days 6–15 p.c.	gavage	Cleft palate	Not relevant for the critical indicator
Folpet	Rabbit developmental ([redacted] 1984)	Days 7–28 p.c.	gavage	Hyoid alae angulated	Not relevant for the critical indicator
Mancozeb	Rat developmental ([redacted] 2015c)	Days 6–19 p.c.	gavage	Hyoid unossified, reduced ossification in the skull	Double staining
Tebuconazole	Mouse developmental ([redacted] 1995c)	Days 6–15 p.c.	gavage	Exencephaly, open eye, acrania, cleft palate	Not relevant for the critical indicators
Thiabendazole	Rabbit developmental ([redacted] 1989)	Days 6–18 p.c.	gavage	Enlarged anterior and posterior fontanelles	Not relevant for the critical indicator
Thiabendazole	Rabbit developmental ([redacted] 1992)	Days 6–15 p.c.	gavage	No effect	-

(a): Reference as given in the source document (DAR/DRAR) from which the information was extracted.
(b): The NOAEL for 2,4-D in this rat generational study is 5 mg/kg bw per day. In developmental toxicity studies in rats, no indicators were observed up to 75 mg/kg bw per day. In developmental toxicity studies in rabbits, a NOAEL of 30 mg/kg bw per day was established, based on cleft palate ([redacted] 1990).

Table F.9: Components of the design of the study used to establish the NOAELs and LOAELs of risk drivers in CAG-DAH

Active substance	Study type and reference[a]	Exposure period	Mode of administration	Critical indicators
2,4-D[b]	Rat generational ([redacted] 1984)[b]	Not clear from the report	Diet	Microphthalmia
Chlorpyrifos	Rat developmental ([redacted] 1983)	Days 6–15 p.c.	gavage	Microphthalmia
Cyproconazole	Chinchilla rabbit developmental ([redacted] 1986)	Days 6–18 p.c.	gavage	Hydrocephalus
Deltamethrin	Rabbit developmental ([redacted] 1977c)	Days 6–19 p.c.	gavage	Hydrocephalus
Deltamethrin	Rabbit developmental ([redacted] 2001)	Days 6–28 p.c.	gavage	No effect
Folpet	Rabbit developmental ([redacted] 1984)	Days 7–28 p.c.	gavage	Hydrocephalus
Thiabendazole	Rabbit developmental ([redacted] 1989)	Days 6–18 p.c.	gavage	Hydrocephalus Dome-shaped head
Thiabendazole	Rabbit developmental ([redacted] 1992)	Days 6–18 p.c.	gavage	No effect

(a): Reference as given in the source document (DAR/DRAR) from which the information was extracted.
(b): The NOAEL for 2,4-D in this rat generational study is 5 mg/kg bw per day. In developmental toxicity studies in rats, no indicators were observed up to 75 mg/kg bw per day. In developmental toxicity studies in rabbits, a NOAEL of 30 mg/kg bw per day was established, based on dome-shaped head and hydrocephalus ([redacted] 1990).

Most of the studies used for the NOAEL/LOAEL-setting were developmental toxicity studies, in which the substance was administered during a period sufficient to cover the full period of organogenesis. In the case of 2,4-D, a two-generational study, with longer duration of exposure, was used, instead of the available developmental toxicity studies because it showed effects at lower doses.

The developmental toxicity studies conducted according to the internationally agreed protocols aim at the identification and characterisation of hazard to the developing embryos and pregnant animals. The test substance is usually administered by gavage to the animals in a vehicle that does not influence its absorption, distribution and metabolism and allows the accurate estimation of the administered dose. The established NOAELs from developmental toxicity studies are always considered for the setting of the ADI and/or ARfD when the data indicate that they should be taken into account. In case of administration of the test substance through the diet (e.g. in generational studies), its oral absorption may be affected (reduced). However, this was not observed in the case of one of the risk drivers for CAG-DAC and CAG-DAH, i.e. 2,4 D for which the generational study was selected for the NOAEL setting instead of the available developmental study since it showed effects at lower doses.

In teratogenicity studies, rodent and rabbit fetal bones are mostly stained with alizarin red S to examine morphological features of the skeleton. The cartilage remains unstained and therefore might be undetectable. In contrast, double staining allows the staining of cartilage (blue, stained with alcian blue) and the bone (red, stained with alizarin red S) to be visible.

There are two types of ossification of the skull bones (endochondral or intramembranous). In the case of endochondral skeletal elements, skeleton is pre-formed in cartilage that ossifies late (ossification by substitution, typical, for example, of the skull basis, otic, optic and nasal regions, ear ossicle, Meckels cartilage of jaw). Physiologically in rodents and rabbits, large part of fetal skeleton is immature at time of birth and immature ossifications are pathological conditions too.

In preparations that are stained only with alizarin red S (staining the ossified elements), as it was usually done, any cartilage that is present remains unstained and, thus, might be invisible to examiners. The non-appearance of alizarin-stained tissue could potentially lead to the reporting of 'agenesis' of the tissue, even when the primary bone tissue or cartilaginous rudiment was present, and the development of that bone was actually only slower than that of controls. By contrasts, some anomalies indicated as delay of ossification can reflect agenesis or dysmorphogenesis (including severe defects like fusion between skeletal elements).

Some parts of the cranium (the skull vault, large part of jaws) ossify by direct ossification of connective without the formation of cartilage. Ossification delays of the skull vault appears like a thinned-out stain. Due to the absence in these districts of cartilage, blue elements are not visible after double staining. Ossification delays, by contrast, have never been reported at the level of jaw.

The indicators of CAG-DAC which are sensitive to the staining method are the following: 'hyoid: any kind of hyoid defects (bent or accentuated curvature, fused, misshapen, short, supernumerary, crooked)', 'extra ossification sites/accessory skull bones or cartilages' and 'abnormalities at the brachial apparatus level visible at embryo stages'.

As the studies were rather old, the staining method in studies used for the characterisation of risk drivers was therefore checked. Indeed, if single staining was used, this may have resulted in the misclassification of a variation or a retarded ossification into a malformation. This can not only result in an erroneous inclusion of a substance in CAG-DAC due to misclassification of delayed ossification as agenesis (to be considered under U2) when this concerns the only indicator observed, but also in the setting of NOAELs at too low levels, when other relevant indicators were observable at higher levels.

It must be noted that the dose spacing, although being a key point of the study design, is not included in the scope of U5, but is inherent part of uncertainty U37 (see Note 36).

Note 6 (Impact of the quality of the key study on the accuracy of NOAELs) – U6

This note deals with the last factor influencing the accuracy of the NOAELS, the uncertainty resulting from eventual shortcomings related to the quality of the key studies (i.e. the studies used for the setting of NOAELs and LOAELs).

Detailed information on the studies used for the characterisation of the substances included in CAG-DAC and CAG-DAH can be found in Annex A. However, for the purpose of the assessment of the impact of U6, the study quality is mainly evaluated on the following criteria:

- Availability of a statistical analysis.
- Clear reference to test guidelines.

- Year of performance of the study: Studies conducted before 2001 may lack of robustness as explained in Note 1. This lack of robustness may impact both the decision to include an active substance in the CAG and the accuracy of the NOAEL setting.
- Availability of HCD.
- Steadiness of the administered dose during the administration period. To demonstrate the reliability of the study results, it is important that the administered doses are proven to be at the nominal levels and to remain constant across the study duration. This requires the use of validated analytical methods and the reporting of analyses of the administered diet/gavage solutions. In the absence of evidence that the administered doses were at nominal levels, the MOET may be overestimated if the substance degraded before administration.

The studies used for the characterisation of risk drivers were checked for these 5 criteria and the findings are reported in Table F.10. The table also includes the judgement of the Working Group experts on the acceptability of these studies for the assessment of craniofacial alterations.

Table F.10: Study quality information regarding the toxicological characterisation of risk drivers for craniofacial alterations

Risk driver/Study reference[a]	Availability of statistical analysis	Test Guideline[b]	Availability of HCD	chemical analysis of tested doses[c]	Acceptability of the study for the assessment of craniofacial alteration
CAG-DAC					
2,4-D/Rat generational ([redacted] 1984)	no	Study not fully in compliance with EU B35 method	no	Information missing	Acceptable
Chlorpyrifos/Rat developmental ([redacted] 1983)	yes	OECD TG 414	no	Information missing	Acceptable
Folpet/Rabbit developmental ([redacted] 1984)	yes	EPA-FIFRA Requirements	no	Yes	Acceptable
Mancozeb/Rat developmental ([redacted] 2015c)	no	OECD TG 414	no	Information missing	Acceptable
Tebuconazole/Mouse developmental ([redacted] 1995c)	yes	EPA 83-3	yes	Information missing	Acceptable
Thiabendazole/ Rabbit developmental ([redacted] 1989)	yes	OECD TG 414	yes	Yes	Acceptable
Thiabendazole/ Rabbit developmental ([redacted] 1992)	n.a.	OECD TG 414	n.a.	Yes	Acceptable
CAG-DAH					
2,4-D/Rat generational ([redacted] 1984)	no	Study not fully in compliance with EU B35 method	no	Information missing	Acceptable
Chlorpyrifos/Rat developmental ([redacted] 1983)	yes	OECD TG 414	no	Information missing	Acceptable
Cyproconazole/Chinchilla rabbit Developmental ([redacted] 1986)	no	OECD TG 414	yes	Study report not available	Acceptable

Risk driver/Study reference[a]	Availability of statistical analysis	Test Guideline[b]	Availability of HCD	chemical analysis of tested doses[c]	Acceptability of the study for the assessment of craniofacial alteration
Deltamethrin/Rabbit developmental ([redacted] 1977c)	no	OECD TG 414	yes	Information missing	Acceptable
Deltamethrin/Rabbit developmental ([redacted] 2001)	n.a.	OECD TG 414	n.a.	Yes	Acceptable
Folpet/Rabbit developmental ([redacted] 1984)	yes	EPA-FIFRA Requirements	no	Yes	Acceptable
Thiabendazole/ Rabbit developmental ([redacted] 1989)	yes	OECD TG 414	yes	Yes	Acceptable
Thiabendazole/ Rabbit developmental ([redacted] 1992)	n.a.	OECD TG 414	n.a.	Yes	Acceptable

(a): Reference as given in the source document (DAR/DRAR) from which the information was extracted.
(b): All the studies were performed according to OECD TG 414 version of 1981 except the study by [redacted] 2015c for mancozeb in CAG DAC.
(c): A 'Yes' means that a chemical analysis was performed and confirmed that the nominal concentration of the test compound was administered.

Note 7 (contribution of the 36 selected commodities to the overall diet of plant origin) – U7

The contribution of the 36 commodities selected for the assessment (see Annexes A1 and A2, Tables A.02) to the daily consumption of plant-based foods has been calculated for the 14 populations assessed, based on the respective consumption survey data and using the RPC model (EFSA, 2019e) to convert the amounts of food as consumed into the respective amounts of RPCs. Sugar plants were excluded from these calculations as residues in sugar are very unlikely due to the extensive processing that is applied to sugar plants.

The calculations reported in Table F.11 show that this contribution ranges, on average, from 75.2 (Finland) to 89.5% (Spain), with standard deviations ranging from 9.5 to 14.7%.

Table F.11: Contribution (in % of the total weight) of the selected 36 commodities to the overall diet of plant origin in the population groups considered in the assessment

Country	Survey	No. of consumption days	Mean contribution (%)	Standard deviation (%)
Belgium	DIET NATIONAL 2004	782	81.2	12.9
Czechia	SISP04	837	85.9	11.2
Germany	NATIONAL NUTRITION SURVEY II	6561	81.7	13.6
Denmark	DANSDA 2005-08	3969	82.7	9.5
Spain	AESAN FIAB	1138	89.5	12.0
Finland	FINDIET2012	710	75.2	13.3
France	INCA2	5603	82.7	13.0
Hungary	NATIONAL REPR SURV	981	78.1	12.0
Ireland	NANS 2012	1603	81.2	11.6
Italy	INRAN SCAI 2005-06	2049	88.2	10.8
Latvia	EFSA_TEST	779	80.4	14.7
Netherlands	VCP BASIS AVL2007-2010	1364	77.5	11.8
Romania	DIETA PILOT ADULTS	2924	77.2	13.8
Sweden	RIKSMATEN 2010	1840	80.3	11.9

In a German study, cumulative probabilistic exposure assessments demonstrated that ≥ 85% of the total chronic exposure is covered by a market basket including 16 RPCs, while a market basket of about 41 RPCs is required to reach a similar coverage of the total acute exposure (Sieke, 2020).

Note 8 (Contribution of animal commodities to the acute exposure to pesticide residues) – U7

Food from animal origin represents a major part of human diet. Its omission from the exposure calculations leads therefore to an underestimation of the risks.

However, the contribution of animal commodities to the dietary exposure to pesticide residues is expected to be much lower than the contribution of plant commodities because the occurrence of pesticide residues in animal commodities is less frequent and at lower levels than in plant commodities.

The EFSA annual European Union reports on pesticide residues in food contain detailed information on pesticide residues in animal products in dedicated sections (EFSA, 2019a, 2020c, 2021b). Information concerning the active substances included in CAG-DAC and CAG-DAH has been compiled in Table F.12.

Table F.12: Occurrence of residues of active substances included in CAG-DAC and CAG-DAH above the LOQ in animal commodities

Year	2017	2018	2019*
Number of samples	Animal fat: 2868 Eggs: 1085 Honey: 659 Kidney: 470 Liver: 378 Milk: 1625 Muscle: 2384	Animal fat: 3626 Eggs: 1665 Honey: 762 Kidney: 1534 Liver: 160 Milk: 1923 Muscle: 484	Animal fat: 5018 Eggs: 1331 Honey: 1301 Kidney: 1420 Liver: 888 Milk: 3525 Muscle: 746
	Number of occurrences above the LOQ		
2,4-D	–	1 (milk)	n.a.
Acetamiprid	35 (honey)	24 (honey)	49 (honey)
Chlorpyrifos	1 (honey)	1 (milk); 1 (kidney); 1 (muscle); 19 (other)	1 (honey); 14 (kidney)
Cyproconazole	–	1 (honey)	n.a.
Deltamethrin	2 (animal fat)	1 (milk)	n.a.
Dieldrin	1 (muscle); 3 (animal fat); 3 (milk); 1 (eggs); 1 (other)	2 (eggs); 1 (animal fat); 2 (other)	2 (eggs); 10 (animal fat); 1 (milk); 1 (muscle); 6 (liver)
Prosulfocarb	–	1 (honey)	n.a.
Tebuconazole	–	1 (honey)	n.a.
Thiacloprid	106 (honey)	106 (honey)	173 (honey)

*: In the 2021 EFSA annual report (corresponding to the 2019 monitoring exercise), information on the number of samples above the LOQ is available only for pesticides with quantifiable residues in at least 10 samples of animal commodities.

In its annual reports, EFSA performed acute risk assessment only for pesticide/commodity combinations included in the respective EUCP, i.e. for chlorpyrifos, deltamethrin and dieldrin in poultry fat and sheep fat in 2017, bovine fat and chicken eggs in 2018, and cattle milk and swine fat in 2019. Short term intakes equal or exceeding 1% of the ARfD were found for dieldrin in one sample of bovine fat in 2018 (1% of the ARfD) and in one sample of swine fat in 2019 (9% of the ARfD). The ARfD of dieldrin used for these calculations was 0.003 mg/kg bw, as established by the EFSA PPR panel in 2007.[23]

Note 9 (Contribution of the 36 selected commodities to the long-term exposure to pesticide residues) – U7

The long-term calculations reported under this note have an indicative value only in the context of the acute CRA of craniofacial alterations.

Based on the occurrence data collected in 2017, 2018 and 2019 under the EUCP and official national programmes according to the objective, selective and suspect sampling strategies (i.e. sample

[23] Available online: https://www.efsa.europa.eu/en/efsajournal/pub/554

strategies ST10A, ST20A and ST30A as defined by EFSA (2013), long-term dietary exposures to substances in CAG-DAC and CAG-DAH were calculated deterministically with the PRIMo model version 3.1 (EFSA, 2019g) using either the full diet or solely the 36 commodities of plant origin selected to perform the present CRA.

These calculations were performed following the lower bound approach described in the 2019 European Union report on pesticide residues in food (EFSA, 2021b). In this approach, measurements reported to be below the LOQ were in all cases considered as true zeros. These calculations, which rely on quantified residues only, and therefore are not biased by the contribution of hypothesised residues under the LOQ, are the most appropriate to provide an insight into the contribution of the 36 commodities considered in the present assessment to the total intake of residues. No processing factor was used in these calculations.

The calculations were conducted for all populations included in the PRIMo model, and the results for the population with the highest intake can be found in Table F.13, in the columns under the heading *'Critical long-term exposure (lower bound calculations)'*. The contribution of the 36 selected commodities varied widely between substances from 3% (flutriafol) to 100% (cymoxanil, fenpropimorph, fenpyrazamine, folpet, paclobutrazole, propargite and spiroxamine), with a median value of 80%. In the interpretation of the results, it must be kept in mind that there might be important variations from one population to the other, due to differences in the consumption pattern of some commodities.

The column *'Remark'* of Table F.13 lists all the unselected commodities that were found to contribute at least 0.01% of the ADI in at least one population of the PRIMo model. This provides some insight into which unselected commodity could be the source of isolated cases of acute exposure.

Table F.13: Contribution of the 36 selected commodities of plant origin to the total long-term exposure to residues of substances included in CAG-DAC and CAG-DAH

Active substance	CAG-DAC	CAG-DAH	Critical long-term exposure (lower bound calculations)				Remarks
			Selected commodities (% ADI)	All commodities (% ADI)	Contribution of selected commodities (%)	Population	
2,4-D	Yes	Yes	0.23	1.74	13	NL toddler	ADI = 0.02 mg/kg bw per day (EFSA conclusions, 2016) Non-selected commodities: Total contribution to long term exposure (all populations): 0.08–1.50% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): lemon 0.01%, cocoa (fermented beans) 0.01% and milk 1.49%
Abamectin	Yes	No	0.063	0.076	83	NL toddler	ADI = 0.0012 mg/kg bw per day (EFSA conclusions, 2020) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01 to 0.02% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): blackberries 0.01%, currants (red, black and white) 0.01%, basil 0.01% and tarragon 0.01%
Acephate	No	Yes	0.14	0.15	98	NL toddler	ADI = 0.0025 mg/kg bw per day (ECCO meeting 93, 2000) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01 to 0.05% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): passion fruit 0.01%, basil 0.04% and bay leaves (laurel) 0.02%
Acetamiprid	No	Yes	0.26	0.36	74	DE child	ADI = 0.025 mg/kg bw per day (EFSA conclusions, 2016) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01 to 0.09% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): cherries 0.03%, currants (red, black and white) 0.01%, kale 0.01%, escarole (broad-leaf endive) 0.01%, rocket (rucola) 0.01%, sage 0.02%, basil 0.01% and cumin seed 0.01%

Active substance	CAG-DAC	CAG-DAH	Critical long-term exposure (lower bound calculations)				Remarks
			Selected commodities (% ADI)	All commodities (% ADI)	Contribution of selected commodities (%)	Population	
Acrinathrin	No	Yes	0.088	0.088	99	NL toddler	ADI = 0.01 mg/kg bw per day (EFSA conclusions, 2013) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01% ADI
Azadirachtin	No	Yes		< 0.001	–	All	ADI = 0.1 mg/kg bw per day (EFSA conclusions, 2018) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01% ADI
Bitertanol	Yes	Yes	0.003	0.004	75	NL toddler	ADI = 0.003 mg/kg bw per day (EFSA conclusions, 2010) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01% ADI
Bromuconazole	Yes	Yes	0.0004	0.0046	9	IE adult	ADI = 0.01 mg/kg bw per day (EFSA conclusions, 2010) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01% ADI
Carbendazim	Yes	Yes	0.19	0.28	68	DE child	ADI = 0.02 mg/kg bw per day (EFSA conclusions, 2010) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01 to 0.09% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): apricots 0.01%, cherries 0.01%, currants (red, black and white) 0.01%, passion fruits 0.03%, bay leaves (laurel) 0.02%, cumin seeds 0.01%
Chlorpyrifos	Yes	Yes	7.8	8.4	92	NL toddler	ADI = 0.001 mg/kg bw per day (EFSA conclusions, 2014) Non-selected commodities: Total contribution to long term exposure (all populations): 0.02–0.63% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): lemons 0.37%, limes 0.01%, quinces 0.03%, currants (red, black and white) 0.04%, table olives 0.02%, mangoes 0.01%, papaya 0.01%, pomegranate 0.01%, cherimoya 0.01%, guava

Active substance	CAG-DAC	CAG-DAH	Critical long-term exposure (lower bound calculations)				Remarks
			Selected commodities (% ADI)	All commodities (% ADI)	Contribution of selected commodities (%)	Population	
							0.06%, pineapples 0.01%, sweet potatoes 0.01%, celeriac 0.02%, parsley roots 0.01%, turnip 0.01%, spring onion 0.01%, gherkins 0.01%, watermelons 0.04%, Brussels sprouts 0.01%, Chinese cabbage 0.03%, other lettuce and other salad plants 0.02%, beet leaves (chard) 0.09%, celery leaves 0.04%, parsley 0.02%, thyme 0.01%, basil 0.03%, bay leaves (laurel) 0.02%, other legume vegetables (fresh) 0.02%, celery 0.02%, fennel 0.01%, globe artichokes 0.03%, lentils 0.02%, peanuts 0.02%, rape seed 0.04%, buckwheat 0.01%, maize 0.19%, tea 0.06%, coffee beans 0.34%, Cocoa (fermented beans) 0.01%, coriander seed 0.01%, cumin seed 0.01%, ginger 0.01%, saffron 0.01%, poultry meat 0.01% and snails 0.01%
Cymoxanil	Yes	Yes	0.002	0.002	100	NL toddler	ADI = 0.013 mg/kg bw per day (EFSA conclusions, 2008) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01% ADI
Cyproconazole	Yes	Yes	0.004	0.005	80	NL toddler	ADI = 0.02 mg/kg bw per day (EFSA conclusions, 2010) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01% ADI
Deltamethrin	Yes	Yes	0.41	1.00	41	NL toddler	ADI = 0.01 mg/kg bw per day (EC review report, 2002) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01 to 0.59% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): apricots 0.01%, cherries 0.01%, peas (dry) 0.01%, lentils 0.01%, sunflower seeds 0.02%, maize 0.57% (To be noted that the contribution of maize in the case of the NL toddler population is much larger than in all other national population groups of the PRIMo model: the second highest contribution of maize concerns UK children and reaches 0.08% ADI only)

Active substance	CAG-DAC	CAG-DAH	Critical long-term exposure (lower bound calculations)				Remarks
			Selected commodities (% ADI)	All commodities (% ADI)	Contribution of selected commodities (%)	Population	
Dieldrin	Yes	No	0.53	0.52	99	DK child	ADI = 0.0001 mg/kg bw per day (JMPR, 1994) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01 to 0.11% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): gherkins 0.08%, pumpkins 0.09%, kale 0.01%, swine fat 0.05% and bovine fat 0.03%
Emamectin	Yes	Yes	0.11	0.11	97	NL toddler	ADI = 0.0005 mg/kg bw per day (EFSA conclusions, 2012) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01 to 0.03% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): chives 0.01% and basil 0.03%
Epoxiconazole	Yes	Yes	0.010	0.070	14	NL child	ADI = 0.008 mg/kg bw per day (EFSA conclusions, 2008) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01 to 0.06% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): sugar beet roots 0.06%
Ethylene oxide	Yes	Yes	Not available				–
Fenpropidin	No	Yes	0.003	0.007	43	NL toddler	ADI = 0.02 mg/kg bw per day (EFSA conclusions, 2008) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01% ADI
Fenpropimorph	Yes	No	0.20	0.20	100	NL toddler	ADI = 0.003 mg/kg bw per day (EFSA conclusions, 2008) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01% ADI

Active substance	CAG-DAC	CAG-DAH	Critical long-term exposure (lower bound calculations)				Remarks
			Selected commodities (% ADI)	All commodities (% ADI)	Contribution of selected commodities (%)	Population	
Fenpyrazamine	Yes	No	0.016	0.016	100	PT general	ADI = 0.13 mg/kg bw per day (EFSA conclusions, 2012) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01% ADI
Fluazifop-P	Yes	Yes	0.053	0.074	72	NL toddler	ADI = 0.01 mg/kg bw per day (EFSA conclusions, 2010) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01 to 0.02% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): turnip 0.01% and rapeseed 0.02%
Flusilazole	Yes	Yes	0.002	0.023	9	NL toddler	ADI = 0.002 mg/kg bw per day (EC review report, 2007) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01 to 0.02% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): elderberries 0.02% and Chinese cabbage 0.01%
Flutriafol	Yes	Yes	0.002	0.072	3	FI adult	ADI = 0.01 mg/kg bw per day (EFSA conclusions, 2010) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01 to 0.07% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): coffee beans 0.07% (To be noted that the contribution of coffee beans in the case of the FI adult population is much larger than in all other national population groups of the PRIMo model: the second highest contribution of coffee beans concerns DE general population and reaches 0.006% ADI only)
Folpet	Yes	Yes	0.37	0.37	100	PT general	ADI = 0.1 mg/kg bw per day (EFSA conclusions, 2009) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01% ADI

Active substance	CAG-DAC	CAG-DAH	Critical long-term exposure (lower bound calculations)				Remarks
			Selected commodities (% ADI)	All commodities (% ADI)	Contribution of selected commodities (%)	Population	
Haloxyfop-P	Yes	yes	0.69	0.70	99	UK toddler	ADI = 0.00065 mg/kg bw per day (EFSA conclusions, 2009) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01 to 0.29% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): sweet potatoes 0.10%, beetroot 0.01%, peas (dry) 0.03%, linseed 0.13%, sunflower seed 0.02%, buckwheat 0.02%
Mancozeb	Yes	Yes	1.1	8.1	12	IT adult	ADI = 0.023 mg/kg bw per day (EFSA conclusions, 2020) Non-selected commodities: Total contribution to long term exposure (all populations): 0.03 to 8.06% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): lemons 0.04%, apricots 0.22%, cherries 0.04%, plums 0.01%, currants (red, black and white) 0.31%, figs 0.42%, passion fruits 0.06%, mangoes 0.01%, papaya 0.01%, pineapples 0.01%, radishes 0.05%, swedes 0.05%, turnip 0.66%, garlic 0.01%, shallots 0.04%, spring onions 0.02%, watermelons 0.01%, Brussels sprouts 0.13%, Chinese cabbage 0.06%, kale 0.13%, escarole (broad-leaf endive) 0.08%, rocket (rucola) 0.04%, other spinach and similar 7.84% (To be noted that the contribution of 'other spinach and similar' - with mean residue of 16 mg/kg in the case of the IT adult population is much larger than in all other national population groups of the PRIMo model), vine leaves (grape leaves) 0.03%, water cress 0.13%, celery leaves 0.03%, parsley 0.06%, basil 0.12%, peas (with pods) 0.02%, celery 0.03%, globe artichokes 0.02%, peas (dry) 0.01% and sugar beet (root) 0.33%

Active substance	CAG-DAC	CAG-DAH	Critical long-term exposure (lower bound calculations)				Remarks
			Selected commodities (% ADI)	All commodities (% ADI)	Contribution of selected commodities (%)	Population	
Maneb	No	Yes	0.50	4.06	12	IT adult	ADI = 0.05 mg/kg bw per day (EC review report, 2005) Non-selected commodities: Total contribution to long term exposure (all populations): 0.03–3.56% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): lemons 0.02%, apricots 0.10%, cherries 0.02%, currants (red, black and white) 0.14%, figs 0.19%, passion fruits 0.03%, papaya 0.01%, radishes 0.02%, swedes 0.02%, turnip 0.29%, garlic 0.01%, shallots 0.02%, spring onions 0.01%, Brussels sprouts 0.06%, Chinese cabbage 0.03%, kale 0.06%, escarole (broad-leaf endive) 0.04%, rocket (rucola) 0.02%, other spinach and similar 3.46% (To be noted that the contribution of 'other spinach and similar' - with mean residue of 16 mg/kg in the case of the IT adult population is much larger than in all other national population groups of the PRIMo model), vine leaves (grape leaves) 0.01%, water cress 0.06%, celery leaves 0.02%, parsley 0.03%, basil 0.06%, peas (with pods) 0.01%, celery 0.01%, globe artichokes 0.01% and sugar beet (root) 0.15%
Metconazole	Yes	Yes	0.003	0.011	27	NL toddler	ADI = 0.01 mg/kg bw per day (EFSA conclusions, 2006) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01 to 0.01% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): rapeseed 0.01%
Myclobutanil	Yes	Yes	0.30	0.31	95	NL toddler	ADI = 0.025 mg/kg bw per day (EFSA conclusions, 2010) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01 to 0.02% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): currants (red, black and white) 0.01% and gooseberries 0.01%

Active substance	CAG-DAC	CAG-DAH	Critical long-term exposure (lower bound calculations)				Remarks
			Selected commodities (% ADI)	All commodities (% ADI)	Contribution of selected commodities (%)	Population	
Paclobutrazole	Yes	No	0.002	0.002	100	NL toddler	ADI = 0.022 mg/kg bw per day (EFSA conclusions, 2010) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01% ADI
Penconazole	No	Yes	0.023	0.025	92	DE child	ADI = 0.03 mg/kg bw per day (EFSA conclusions, 2008) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01% ADI
Propargite	Yes	No	0.008	0.008	100	NL toddler	ADI = 0.03 mg/kg bw per day (EFSA reasoned opinion 2018) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01% ADI
Propiconazole	Yes	No	0.78	0.83	94	DE child	ADI = 0.04 mg/kg bw per day (EFSA conclusions, 2017) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01 to 0.07% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): lemon 0.07%
Propineb	No	Yes	1.1	9.1	12	IT adult	ADI = 0.025 mg/kg bw per day (EFSA conclusions, 2016) Non-selected commodities: Total contribution to long term exposure (all populations): 0.03–7.94% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): lemons 0.04%, apricots 0.22%, cherries 0.04%, plums 0.01%, currants (red, black and white) 0.31%, figs 0.42%, passion fruits 0.06%, mangoes 0.01%, papaya 0.01%, pineapples 0.01%, radishes 0.05%, swedes 0.05%, turnip 0.65%, garlic 0.01%, shallots 0.04%, spring onions 0.02%, watermelons 0.01%, Brussels sprouts 0.13%, Chinese cabbage 0.06%, kale 0.13%, escarole (broad-leaf endive) 0.08%, rocket (rucola) 0.04%, other spinach and similar 7.72% (To be noted that the contribution of 'other

Active substance	CAG-DAC	CAG-DAH	Critical long-term exposure (lower bound calculations)				Remarks
			Selected commodities (% ADI)	All commodities (% ADI)	Contribution of selected commodities (%)	Population	
							spinach and similar' - with mean residue of 16 mg/kg in the case of the IT adult population is much larger than in all other national population groups of the PRIMo model), vine leaves (grape leaves) 0.03%, water cress 0.13%, celery leaves 0.03%, parsley 0.06%, basil 0.12%, peas (with pods) 0.02%, celery 0.03%, globe artichokes 0.02%, peas (dry) 0.01% and sugar beet roots 0.33%
Prosulfocarb	Yes	Yes	0.060	0.086	70	NL toddler	ADI = 0.005 mg/kg bw per day (EFSA conclusions, 2007) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01 to 0.04% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): celeriac 0.02%, parsnip 0.01%, celery 0.01% and sugar beet roots 0.03%
Prothioconazole	Yes	Yes	Not available				–
Prothioconazole-desthio	Yes	Yes	0.001	0.008	13	IE adult	ADI = 0.01 mg/kg bw per day (EFSA conclusions, 2007) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01% ADI
Spirotetramate	Yes	Yes	0.083	0.109	76	DE child	ADI = 0.05 mg/kg bw per day (EFSA conclusions, 2013) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01 to 0.03% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): kale 0.02% and sage 0.01%
Spiroxamine	Yes	Yes	0.021	0.021	100	PT general	ADI = 0.025 mg/kg bw per day (EFSA conclusions, 2010) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01% ADI
Tebuconazole	Yes	Yes	0.21	0.26	80	NL toddler	ADI = 0.03 mg/kg bw per day (EFSA conclusions, 2014) Non-selected commodities:

Active substance	CAG-DAC	CAG-DAH	Critical long-term exposure (lower bound calculations)				Remarks
			Selected commodities (% ADI)	All commodities (% ADI)	Contribution of selected commodities (%)	Population	
							Total contribution to long term exposure (all populations): < 0.01 to 0.09% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): apricots 0.01%, cherries 0.04%, plums 0.01%, currants (red, black and white) 0.02%, gooseberries 0.01%, passion fruit 0.01% and kale 0.01%
Tebufenpyrad	Yes	Yes	0.052	0.053	98	DE child	ADI = 0.01 mg/kg bw per day (EFSA conclusions, 2009) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01% ADI
Thiabendazole	Yes	Yes	1.3	1.3	98	DE child	ADI = 0.1 mg/kg bw per day (EFSA conclusions, 2014) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01 to 0.21% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): lemons 0.02%, limes 0.01%, mangoes 0.01% and sweet potatoes 0.19%
Thiacloprid	No	Yes	0.38	0.54	70	NL toddler	ADI = 0.01 mg/kg bw per day (EFSA conclusions, 2019) Non-selected commodities: Total contribution to long term exposure (all populations): < 0.01 to 0.16% ADI Commodities contributing ≥ 0.01% (all populations, highest observed contributions): quinces 0.01%, apricots 0.02%, cherries 0.02%, raspberries 0.01%, currants (red, black and white) 0.12%, kale 0.02%, rosemary 0.01%, basil 0.08% and tea 0.04%

Prothioconazole, ethylene oxide as well as the metabolites 1,2,4-triazole, 3,5,6-TCP, delta 8,9 isomer of avermectin B1a, ETU, prothioconazole-sulfonic acid, PTU and triazole alanine are not reported in this table because they are not monitored.

Note 10 (Ambiguity of consumption and occurrence data) – U8 and U18

Part B of annex I to Regulation (EC) No 396/2005 defines groups of commodities containing a main product (e.g. tomatoes) and other similar products to which the same MRL applies (e.g. ground cherries, cape gooseberries, cherry tomatoes, etc.). Each group has a code number.

The EFSA SSD (EFSA, 2014b) defines a matrix code ProdCode, derived from the group code number of the Regulation, and requires this code to be used for the sample description in the reporting of occurrence data. For the monitoring data from 2017 to 2019, a systematic mechanism to differentiate commodities within each group listed in part B of Annex I was not in place, and therefore, the occurrence data of all commodities of the group were merged and reported under the same code.

The EFSA comprehensive food consumption database contains similar ambiguities and is built on a similar level of aggregation of RPCs as for occurrence data. The consequence is that probabilistic modelling combines indiscriminately occurrence and consumption data for different commodities of a same group, although the residue profiles and consumption level may differ between these commodities.

The proportion of occurrence data that are assigned to a consumed commodity which is not the same as the commodity which has been analysed is expected to be low (less than 5%, based on rough estimation), but precise information about the exact cases and proportions is not available.

Note 11 (Methodological characteristics food consumption surveys, quality check of consumption data) – U9

Basic information (survey method, period, number of subjects, number of survey days per subject) on the 14 dietary surveys from which the population groups were extracted to perform the present CRAs is provided in Tables A.04 of Annexes B1 and B2. Additional information, as well as references and links to the original survey reports, are also available on the 'Survey details' sheet of the Comprehensive Database.[24]

Additional methodological features (e.g. days between non-consecutive days, interview administration, portion size estimation, dietary software and related databases, additional food information (brand, household processing, packaging), evaluation of under-reporting) characterising 8 of these surveys (Belgium (Diet National 2004), Czech Republic (SISP04), France (INCA2), Germany (German National Nutrition Survey II), Hungary (NATIONAL REPR SURV), Italy (INRAN-SCAI 2005–06), Latvia (EFSA_TEST) and Spain (AESAN FIAB)) were described and critically discussed by EFSA (European Food Safety Authority) (2011) and Merten et al. (2011). This information is important to understand the level of robustness and accuracy of food consumption data.

In addition, food consumption data provided to EFSA are subject to a validation process upon reception. First, the food classification is compared to the food description reported by the data provider. Any inconsistency identified is reported to the data provider for confirmation or correction. Furthermore, the amounts of food reported are validated against several maximum limits, which are derived from the food consumption data already available to EFSA. These limits are defined for each food category per eating occasion and per day. If one of these limits is exceeded, the data provider is requested to provide a justification or to correct the amount reported if necessary.

Note 12 (Psychological factors influencing food consumption surveys) – U9

In its guidance on the EU Menu methodology, EFSA collected information on the magnitude, nature and determinants of misreporting (EFSA, 2014c), including both under- and over-reporting. This information suggests that over-reporting occurs much less often than under-reporting, and that the importance of under- and over-reporting varies between population subgroups and commodities (tendency to under-report foods with high content of fat or sugar). It was estimated that when a food consumption database is used to assess dietary exposure, the presence of under-reporting may lead to the under-estimation of mean dietary exposure in the population, and to the under-estimation of the percentage of consumers of some foods high in fat or in sugar. Under-reporting is however likely to have little effect on the assessment of high percentiles of dietary exposure per kilogram body weight.

When available, information about the proportion of under-reporters is available on the 'Survey details' sheet of the Comprehensive Database. For 8 of the surveys used in the present assessment (same surveys as those mentioned in second paragraph of Note 11), more details were reported by Merten et al. (2011) (method of identification of under-reporters, cut-off values and exclusion).

[24] Available online: https://www.efsa.europa.eu/en/microstrategy/food-consumption-survey

Note 13 (Representativeness of consumption data/Sampling bias) – U10

Biases can arise from a survey sample that is not representative of the whole population it is extracted from.

For 8 of the surveys used in the present assessment (same surveys as those mentioned in paragraph 2 of Note 11), information about the sampling strategy has been reported by EFSA (European Food Safety Authority) (2011) and Merten et al. (2011). The information of interest related to the representativeness of the consumption data includes the sampling design (sampling method, sampling frame), the response rate, the sample stratification variables (gender, age, geographical areas, day of the week and season, other parameters (education level, urban vs rural residence, ethnicity), the existence of excluded groups (e.g. institutionalised persons, pregnant or breastfeeding women), and the inclusion/exclusion of subjects with specific long-term dietary pattern (e.g. vegetarian, health related or slimming). Similar information for the other 6 populations under consideration in the present assessment can be found in the original survey reports referred to in the 'Survey details' sheet of the Comprehensive Database.

Another factor affecting the representativeness of consumption data is the temporal gap between the period of the survey and the reference period of the assessment (2017–2019). Depending on the survey, the consumption data used in this CRA were collected from 2003 to 2012. Possible changes in food consumption practices over time need therefore to be considered. In the Netherlands, the evolution in food consumption was reported by RIVM by comparing the results of surveys conducted from 2007 to 2010 and from 2010 to 2016.[25] Over this period of about 5 years, the consumption of cereal products and vegetables (increase of 3%) was rather stable, while a slight increase of the fruit consumption, including nuts and olives (increase of 9%) were noted. A decrease in the consumption of potatoes, milk products and meat products was also noted. These observations are supported by the observation of an overall positive trend in the prevalence of daily fruit and vegetable consumption between 2002 and 2010 by adolescents in 33 countries (Vereecken et al., 2015).

Note 14 (Statistics for pregnancies before the age of 18 years and after the age of 45 years) – U11

Eurostat, the statistical office of the European Union collects data on live births by mother's age and citizenship. Numbers of live births for mothers aged 45–49 and 15–19 clusters were extracted and calculated in percentage of the total number of live births for 2017, 2018 and 2019 (Table F.14). Additionally, for the 10–14 age cluster, data from 2019 were extracted showing that the percentage of pregnancies is minimal.

Table F.14: Percentage of live births in 2017, 2018 and 2019 for mothers aged 45–49, 15–19 and 10–14 years in EU

Country	% Mothers 45–49 years old			% Mothers 15–19 years old			% Mothers 10–14 years old
	2017	2018	2019	2017	2018	2019	2019
BE – Belgium	0.2	0.3	0.3	1.5	1.4	1.3	0.00
CZ – Czechia	0.2	0.2	0.3	2.3	2.1	2.0	0.02
DE – Germany	0.2	0.2	0.2	2.0	1.8	1.7	0.01
DK – Denmark	0.2	0.2	0.3	0.8	0.7	0.6	0.00
ES – Spain	0.7	0.8	0.8	2.0	1.9	1.9	0.02
FI – Finland	0.3	0.2	0.3	1.4	1.3	1.3	0.00
FR – France	0.3	0.3	0.3	2.1	2.0	2.0	0.03
HU – Hungary	0.2	0.2	0.2	5.8	5.6	5.4	0.06
IE – Ireland	0.5	0.5	0.6	1.7	1.6	1.4	0.01
IT – Italy	0.7	0.8	0.8	1.3	1.3	1.2	0.00
LV – Latvia	0.2	0.3	0.2	3.0	2.7	2.9	0.01
NL – Netherlands	0.2	0.2	0.2	0.8	0.8	0.7	0.00
RO – Romania	0.2	0.1	0.2	9.3	9.1	9.0	0.38
SE – Sweden	0.3	0.3	0.3	1.0	1.0	0.8	0.00

[25] https://www.wateetnederland.nl/resultaten/voedingsmiddelen/verandering

Note 15 (Diet during the vulnerability period of pregnancy to craniofacial alterations) – U12

Consumption surveys specially focused on pregnant women are not available to EFSA. Therefore, the exposure calculations used consumption data of women irrespective of the pregnancy status and collected from surveys in general adult populations. In addition, in some of these surveys, pregnant women were excluded. Therefore, the consumption data that were used may not be fully representative of the actual food consumption of pregnant women during the period of vulnerability to craniofacial alterations (see Section 3.1.1.2).

There is an uncertainty in dietary preferences changing during the pregnancy, either while pregnant women start to follow national dietary recommendations or as a consequence of individual hormonal imbalance during pregnancy. Women might change their dietary intake pattern after they learn they are pregnant, after they receive advice at the prenatal visits or because they suffer nausea or vomiting which might resolve after the 1st trimester of pregnancy or continue. Women who suffer nausea or vomiting following hormonal imbalance may avoid special food or reduce their food consumption in general. There is also an uncertainty in how many women are aware of their pregnancy during the vulnerability period and therefore prone to think about adapting their diet.

No systematic literature review from published studies has been done to collect and analyse all available information on changes in dietary preferences during pregnancy. The literature in this area in general seems to be limited to a handful of studies using a variety of dietary intake recording methods on a wide range of dietary variables to collect data from both prospective and retrospective studies. Age, educational status and economic status are variables, which additionally influence dietary habits and their potential adaptations.

Nevertheless, some indications could be retrieved from available literature and are summarised as follows:

- Most of the studies report increased consumption for fruits and fruit juices (Crozier et al., 2009a; Forbes et al., 2018; Hillier and Olander, 2017; Pinto et al., 2008, Rifas-Shiman et al., 2006; Saunders et al., 2019; Skreden et al., 2015; Verbeke and De Bourdeaudhuij, 2007), milk and dairy products (Chan-Hon-Tong et al., 2013, Crozier et al., 2009a; Forbes et al., 2018; Hillier and Olander, 2017; Pinto et al., 2008, Rifas-Shiman et al., 2006; Saunders et al., 2019; Skreden et al., 2015; Verbeke and De Bourdeaudhuij, 2007) and white bread and breakfast cereals (Chan-Hon-Tong et al., 2013, Crozier et al., 2009a; Forbes et al., 2018; Hillier and Olander, 2017; Pinto et al., 2008, Rifas-Shiman et al., 2006; Saunders et al., 2019; Skreden et al., 2015; Verbeke and De Bourdeaudhuij, 2007) during pregnancy in general. All these studies (except Chan-Hon-Tong et al., 2013, Forbes et al., 2018 and Pinto et al., 2008) also report increased consumption of cooked red meat and processed meat. These adaptations in diet are in line with national recommendations for increased consumption of fibres, calcium and iron during pregnancy.
- Only few studies addressed changes in diet from pre-pregnancy over early pregnancy to late pregnancy. In the early pregnancy, increase in consumption of fruits and fruit juices, especially from citrus fruits (Crozier et al., 2009a, Skreden et al., 2015), milk (Skreden et al., 2015), white bread, cereals, processed meat (Crozier et al., 2009a) is reported, while no change in consumption of dairy products and red meat was recorded in this period (Crozier et al., 2009a).
- Pregnant women tend to almost abandon from their diet raw meat, organ meat (kidney, liver), raw fish, raw milk cheese and raw vegetables (Verbeke and De Bourdeaudhuij, 2007; Forbes et al., 2018) and to reduce rice, pasta and potatoes (Pinto et al., 2008; Crozier et al., 2009b) as well as eggs (Pinto et al., 2008; Hillier and Olander, 2017).
- While some studies report an increase in consumption of vegetables (Hillier and Olander, 2017; Saunders et al., 2019) the others report either a decrease (Verbeke and De Bourdeaudhuij, 2007; Crozier et al., 2009a) or no change (Pinto et al., 2008; Crozier et al., 2009b; Chan-Hon-Tong et al., 2013) or both increase and decrease in the same survey (Forbes et al., 2018). These diverging records are probably due to ambiguous information on whether vegetables were cooked or were consumed raw.
- As for vegetables, studies report either an increased (Saunders et al., 2019) or unchanged (Verbeke and De Bourdeaudhuij, 2007; Pinto et al., 2008; Chan-Hon-Tong et al., 2013) consumption of (cooked) fish. The differences in perception of fish in a diet during pregnancy might have a traditional food aspect and might also derive from the fact that maternal fish

intake in pregnancy has been associated with positive fetal neurodevelopmental outcome but at the same time with consumption of mercury which can have negative impact on fetal development.

Note 16 (Alcohol consumption during the vulnerability periods of pregnancy to craniofacial alterations) – U13

The vulnerability period to craniofacial alterations is described in Section 3.1.1.2.

Recommendations from public authorities are to drastically limit or avoid the alcohol consumption during pregnancy because of its relationship with the risk of abortion and severe health issues such as the alcohol spectrum disorders, including birth defects that involve central nervous system impairment, behavioural disorders, and impaired intellectual development (See also Section 4.3.3).

Many studies have been published regarding changes in the alcohol consumption pattern during pregnancy. No systematic literature review has been performed on the subject for reason of resources. Instead, a sample of scientific publications were identified from which the following indications were derived:

Almost 16% of women resident in Europe consumed alcohol during pregnancy (Mårdby et al., 2017), with large cross-country variations (United Kingdom: 29%, Italy: 18%, Finland: 14%, France: 11.5%, Poland: 10%, Sweden: 7%).

There is a strong reduction in the weekly consumption of alcoholic beverages during pregnancy. In a Southampton Women's Survey, there was a significant reduction in alcohol consumption: before pregnancy 54% of women drank more than four units of alcohol (one unit equals 10 ml or 8 g of pure alcohol) per week, whereas during first 11 weeks of pregnancy they were 10% only (Crozier et al., 2009b). In Copenhagen, 70% of women reported weekly alcohol consumption before pregnancy, but this prevalence decreased to 3% during early pregnancy (in average during the first 10 gestational weeks) (Iversen et al., 2015). In Ireland, alcohol consumption was markedly reduced from 81% before pregnancy to 12% during the first trimester of pregnancy, with the majority of drinkers (92%) consuming 5 units per week or less (Murphy et al., 2014). In Porto, the percentage of women who reported ever drinking alcoholic beverages fell from 36.3% prior to pregnancy to only 13.3% during it, with the median intake among drinkers declining from 3.7 g to 0.9 g between the two time periods (Pinto et al., 2008).

Episodes of binge drinking are however frequent during pregnancy. This was in particular investigated in Denmark. During years 1996–2002, approximately one quarter of the women reported binge drinking at least once during pregnancy, most of these in the pre-recognised part of pregnancy (Strandberg-Larsen et al., 2008). It was found that binge drinking is occurring mainly during the first 5 weeks of pregnancy (gestational age calculated from the last menstrual period) and becomes rare events from week 7 (Kesmodel, 2001). In Copenhagen, in 2012–2013, despite low weekly consumption, the overall proportion of women reporting binge drinking during early pregnancy was 35% (Iversen et al., 2015).

The change in the alcohol consumption seems to occur after several weeks of pregnancy. In a study covering 8 metropolitan areas in United States, about 50% of the participants reported using alcohol during early pregnancy. The median gestational age at the change in alcohol use was 29 days (interquartile range, 15–35 days) (Denny et al., 2019).

To quantify the potential impact of total abstinence of alcohol during pregnancy, a sensitivity analysis was performed (See sensitivity analyses G in Section 3.2.3).

Note 17 (Sampling uncertainty – Consumption and occurrence data) – U14 and U21

Even with a perfect sampling method, a sample is never perfectly representative of the population it is extracted from. In other words, statistical properties estimated from a sample (e.g. average, standard deviation, percentiles) are not the true statistical properties of the population that was sampled. This is referred to as *sampling uncertainty*. The size of the sample has a crucial importance in this respect.

With respect to consumption data, the number of subjects in the 14 populations used to perform CRA ranges from 327 (Hungary) to 3,285 (Germany). The Guidance on the use of the comprehensive food consumption database contains a section on the reliability of high percentiles in food consumption. The minimum number of subjects in a population needed to achieve a 95% confidence interval (significance level (α) at 0.05) increases with the percentile to be computed. This is achieved for $n \geq 59$ and $n \geq 298$ for the 95th or 99th percentiles, respectively (EFSA, 2011). The number of subjects needed to achieve similar statistical robustness at the 99.9th percentile is approximately 3000.

Beside the number of subjects in the populations, there are 2 additional elements to be considered:

- The number of days/replicates within each survey, which varies between 2 and 7. In the context of acute exposure assessments, the size of the consumption data set corresponds to the number of individuals/days, rather than to the number of consumers.
- Within the consumption data set, the number of individuals/days with effective consumption of a certain RPC may be much lower than the total number of individuals/days. For commodities which are rarely consumed, the amount of data with effective consumption may be very low and create a rather large uncertainty.

With respect to occurrence data, the number of data (measurements) for each pesticide/commodity combination in the scope of the present CRAs varies widely, from zero (see Note 24) to several thousands. The precise number of measurements available for each combination can be found in Tables A.09 of Annexes B1 and B2. Table F.15 gives an overview of these numbers.[26]

Table F.15: Number of measurements available for pesticide/commodity combinations under the scope of the present assessment

Number of measurements	Number of pesticide/commodity combinations (CAG-DAC)	Number of pesticide/commodity combinations (CAG-DAH)
Less than 100	25 – Mainly pesticide/commodity combinations involving olives for oil production	33 – Mainly pesticide/commodity combinations involving olives for oil production
At least 100 and less than 300	72 – Many pesticide/commodity combinations involving olives for oil production or fluazifop-P and fluazifop-P-butyl – Includes mancozeb/ head cabbages	79 – Many pesticide/commodity combinations involving olives for oil production or acrinathrin, azadirachtin, fluazifop-P and fluazifop-P-butyl
At least 300 and less than 1000	327 – Includes folpet/red and white wine	355 – Includes folpet/red and white wine, 2,4-D/mandarins
At least 1000 and less than 3000	558 – Includes 2,4-D/oranges, mancozeb/ lettuce, mancozeb/oranges	532 – Includes 2,4-D/oranges
More than 3000	305 – Includes chlorpyrifos/potatoes, thiabendazole/oranges, tebuconazole/ peaches, tebuconazole/apples, folpet/apples	288 – Includes chlorpyrifos/tomatoes, chlorpyrifos/potatoes, deltamethrin/wheat, thiabendazole/mandarins and thiabendazole/ oranges

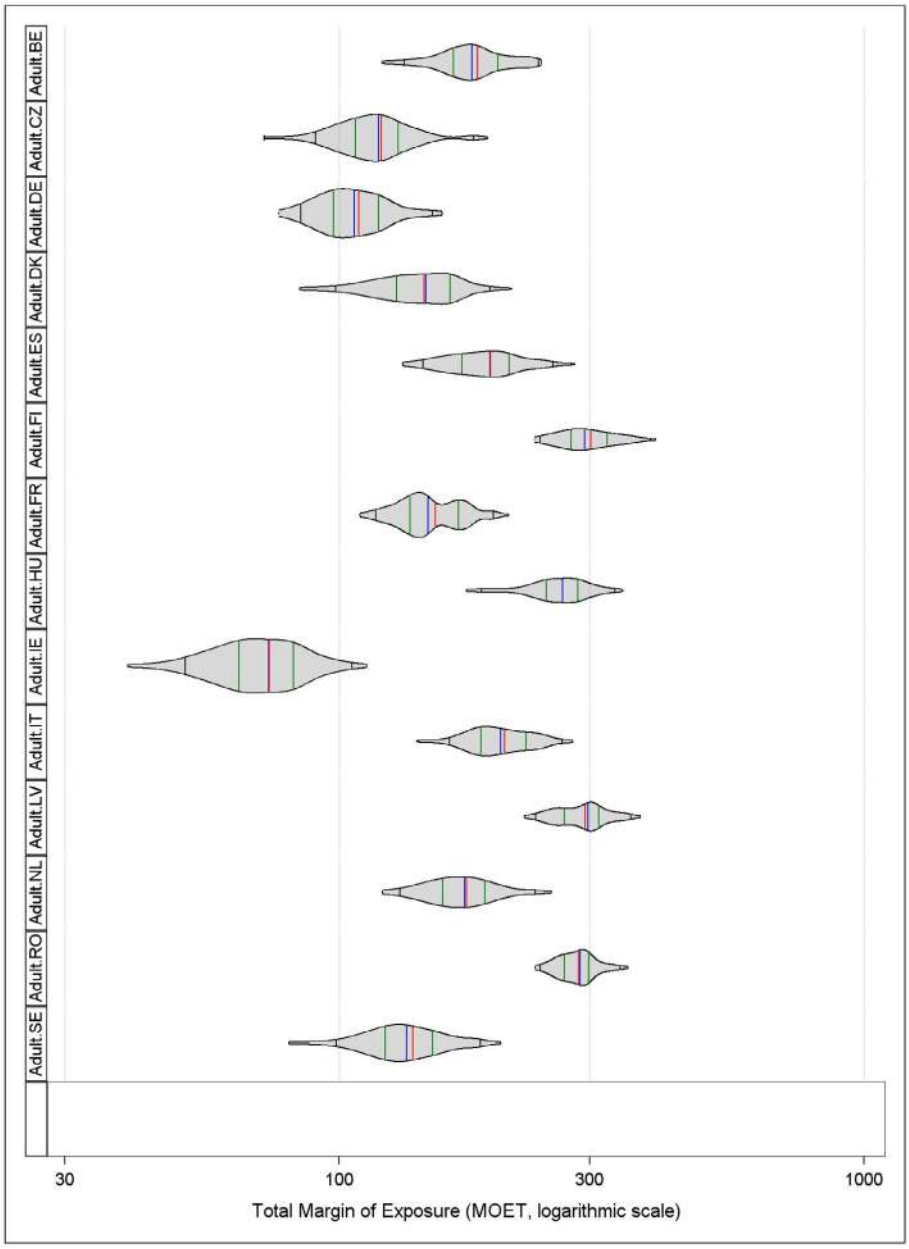
The first component of sampling uncertainty is *sampling variability*, i.e. how much the estimated parameters vary between samples. The overall sampling variability, associated with consumption and occurrence data, was quantified by outer-loop execution and the resulting confidence intervals are reported in Section 3.2.2. It is acknowledged, however, that bootstrapping performs less well for small data sets (EFSA Scientific Committee, 2018b), especially when the focus is on the tail of the variability distribution as is the case here (99.9th percentile). It is therefore important to check the density distributions of MOET confidence intervals at the 99.9th percentile of the exposure distribution, as shown by the violin plots in Figures F.2 and F.3.

Sampling variability is negatively correlated to the sample size, meaning that the sampling variability (and the associated confidence interval) will be large when the sample size is small. This is well reflected in the current assessment of CAG-DAH where the confidence intervals for the German survey (3,285 subjects) are small compared to the Finnish survey (356 subjects). Considering that the same occurrence data set is used for all population groups and that risk drivers are comparable, this seems to suggest that, for the current assessment of CAG-DAH, the overall sampling variability is primarily driven by the sampling variability of the consumption data.

Furthermore, when the confidence interval is very wide and the density distribution within that interval is bimodal or multimodal, this may indicate a strong impact of some individual consumption (or occurrence) data points. However, bimodality of the confidence intervals should be considered carefully, as it may also derive from the size of the data set. Small data sets tend to be more unstable,

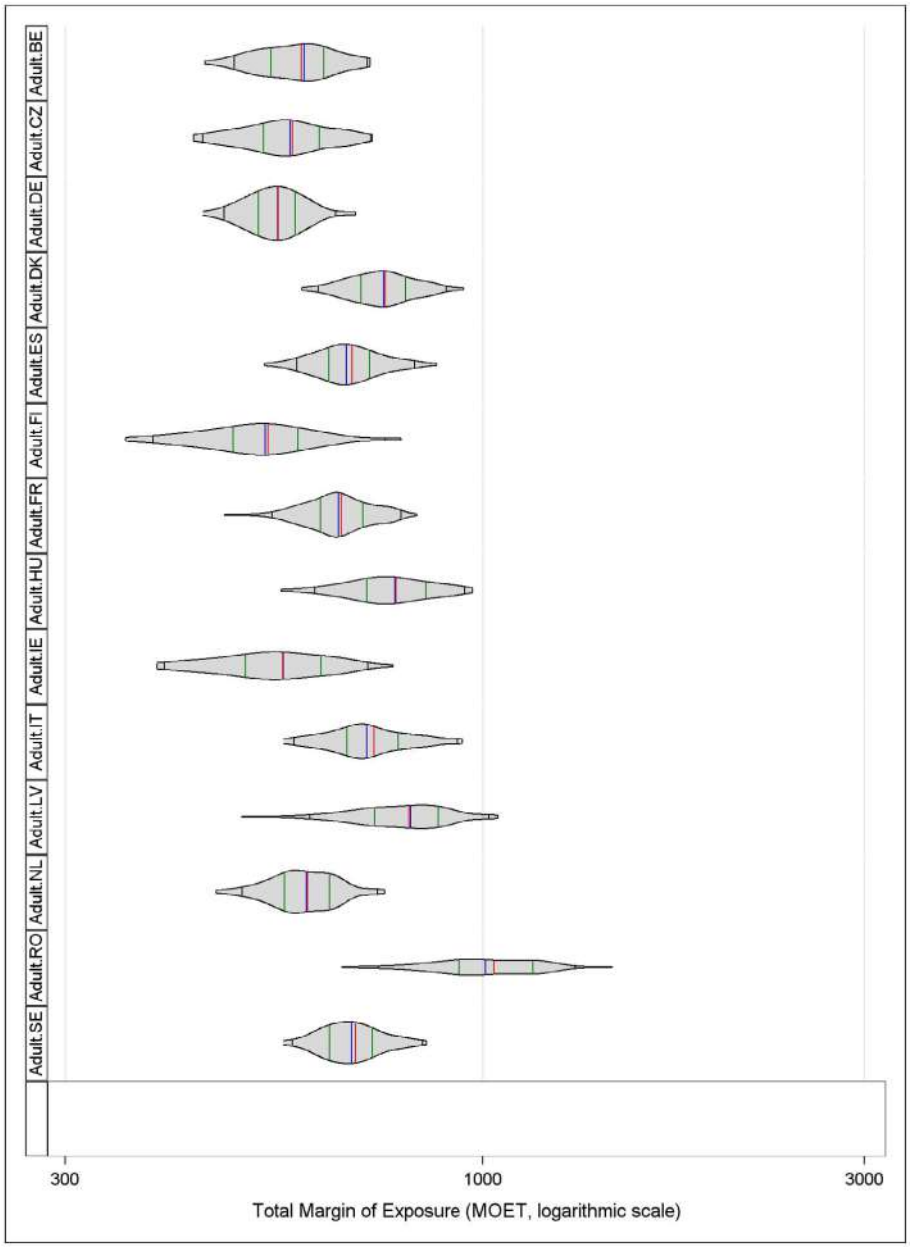
[26] Available online: Food intended for infants and young children are excluded from this table as a legal limit of 0.01 mg/kg applies for pesticide residues in these commodities (Commission Directives 2006/125/EC and 2006/141/EC). Pesticide/ commodity combinations for which no measurements are available are also excluded from the table. For specific information about these combinations, see Note 24.

even when there are no extreme values. Therefore, special consideration should only be given when the distribution is stretched, and bimodality is clearly marked. As this is not the case for any of the dietary surveys, it can be concluded that, in the current assessment, the sampling variability was well captured by the bootstrapping method. Furthermore, sensitivity analyses H (see Section 3.2.3) showed that extreme consumers of particular commodities in some populations had no significant impact on the MOET estimates at the 99.9th percentile of exposure.



Legend: The width of violin is proportional to density of observation for each value of the MOET at the 99.9th percentile of the exposure distribution. The 95% confidence interval is delimited by the black vertical lines, whereas the quartiles are highlighted in green. Mean and median values are indicated by a red and a blue line, respectively. The confidence intervals are plotted on a logarithmic axis.

Figure F.2: Violin plots for the confidence intervals of the MOET at the 99.9th percentile of the exposure distributions for the Tier II scenario of CAG-DAC in women of childbearing age, presented by country



Legend: The width of violin is proportional to density of observation for each value of the MOET at the 99.9th percentile of the exposure distribution. The 95% confidence interval is delimited by the black vertical lines, whereas the quartiles are highlighted in green. Mean and median values are indicated by a red and a blue line, respectively. The confidence intervals are plotted on a logarithmic axis.

Figure F.3: Violin plots for the confidence intervals of the MOET at the 99.9th percentile of the exposure distributions for the Tier II scenario of CAG-DAH in women of childbearing age, presented by country

In addition to the sampling variability, sampling uncertainty can be (partially) driven by a *sampling bias*, i.e. the bias that occurs when some members of the intended population have a lower or higher probability of being sampled. It is known that for skewed distributions (like the populations of consumers and occurrence data) there is a high probability that values from the upper tail of the distribution will not be sampled, which will lead to an underestimation of the highest percentiles. To illustrate the problem, a simulation starting from a skewed parametric distribution (in this case a lognormal distribution with a true 99.9th percentile of 646.9, see Figure F.4) was performed. From this distribution 1000 values were sampled at random and the observed 99.9th percentile of the sample was computed. This process was repeated 1000 times and the 99.9th percentile for the 1000 samples

were plotted and compared to the true 99.9th percentile of this distribution (see Figure F.5). It turned out that by selecting 1000 values from the distribution, the observed 99.9th percentile will be underestimated in around 75% of the cases and this underestimation may be by a factor up to 2. Although this is only a theoretical simulation, it clearly shows that the 99.9th percentile of the exposure distribution, which is skewed, is likely to be underestimated.

Such a sampling bias cannot be captured by the bootstrapping method applied in the current assessment.

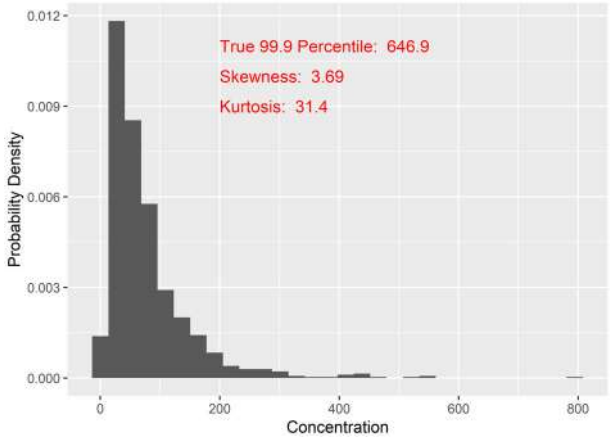


Figure F.4: Density plot for a skewed distribution (lognormal)

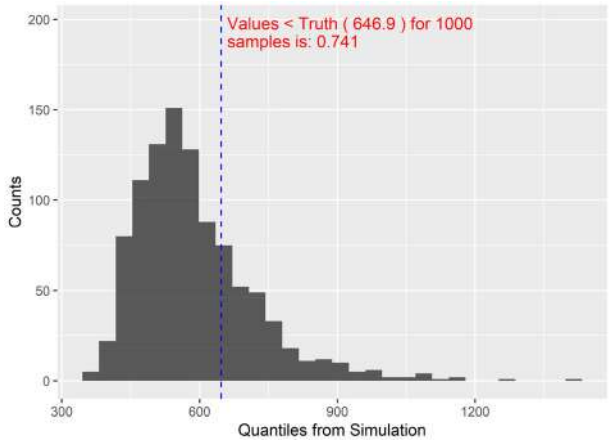


Figure F.5: Density plot of the observed 99.9th percentile of 1000 simulated samples (each with a sample size of 1000 values)

Note 18 (RPC model) – U15

In order to perform cumulative exposure assessments, the EFSA RPC model (EFSA, 2019e) was used to convert the consumption data for composite foods (i.e. foods consisting of multiple components, for example apple strudel) and RPC derivatives (i.e. single-component foods which have been physically changed by processing, for example apple juice) into the equivalent quantities of RPCs (i.e. single-component foods which are unprocessed or whose nature has not been changed by processing, for example apples).

The main sources of uncertainty of the RPC model result from the following:

- The RPC model still relies on the FoodEx coding system, which is less accurate than the more recent FoodEx2 coding system. Although the FoodEx classification system has been expanded to include intermediate codes, the specificity of the RPC model is still limited by the FoodEx classification system applied in the comprehensive European food consumption database at the time of the model's development. Food consumption data in the comprehensive database have since been updated to include dietary surveys coded with the revised FoodEx2 system (EFSA, 2015b). Meanwhile, RPC consumption data resulting from composite foods that could

not be assigned with a more accurate classification code may either be over- or underestimated.

- When a food code reported in the comprehensive database was not sufficiently detailed for disaggregation, more specific foods and food components were assigned using probabilities. This probabilistic assignment introduces an element of uncertainty. Although foods are selected based on the reported consumption records in the food consumption database, a food which is not representative of what was actually consumed may be selected. Some sensitivity tests demonstrated that results obtained through the RPC model may be very variable when low probabilities are considered. This instability was addressed by excluding foods and food components that had probabilities below 10%. This approach increased the reliability of the RPC model. However, the exclusion of certain foods also implies that consumption data for frequently consumed RPCs (e.g. apples) may be slightly overestimated. Likewise, RPCs that are not frequently consumed (e.g. cherries) are likely to be underestimated. In practice, in the present case, as only 36 major commodities are considered, the exclusion or rare food components results in possible overestimation of the actual consumption of these commodities.
- The RPC model does not consider inter-country variation, consumer habits, personal preferences, and product or recipe variation. Furthermore, differences between commercial products and household prepared foods are not accounted for. This may lead to either over- or underestimations of the RPC consumption.
- In the final step of the RPC conversion, amounts of RPC derivatives are converted to corresponding amounts of RPC, using reverse yield factors. There is currently no harmonised list of reverse yield factors available on either European or worldwide level and reverse yield factors sourced in the conversion table of the model may not be accurate. Furthermore, the RPC model uses one single factor for each processing technique. In reality, yields vary among households and industrial manufacturers. This uncertainty is not expected to have a major impact on average consumption/exposure, but it is expected to underestimate upper tail consumption/exposure.

Consumers with the highest consumption of RPC derivatives and composite foods are the most sensitive to this source of uncertainty.

Note 19 (Missing occurrence data) – U16

Some substances included in the CAGs were not considered in the cumulative exposure assessments because monitoring data were not available or were not used, causing an underestimation of the risk.

Occurrence data are missing for 1,2,4-triazoles (CAG-DAC and CAG-DAH), 3,5,6-TCP (CAG-DAC and CAG-DAH), ETU (CAG-DAC and CAG-DAH), prothioconazole-sulfonic acid (CAG-DAC and CAG-DAH), PTU (CAG-DAH only) and triazole alanine (CAG-DAC only), because these substances are not monitored by Member States. As these substances are metabolites, the impact of these missing data is however addressed under U17.

Occurrence data are missing for the active substance prothioconazole (CAG-DAC and CAG-DAH) because this substance is not included in the residue definition for monitoring. This is justified by the fact that it is extensively metabolised and has a lower toxicological potency than its metabolite prothioconazole-desthio (EFSA conclusion, 2007).

Ethylene oxide is included in CAG-DAC and CAG-DAH, but the NOAELs that were assigned for the 2 types of craniofacial alterations cannot be used for the reason explained in Section 3.1.4. Anyway, only very few monitoring data available for this compound. Residues are essentially found in sesame seeds or spices, but ethylene oxide being a rather unstable compound, 2-chloroethanol is the major component the consumer is exposed to (BfR, 2021). For this reason, the EU regulation defines the residues for monitoring as the sum of ethylene oxide and 2-chloro-ethanol expressed as ethylene oxide. With respect to developmental toxicity, no craniofacial alterations were reported in 2 studies in mice with 2-chloroethanol (U.S. EPA, 2012).

For all other substances included in the CAGs, monitoring data were available for all 36 selected RPCs, as well as in olive oil and red and white wine.

Note 20 (Contribution of metabolites to the risk) – U17

Developmental toxicity studies showed craniofacial alterations for 8 metabolites of the 85 active substances in the scope of this assessment: 1,2,4-triazole (metabolite of triazole fungicides), 3,5,6-TCP

(metabolite of chlorpyrifos, chlorpyrifos-methyl and triclopyr), delta 8,9 isomer of avermectin B1a (metabolite of abamectine), ETU (metabolite of ethylene-bis-dithiocarbamates (EBDCs) fungicides such as maneb, mancozeb, and metiram and zineb), prothioconazole-dethio and prothioconazole-sulfonic acid (metabolites of prothioconazole), PTU (metabolite of propineb) and triazole alanine (metabolite of triazole fungicides).

- Two of these metabolites (delta 8,9 isomer of avermectin B1a and prothioconazole-desthio) are included in the residue definition for enforcement and have therefore been covered by the exposure calculations. In these calculations, the contribution of the delta 8,9 isomer of avermectin B1a is however overestimated because the occurrence data are reported as the sum of the active substance and the metabolite and the RPI is calculated using the NOAEL of active substance (0.8 mg/kg bw per day), which is about 2 times lower than the NOAEL of the metabolite (1.5 mg/kg bw per day). In contrast, the contribution of the metabolite prothioconazole-desthio is accounted at the right magnitude as it is the only constituent of the residue definition.
- 1,2,4-triazole and triazole alanine are two of the four TDMs which are common to fungicides containing the 1,2,4-triazole moiety (triazole fungicides). They are known to be very frequently present in food commodities, as a result of the use of triazole fungicides on the crop or their uptake from the soil. They are not covered by the EUCPs and were not included in the exposure calculations. The EU Reference Laboratory for pesticides requiring Single Residue Methods (EURL-SRM) (hosted by the CVUA (Chemisches un Veterinäruntersuchungsamt) Stuttgard) reported in 2016 a survey conducted on more than 4600 conventional and organically labelled products from the local market which were analysed for TDM residues (Ströher Kolberg et al., 2016). A high percentage of the samples were found to contain residues exceeding the LOQ. Triazole alanine (included in CAG-DAC only) was the most frequently detected TDM at levels up to or exceeding 1 mg/kg in pome fruits, stone fruits, exotic fruits, leafy vegetables, fruiting vegetables, sprout vegetables, cereals and potatoes. Supposing a pregnant woman of 60 kg consuming an unprocessed commodity unit of 200 g from a lot containing 1 mg/kg of triazole alanine (NOAEL = 30 mg/kg bw) and a VF of 7, the margin of exposure would be around 1,300. 1,2,4-triazole (included in CAG-DAC and CAG-DAH) exceeded the LOQ only rarely, with the highest levels (0.035–0.064 mg/kg) in berries and leafy vegetables.
- ETU and PTU can be generated by the degradation of dithiocarbamates, and their toxicological potency differ from that of the parent compound. As can be seen in Tables A.09 of Annexes B1 and B2, dithiocarbamates are found in most commodities with relatively high frequency of quantifiable measurements (above 10% of the total number of samples in apples, lettuces, cucumbers, mandarins, leeks, table grapes, wine grapes, peaches, oranges, onions, grapefruits, pears, head cabbages, cauliflower and broccoli). The levels measured as CS2 are equal to or above 1 mg/kg at the 99th percentile of distribution of measurements in beans (with pods), pears, beans (dry), lettuces. In peas (without pods) and broccoli, the number of samples is too small to derive a reliable value at 99th percentile, but levels are above 1 mg/kg at 95th percentile. Considering the large presence of dithiocarbamates in food commodities, it was found appropriate to perform sensitivity analyses to quantify the impact of their degradation into ETU or PTU in food products derived from a process involving a heating step (sensitivity analyses J, see Section 3.2.3). Furthermore, sensitivity analyses K (see Section 3.2.3) were performed, assuming, additionally, that propineb and thiram were still approved during the reference period (actually, they were approved during a significant part of the reference period).
- Prothioconazole-sulfonic acid is not enforced. Its toxicity is however low (NOAEL at 150 mg/kg bw per day in in both CAGs).
- Resources to collect information about the possible occurrence of 3,5,6-TCP in commodities have been lacking during the present assessment.

In addition to the 8 metabolites mentioned above, other metabolites and degradation products for which developmental toxicity studies are not available may also contribute to the risk. Ideally, a residue definition tailored to the toxicological effect under consideration should be established for all the investigated active substances. In the present exercise, for reason of resources, residues definition for the assessment of the risk of craniofacial alterations were not established and the exposure

calculations were conducted with the occurrence data, as measured according to the residue definition for enforcement, without any correction to take account of the contribution of metabolites.

For information, the residue definition for risk assessment of all substances included in CAG-DAC and CAG-DAH, for their respective critical effects (which are not necessarily craniofacial alterations), have been collected from earlier EFSA outputs and compared to the respective residue definitions for enforcement in Table F.16. When available, conversion factors to recalculate the residue concentrations expressed following the residue definition for enforcement into their counterparts for risk assessment were also collected when available. This table shows that for about 30% of the active substances (acrinathrin, azadirachtin, chlorpyrifos (processed commodities only), deltamethrin, emamectin, fenpropimorph, fenpyrazamine, myclobutanil, penconazole, propiconazole, prothioconazole, spiroxamine and thiacloprid), the residue definition for risk assessment includes compounds, other than the 8 metabolites mentioned above, not included in the residue definition for enforcement, and therefore not included in the calculations. Three of these substances are risk drivers (chlorpyrifos, deltamethrin and thiabendazole). In the case of chlorpyrifos, the additional relevant metabolites are present in processed commodities only, but the applicable conversion factor is not available. For deltamethrin, a conversion factor of 1.25 was established. For thiabendazole, the additional relevant metabolites occur in case of pre-harvest treatment only, but conversion factors are not available.

Table F.16: Residue definition for enforcement and risk assessment (of the critical effect) in plant commodities of substances included in CAG-DAC and CAG-DAH

Substance	Residue definitions for enforcement during the reference period	Residue definitions for risk assessment	Conversion factor	References/Comments
1,2,4-triazole (CAG-DAC, CAG-DAH)	Not enforced	1,2,4-triazole	Not necessary	Peer review of the pesticide risk assessment for the triazole derivative metabolites in light of confirmatory data submitted (EFSA conclusions, 2018)
2,4-D (CAG-DAC (*risk driver*), CAG-DAH (*risk driver*))	Sum of 2,4-D, its salts, esters and conjugates, expressed as 2,4-D	Sum of 2,4-D, its salts, esters and conjugates, expressed as 2,4-D	Not necessary	Peer review of the pesticide risk assessment of the active substance 2,4-D (EFSA conclusions, 2014)
3,5,6-TCP (CAG-DAC, CAG-DAH)	Not enforced	sum of 3,5,6- TCP and its conjugates, expressed as 3,5,6-TCP	Not available	Article 12 reviews chlorpyrifos and chlorpyrifos-methyl (EFSA reasoned opinions, 2017)
Delta 8,9 isomer of avermectin B1a (CAG-DAC)	sum of avermectin B1a, delta 8,9 isomer of avermectin B1a, and avermectin B1b, expressed as avermectin B1a	sum of avermectin B1a, delta 8,9 isomer of avermectin B1a, and avermectin B1b, expressed as avermectin B1a	Not necessary	Peer review of the pesticide risk assessment of the active substance abamectin (EFSA conclusions, 2020)
Abamectin (CAG-DAC)	sum of avermectin B1a, delta 8,9 isomer of avermectin B1a, and avermectin B1b, expressed as avermectin B1a	sum of avermectin B1a, delta 8,9 isomer of avermectin B1a, and avermectin B1b, expressed as avermectin B1a	Not necessary	Peer review of the pesticide risk assessment of the active substance abamectin (EFSA conclusions, 2020)
Acephate (CAG-DAH)	Acephate	1) Acephate 2) Methamidophos	Not necessary	JMPR (2003) Methamidophos not teratogenic (JMPR, 2002)
Acetamiprid (CAG-DAH)	Acetamiprid	Acetamiprid	Not necessary	Peer review of the pesticide risk assessment of the active substance acetamiprid (EFSA conclusions, 2016)
Acrinathrin (CAG-DAH)	Acrinathrin	Fruits and leafy crops: Acrinathrin and all isomers	1.1	Peer review of the pesticide risk assessment of the active substance acrinathrin (EFSA conclusions, 2013) Modification of the existing MRLs for acrinathrin in peaches and sweet peppers (EFSA reasoned opinion, 2021)

Substance	Residue definitions for enforcement during the reference period	Residue definitions for risk assessment	Conversion factor	References/Comments
Azadirachtin (CAG-DAH)	Azadirachtin	Provisional: Azadirachtin (sum of active components in the extract, determined as Azadirachtin A x CF 9 (worst case, depends on the extract))	9	Peer review of the pesticide risk assessment of the active substance azadirachtin (Margosa extract) (EFSA conclusions, 2018)
Benomyl (CAG-DAC, CAG-DAH)	Sum of benomyl and carbendazim, expressed as carbendazim	Sum of thiophanate-methyl, carbendazim and benomyl, expressed as carbendazim	Not necessary	JMPR (1998) Modification of the existing MRLs for thiophanate-methyl and carbendazim in apples and pears (EFSA reasoned opinion, 2014)
Bitertanol (CAG-DAC, CAG-DAH)	Bitertanol (sum of isomers)	Bitertanol	Not necessary	Peer review of the pesticide risk assessment of the active substance bitertanol (EFSA conclusions, 2010) Contribution of TDMs considered separately
Bromuconazole (CAG-DAC, CAG-DAH)	Bromuconazole (sum of diasteroisomers)	Cereals only: bromuconazole (any ratio of constituent isomers)	Not necessary	Art. 12 MRL review (EFSA reasoned opinion, 2017) Contribution of TDMs considered separately
Carbendazim (CAG-DAC, CAG-DAH)	Sum of carbendazim and thiophanate-methyl, expressed as carbendazim Sum of benomyl and carbendazim, expressed as carbendazim	Sum of thiophanate-methyl, carbendazim and benomyl, expressed as carbendazim	Not necessary	JMPR (1998) Modification of the existing MRLs for thiophanate-methyl and carbendazim in apples and pears (EFSA reasoned opinion, 2014)
Chlorpyrifos (CAG-DAC (*risk driver*), CAG-DAH (*risk driver*))	Chlorpyrifos	Raw commodities: chlorpyrifos Processed commodities: sum of chlorpyrifos and its desethyl metabolite, expressed as chlorpyrifos (tentative)	Raw commodities: Not necessary Processed commodities: Not available	Art. 12 MRL review (EFSA reasoned opinion, 2017) Peer review of the pesticide risk assessment of the active substance chlorpyrifos (EFSA conclusions, 2014)
Cymoxanil (CAG-DAC, CAG-DAH)	Cymoxanil	Cymoxanil	Not necessary	Evaluation of confirmatory data following the Article 12 MRL review (EFSA reasoned opinion, 2019)
Cyproconazole (CAG-DAC, CAG-DAH)	Cyproconazole	Cyproconazole	Not necessary	Art. 12 MRL review (EFSA reasoned opinion, 2021) Contribution of TDMs considered separately

Substance	Residue definitions for enforcement during the reference period	Residue definitions for risk assessment	Conversion factor	References/Comments
Deltamethrin (CAG-DAC, CAG-DAH (*risk driver*))	Deltamethrin (cis-deltamethrin)	Sum of cis-deltamethrin and its alpha-R-isomer and trans-isomer (provisional)	1.25 (provisional)	Art. 12 MRL review (EFSA reasoned opinion, 2015) Modification of the existing MRL for deltamethrin in carobs/Saint John's breads (EFSA reasoned opinion, 2020)
Dieldrin (CAG-DAC)	Dieldrin, singly or combined with aldrin, expressed as dieldrin	Dieldrin, singly or combined with aldrin, expressed as dieldrin	Not necessary	Opinion of the Scientific Panel on Plant protection products and their Residues on a request from the Commission on the risks associated with an in-crease of the MRL for dieldrin on courgettes (EFSA Scientific opinion, 2007)
Emamectin (CAG-DAC, CAG-DAH)	Emamectin benzoate B1a, expressed as emamectin	Sum of emamectin B1a, emamectin B1b, 8,9-Z-MAB1a, plus 3 times AB1a, plus 3 times MFB1a and 3 times FAB1a, expressed as emamectin B1a (free base)	1–1.5 depending on the commodity	Art. 12 MRL review (EFSA reasoned opinion, 2019)
Epoxiconazole (CAG-DAC, CAG-DAH)	Epoxiconazole	Epoxiconazole	Not necessary	Modification of the existing MRL for epoxiconazole in beetroots (EFSA reasoned opinion, 2018) Peer review of the pesticide risk assessment for the active substance epoxiconazole in light of confirmatory data submitted (EFSA conclusions, 2015) Contribution of TDMs considered separately
Ethylene oxide (CAG-DAC, CAG-DAH)	Ethylene oxide (sum of ethylene oxide and 2-chloro-ethanol expressed as ethylene oxide)	Not established	Not available	Ethylene oxide is banned in the EU since 1986. In 2004, the active substance has been included in a MRL Directive which set the EU MRLs at the LOQ for a range of forbidden active substances (Directive 2004/61).
ETU (CAG-DAC, CAG-DAH)	Not enforced	ETU	Not necessary	Modification of the existing MRLs and setting import tolerances for metiram in various crops (EFSA reasoned opinion, 2021)

Substance	Residue definitions for enforcement during the reference period	Residue definitions for risk assessment	Conversion factor	References/Comments
Fenpropidin (CAG-DAH)	Sum of fenpropidin and its salts, expressed as fenpropidin	Sum of fenpropidin and its salts, expressed as fenpropidin	Not necessary	Art. 12 MRL review (EFSA reasoned opinion, 2011)
Fenpropimorph (CAG-DAC)	Fenpropimorph (sum of isomers) Fenpropimorph carboxylic acid (BF 421-2) expressed as fenpropimorph	Sum of fenpropimorph, metabolite BF 421-1[(a)] (free and conjugated) and 2,6-dimethylmorpholine, expressed as fenpropimorph	5 (tentative) for strawberries, cane fruit (raspberries, dewberries, blackberries), other small fruit and berries (currants, blueberries, cranberries, gooseberries), leek and hops. Not necessary for root and tuber vegetables, cereal grains and bananas.	Peer review of the pesticide risk assessment of the active substance fenpropimorph (EFSA conclusions, 2008) Art. 12 MRL review (EFSA reasoned opinion, 2015)
Fenpyrazamine (CAG-DAC)	Fenpyrazamine	Sum of fenpyrazamine and S-2188-DC[(b)], expressed as fenpyrazamine	1–1.3, depending on the crop	Art. 12 MRL review (EFSA reasoned opinion, 2017)
Fluazifop-P (CAG-DAC, CAG-DAH)	Fluazifop-P (sum of all the constituent isomers of fluazifop, its esters and its conjugates, expressed as fluazifop) Fluazifop-P-butyl (fluazifop acid (free and conjugate))	Sum of all the constituent isomers of fluazifop, its esters and its conjugates, expressed as fluazifop	Not necessary	Modification of the existing MRLs for fluazifop-P in various products of plant and animal origin (EFSA reasoned opinion, 2017) Modification of the existing MRL for fluazifop-P in tomato (EFSA reasoned opinion, 2018)
Flusilazole (CAG-DAC, CAG-DAH)	Flusilazole Flusilazole (sum of flusilazole and its metabolite IN-F7321 ([bis-(4-fluorophenyl)methyl] silanol) expressed as flusilazole)	Flusilazole	Not necessary	Art. 12 MRL review (EFSA reasoned opinion, 2013) Contribution of TDMs considered separately
Flutriafol (CAG-DAC, CAG-DAH)	Flutriafol	Flutriafol	Not necessary	Evaluation of confirmatory data following the Article 12 MRL review (EFSA reasoned opinion, 2020) Contribution of TDMs considered separately

Substance	Residue definitions for enforcement during the reference period	Residue definitions for risk assessment	Conversion factor	References/Comments
Folpet (CAG-DAC (*risk driver*), CAG-DAH (*risk driver*))	Folpet (sum of folpet and phthalamide, expressed as folpet) Phthalimide, expressed as folpet	Folpet (sum of folpet and phthalamide, expressed as folpet)	Not necessary	Modification of the existing MRLs for folpet in barley, oat, rye and wheat (EFSA reasoned opinion, 2021)
Haloxyfop-P (CAG-DAC, CAG-DAH)	Sum of haloxyfop, its esters, salts and conjugates expressed as haloxyfop (sum of the R- and S-isomers at any ratio) Haloxyfop (Sum of haloxyfop, its esters, salts and conjugates expressed as haloxyfop (sum of the R- and S- isomers at any ratio))	Sum of haloxyfop, its esters, salts and conjugates expressed as haloxyfop (sum of the R- and S-isomers at any ratio)	Not necessary	Setting of import tolerances for haloxyfop-P in linseed and rapeseed (EFSA reasoned opinion, 2018)
Mancozeb (CAG-DAC (*risk driver*), CAG-DAH)	Dithiocarbamates (dithiocarbamates expressed as CS2, including maneb, mancozeb, metiram, propineb, thiram and ziram)	Mancozeb	1.78 (for conversion of CS_2 to mancozeb - not for accounting metabolites)	Conclusion on the peer review of the pesticide risk assessment of the active substance mancozeb (EFSA conclusions, 2020) Contribution of ETU considered separately
Maneb (CAG-DAH)	Dithiocarbamates (dithiocarbamates expressed as CS2, including maneb, mancozeb, metiram, propineb, thiram and ziram)	Maneb	1.78 (for conversion of CS_2 to maneb – not for accounting metabolites)	Contribution of ETU considered separately
Metconazole (CAG-DAC, CAG-DAH)	Metconazole (sum of isomers)	Metconazole (sum of isomers)	Not necessary	Modification of existing MRLs (EFSA reasoned opinion, 2016) Contribution of TDMs considered separately
Myclobutanil (CAG-DAH)	Myclobutanil (sum of constituent isomers)	Sum of myclobutanil and metabolite RH-9090 (free and conjugated), expressed as myclobutanil (tentative for leafy vegetables, pulses and oilseeds and post-harvest treatment)	1.5–2 depending on the crop	Art. 12 MRL review (EFSA reasoned opinion, 2018)

Substance	Residue definitions for enforcement during the reference period	Residue definitions for risk assessment	Conversion factor	References/Comments
Paclobutrazol (CAG-DAC)	paclobutrazol (sum of constituent isomers)	Paclobutrazol (sum of constituent isomers) (limited to oilseeds, tentative for fruit crops)	Not necessary	MRLs review art. 12 (EFSA reasoned opinion, 2017) Contribution of TDMs considered separately
Penconazole (CAG-DAH)	Penconazole (sum of all constituent isomers)	Sum of penconazole and free and conjugated CGA 132465[(c)], CGA 190503[(d)] and CGA 127841[(e)], expressed as penconazole	Fruits, fruiting vegetables: 6 (tentative) Other crops: not available	Art. 12 MRL review (EFSA reasoned opinion, 2017) Contribution of TDMs considered separately
Propargite (CAG-DAC)	Propargite	Fruit crops: sum of propargite and metabolites TBPC[(f)], TBPC-diol[(g)], HOMe-TBPC[(h)], HOMe-TBPC-diol[(i)], carboxy-TBPC[(j)], carboxy-TBPC-diol[(k)], carboxy-TBPC trio[(l)], expressed as propargite. Tea: sum of propargite and metabolites TBPC, TBPC-diol, HOMe-TBPC, HOMe-TBPC-diol, HOMe-TBPC-glucoside, carboxy-TBPC-diol, expressed as propargite.	Not available	Conclusion on the peer review of the pesticide risk assessment of the active substance propargite (EFSA conclusions, 2011) Setting of MRLs for propargite in citrus fruits and tea (EFSA reasoned opinion, 2018)
Propiconazole (CAG-DAC)	Propiconazole (sum of isomers)	Propiconazole (sum of isomers) (provisional, pending decision on whether to include CGA118244[(m)] free and glucoside conjugated)	Not available	Peer review of the pesticide risk assessment of the active substance propiconazole (EFSA conclusions, 2017) Contribution of TDMs considered separately
Propineb (CAG-DAH)	Dithiocarbamates (dithiocarbamates expressed as CS2, including maneb, mancozeb, metiram, propineb, thiram and ziram)	Propineb (provisional)	2.01 (conversion of CS2 to propineb)	Art. 12 MRL review (EFSA reasoned opinion, 2020) Contribution of PTU considered separately
Prosulfocarb (CAG-DAC, CAG-DAH)	Prosulfocarb	Prosulfocarb	Not necessary	Art. 12 MRL review (EFSA reasoned opinion, 2011)

Substance	Residue definitions for enforcement during the reference period	Residue definitions for risk assessment	Conversion factor	References/Comments
Prothioconazole (CAG-DAC, CAG-DAH)	Prothioconazole-desthio (sum of isomers)	Sum of prothioconazole-desthio and all metabolites containing the 2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl-2H-1,2,4-triazole moiety, expressed as prothioconazole-desthio (sum of isomers)	1–3 depending on the commodity	Art. 12 MRL review (EFSA reasoned opinion, 2014) Modification of the existing MRLs for prothioconazole in sunflower seeds (EFSA reasoned opinion, 2015) Evaluation of confirmatory data following the Article 12 MRL review and modification of the existing MRLs for prothioconazole in celeriacs and rapeseeds (EFSA reasoned opinion, 2020). Contribution of TDMs considered separately
Prothioconazole-dethio (CAG-DAC)	Prothioconazole-desthio (sum of isomers)	Sum of prothioconazole-desthio and all metabolites containing the 2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl-2H-1,2,4-triazole moiety, expressed as prothioconazole-desthio (sum of isomers)	2 for sunflower seeds	Art. 12 MRL review (EFSA reasoned opinion, 2014) Modification of the existing MRLs for prothioconazole in sunflower seeds (EFSA reasoned opinion, 2015) Evaluation of confirmatory data following the Article 12 MRL review and modification of the existing MRLs for prothioconazole in celeriacs and rapeseeds (EFSA reasoned opinion, 2020).
Prothioconazole-sulfonic acid (CAG-DAC, CAG-DAH)	Not enforced			
PTU (CAG-DAH)	Not enforced	PTU	Not necessary	See propineb
Spirotetramat (CAG-DAC, CAG-DAH)	Spirotetramat and its 4 metabolites BYI08330-enol, BYI08330-ketohydroxy, BYI08330-monohydroxy, and BYI08330 enol-glucoside, expressed as spirotetramat Spirotetramat (spirotetramat and its metabolite BYI08330-enol expressed as spirotetramat)	Spirotetramat and its 4 metabolites BYI08330-enol, BYI08330-ketohydroxy, BYI08330-monohydroxy, and BYI08330 enol-glucoside, expressed as spirotetramat	Not necessary	Peer review of the pesticide risk assessment for the active substance spirotetramat (EFSA conclusions, 2013)

Substance	Residue definitions for enforcement during the reference period	Residue definitions for risk assessment	Conversion factor	References/Comments
Spiroxamine (CAG-DAC, CAG-DAH)	Spiroxamine (sum of isomers) Spiroxamine carboxylic acid metabolite M06, expressed as spiroxamine (sum of isomers)	Cereals: Sum of spiroxamine and all metabolites containing the tert-butyl-cyclohexanone moiety, expressed as spiroxamine (sum of isomers) Fruits: - Spiroxamine - Sum of metabolites containing the aminodiol (N-ethyl-N-propyl-1,2-dihydroxy-3-amino-propane moiety, expressed as spiroxamine aminodiol - Sum of 4-tert-butylcyclohexanol and its hydroxy-metabolites, their esters and conjugates, expressed as 4-tert-butylcyclohexanol	Assessment unfinalised	Art. 12 MRL review (reasoned opinion, 2015) Peer review of the pesticide risk assessment for the active substance spiroxamine in light of confirmatory data submitted (EFSA conclusions, 2021)
Tebuconazole (CAG-DAC (*risk driver*), CAG-DAH)	Tebuconazole	Tebuconazole	Not necessary	Peer review of the pesticide risk assessment of the active substance tebuconazole (EFSA conclusions, 2014) Contribution of TDMs considered separately
Tebufenpyrad (CAG-DAC, CAG-DAH)	Tebufenpyrad	Tebufenpyrad	Not necessary	Art. 12 MRL review (EFSA reasoned opinion, 2016)
Thiabendazole (CAG-DAC (*risk driver*), CAG-DAH (*risk driver*))	Thiabendazole Thiabendazole (sum of thiabendazole and 5-hydroxythiabendazole)	Post-harvest treatments: thiabendazole Pre-harvest treatments and rotational crops: - thiabendazole - benzimidazole, including its conjugates (tentative)	Post-harvest treatments: not necessary Pre-harvest treatments: assessment not finalised	Art. 12 MRL review (EFSA reasoned opinion, 2016)

Substance	Residue definitions for enforcement during the reference period	Residue definitions for risk assessment	Conversion factor	References/Comments
Thiacloprid (CAG-DAH)	Thiacloprid	Cereals (except rice): thiacloprid Oilseeds: thiacloprid and M03[(n)] (free and conjugated) (provisional)	Cereals: not necessary Oilseeds: Not available	Peer review of the pesticide risk assessment of the active substance thiacloprid (EFSA conclusions, 2019)
Triazole alanine (CAG-DAC)	Not enforced	Triazole alanine and triazole lactic acid	Not available	Peer review of the pesticide risk assessment for the triazole derivative metabolites in light of confirmatory data submitted (EFSA conclusions, 2018)

(a): 4-{3-[4-(2-hydroxy-1,1-dimethyl)ethylphenyl]-2-methylpropyl}-cis-2,6-dimethylmorpholine.
(b): 5-amino-4-(2-methylphenyl)-2-(propan-2-yl)-1,2-dihydro-3H-pyrazol-3-one.
(c): 4-(2,4-Dichlorophenyl)-5-(1H-1,2,4-triazol-1-yl)-2-pentanol.
(d): 2-(2,4-Dichlorophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-pentanol.
(e): 4-(2,4-Dichlorophenyl)-5-(1H-1,2,4-triazol-1-yl)-1-pentanol.
(f(: (1RS,2RS;1RS,2SR)-2-[4-(2-methyl-2-propanyl)phenoxy]cyclohexanol.
(g): 4-[4-(2-methyl-2-propanyl)phenoxy]-1,xcyclohexanediol.
(h): (1RS,2RS;1RS,2SR)-2-[4-(1-hydroxy-2-methyl-2-propanyl)phenoxy]cyclohexanol.
(i): 4-[4-(1-hydroxy-2-methyl-2-propanyl)phenoxy]-1,xcyclohexanediol.
(j): 2-(4-{[(1RS,2RS;1RS,2SR)-hydroxycyclohexyl]oxy}phenyl)-2-methylpropanoic acid.
(k): 2-{4-[(2,xdihydroxycyclohexyl)oxy]phenyl}-2-methylpropanoic acid.
(l): 2-methyl-2-{4-[(2,x,ytrihydroxycyclohexyl)oxy]phenyl}propanoic acid.
(m): 3,5-dideoxy-1,2-O-[(1RS)-1-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethylidene]-D,L-pentitol.
(n): 6-chloronicotinic acid.

Note 21 (Laboratory analytical uncertainty) – U19

In accordance with Article 37 of Regulation (EU) 2017/625[27], laboratories designated for official control of pesticide residues must be accredited to ISO/IEC 17025[28].

The guidance on the use of the EFSA SSD (EFSA, 2014b) provides official laboratories in Member States with a standardised model for the reporting of harmonised data on analytical measurements of chemical substances occurring in food, feed and water. It provides that laboratories must always analyse and quantify pesticide residues according to the harmonised EU residue definitions, as provided by annexes II and III of Regulation (EC) No 396/2005. In reporting the results, and for the sake of comparability of data, the analytical uncertainty shall not be taken into account. However, the sample is reported to be compliant or not (considering the analytical uncertainty) under a dedicated field of the reporting model.

Furthermore, the Guidance document of the European Commission on analytical quality control and method validation procedures for pesticide residues and analysis in food and feed proposes a default measurement uncertainty of 50% (corresponding to a 95% confidence level and a coverage factor of 2), calculated from EU proficiency tests (European Commission, 2019) for multiresidues analytical method. In general, this 50% value covers the interlaboratory variability between the European laboratories and is recommended to be used by regulatory authorities in cases of enforcement decisions (MRL exceedances).

Note 22 (Sampling strategy and representativeness of occurrence data) – U20

Various sampling strategies are used by Member States (objective sampling, selective sampling, suspect sampling, convenient sampling and census). These types of sampling are described in the Guidance on the use of the EFSA SSD (EFSA, 2013) and Member States need to indicate under which sampling strategy each sample reported to EFSA has been collected using dedicated codes. To perform the CRAs reported in the present document, EFSA used samples taken according to the following sampling strategies:

- ST10A (objective sampling): Strategy based on the selection of a random sample from a population on which the data are reported. Random sample is a sample which is taken under statistical consideration to provide representative data.
- ST20A (selective sampling): Strategy based on the selection of a random sample from a subpopulation (or more frequently from subpopulations) of a population on which the data are reported. The subpopulations may or may not be determined on a risk basis. The sampling from each subpopulation may not be proportional: the sample size is proportionally bigger for instance in subpopulations considered at high risk.

Under the selective sampling strategy, it is common that some food products, production methods, producers or countries are more targeted than others, and this affects the overall representativeness of the monitoring data. There are however inconsistencies in the interpretation of the term 'selective sampling' at member-state level, as indicated by large differences in the proportion of samples coded ST20A between countries.

Although a representative sampling of occurrence data includes lots of commodities pertaining to various distribution channels (e.g. products for local consumption, grocery stores, specialised in foods imported from third countries) or produced following various method, including organic farming and a representative survey of consumption data includes consumers adhering to the respective distribution channels or methods of production, occurrence and consumption data are randomly associated by the model. The existing relationships between preferential consumption practices and the associated methods of productions and respective residue patterns are therefore lost. This was considered and it

[27] Regulation (EU) 2017/625 of the European Parliament and of the Council of 15 March 2017 on official controls and other official activities performed to ensure the application of food and feed law, rules on animal health and welfare, plant health and plant protection products, amending Regulations (EC) No 999/2001, (EC) No 396/2005, (EC) No 1069/2009, (EC) No 1107/2009, (EU) No 1151/2012, (EU) No 652/2014, (EU) 2016/429 and (EU) 2016/2031 of the European Parliament and of the Council, Council Regulations (EC) No 1/2005 and (EC) No 1099/2009 and Council Directives 98/58/EC, 1999/74/EC, 2007/43/EC, 2008/119/EC and 2008/120/EC, and repealing Regulations (EC) No 854/2004 and (EC) No 882/2004 of the European Parliament and of the Council, Council Directives 89/608/EEC, 89/662/EEC, 90/425/EEC, 91/496/EEC, 96/23/EC, 96/93/EC and 97/78/EC and Council Decision 92/438/EEC (Official Controls Regulation). OJ L 95, 7.4.2017, pp. 1–142.

[28] General Requirements for the Competence of Testing and Calibration Laboratories; International Organisation for Standardization (ISO): Geneva, Switzerland, 2005.

was concluded that this has a very minor impact at overall population level, especially at the percentile of interest of the cumulative exposure distribution.

To quantify the impact of samples belonging to the selective sampling strategy, sensitivity analyses were performed, from which these samples were excluded (See sensitivity analyses E in Section 3.2.3).

Note 23 (Pooling of occurrence data from all EU Member States) – U22

Occurrence data from all countries were pooled into one single data set that was used to calculate the cumulative risk for the 14 populations. This was done to increase the statistical robustness of the outcomes. Although this leads to losing the country specificity of the residue concentrations in commodities, this is not considered to be a major issue since most of the EU population is purchasing and consuming a mixture of local and imported commodities that is drawn from, and similar to, the mixture that is represented by the single data set with pooled occurrence data ('common market').

It should be also noted that samples analysed and reported in national monitoring programmes are not only taken from lots intended for the internal market, but also from lots which are in transit or intended for export. This makes very difficult to make national risk assessments based on occurrence data reflecting exactly the residue level in commodities consumed in this country. Such assessments would require a specific data extraction based on information provided about the sampling point.

Note 24 (Imputation of missing measurements) – U23

In many samples, the occurrence levels of certain active substances are missing because they were not measured, while they are available in other samples of the same commodities. In these cases, missing values were imputed by various approaches according to the Tier. In Tier I, a worst-case approach was used, and in Tier II, the imputation was done randomly, by drawing one of the available occurrence data for the respective substance/commodity combinations. Only empirical data were imputed. All details of the implementing procedure are explained in Section 2.2.4.1.3 and in Appendix D.

Tables A.09 of Annexes B1 and B2 give the total number of samples available for each commodity and the number of these samples which were analysed for each pesticide. This gives an insight into the proportion of missing values.

Note 25 (Unspecific residue definitions for enforcement) – U24

In Tier II of the exposure calculations, in the absence of information related to the use frequency of pesticides, occurrence data with unspecific residue definition for enforcement were randomly assigned to one of the active substances included in the residue definition and authorised to be used on the respective commodity. All details of the implementing procedure are given in Section 2.2.4.1.1 and Appendix B.

With respect to the active substances included in CAG-DAC and CAG-DAH, the following residue definitions are unspecific because they cover/include more than one active substance (Tables A.03 of Annexes B1 and B2):

- Aldrin and Dieldrin (Aldrin and dieldrin combined expressed as dieldrin): Both substances are phased out for more than 10 years. Historical contamination is still possible due to their persistency. As aldrin metabolises into dieldrin, any residue measured under this residue definition was considered to be dieldrin.
- (Sum of) carbendazim and thiophanate-methyl, expressed as carbendazim: Approval of carbendazim expired in 2014. During the reference period, only thiophanate-methyl was authorised for being used on 24 of the 36 RPCs in the scope of this assessment (see tables A.06 of Annexes B1 and B2). For these 24 RPCs, as thiophanate-methyl can be metabolised into carbendazim, any measurement under this residue definition was assigned in proportions of 0.5 to each substance. Measurements in the 12 RPCs for which the use of thiophanate methyl was not authorised were considered to result from treatment with carbendazim in 50% of the cases (and in such case the measurement was entirely assigned to carbendazim) or from treatment with thiophanate-methyl in the other 50% of cases (and in such case the proportion of 0.5 for each substance applied).
- Carbendazim and benomyl (sum of benomyl and carbendazim expressed as carbendazim): None of these substances was approved during the reference period (expiration of approval of carbendazim in 2014 and non-inclusion of benomyl in 2002). Any residue measured under this residue definition was considered to be carbendazim, resulting from the use of thiophanate

methyl. As it was phased out since more than 10 years, benomyl was totally disregarded in the present assessment.

- Dithiocarbamates (dithiocarbamates expressed as CS2, including maneb, mancozeb, metiram, propineb, thiram and ziram): Three substances were assumed to have authorised uses during the reference period: mancozeb, metiram and ziram in Tier II. In 31 of the 36 RPCs in the scope of this assessment, at least one of these substances was assumed to be authorised to be used. In these commodities, measurements were assigned with equal probability to these substances. In head cabbage, as mancozeb was the only substance assumed to be authorised for use in head cabbage, all CS2 measurements were therefore assigned to mancozeb. In lettuce, as mancozeb and metiram were both assumed to be authorised, CS2 measurement were randomly assigned with equal probability to either mancozeb or metiram. For the remaining commodities for which no authorised use was assumed for dithiocarbamates, measurements were assigned with equal probability to the 6 active substances generating CS2.
- Fluazifop-P (sum of all the constituent isomers of fluazifop, its esters and its conjugates, expressed as fluazifop): only fluazifop-P was approved during the reference period. Any residue measured under this residue definition was considered to be fluazifop-P. As it was phased out since more than 10 years, fluazifop was totally disregarded in the present assessment.
- Haloxyfop (Sum of haloxyfop, its esters, salts and conjugates expressed as haloxyfop (sum of the R- and S- isomers at any ratio)): only haloxyfop-P was approved during the reference period. Any residue measured under this residue definition was considered to be haloxifop-P. As it was phased out since more than 10 years, haloxyfop was totally disregarded in the present assessment.

Note 26 (Assumptions of the authorisation status of pesticide/commodity combinations) – U25

The handling of left-censored data requires 3 types of assumption, each of them creating a source of uncertainty:

- Assumption of the authorisation status at pesticide/commodity combination level
- Assumption of the use frequency for authorised pesticide/commodity combinations
- Assumption of the residue level in treated samples of authorised pesticide/commodity combinations with residues below the LOQ.

The present note deals with the first type of assumption. The assumption of the authorisation status determines pesticide/commodity combinations for which samples with results below the LOQ may be imputed with non-zero values as explained in Appendix C. In practice, it was first assumed that an authorisation exists in all EU countries for an active substance/commodity combination when the MRL in place on 31 December 2019 was above the LOQ. Additionally, authorisation in all EU countries was also assumed for active substance/commodity combinations with MRLs set at the LOQ, but for which a use had been reported to EFSA in the context of article 12 and/or subsequent article 10 reasoned opinions. The full description of the assumption process is given in Section 2.2.4.1.2. The full list of the assumed authorised uses is given in Tables A.06 of Annexes B1 and B2.

The assumption of the authorisation status is however uncertain and does not necessarily reflect the precise authorised uses of pesticides at national level.

On one hand, the assumption on authorisations, as described above, leads to an overestimation of the risk because authorisations for any active substance/commodity combination are not necessarily granted in all Member States, but more often in certain Member States only. On the other hand, it also leads to an underestimation of the risk when an authorisation does not result in an MRL above the LOQ and when this authorisation has not been reported to EFSA. Finally, even in the absence of authorisation, residues may be present in commodities because of their uptake from the soil.

The magnitude of the over- or underestimation due to this source of uncertainty is however limited as it concerns residues at very low level (typically below 0.01 mg/kg). Even with the most potent active substances in CAG-DAC and CAG-DAH (abamectin and cyproconazole, respectively), the consumption by a pregnant woman of 60 kg of a commodity unit of 200 g from a lot containing a residue level of 0.01 mg/kg, assuming a VF of 3.6, would result in MOEs of 6700 and 1700 in the case of abamectin and cyproconazole, respectively.

For substances with residues covered by an unspecific residue definition, it was assumed that an authorisation was existing for an active substance/commodity combination when a MRL was in place

above the LOQ, and the substance was approved under Regulation 1107/2009 at the end of the reference period (i.e. on 31 December 2019). Therefore, an active substance which was authorised during a part of the 3-year cycle during which the occurrence data were collected, but the approval period of which expired before 31 December 2019, was considered as not having any authorised use during the 3-year cycle. Consequently, this active substance was not allocated to any measurement. This is particularly the case of propineb for which the approval expired on 22/03/2018 and the authorisations had to be withdrawn by 22 June 2018 with a period of grace until 22 June 2019. This was also the case of thiram for which the approval expired on 30/10/2018 and the authorisations had to be withdrawn by 30 January 2019 with a period of grace until 30 April 2019 or 30/01/2020, depending on the type of use.

To quantify the potential impact of considering propineb and thiram as approved during the reference period, sensitivity analyses were performed (See sensitivity analyses I in Section 3.2.3).

Note 27 (Assumption of the use frequency of pesticides and of the residue level (1/2 LOQ) as imputed value) – U26 and U27

This note concerns the second and third types of assumptions concerning left-censored data.

With respect to the use frequency of pesticides on crops, as statistics are not available to EFSA, the European Commission and Member States have defined the assumptions to be made in Tiers I and II of the exposure calculations (European Commission, online). All details of the implementing procedure can be found in Section 2.2.4.1.2 and Appendix C.

As part of the implementing procedure, residue levels equal to 1/2 LOQ are assigned to samples considered as having been treated. The choice of a level equal to 1/2 LOQ is also an assumption as the actual residue level may take any value comprised between zero and the LOQ.

The sensitivity of the cumulative exposure calculations to the assumptions of the use frequency and of the residue level was quantified in sensitivity analyses A and B in Tables 20 and 21 of Section 3.2.3.

Note 28 (Assumption regarding residues of pesticides in drinking water) – U28

EFSA does not have access to detailed monitoring data on pesticides in drinking water. Therefore, assumptions were used to impute occurrence values in drinking water. These assumptions were based on Council Directive 98/83/EC[29] of 3 November 1998 on the quality of water intended for human consumption. This Directive sets an MRL of 0.1 μg/L to each individual pesticide and its relevant metabolites, degradation and reaction products, and of 0.5 μg/L to the sum of all these substances detected and quantified. In Tier I, it was assumed that the five most potent pesticides of the CAG approved in EU (abamectin, folpet, tebuconazole, prothioconazole-desthio and chlorpyrifos for CAG-DAC; cyproconazole, flusilazole, acephate, chlorpyrifos and emamectin for CAG-DAH) were at the level of 0.1 μg/L. This corresponds to the worst possible exposure complying with the legal provisions. In Tier II, it was assumed that the same pesticides were at 50% of the allowed level (0.05 μg/L).

Based on these assumptions, the contribution of drinking water to the exposures exceeding the 99th percentile in Tier II was the highest in Finland for CAG-DAC (0.3%) and in Denmark for CAG-DAH (1.2%). For Germany, the contribution of drinking water was 0.1% and 0.7% for CAG-DAC and CAG-DAH, respectively (Tables C.02 of Annexes D1 and D2).

Member States are obliged under the Drinking Water Directive to monitor on a regular basis the quality of the drinking water that is supplied to consumers and to report triennially the results to the Commission, which produces a synthesis report.[30] The last available report of the drinking water quality in EU Member States covers the 2011–2013 period (European Commission, 2016). This report states that '*Member States monitor a considerable number of pesticides and metabolites (degradation and reaction products) in drinking water that are chosen at national level and are thus specific for each Member State. However, only those pesticides that are likely to be present in a given supply need to be monitored. For reporting purposes, a short list of 13 pesticides*[31] *was agreed between European Commission and Member States. For these, monitoring frequency and information on non-compliance were reported for 2011–2013. Even though the reporting of pesticides' short list is a harmonized approach and comparable, it does not show the full picture of all pesticides and all relevant metabolites occurring in a country. Nevertheless, the reported compliance rates are consistently high*'.

[29] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A31998L0083
[30] https://ec.europa.eu/environment/water/water-drink/reporting_en.html
[31] This list is composed exclusively of herbicides, which, due their physico-chemical properties, are the most prone to be present in water.

The compliance rate for total pesticides is indeed above 99.9% and for individual pesticides above 99.5%. Although this information is of very qualitative nature, it suggests that the assumptions used under Tier II calculations are conservative.

Note 29 (Unit-to-unit variability of pesticide residues) – U29

Fixed values (and not a distribution) have been used for the VF. In Tier II, the value was 3.6, the average estimate of observed VFs in market samples (EFSA PPR Panel, 2005). The EFSA 2005 opinion does not give credible intervals or confidence intervals for the average of 3.6. However, a median VF was also reported as 3.4 with a 95% credible interval of 3.1–3.7. This credible interval reflects the uncertainty in estimating the VFs in the data sets available to the Panel and the sampling variability in estimating the distribution of the 'true' VFs between data sets but does not take account of the contribution of 6 other sources of uncertainty. The combined effect of these uncertainties was not quantified. However, while some of them might, if quantified, contribute noticeably to increasing the credibility intervals on the results, most of them would not be expected to introduce significant bias. The important exception to this is the uncertainty about whether a real difference exists between VFs for medium and large sized commodities.

To quantify the overall impact of the unit-to-unit variability in the present assessment, sensitivity analyses were performed, in which it was assumed that all commodity units contained the same residue level (i.e. the level measured in the sample) (See sensitivity analyses F in Section 3.2.3).

Note 30 (Commodity unit weights) – U30

As indicated in Section 2.2.3.4, one single value for the unit weight of each commodity above 25 g was retrieved from the Pesticide Residues Intake Model (EFSA, 2018b).

Note 31 (Missing information about the effect of processing on pesticide residues) – U31

To perform calculations, a PF for a pesticide/raw commodity/processing technique combination has been used if:

- A reliable median value was available in the database of processing techniques and PFs compatible with the EFSA food classification and description system FoodEx 2 (Scholz et al., 2018a) or in EFSA outputs published after June 2016. To be reliable, the PF had to be based on three or more acceptable individual PF values or on two acceptable individual PF values with a variation of less than 50%.
- The processing techniques reported in the PF database was matching the processing techniques reported in the RPC consumption data set for the food item consumed. The processing techniques from both databases were matched according to principles described in Section 2.2.3.3.

Of course, when occurrence data measured directly on processed commodities (i.e. on wine and olive oil) were used in the calculation of cumulative exposure, the use of PFs is not necessary.

In the absence of PFs, it was assumed in the model that all residues in the raw commodity are quantitatively transferred to the processed commodity and reach the consumer.

The list of all PFs used to perform the calculations are given in Tables A.07 Annexes B1 and B2.

For CAG-DAC, PFs were used for the following risk drivers:

- Folpet/apples: PF of 0.75 for juicing, canning/jarring and pulping/mashing
- Thiabendazole/oranges: PF of 0.17 for peeling

For CAG-DAH, PFs were used for the following risk drivers:

- Thiabendazole/oranges: PF of 0.17 for peeling
- Thiabendazole/mandarins: PF of 0.075 for peeling

The largest possible impact of this source of uncertainty was quantified by sensitivity analyses which assumed that no residue is present in any pesticide/commodity/treatment type other than '*PROCESS=Unspecified*' combinations for which PFs are not available (sensitivity analyses C in Section 3.2.3).

Note 32 (Applicability of PFs in the EFSA food classification and description system (FoodEx)) – U32

The database of validated PFs developed by Scholz et al. (2018a) has been developed to be compatible with the EFSA food classification and description system FoodEx 2.

In the first part of the project, a compendium of representative processing techniques was elaborated based on the standard protocols used in regulatory processing studies (Scholz et al., 2018b). The original study reports of a representative set of processing studies covering the most important processes in food processing, in terms of consumption and production of the processed products, were reviewed to identify the main food processing types (cooking in water, steaming, canning of fruits and vegetables (including jam/jelly/marmalade production as well as purée and paste production), dehydration/drying of fruits, vegetables, herbs and spices, frying and deep-frying, baking and roasting, microwaving, production of fruit and vegetable juices, wine manufacturing, fermentation and pickling, oil production including essential oils, soya milk and tofu production, beer brewing, milling processes, starch production, cocoa powder production, sugar production).

For each process, a typical set of processing conditions was provided based on published literature and/or inquiry in the food processing industry. Detailed descriptions of processing conditions were given, and the processes were visualised in flowcharts.

In a second step of the project, the food/feed items and processes as described in the compendium were coded using the FoodEx2 coding system (Donkersgoed et al., 2018), and therefore linked with each other. Additionally, a key facet was added in order to be able to link food and feed items to the EFSA RPC-model.

The sources used to code the foods, feeds and processes are described, as well as the coding decisions. The results of the coding are listed as appendix A to Scholz et al. (2018b).

Linking processing techniques investigated in regulatory studies with processing techniques of the EFSA RPC-model, includes uncertainties, first from the fact that PFs derived from processing studies conducted according to a limited number of standardised protocols are assigned to food as consumed which may have been processed following conditions diverging to varying extent from these standard conditions. A second source of uncertainty is associated with extrapolations of PFs derived for commodities investigated in processing studies to other commodities.

To perform the present assessment, processing techniques reported in the PF database were matched with the processing techniques reported in the RPC consumption data set according to the principles described in Section 2.2.3.3.

Note 33 (Accuracy of PFs) – U34

PFs are calculated as the ratio between the residue concentrations in the processed commodity and in the RPC.

In case of residue levels below the LOQ either in the processed or raw commodity, the approach in Scholz et al. (2018a) was as follows:

- When residues in the processed commodity were below the LOQ, the calculation assumed as worst case that the actual residue concentration in the processed commodity was equal to the LOQ and in this case the calculated PF represented the maximum possible value. In the present assessment, this concerned the following pesticide/commodity/processing type combinations (relevant for both CAG-DAC and CAG-DAH):
  - emamectin/oranges, mandarins, grapefruit, melons/peeling (PF<0.25)
  - folpet/apple/ juicing, canning, jarring (PF<0.75)
  - mancozeb/tomatoes/pulping, mashing (PF<0.36)
  - mancozeb/wheat, rye/white bread, whole meal bread (PF<0.70)
  - propineb/apples, pears/juicing (PF<0.27)
  - propineb/apples, pears/pulping, mashing (PF<0.22)
  - propineb/table grapes/juicing (PF<0.18)
  - propineb/tomatoes/canning, jarring (PF<0.12)
  - tebuconazole/orange/juicing (PF<0.21)
- When residues in the raw commodity were below the LOQ, the calculation assumed as best-case scenario that the actual residue concentration in the raw commodity was equal to the LOQ and in this case the calculated PF represents the minimum possible value. In such case, the PF was not considered reliable in the PF database and therefore was not used in the calculations.

Note 34 (Use of fix values of PFs) – U35

Only one value of PF is used for each pesticide/commodity/processing type, corresponding to the median of the distribution of values derived from the available processing studies considered as reliable or indicative by Scholz et al., 2018a. Information on the number of independent trials performed to determine PFs and individual results can be found in Scholz et al., 2018a.

With respect to risk drivers for which PFs are available, the numbers of independent trials from which the median values were defined were as follows:

For CAG-DAC:

- folpet/apples/juicing: 3 independent trials
- folpet/apples/canning/jarring: 3 independent trials
- folpet/apples/pulping/mashing: 3 independent trials
- Thiabendazole/oranges/peeling: 3 independent trials

For CAG-DAH:

- Thiabendazole/oranges/peeling: 3 independent trials
- Thiabendazole/mandarin/peeling: 8 independent trials

Note 35 (Effect of washing and peeling on pesticide residues in/on commodities with edible peel) – U36

Sensitivity analysis C does not cover all possible processes which can decrease the residue level in the commodity as consumed. Generally, the model considers any consumption event of a commodity for which information about the nature of processing is not given (i.e. associated with the facet '*PROCESS=Unspecified*') as the consumption of the raw commodity, and, under sensitivity analysis C, the exposure related to this consumption event is the same as in the Tier II calculation.

U36 concerns the uncertainty related to treatments/preparations of the commodities before consumption which are not covered by sensitivity analysis C. This includes:

- The effect of peeling and washing on pesticide residue levels for fruits and vegetables with edible peel and which are consumed raw (e.g. apples).
- The effect of washing of commodities eaten raw (e.g. lettuce).
- The effect of the usual processing when the consumption event of a commodity is reported without information about the processing type (facet '*PROCESS=Unspecified*'). This can for instance concern potatoes when no processing type has been reported/recorded for the consumption event during the consumption survey. In such case, although it is very likely that the potatoes have at least been cooked, the effect of the processing has not been accounted in sensitivity analysis C.

Information about the contributions of consumption events of commodities with unspecified processing type to the exposures exceeding the 99th percentile can be found in Tables C.02 of Annexes D1 and D2. For the reasons explained above, these contributions are overestimated.

The following risk drivers are concerned by this source of uncertainty:

- CAG-DAC: folpet/wine grapes (Germany only), tebuconazole/peaches, mancozeb/head cabbages, mancozeb/lettuce, chlorpyrifos/potatoes, folpet/apples, tebuconazole/apples.
- CAG-DAH: folpet/wine grapes (Germany only), chlorpyrifos/potatoes, chlorpyrifos/tomatoes.

Information on the effects of washing of fruits and vegetables on pesticide residue levels from published literature was combined and analysed in a meta-analysis review (Keikotlhaile et al., 2010); however, the analysis did not distinguish different types of active substances or different commodity types and therefore only a general conclusion could be drawn. It was reported that overall, washing leads to a combined reduction of pesticide residue levels by a weighted mean response ratio of 0.68.

Information from published literature on the effects of washing and peeling was reviewed for specific identified pesticide/commodity combinations (Chung, 2018). A correlation between water solubility of the active substance and pesticide decrease after washing could not be observed. The reduced effect of washing on residue levels for some pesticide/commodity combinations was reported to be attributed to penetration of active substances into the waxy surface of some fruits or translocation of the active substance into plant tissues. It was reported that the partition coefficient (Kow) of active substances may be an indicative factor of the residues partitioning into the waxy surface of some fruits, although a correlation with pesticide decrease after washing was not

demonstrated. The time after pesticide spray application was reported to be a contributing factor for a variety of crops, with the decline in time in the proportion of residues reduced by washing being attributed to translocation of residues deeper into the crop surface. The behaviour of the active substance in terms of whether it is systemic or non-systemic was one of several factors used to explain the differences in PFs for various household processing conditions, including washing and peeling, for various pesticide/commodity combinations.

Information on the frequency of peeling and washing of commodities with edible peel which are consumed raw is not available to EFSA.

Although not related to the effect of processing, it is known that residue levels decline between the market distribution and the time of consumption. Therefore, the consumer might be exposed to residue level lower than those measured and reported by official laboratories. Not taking account of this decline leads to an overestimation of the risk, which was considered to be minor. There are theoretical reasons to this: this decline is governed by photolysis, volatilisation and to some extent to chemical degradation, but these processes start directly after treatment in field, and not only after marketing or purchase of the commodity by the consumer. When they are major degradation/ dissipation routes (e.g. volatility of dichlorvos), residues decline shortly after harvest and are low at any other point of the distribution channel and later at point of consumption. When the substance is more stable, these processes are expected to play a minor role and to be less efficient than industrial or household processing with hydrolysing conditions or physical treatments such as fractionation of commodities, peeling or washing. Collecting factual information on the degradation of residues after retail store would be cumbersome, due to the complexity of this phenomenon, its substance-specific nature and the multiple influencing factors.

Note 36 (uncertainty on how well NOAELs represent true BMDL50s) – U37

In toxicology, the BMD is a dose level estimated from the fitted dose–response curve and associated with a specified change in response, the BMR. Different metrics can be used to express the magnitude of the BMR (EFSA Scientific Committee, 2017a). For quantal data, the BMR is defined in terms of an increase in the incidence of the lesion/response scored, compared with the background incidence. The two common metrics for reflecting such an increase are the *additional risk* (incidence at a given dose minus incidence in the controls) and the *extra risk* (the additional risk divided by the non-affected fraction of the population). For example, when the additional risk is 8.5% and the background response is 15%, then the extra risk is 8.5/(100–15) = 10%.

The BMDL is the BMD's lower confidence bound, and this value is normally used as the reference point when BMD modelling is used to characterise substances toxicologically. Generally, the EFSA Scientific Committee (2017a) suggests the use of BMDL10s (lower confidence bounds of BMDs for 10% response level) for risk assessment purposes of effects measured by quantal data.

For optimal accuracy of CRAs, following the recommendations of the EFSA Scientific Committee (2017a), BMDLs should be the preferred point of departure (PoD) for the characterisation of substances included in the CAGs. In the specific case of craniofacial alterations, a 5% extra risk would be - a priori - an appropriate BMR for the reasons given in Section 2.3.4.

In the present assessments, the cumulative exposures were calculated using NOAELs, and it is uncertain how different the result would have been if robust BMDLs for the craniofacial alterations would have been used. To quantify the impact of this uncertainty, the Working Group undertook to derive BMDL05s for the risk drivers identified by the cumulative exposure calculations. The intention was to perform a sensitivity analysis in which the calculations would have been repeated after substitution of the NOAELs of risk drivers by their BMDL05s.

In order to derive BMDL05s for risk drivers, data were collected according to the modalities described in Note 2 for the assessment of the dose–response relationship. Individual findings were therefore retrieved from the original raw data and carefully reviewed to avoid double or triple counting of the incidences (Example: If 3 fetuses out of 13 in a dam had cleft palate and 3 fetuses in this same dam had cleft lip, but one of these fetuses had both, cleft palate and cleft lip, the entry would be 5 affected fetuses/of 13 fetuses/dam). Data could not be collected for cyproconazole (CAG-DAH).

BMD modelling was performed using PROAST software (v 67) in MENU option.[32] A BMR of 5% was set and quantal data were modelled including litter effects. As BMD approach does not aim to find the

[32] PROAST (copyright RIVM National Institute for Public Health and the Environment) is a software package for the statistical analysis of dose-response data. See https://www.rivm.nl/en/proast

single statistically best estimate of the BMD but rather all plausible values that are compatible with the data, the Model Averaging approach was applied according to the EFSA Scientific Committee (2017a).

This exercise was done both on single data sets from individual studies and combined data sets from sets of studies of equivalent quality as defined in Section 2.1.3.

The results obtained for risk drivers in CAG-DAC are given in Table F.17. A model average BMD05 confidence interval was obtained for tebuconazole only. Both single data set modelling and combined data set modelling performed on folpet data failed to give appropriate dose response curves to describe the data-points as none of the models passed the acceptability cut-off criteria. Both single data set modelling and combined data set modelling performed on mancozeb and thiabendazole data resulted only in a range (BMDLs-BMDUs intervals) of BMD05s as model averaging approach failed in giving a BMD05 confidence interval; moreover, in particular for thiabendazole, BMDLs-BMDUs intervals indicated the high modelling uncertainty. For chlorpyrifos and 2,4-D, effects were found in only one fetus at the highest dose in only one study, leading to the unfeasibility of BMD modelling.

Table F.17: Results of BMD modelling for risk drivers in CAG-DAC

Substance	Data set	Acceptable models	BMD05 range (BMDL-BMDU)	BMD05 confidence interval by model averaging
Tebuconazole	Combined studies ([redacted] (1988b) and [redacted] (1995c))	2	67–107	66.1–106
Folpet	Combined studies ([redacted] (1984) and [redacted] (1985c))	0	na	na
Folpet	Single study ([redacted] (1984))	0	na	na
Mancozeb	Combined studies ([redacted] (1980) and [redacted] (2015c)	3	417–510	na
Mancozeb	Single study ([redacted] (2015c))	8	179- inf*	na
Thiabendazole	Combined studies ([redacted] (1989) and [redacted] (1992))	6	614- inf*	na
Thiabendazole	Single study ([redacted] (1989))	8	328–565000	na

*: Inf: Infinity.

The results obtained for risk drivers in CAG-DAH are given in Table F.18. Single data set modelling performed on folpet data resulted only in a wide (and highly uncertain) range of BMD05 as model averaging approach failed in giving a BMD05 confidence interval. When the analysis was performed on combined data sets, none of the models passed the acceptability cut-off criteria. Single data set modelling performed with thiabendazole data gave only wide BMDLs-BMDUs intervals as model averaging approach failed in giving a BMD05 confidence interval. BMD modelling for the other risk drivers of CAG-DAH were not performed because effects were seen in only one or few fetuses at the highest dose.

Table F.18: Results of BMD modelling for risk drivers in CAG-DAH

Substance	Data set	Acceptable models	BMD05 range (BMDL-BMDU)	BMD05 confidence interval by model averaging
Folpet	Combined studies ([redacted] (1984) and [redacted] (1985c))	0	na	na
Folpet	Single study ([redacted] (1984))	8	33.2 - 3.44e+09	na
Thiabendazole	Single study ([redacted] (1989))	8	199–18200	na

The poorly reliable results of BMD modelling are explained by the lack of clear dose–response relationship in case of craniofacial alterations or the low response incidence (at the highest tested

dose), which appears similar to, or below the selected BMR (resulting in very wide BMDL-BMDU intervals and BMDL values outside the dose range of the study).

The outcome of BMD modelling reported above contrast with observations of the EFSA Scientific committee (2017a), which reported that various studies estimated that, on average, the median of the upper bound of extra risk at the NOAEL was close to 10% in the case of quantal data. This might be explained by the rare incidence of craniofacial alterations and the principles used to establish NOAELs in the present assessment, which considered the biological relevance of the observations rather than their statistical significance. Indeed, in the present assessment, one single observation of any of the indicator of craniofacial alteration was considered as relevant and sufficient to reflect an effect of the treatment. Assuming therefore a study with 25 dams per treatment group and an average of 10 pups per dam, 1 hit would indicatively correspond to an incidence increase of 0.4% i.e. 10 times lower than a BMR of 5%.

Note 37 (Adequacy of the dose-addition model) – U38

The rationale behind the use of dose-addition to perform CRA, has been given by the PPR panel in its opinions on the establishment of CAGs (EFSA PPR Panel, 2013a) and on the relevance of dissimilar modes of action (EFSA PPR Panel, 2013b).

Dose-addition occurs when the individual compounds in a mixture share the same MoA for their toxicological effects and differ only in their potencies. The components of such mixtures can be considered as dilutions of one another, and one chemical can be replaced with an equally effective concentration of another chemical of the mixture without changing the overall combined effect. The approach also assumes no chemical interaction between the co-occurring chemical components and does not consider potential synergism or antagonism between the components of the mixture. Dose-addition has found widespread acceptance as an assessment concept for combined exposures to multiple chemicals and is extensively used by regulatory authorities as a protective default approach.

The appropriateness of the dose-addition model as the default assumption for mixtures of compounds which do not necessarily share the same MoA but lead to a common phenomenological effect or adverse outcome, was investigated in the EuroMix collaborative EU research project.[33] The EuroMix project implemented a methodology based on the dose-addition hypothesis using RPFs for substances grouped into the same assessment group (Zilliacus et al., 2019) as recommended model for mixture risk assessment (Rotter et al., 2018; EFSA Scientific Committee, 2019; Beronius et al., 2020). Results of a range of bioassays investigating the liver steatosis, craniofacial alterations and endocrine-related effects were in agreement with the dose-addition model. As it has been shown, the analyses of mixture effects revealed additivity for all the different combinations of MoA and endpoints that were tested (Zoupa et al., 2020; Luckert et al., 2019; Lichtenstein et al., 2020; van Oostrom et al., 2020; Moretto et al., 2013; Metruccio et al., 2020; Van Der Ven et al., 2022). Thus, the dose-addition model was found to be adequate in the tested cases, in mixtures containing substances eliciting the common adverse effect through both similar and dissimilar modes of action.

As part of the EuroMix project, an Expert Panel Meeting was organised involving 8 EU and 4 non-EU scientists on 16–18 April 2019 at WHO, Geneva. The Panel agreed that the available information supports the application of the dose-addition assumption for risk characterisation of chemicals of an established group or of those with sufficient similarity to that group also when there are differences in the MIEs or some of the KEs in the respective AOPs of those substances (FAO/WHO, 2019). This suggests that the concept of AOP networks can be useful for mixture risk assessment to support grouping of substances into assessment groups and to identify upstream KEs to be considered for this purpose.

Adequacy of the dose-addition model for craniofacial alterations due to abnormal skeletal development

Craniofacial development entails a complex three-dimensional morphogenetic process, regulated by the morphogen RA (see Section 3.1.1.1). A specific relationship has been described between RA gradient in different hindbrain areas, Hox gene expression, NCCs migration, pharyngeal arch formation and facial morphogenesis (Osumi-Yamashita, 1996).

In the frame of EuroMix project, specific RA-like teratogenic effects at the level of the branchial structures were correlated to exposure to certain antifungal azoles (triadimefon, cyproconazole and flusilazole) selected on the basis of results from previous Whole Embryo Culture (WEC) experiments

[33] Available online: https://www.rivm.nl/en/international-projects/euromix

(Di Renzo et al., 2019), the histone deacetylases inhibitor valproic acid, and RA (as reference molecule). The suggested hypothetical pathogenic pathway for azoles, which includes CYP26 inhibition as MIE (Menegola et al., 2006), was the basis for developing AOP for craniofacial malformations (Metruccio et al., 2020).

PROAST analysis on branchial outcomes was first performed to compare the fit to the single data set with the fit to the combined data set to calculate RPF, using in both cases exponential model family tests. As the log-likelihood ratio test did not reject the equal steepness assumption, RPFs were estimated using the combined model fit (Metruccio et al., 2020). This step is actually necessary as the dose-addition model assumes that, when the dose–response curves are normalised for potency, they are all identical, with the same shape and slope.

Dose additivity appears to be adequate for describing craniofacial malformations in WEC embryos exposed to antifungal azoles (cyproconazole, triadimefon) and valproic acid mixtures (Luckert et al., 2019). Importantly, dose-addition was observed irrespectively of MoA of the contributing chemicals (Zoupa et al., 2020). Craniofacial malformations were studied in zebrafish embryos from combined exposure to chemicals with similar MoA (the triazoles cyproconazole, triadimefon and flusilazole), or dissimilar MoA (cyproconazole or triadimefon and dissimilarly acting compounds, TCDD, thiram, valproic acid, prochloraz, fenpropimorph, PFOS or endosulfan). All tested compounds induced an increase of the Meckel's–palatoquadrate angle as an indicator of head skeleton malformations in zebrafish (Staal et al., 2018) with varying potency and specificity. Their mixtures were designed as (near) equipotent combinations of the contributing compounds in a range of cumulative concentrations. Dose-addition was assessed by evaluation of the overlap of responses of each of the tested binary mixtures with those of the single compounds. The mixture responses did not deviate from the prediction by the dose-addition model. This conformed the validity of this model, irrespectively of the MoA of the contributing chemicals.

Adequacy of the dose-addition for head soft tissue alterations and brain neural tube defects

Regarding this particular outcome, experimental results dealing with dose additivity predictions are lacking. There is in this case uncertainty regarding the slope and the shape of the dose–response curves for the substances included in the assessment as, differently from the skeletal craniofacial malformations, no evidence reassuring on comparable steepness of the dose response curve has been produced in EuroMix project. As stated above, the dose-addition model assumes that, when the dose–response curves are normalised for potency, they have similar shape and slope (this assumption is sometimes expressed as requiring that the dose–response curves are parallel, e.g. EFSA PPR Panel, 2008).

However, even if empirical evidence is lacking, the current common agreement is that substances that act via different AOPs (i.e. by different modes of action) leading to the same adverse outcome can be grouped together and can be assumed to combine their effects according to the dose-addition model (EFSA PPR panel, 2013b; EFSA Scientific Committee, 2019). A survey conducted by the Joint Research Centre of the EU Commission showed that several experts would not even recommend the further use of independent action-based approaches, mainly because of the higher need for input data for independent action but also considering the small differences in predictions by independent action compared to combined action (Bopp et al., 2015). Also, Backhaus and Karlsson (2014) described how ignoring independent action or even using the sum of individual risk quotients as a rough approximation of dose-addition does not have a major impact on the final risk estimate of the examined mixtures. It is however acknowledged that the Scientific Committees on Health and Environmental Risks, on Emerging and Newly Identified Health Risks and on Consumer Safety of the European Commission (2011) considered that, in certain cases, the dose-addition model may not appropriately describe the combined effect of substances causing a same adverse outcome via separate independent AOPs. In such cases, the substances would be grouped based on the specific MoA/AOP and the model for response addition could potentially be used.

Interactions

Although interactions and effects of different magnitude than what can be predicted by dose-addition modelling have low relevance for the risk assessment of pesticide residue levels in food (EFSA PPR Panel, 2008), this cannot be fully excluded and should be considered on a case-by-case basis (Boobis et al., 2008). Boobis et al. (2011) reviewed 90 studies that reported evidence of synergy in mammalian test systems performed at low doses (i.e. close to the PoD) for individual chemicals. Only in 6 studies, useful quantitative information on the magnitude of synergy was reported and indicated that the difference between observed synergisms and predictions by dose-addition did not deviate by

more than a factor of 4. In a later systematic review about synergisms and antagonisms in chemical mixtures, no additional, new in vivo low dose studies evidencing synergistic interactions and not already reviewed by Boobis et al. (2011) were identified by the authors (Martin et al., 2021).

For the specific effects under consideration in the present assessment, no biologically plausible hypothesis for potential synergistic action between active substances included in the CAGs or with other chemicals present in food is known.

Pattern of exposure at the percentiles of interest of the exposure distribution

Tables C.03 of Annexes D1 and D2 contain detailed records of subjects with cumulative exposures exceeding the 99th percentile. They show that in a large majority of cases, consumers are essentially exposed to one single substance: the proportion of cases where consumers are exposed to at least 2 substances each contributing to at least 20% of the cumulative exposure is less than 10% in the case of CAG-DAC and less than 20% in the case of CAG-DAH. This indicates that the fraction of cases, where the uncertainty about the adequacy of the dose-addition model may have an impact, is small.

Note 38 (Adequacy of the acute exposure calculation model) – U39

The acute exposure model calculates exposures within a time window of 24 h, and it is uncertain if this model is adequate to correctly assess the risks of craniofacial alterations.

On one hand, at the 99.9th percentile of the distribution, the calculated human exposures represent exceptionally high exposures, which can reasonably be expected to be much higher than the exposures during the preceding and following days of the concerned consumers. Therefore, for the fraction of consumers of interest in the present assessment, in most circumstances, the practical exposure pattern corresponds to one isolated dose calculated for a 24-h period.

On the other hand, the NOAELs characterising the substances in the CAGs are based on developmental toxicity studies, in which the exposure of animals is repeated during the whole duration of organogenesis (e.g. gestational days 5–15 in the rodent, and 6–18 in the rabbit), mostly via daily administration of a constant dose of the test chemical.

It is nonetheless plausible that the relevant exposure window for developing craniofacial alterations is narrower than the full duration of organogenesis. In support of this, a stage-specific trend in the occurrence of craniofacial malformations has been demonstrated in mice at term after a single dose of the fungicide triadimefon at gestational stages E8, E9, E10, E11 or E12 (Di Renzo et al., 2011). Cleft palate peaked on E8 (associated with disruption of skull elements) and E12 while it was not induced on E9. Other cranial malformations (fusions abnormalities or agenesis of bones) were detected in E8–E10 group. Interestingly, the authors noted a good correlation between stage of migrating NCCs at the time of treatment and abnormal skeletal elements at term. An earlier study (Tiboni and Giampietro, 2005) with a single high dose of fluconazole demonstrated phase-specific teratogenic effects. Malformations of the middle ear apparatus were observed only after dosing on gestational day 8. Cleft palate showed a broader gestational phase of sensitivity, which encompassed gestation days 8–11, but peaked on gestation day 10. These observations of gestational age-specificity suggest that craniofacial facial alterations are triggered by exposures during very short time windows, compatible with the time window of 24 h which is the basis of the acute exposure model.

Another important factor is whether the teratogenic response depends on the peak exposure concentration (maximum concentration, Cmax) or the total exposure (area under the concentration-time curve, AUC).

Theoretically, if the determining teratological correlate is the Cmax, the difference between the exposure pattern in developmental toxicity studies and the acute exposure model in humans may not have a high impact, at least for short-lived compounds. In this case, a series of narrow and high peak levels would be obtained in daily exposed experimental animals, each peak being on its own capable of triggering the effect, if sufficiently high. For example, for valproic acid peak concentrations correlated with teratogenicity in mouse, i.e. exencephaly (Nau, 1986). However, for other teratogenic compounds like cyclophosphamide and possibly retinoids, the AUC rather than Cmax seems to better correlate with teratogenicity. If the AUC values (or doses) are the decisive factors, then toxicity could possibly be inversely related to the compound clearance, and the effects may be enhanced by repeated daily exposures to a constant dose, when the metabolisation and excretion rates are not sufficient to impede an accumulation of the substance over time.

ADME properties of the substances included in the CAGs are therefore important parameters to consider in the quantification of the impact of the uncertainty due to the acute exposure calculation model. They are summarised below for risk drivers:

2,4-D (CAG-DAC and CAG-DAH) is rapidly (peak plasma levels at 4-h post dosing) and almost completely absorbed (> 90%) after oral administration. The active substance is poorly metabolised and eliminated rapidly, mainly via urine excretion. Following single low or single high administration of 2,4-D acid in rats, over 94% of the administered dose was recovered by 48-h post dosing and half-life for urinary excretion was approx. 5 hrs (EFSA conclusions 2014).

Chlorpyrifos (CAG-DAC and CAG-DAH) is extensively absorbed in rats after oral administration (84–93%), widely distributed, moderately to extensively metabolised by oxidation and hydrolysis and eliminated mostly through urine within 48 h (approx. 80%). There is no evidence for accumulation (EFSA statement 2019).

Deltamethrin (CAG-DAH) is rapidly absorbed and excreted after oral administration in rats (19–47% in urine and 32–55% in faeces within 24 h after dosing), and rapidly and extensively metabolised in rats.[34] The main routes of metabolism include cleavage, oxidation and conjugation. The amounts of radiolabel retained in tissues and carcass 7 days after dosing are generally low, representing only 0.59–1.9% of the total dose administered. Fat contains the highest concentration of residues.

Folpet (CAG-DAC and CAG-DAH) is rapidly absorbed (> 80%), widely distributed and rapidly excreted after oral administration. Metabolism proceeds via cleavage of the nitrogen–sulfur bond to phthalimide, which is further metabolised to phthalamic acid and phthalic acid. Derivatives of phthalimide are excreted rapidly and extensively. Folpet does not show any potential for accumulation in tissues due to the fast excretion (EFSA conclusions 2009).

Mancozeb (CAG-DAC) is partially (50%) but rapidly (3–6 h) absorbed after single oral administration in rats. It is widely distributed with the thyroid having the highest levels of radioactivity and rapidly and extensively excreted (74–94% within 24 h), mainly via urine and via faeces. Mancozeb is extensively metabolised (> 95%) through two common metabolic pathways (hydrolysation and oxidation). ETU, ethylene urea, ethylenediamine and N-acetyl ethylenediamine are the major metabolites (EFSA conclusions 2020).

Tebuconazole (CAG-DAC) is extensively absorbed (> 98%) and widely distributed after oral administration. It is extensively metabolised and rapidly excreted within 48 h. It does not show any potential for accumulation (EFSA conclusions 2014).

Thiabendazole (CAG-DAC and CAG-DAH) has an oral absorption rate of 70% in rats and is widely distributed. It is extensively metabolised by oxidation and conjugation. Majority (85–92%) of the absorbed dose is excreted within 24h, mainly via urine (EFSA conclusions 2014).

Note 39 (Combination of consumption and occurrence data) – U40

According to calculation method of the RPI (Section 2.2.4), one distinct sample from the set of occurrence data is randomly assigned to each processing type of the commodities consumed during the 24-h period. This is considered to be the most frequent scenario, although consumption, within a same day, of various forms (either raw or processed) of a commodity originating from a same lot is possible.

Note 40 (UF for intra- and interspecies variability in toxicological sensitivity) – U41

The Working Group is not aware of any chemical-specific data allowing inter- and intra-species comparison of toxicokinetic and toxicodynamic properties of the substances included in CAG-DAC and/or CAG-DAH or of any ad hoc information on genetic polymorphisms possibly affecting their kinetics (e.g. plasma concentrations, placental transfer) or dynamics during pregnancy.

Weinberg et al. (2018) indicated that many craniofacial disorders are characterised by highly variable phenotypic expression. Phenotypic variability may be due to the impact of many other normally functioning genes that influence how the face grows acting either independently or interactively with mutated genes and environmental factors to produce an outcome. Thus, there might be some grounds to consider an additional UF for specific genetic polymorphism for the genes involved in craniofacial phenotypes.

Nevertheless, the Working Group considers generally the recommendation of using of the overall default UF of 100 (10x10) for inter and intra species extrapolation (EFSA Scientific Committee, 2012) as appropriate to cover the possible inter- and intra-species differences. The exception identified for infants below the age of 16 weeks (EFSA Scientific Committee, 2017b) is not relevant in the context of the present assessment.

[34] Scientific Opinion of the Panel on Panel on Plant Protection Products and their Residues (PPR) on a request from the European Commission on potential developmental neurotoxicity of deltamethrin. The EFSA Journal (2009) 921, 1–34.

Even though no empiric evidence questioning the validity of the default UF of 100 is available, it was decided to perform an assessment of the probabilities of the MOET being below 500, due to the severity of the effects under consideration and by analogy to the practices prevailing in the assessment of the risk of individual substances in the context of Regulation (EC) 1109/2009.

Appendix G1 – EKE Q1 CAG-DAC: Outcome of the impact assessment of individual sources of uncertainty

The ranges for the values of multiplicative factors that would adjust the median estimate of the MOET at the 99.9th percentile of exposure in Tier II for CAG-DAC if each source of uncertainty identified in Section 3.3.1 was fully resolved and addressed in the modelling, have been elicited.

These judgements were first conducted for the German population (EKE Q1A), based on information specific to the cumulative exposure of this population (Sections 3.2.2 and 3.2.3). The scale and methods used for this estimation are described in Section 2.3.3. For example: '−−−/•' means at least a 90% chance the true factor is between x1/10 and +20%; '++/++' means ≥ 90% chance between 2x and 5x, etc. It was secondly assessed whether the same multiplicative factor would apply to the other thirteen populations for which the cumulative exposure was modelled (EKE Q1B). The outcome of these judgements and the respective rationales are given in the second and third columns of Table G.1. In the last column of Table G.1, reference is given to notes in Appendix F which summarise information used to address EKE Q1A and Q1B.

Table G.1: Impact of individual sources of uncertainties on the MOET at the 99.9th percentile of exposure in Tier II for CAG-DAC

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
U1 (adequacy of the CAG: missing substances)	−/• or •/• (range of opinions)	a) If the CAG would contain all substances causing the effect, the MOET could only be decreased. The extent of this decrease could marginally exceed 20% for some experts or not exceed this threshold for some others. Substances with HQ above 0.1 in at least one European population of adult consumers at 99.9th percentile that could decrease the MOET for CAG-DAC are amitrole, endrin, fenamiphos, hexachlorobenzene, mecarbam and phorate. The HQs were however calculated on the basis of the ARfD or these substances, which are generally based on a NOAEL lower than the NOAEL associated with craniofacial effects. Other substances with HQ below 0.1 and not considered in the establishment of CAGs could also, although to a lesser extent, contribute to a further decrease of the MOET as suggested in te Biesebeek (2021). b) No differences are expected between populations.	Note 1
U2 NOAEL (adequacy of the CAG: substances included in the CAG not causing the effect as primary toxicity)	Not assessed	See Section 3.3.2	Note 2
U3 (Uncertainties related to the data collection methodology)	•/• (consensus)	a) The uncertainties concerning the different steps of the data collection methodology have a limited and undirected impact, below 20%, for several reasons: • The endpoints of interest are clear and unlikely to be misinterpreted, despite possible varying terminologies. • Key studies for risk drivers were in most cases conducted under GLP conditions, and the required quality checks reduce the risk of mistakes at laboratory level. • The evaluation of laboratory studies in the context of the peer review implies independent assessments by multiple experts	Note 3

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
		(EFSA, RMS, Co-RMS, Member States, public consultations). • Clear criteria were used by the authors of this report to prepare the database in Annex A, minimising the risk of human errors. b) No differences are expected between populations.	
U4 (Uncertainty related to the NOAEL-setting principles)	•/+ (consensus)	a) Several factors were considered: (1) In many cases, the indicators of the effect are present at very low incidence only. In such case, the assignment of NOAEL is affected by a generally higher level of uncertainty because it is not supported by statistical analysis. (2) The combination of studies, where possible and under the conditions defined by the Working Group, allows a better use of the available information and reduces the magnitude of the uncertainty. In the present case the combination of studies has however an extremely weak impact as it concerns only one of the risk drivers (thiabendazole) contributing to less than 2% of the exposure above the 99.9th percentile in the German population. (3) For 2 risk drivers (folpet and tebuconazole), a NOAEL could not be identified in the critical study, and it was set by dividing the LOAEL by a default factor of 10. This factor is considered to lead to an overestimation of the toxicological potency of the substance. As folpet is a major risk driver, the availability of a study with adequate dose spacing would likely result in a higher NOAEL and the MOET would be increased, possibly by (slightly) more than 20%. b) The impact in other populations depends on the contribution of folpet (•/+ applicable in most cases)	Note 4
U5 (Uncertainty related to the study design of the critical study)	•/• or •/+ (range of opinions)	a) Two factors were considered: (1) Gavage, as mode of administration in developmental toxicity studies, is not perfectly representative of the kinetics after ingestion of the substance as a residue in diet. Generally, the NOAELs and MOETs tend to be underestimated. (2) For some experts, the indicator on which the NOAEL of folpet (hyoid alae angulated, 1 mg/kg bw) is sensitive to the staining method, and the study in which it was observed does not contain information about the staining method. Therefore, there is some possibility that a variation or retarded ossification could have been misclassified as a malformation. If this would have been the case, the NOAEL of folpet would have been set at 150 g/kg bw based on skull defects (anterior fontanelle large) in rats ([redacted] 1985b). This view was not supported by other experts. b) •/• for Latvia, Finland, Hungary and Romania populations as the contribution of folpet to the exposure/risk is lower.	Note 5

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
U6 (Uncertainties related to original studies/data quality)	•/• to –/+ (range of opinions)	No consensus discussion took place. The rationale is derived from the individual judgements. a and b) The key studies available for risk drivers were all considered acceptable. They were all performed under GLP. Except in the case of mancozeb, which was tested in 2015, the studies may lack robustness/reliability to some extent, considering that they were performed in the years 1983–1995. OECD TG or US EPA guideline in force at the time of the conduct of the studies were followed, except for the 2-generation study with 2,4-D (not fully in compliance with EU B35 method). Statistical analysis and HCD were available for some studies only, although it is acknowledged that the availability of HCD and statistical significance are not major criteria to assess rare developmental findings (malformations). In the absence of such information, it is however common practice to set NOAELs conservatively, considering the effects as being adverse. Information on the steadiness of the administered dose in the critical study is missing for some substances. An eventual degradation of the substance in these studies would have therefore been missed, and the NOAEL overestimated. For each substance, there are different factors with impacts affecting the MOET in opposite directions. The interplay between these factors differs from country to country, depending on the relative weights of the risk drivers. Some experts estimated that the impact may marginally exceed 20%, while the other estimated that it would not exceed this threshold.	Note 6
U7 (omitted commodities)	–/• (consensus)	Solving this source of uncertainty can only decrease the MOET. This decrease can marginally exceed 20%. a) The mean contribution of the 36 commodities to the diet of plant origin is around 80%. Levels in animal commodities are infrequent and generally very low. Data in animal commodities are however lacking for abamectin and emamectin which are registered as veterinary drugs. As acute intake calculations are not available in the context of the annual monitoring report for commodities not covered by the EUCP, it is very difficult to identify if one of the unselected commodities could play a significant role around the 99.9th percentile. Chronic calculations reported in Note 9 suggest that unselected commodities with chronic intake > 0.01% are often commodities with unit weights < 25 g and/or for which consumption of large portions are unlikely. In the case of the German population, this is supported by sensitivity analyses suggesting that	Notes 7–9

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
		the 36 selected RPCs can be considered as covering about 90% of the total chronic and acute daily exposure to pesticide residues (Sieke, 2020). The experience has however shown that in case of acute CRAs, few samples may have a significant impact at the upper end of the exposure distribution. b) No differences are expected between populations	
U8 (ambiguity in consumption data)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. The rationale is derived from the individual judgements. a) perfect information can change the MOET at 99.9th percentile in both directions, but the change would be small and not exceeding 20% because this affects a small proportion of the samples and the pesticide/commodity combinations driving the risk are generally not sensitive to this source of uncertainty. Exception might be mancozeb in lettuce (cutting lettuce residues are reported under lettuce, but both the residue levels and the consumption amounts are expected to be different). b) No differences are expected between populations.	Note 10
U9 (accuracy of consumption data)	–/• or •/• (range of opinions)	a) Two factors were considered: (1) Misreporting for psychological reasons is a first factor contributing to the uncertainty. Under-reporting is generally more frequent than over-reporting. Under-reporting concerns mainly commodities with high content of fat and sugar and normally affects mainly the estimations of mean dietary exposures. However, as wine contributes greatly to the exposure at these high percentiles, an eventual under-reporting of wine consumption might also be influential at the percentiles of interest in the present assessment. This could be cancelled out to a certain extent by an over-reporting of food with healthy profile such as fruits, vegetables and cereals. (2) A second factor contributing to the uncertainty is the fact that the portion sizes in surveys are rarely weighted precisely but are rather estimated by various means suffering from methodological limitations. Perfect information on sample sizes could change the MOET at 99.9th percentile in both directions. Because survey results are subject to robust quality checks, the impact of mistakes in portion size estimations is however expected to be low. Overall, it was concluded that solving this source of uncertainty would decrease the MOET, due to the effect of under-reporting of wine consumption. There were different opinions on the magnitude of the impact, some experts	Notes 11, 12

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
		considering that it could marginally exceed 20% and others not. b) Some differences are expected between populations, depending on wine consumption.	
U10 (Representativeness of the consumption data)	•/• (consensus)	a) From all parameters of relevance concerning the representativeness of the consumption data, the stratification of the surveys over seasons (some commodities are consumed with high degree of seasonality) and the response rate to the survey (non-respondents often have lower-quality health profiles (EFSA, 2014c), presumably associated with lower consumption amounts and frequency of fruits/vegetables, but also with lower diversity of commodities) are considered as being the most important to ensure the representativeness of the consumption data. In the German survey, some imbalance was noted regarding seasonality (only 13% of records were made during winter), and survey response rate as rather low (42%). The fact that this survey took place in 2007 has minor impact because the change in the consumption pattern over years is low. Using a perfectly representative survey would either increase or decrease the MOET, but to an extent not exceeding 20%. b) No differences are expected between populations, except for Finland population for which a higher impact is expected because the survey covers 4 months only.	Note 13
U11 (exclusion of women below the age of 18 and above the age of 45)	•/• (consensus)	Toxicology experts: a) Mothers above the age of 45 years show an extremely low frequency of live births and are not expected to have dietary practices differing from women between 18 and 45 years. Below the age of 18, a lower degree of awareness of dietary recommendations for pregnancy and a less varied diet cannot be excluded. This can result in lower or higher consumption of some type of foods, e.g. lower consumption of vegetables or higher consumption of alcohol, with impact on the MOET at 99.9th percentile in both directions. Nevertheless, the frequency of live births below 18 years remains very low. b) The impact may be higher in the Romania and the Hungary populations, due to the higher percentage of live births below 18 years, but still within 20%.	Note 14
	•/• (consensus)	Exposure experts: a) Inclusion of women below the age of 18 and above the age of 45 could change the MOET at 99.9th percentile in both directions. However, the expected change is extremely small because the percentage of live births in the excluded age ranges is very low in Germany and because the variability of the consumption pattern between 18	

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
		and 45 years is expected to cover that of excluded women. b) The impact may be higher in the Romania and the Hungary populations, due to the higher percentage of live births below 18 years, but still within 20%.	
U12 (representativeness of pregnancy diet)	•/• (consensus)	Toxicology experts: No consensus discussion took place, but all individual judgements were identical. The rationale is derived from the individual judgements. a) Studies report an increase consumption of fruits, fruit juices and breakfast cereals during pregnancy. The increase consumption of citrus juice is consistent with the recommendation for pregnant women to increase vitamin C consumption. This change of diet during pregnancy is expected to result in a decrease of the MOET at 99.9th percentile. However, (1) as the exposure at the percentile of interest is largely related to the consumption of wine, (2) as the vulnerability window to craniofacial alteration occurs very early during pregnancy, plausibly when the diet has not been modified yet, the decrease is expected to be small and below 20%. b) –/• in Finland, Latvia, Romania and Hungary populations because the contribution of (citrus) fruits to the risk is higher.	Note 15
	•/• (consensus)	Exposure experts: a) The impact of an increase of the consumption of fruits and wheat during pregnancy is of nature to increase the exposure and reduce the MOET. The impact is however expected to be below 20% because (1) the vulnerability period is very early in pregnancy, and possibly anterior to changes in diet; (2) the change in diet is anticipated to consist mainly in an increase of the daily consumption, rather than in an increase of the frequency of large portions; (3) women frequently suffer nausea starting at the same time as the vulnerability window and may therefore decrease their overall food consumption during this period; (4) In the German population, the main risk driver is folpet in wine (specifically covered in U13) b) No differences are expected between populations	
U13 (representativeness of alcohol consumption during pregnancy)	•/• to •/++ (range of opinions)	Toxicology experts: No consensus discussion took place. The rationale is derived from the individual judgements. a) Sensitivity analysis G informs about the maximum possible impact of complete abstinence of alcohol during pregnancy. However, in reality, either unawareness of the pregnancy status or episodes of binge drinking may result in exposure	Note 16

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
		from wine drinking. The degree of this exposure is difficult to appreciate, leading to a range of opinions. b) For Ireland population, the range of opinions extend to •/+++.	
	•/+ to •/++ (range of opinions)	Exposure experts: a) several factors were considered: 1) The outcome of sensitivity analysis G showing an increase of MOET from 107 to 140; 2) Studies reported in Note 16 generally indicate a strong reduction of the weekly consumption of alcohol during pregnancy, but also, in contrast, episodes of binge drinking taking place during early pregnancy; 3) The possible unawareness of pregnancy during the critical window of craniofacial effects; 4) the possible substitution of alcohol by citrus juice, possibly containing 2,4-D or thiabendazole by pregnant women. Some experts also considered that sensitivity analysis G underestimated the effect of alcohol abstinence during pregnancy specifically in the case of the German population. A range of opinion was expressed, reflecting the complexity of this source of uncertainty. b) For Ireland population, the range of opinions extend to •/+++.	
U14 (sampling uncertainty of consumption data)	–/• (consensus)	a) It was agreed to consider U14 and U21 in one single combined impact assessment, as they present a lot of commonalities, and the confidence interval of Tier II calculations do not discriminate between the sampling variability affecting consumption and occurrence data. Solving U14 and U21, by including all consumers of the considered populations and occurrence data for all lots of commodities consumed would result in a decrease of the MOET, possibly by more than 20%. The main reason is the sampling bias affecting the sampling of a fraction of the populations of consumers and a fraction of the occurrence data, which results in a higher probability of underestimating the extreme high of the true distribution than the probability of overestimating it. b) No differences are expected between populations	Note 17
U15 (use of invariable recipes and conversion factors by the RPC model)	•/• (consensus)	a) The RPC model uses invariable recipes and fixed values for yield factors to convert food as consumed to the respective amounts of raw commodities. In practice, however, important variations are possible between recipes and yield factors. Perfect information could alter the calculation of RPI of individual person/days. It results that the MOET at 99.9th percentile could change in both directions, but only marginally in this case because the main risk driver (folpet in wine) is not sensitive to this uncertainty.	Note 18

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
		b) –/+ (impact possibly exceeding marginally 20% in both direction) for Finland, Hungary, Ireland, Latvia, Netherlands, Romania and Spain populations considering the contribution of distillates from wine grapes. No differences with other populations.	
U16 (pesticide/commodity combinations without occurrence data or with unused data)	–/• to •/• (range of opinions)	a) information or data on the occurrence of ethylene oxide and its metabolite 2-chloro-ethanol are lacking and an assessment of the impact of this uncertainty is difficult. This explains that there is a range of opinions about this source of uncertainty. b) No differences are expected between populations	Note 19
U17 (metabolites not accounted)	•/• (consensus)	a) Solving this source of uncertainty can only decrease the MOET. For the German population, this decrease is expected to be smaller than 20%. The main contributor to this decrease is the degradation of dithiocarbamates into ETU which can decrease the MOET by 10% at the most, as quantified by sensitivity analyses J and K. To a lesser extent, the metabolites included in the residue definition for risk assessment, but not monitored, could also participate to this decrease. This concerns 2 (minor) risk drivers, chlorpyrifos (but for processed products only) and thiabendazole (but for residues resulting from pre-harvest treatments only – and therefore not applicable to citrus fruit). The contribution of 1,2,4-triazole and triazole alanine to the exposure at the percentiles of interest is small because despite occurrence levels up to 1 mg/kg in the case of triazole alanine, their toxicological potency is moderate (100 mg/kg bw and 30 mg/kg bw for 1,2,4-triazole and triazole alanine, respectively). Occurrence data are lacking for 3,5,6-TCP, but its toxicological potency is also moderate (100 mg/kg bw). b) –/• for Belgium, Finland, France, Hungary, Italy, Latvia, Netherlands, Romania and Spain populations, based on the outcome of sensitivity analyses J and K.	Note 20
U18 (ambiguity of occurrence data)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) Same rationale as for U8 (ambiguity of consumption data) based on the individual judgements b) Same rationale as for U8 (ambiguity of consumption data) based on the individual judgements	Note 10
U19 (analytical uncertainty for occurrence data)	•/• to –/+ (range of opinions)	a) If residue levels in food samples were corrected for the actual analytical uncertainty, the MOET at 99.9th percentile could change in both directions with equal probability. The default 50% measurement uncertainty considered for decision on compliance is considered larger than the	Note 21

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
		actual uncertainty. The analytical uncertainty is also expected to decrease with the magnitude of the residue levels and the highest residue levels are those which are the most influential in the case of acute exposure assessments. Even if RPIs calculated for individual person/days could be significantly affected, the impact on the MOET at 99.9th percentile will be levelled out considering the high number of measurements. The overall impact was anticipated to be lower than 20% by a part of the experts and to marginally exceed this value by others. b) No differences are expected between populations.	
U20 (representativeness of the occurrence data)	•/• or •/+ (range of opinions)	No consensus discussion took place. The rationale is derived from the individual judgements. a) The interpretation of sensitivity analysis E is difficult. On one hand, as monitoring data from all Member States have been pooled in one single data set, very small differences between populations were expected. This is not really the case as the impact on the MOET ranges from a decrease of 6% (Denmark) to an increase of 19% (Ireland). On the other hand, as the majority of substances (75%) included in CAG-DAC and CAG-DAH are identical and as the risk drivers in both CAGs are essentially the same, the results of sensitivity analysis E were expected to be rather similar between CAG-DAC and CAG-DAH. This is again not the case as the sensitivity analysis results generally in an increase of the MOET (what is expected if sampling strategy ST20A is actually risk-based) in the case of CAG-DAC, but in a counter-intuitive decrease of the MOET in the case of CAG-DAH. All this suggest that 1) the use of the samples collected according to sampling strategy ST20A in the exposure calculation does not result in an obvious underestimation of the MOET and 2) that the sensitivity analyses reveal the influence of a factor which is unrelated to the sampling strategy. In any case, the sensitivity analysis affected the MOET by less than 20% in all populations. b) No differences are expected between populations	Note 22
U21 (sampling uncertainty of occurrence data)		See U14	Note 17
U22 (pooling of occurrence data from all Member States)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) This source of uncertainty has a small impact, below 20% and in both directions. Indeed, populations usually consume a mixture of imported and local commodities. In addition, the highest exposures are largely determined by the magnitude of the MRLs which are regulated at EU level.	Note 23

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
		b) No differences are expected between populations	
U23 (imputation of residue levels to food samples with missing measurements)	•/• or –/+ (range of opinions)	No consensus discussion took place. The rationale is derived from the individual judgements. a) The uncertainty related to the imputation itself is covered by the confidence interval around the MOET. The remaining uncertainty is therefore whether imputing at random is correctly reflecting the actual co-occurrence pattern or is a source of overestimation of the MOET (e.g. in case 2 substances would be used in co-formulation, their co-occurrence would occur) or underestimation (e.g. in case of pest resistance management, co-occurrence of specific groups of pesticides would rather be excluded). This source of uncertainty affects the MOET at the 99.9th percentile in both directions, but the magnitude of the impact is expected to be below 20% for most experts, considering that the observed exposures around the 99.9th percentiles are strongly driven by one single substance in a certain food sample. One expert considered that the impact on the MOET could marginally exceed 20% considering the ratios total measurements/total samples for risk drivers. b) No differences are expected between populations	Note 24
U24 (unspecific residue definitions for monitoring)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) The uncertainty related to the assignment of active substances to the occurrence data with unspecific residue definition is covered by the confidence interval around the MOET. The remaining uncertainty is therefore related to the assumptions behind the assignment (i.e. random assignment using equal probabilities). This source of uncertainty concerns one pesticide/commodity combination mentioned in Table 17, mancozeb/lettuce, because mancozeb and metiram are both authorised to be used on this crop. As contribution of mancozeb in lettuce, as calculated assuming equal probability of use between mancozeb and metiram is 3% above the 99th percentile of the exposure distribution, knowing the precise use frequency of the 2 compounds could impact the MOET at 99.9th percentile in one or the other direction, but by much less than 20%. b) Slightly higher impact in Finland, Italy, Latvia, Romania, Spain and Sweden populations because the contribution of mancozeb in lettuce is higher than in Germany, but the same range (•/•) is still applicable.	Note 25
U25 (left-censored data: assumption of the authorisation status of	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical.	Note 26

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
pesticide/commodity combinations)		a) for substances with specific residue definition, the impact of erroneous assumptions of the authorisation status concerns only the handling of determinations below the LOQ. As the exposure at the 99,9th percentile is mainly driven by the highest quantified residues levels, their impact is minimal, considering in addition that the NOAELs for craniofacial alterations are generally high. For substances with unspecific residue definition, erroneous assumptions also concern the measurements above the LOQ and are therefore more prone to have an impact. For this reason, sensitivity analysis I was conducted assuming that thiram and propineb were authorised (this was the case for a part of the reference period). This sensitivity analysis resulted in a small increase of the MOET (5%), consistent with the fact that neither propineb nor thiram are included in the CAG. b) Very small differences are expected between populations, as indicated by sensitivity analysis I, but the same range (•/•) is still applicable in all cases	
U26 (left-censored data: assumption about the use frequency)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) The use frequencies in Tier II (based on the assumption that each commodity has been treated by at least one substance included in the CAG) are considered to be conservative. Solving this source of uncertainty would therefore more likely increase than decrease the MOET at the 99.9th percentile, and sensitivity analysis B is in this respect more informative than uncertainty analysis A. The increase of the MOET is however expected to be very small (maximum 4% based on sensitivity analysis B). b) No differences are expected between populations	Note 27
U27 (left-censored data: assumption on the residue level)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) Knowing and using in the exposure calculations the real residue levels in treated samples with determinations below the LOQ would not have a significant effect on the MOET at the 99.9th percentile. A first reason is that the impacts on the Tier II calculations of residues, being either above or below 1/2 LOQ in individual samples, would collectively cancel each other out to a large extent. A second reason is the fact that the high percentiles of the exposure distribution are driven by samples with residues well above the LOQ. b) No differences are expected between populations	Note 27
U28 (assumption about pesticides in drinking water)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical.	Note 28

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
		a) The assumptions for residues present in drinking water can be considered as conservative in view of the (qualitative) information available from the EC in its synthesis reports on the quality of drinking water. Under these assumptions, drinking water does not appear as a risk driver in Tier II for any of the 14 populations. The largest contribution of drinking water to the exposure above the 99th percentile is seen for Finland (0.3%). In Germany, this contribution is 0.1% only. Using perfect information about the presence of pesticides and metabolites in drinking water would therefore have a minimal impact (most probably an increase) on the MOET at 99.9th percentile. b) No differences are expected between populations.	
U29 (use of fixed values for the VF)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) As the risk is essentially related to blended processed food commodities (wine), the impact of the unit-to-unit variability on the MOET at 99.9th percentile is expected to be small. This is confirmed by the outcome of sensitivity analysis F which shows that the MOET would be very marginally increased if calculations would be conducted without using any VF. This means that using a (parametric) distribution for the VF instead of one single fixed value wouldn't have any effect. b) No differences are expected between populations.	Note 29
U30 (use of fixed values for individual unit sizes)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) Risk drivers consist essentially in blended processed commodities. The use of actual unit weights above or below the fixed value for other commodities could either increase or decrease the MOET but not by more than 20%. b) No differences are expected between populations	Note 30
U31 (missing PFs)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) Solving this source of uncertainty can only increase the MOET. However, as indicated by sensitivity analysis C, the impact is very minor in the case of the German population. This is explained by the fact that the exposure is essentially driven by residues in wine (no PF applicable), and by other commodities consumed raw. b) In most other countries, the effect of processing is expected to be higher than in	Note 31

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
		Germany based on sensitivity analysis C but the effect will not exceed 20% (•/•, consensus) In Ireland and Finland, however, some experts estimated that the impact may exceed 20% (•/• or •/+, range of opinions), based on sensitivity analysis C. This is particularly valid for Ireland because 38% of the exposure is related to wine grape distillates (type of processing associated with a minimal transfer of residues)	
U32 (Use of PFs in the EFSA food classification and description system (FoodEx))	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) Only two PFs were used for pesticide/commodity combinations driving the risk (folpet/apples/juicing, canning/jarring and pulping/mashing; thiabendazole/oranges/peeling). Generally, the use of PFs derived from laboratory studies in FoodEx can result in either an underestimation or an overestimation of the intake at individual commodity/processing type level. At global level the effects will cancel each other out for a major part. Moreover, the main risk driver is a processed commodity. b) No differences are expected between populations	Note 32
U33 (analytical uncertainty for PFs)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) A limited number of PFs have been used. Analytical methods in regulatory studies are expected to be validated according to SANTE/2020/12830. Moreover, the main risk driver is a processed commodity. This source of uncertainty has a minimal, undirected impact. b) No differences are expected between populations	–
U34 (accuracy of PFs)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) This source of uncertainty concerns PFs for pesticide/commodity/processing type combinations with residues below the LOQ in the processed commodity. These combinations are unlikely to play a role at the percentiles of the exposure distribution of interest. Solving this source of uncertainty would increase the MOET, but the impact would be very minimal. b) No differences are expected between populations	Note 33
U35 (use of fixed values of PFs)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) A limited number of PFs have been used. Moreover, the main risk diver is a processed commodity. This source of uncertainty has a minimal, undirected impact. b) No differences are expected between populations	Note 34

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
U36 (effect of peeling of commodities with edible peel and of washing disregarded)	•/• to •/+ (range of opinions)	No consensus discussion took place. The rationale is derived from the individual judgements. a and b) Solving this source of uncertainty can only increase the MOET. Some experts estimated that the impact would be smaller than 20%, and others that it could exceed this threshold. The impact can be larger in some countries than in Germany. The contribution, to the exposures exceeding the 99th percentile, of consumption events of commodities for which the processing is not reported (identifiable by the facet '*PROCESS=Unspecified*' in Table C.02 of Annex D1), and therefore not covered by sensitivity analysis C, is variable from one country to the other. This contribution gives insight into the potential impact on the washing and peeling of commodities which are not further processed. It is likely that pregnant women wash and peel commodities more frequently than the general population for reason of hygiene. However, the available information indicates that washing and peeling of commodities do not necessarily remove all residues present. The issue caused by the large contribution to exposures above the 99th percentile (39%) of consumption events of wine grapes with the facet '*PROCESS=Unspecified*' in the German population was raised during the expert discussion, but not integrated in the consensus judgement. It was rather agreed to considered it under EKE Q2 and EKE Q3.	Note 35
U37 (Use of NOAEL to characterise the substances in the CAG)		Assessment not possible. See Section 3.3.2.	Note 36
U38 (adequacy of the dose-addition model)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) This source of uncertainty has a small impact. For this effect, empirical evidence is available supporting the validity of the dose-addition model, irrespective of differences in MIE or KE. In addition, the observation of the pattern of exposure indicates that less than 10% consumers at the percentiles of interest are exposed within the same day to at least 2 substances contributing to at least 20% of the cumulative exposure. b) No differences are expected between populations.	Note 37
U39 (adequacy of the exposure calculation model)	•/• to –/+ (range of opinions)	a) The vulnerability window to craniofacial alterations during the organogenesis is narrow and requires exposure during precise gestational stages. As the clearance of risk drivers is generally almost complete within 24–48 h, the acute exposure model fits well the present assessment. Some experts considered that perfect adequacy of the exposure model would	Note 38

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
		either increase or decrease the MOET by less than 20%, but some others considered that a marginal exceedance of this threshold was possible. b) No differences are expected between populations	
U40 (adequacy of the combination of occurrence and consumption data)	•/• (consensus)	a) The likelihood of consuming, within the same day, a commodity from a same lot in various forms (i.e. raw and/or after various types of processing) is deemed to be very low. Moreover, if this is the case, it is unlikely that large portions of the different processing types would be consumed. b) No differences are expected between populations.	Note 39
U41 (adequacy of the UF for intraspecies variability)	Not assessed	See Section 3.3.1	Note 40

Appendix G2 – EKE Q1 CAG-DAH: Outcome of the impact assessment of individual sources of uncertainty

The ranges for the values of multiplicative factors that would adjust the median estimate of the MOET at the 99.9th percentile of exposure in Tier II for CAG-DAH were estimated for each source of uncertainty identified in Section 3.3.1, assuming that it was fully resolved and addressed in the modelling.

These judgements were first conducted for the German population (EKE Q1A), based on information specific to the cumulative exposure of this population (Sections 3.2.2 and 3.2.3). The scale and methods used for this estimation are described in Section 2.3.3. For example: '– – –/•' means at least a 90% chance the true factor is between x1/10 and +20%; '++/++' means ≥ 90% chance between 2x and 5x, etc. It was secondly assessed whether the same multiplicative factor would apply to the other thirteen populations for which the cumulative exposure was modelled (EKE Q1B). The outcome of these judgements and the respective rationales are given in the second and third columns of Table G.2. In the last column of Table G.2, reference is given to notes in Appendix F which summarise information used to address EKE Q1A and Q1B.

Table G.2: Impact of individual sources of uncertainties on the MOET at the 99.9th percentile of exposure in Tier II for CAG-DAH

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
U1 (adequacy of the CAG: missing substances)	–/• or •/• (range of opinions)	a) If the CAG would contain all substances causing the effect, the MOET could only be decreased. The extent of this decrease could marginally exceed 20% for some experts or not exceed this threshold for some others. Substances with HQ above 0.1 in at least one European population of adult consumers at 99.9th percentile that could decrease the MOET for CAG-DAC are amitrole, clopyralid, endrin, methamidophos, oxydemeton-methyl, phosmet and phosphamidon. The HQs were however calculated based on the ARfD or these substances, which are generally based on a NOAEL lower than the NOAEL associated with craniofacial effects. Other substances with HQ below 0.1 and not considered in the establishment of CAGs could also, although to a lesser extent, contribute to a further decrease of the MOET as suggested in te Biesebeek (2021). b) No differences are expected between populations.	Note 1
U2 NOAEL (adequacy of the CAG: substances included in the CAG not causing the effect as primary toxicity)	Not assessed	See Section 3.3.2	Note 2
U3 (Uncertainties related to the data collection methodology)	•/• (consensus)	a) Same rationale as for CAG-DAC b) Same rationale as for CAG-DAC	Note 3
U4 (Uncertainty related to the NOAEL-setting principles)	–/• or •/• (range of opinions)	a) Several factors were considered: 1) In many cases, the indicators of the effect are present at very low incidence only. In such case, the assignment of NOAEL is affected by a generally higher level of uncertainty because it is not supported by statistical analysis. 2) For some experts, the combination of studies, where possible and under the conditions defined by the Working Group, allows a better use of the available information and reduces the magnitude of the uncertainty. In the present case, different	Note 4

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
		studies were used to set the LOAEL and the NOAEL for 2 risk drivers (thiabendazole and deltamethrin). Other experts considered the contribution of these substances to the risk above the 99.9th percentile and estimated that the MOET could decrease, by possibly more than 20%, if, instead of several studies, only the study, with the most critical NOAEL, would have been available (NOTE: in this judgement, experts deviated from the sense of the elicitation question which asks what would be the multiplicative factor if *perfect* information was available, because the motivation of their judgement, implies using one study only, although several studies, of equivalent quality are available) 3) Cyproconazole is the only risk driver for which a NOAEL could not be identified in the critical study and was set by dividing the LOAEL by a default factor of 10. This factor is considered to lead to an overestimation of the toxicological potency of the substance. However, as cyproconazole has a low contribution to the risk in the German population (about 4%), the impact is not significant. b) The impact in other populations depends on the contribution of deltamethrin, thiabendazole and cyproconazole, but is in the same range as Germany (–/• or •/• (range of opinions))	
U5 (Uncertainty related to the study design of the critical study)	•/• or •/+ (range of opinion)	No consensus discussion took place. The rationale is derived from the individual judgements a) The NOAEL of 2,4-D is derived from a generational study in rats, which is considered to be less appropriate than developmental toxicity study for the characterisation of substances included in the CAG. Even though the substance was administered via the diet in this study and that it is considered that gavage studies tend to lead to lower NOAELs, the NOAEL was set at 5 mg/kg bw per day, while in developmental studies with rats no effects were observed up to 75 mg/kg bw per day. If only developmental toxicity studies would have been considered, the NOAEL would have been set at 30 mg/kg bw per day based on dome-shaped head in rabbits ([redacted] 1990). For all other risk drivers in CAG-DAH, NOAELs were derived from developmental toxicity studies by gavage. b) The impact in other populations depend on the contribution of 2,4-D to the exposure/risk, but is in the same range as Germany (•/• or •/+ (range of opinion))	Note 5
U6 (Uncertainties related to original studies/data quality)	•/• to –/+ (range of opinions)	No consensus discussion took place. The rationale is derived from the individual judgements. a and b) The key studies available for risk drivers were all considered acceptable. They were all performed under GLP. Except in the case of deltamethrin, which was tested in 2001, the studies may lack robustness/reliability to some extent, considering that they were performed in the years	Note 6

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
		1977–1992. OECD TG or US EPA guideline in force at the time of the conduct of the studies were followed, except for the 2-generation study with 2,4-D (not fully in compliance with EU B35 method). Statistical analysis and HCD were available for some studies only, although it is acknowledged that the availability of HCD and statistical significance are not major criteria to assess rare developmental findings (malformations). In the absence of such information, it is however common practice to set NOAELs conservatively, considering the effects as being adverse. Information on the steadiness of the administered dose in the critical study is missing for some substances. An eventual degradation of the substance in these studies would have therefore been missed, and the NOAEL overestimated. For each substance, there are different factors with impacts affecting the MOET in opposite directions. The interplay between these factors differs from country to country, depending on the relative weights of the risk drivers. The majority of experts estimated that the resulting multiplicative factor may marginally exceed 1.2, but only one estimated that it could be marginally below 0.8.	
U7 (omitted commodities)	–/• (consensus)	Solving this source of uncertainty can only decrease the MOET. This decrease can marginally exceed 20%. a) The mean contribution of the 36 commodities to the diet of plant origin is around 80%. Levels in animal commodities are infrequent and generally very low, except for honey (thiacloprid and acetamiprid) which is consumed in small amounts. Data are however lacking for emamectin which is registered as a veterinary drug. As acute intake calculations are not available in the context of the annual monitoring report for commodities not covered by the EUCP, it is very difficult to identify if one of the unselected commodities could play a significant role around the 99.9th percentile. Chronic calculations reported in Note 9 suggest that unselected commodities with chronic intake > 0.01% are often commodities with unit weights < 25 g and/or for which consumption of large portions are unlikely. In the case of the German population, this is supported by sensitivity analyses suggesting that the 36 selected RPCs can be considered as covering about 90% of the total chronic and acute daily exposure to pesticide residues (Sieke, 2020). The experience has however shown that in case of acute CRAs, few samples may have a significant impact at the upper end of the exposure distribution. b) No differences are expected between populations	Notes 7–9
U8 (ambiguity in consumption data)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. The rationale is derived from the individual judgements.	Note 10

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
		a) perfect information can change the MOET at 99.9th percentile in both directions, but the change would be small and not exceeding 20% because this affects a small proportion of the samples and the pesticide/commodity combinations driving the risk are generally not sensitive to this source of uncertainty. Exception might be chlorpyrifos in tomatoes (cherry tomatoes residues are reported under tomatoes, but both the residue levels and the consumption amounts are expected to be different). b) No differences are expected between populations.	
U9 (accuracy of consumption data)	–/• or •/• (range of opinions)	a) Same rationale as for CAG-DAC b) No differences are expected between populations.	Notes 11, 12
U10 (Representativeness of the consumption data)	•/• (consensus)	a) Same rationale as for CAG-DAC b) Same rationale as for CAG-DAC	Note 13
U11 (exclusion of women below the age of 18 and above the age of 45)	•/• (consensus)	Toxicology experts: a) Same rationale as for CAG-DAC b) Same rationale as for CAG-DAC	Note 14
	•/• (consensus)	Exposure experts: a) Same rationale as for CAG-DAC b) Same rationale as for CAG-DAC	
U12 (representativeness of pregnancy diet)	–/• (consensus)	Toxicology experts: No consensus discussion took place, but all individual judgements were identical. The rationale is derived from the individual judgements. a) Studies report an increase consumption of fruits, fruit juices and breakfast cereals during pregnancy. The increase consumption of citrus juice is consistent with the recommendation for pregnant women to increase vitamin C consumption. This change of diet during pregnancy is expected to result in a decrease of the MOET at 99.9th percentile. Considering the important contribution of fruits and cereals to the exposure, it is estimated that using consumption data collected from pregnant women only could decrease the MOET by more than 20%. However, this decrease should not largely exceed 20% because the vulnerability window to craniofacial alteration occurs very early during pregnancy, plausibly when the diet has not been modified yet in a fraction of pregnant women. b) The impact in the other populations depend on the contribution of fruits and cereals to the calculated exposure. No differences in Belgian, Czech, Danish, French, Hungarian, Italian, Latvian, Dutch, Spanish and Swedish populations (–/•). Range of opinion for Finnish population (––/• or –/•), and for Romanian and Irish populations (–/•or •/•).	Note 15

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
	•/• (consensus)	Exposure experts: a) The impact of an increase of the consumption of fruits and wheat during pregnancy, as encouraged by physicians' recommendations, is of nature to increase the exposure and reduce the MOET. The impact is however expected to be below 20% because 1) the vulnerability period is very early in pregnancy, and possibly anterior to changes in diet; 2) the change in diet is anticipated to consist mainly in an increase of the daily consumption, rather than in an increase of the frequency of large portions; 3) women frequently suffer nausea starting at the same time as the vulnerability window and may therefore decrease their overall food consumption during this period; 4) In the German population, one of the main risk drivers is folpet in wine (specifically covered in U13) b) No differences are expected between populations	
U13 (representativeness of alcohol consumption during pregnancy)	•/• (consensus)	Toxicology experts: a) Same rationale as for CAG-DAC, having in mind that the contribution of folpet in wine in the case of the German population is about 10% (4 times lower than in the case of CAG-DAC) b) No differences between populations, except Iris population (•/+) (consensus)	Note 16
	•/• (consensus)	Exposure experts: a) Same rationale as for CAG-DAC, having in mind that the contribution of folpet in wine in the case of the German population is about 10% (4 times lower than in the case of CAG-DAC) b) No differences between populations, except Iris population (•/+) (consensus)	
U14 (sampling uncertainty of consumption data)	–/• (consensus)	a) Same rationale as for CAG-DAC b) Same rationale as for CAG-DAC	Note 17
U15 (use of invariable recipes and conversion factors by the RPC model)	–/+ (consensus)	a) The RPC model uses invariable recipes and fixed values for yield factors to convert food as consumed to the respective amounts of raw commodities. In practice, however, important variations are possible between recipes and yield factors. Perfect information could significantly alter the calculation of RPI of individual person/days. It results that the MOET at 99.9th percentile could change in both directions, with a magnitude potentially exceeding 20%, but only marginally. b) No differences are expected between populations.	Note 18
U16 (pesticide/ commodity combinations without occurrence data or with unused data)	?(–)/• to •/• (range of opinions)	a) Same rationale as for CAG-DAC b) Same rationale as for CAG-DAC	Note 19
U17 (metabolites not accounted)	–/• (consensus)	a) Solving this source of uncertainty can only decrease the MOET. For the German population, this decrease is expected to possibly exceed 20%. The	Note 20

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
		main contributor to this decrease is the degradation of dithiocarbamates into ETU and PTU which can decrease the MOET by about 30% at the most, as quantified by sensitivity analyses J and K. To a lower extent, the metabolites included in the residue definition for risk assessment, but not monitored, could also participate to this decrease. This concerns 3 risk drivers, chlorpyrifos (but for processed products only), deltamethrin (provisional conversion factor of 1.25) and thiabendazole (but for residues resulting from pre-harvest treatments only – and therefore not applicable to citrus fruit). The contribution of 1,2,4-triazole to the exposure at the percentiles of interest is negligible considering the occurrence levels and the moderate toxicological potency (30 mg/kg bw). Occurrence data are lacking for 3,5,6-TCP, but its toxicological potency is moderate (25 mg/kg bw). b) There are differences between populations, as indicated by sensitivity analyses J and K, but the range of impact is the same as for Germany (–/•).	
U18 (ambiguity of occurrence data)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) Same rationale as for U8 (ambiguity of consumption data) based on the individual judgements b) Same rationale as for U8 (ambiguity of consumption data) based on the individual judgements	Note 10
U19 (analytical uncertainty for occurrence data)	•/• to –/+ (range of opinions)	a) Same rationale as for CAG-DAC b) Same rationale as for CAG-DAC	Note 21
U20 (representativeness of the occurrence data)	•/• or •/+ (range of opinions)	No consensus discussion took place. The rationale is derived from the individual judgements. a) The interpretation of sensitivity analysis E is difficult. On one hand, as monitoring data from all Member States have been pooled in one single data set, very small differences between populations were expected. This is not really the case as the impact on the MOET ranges from a decrease of 11% (Belgium) to an increase of 6% (Ireland). On the other hand, as the majority of substances (75%) included in CAG-DAC and CAG-DAH are identical and as the risk drivers in both CAGs are essentially the same, the results of sensitivity analysis E were expected to be rather similar between CAG-DAC and CAG-DAH. This is again not the case as the sensitivity analysis results generally in an increase of the MOET (what is expected if sampling strategy ST20A is actually risk-based) in the case of CAG-DAC, but in a counter-intuitive decrease of the MOET in the case of CAG-DAH. All this suggest that (1) the use of the samples collected according to sampling strategy ST20A in the exposure calculation does not result in an obvious underestimation of the MOET and (2) that the sensitivity analyses reveal the influence of a factor which is unrelated to the sampling strategy. In any	Note 22

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
		case, the sensitivity analysis affected the MOET by less than 20% in all populations. b) No differences are expected between populations	
U21 (sampling uncertainty of occurrence data)		See U14.	Note 17
U22 (pooling of occurrence data from all Member States)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) Same rationale as for CAG-DAC b) Same rationale as for CAG-DAC	Note 23
U23 (imputation of residue levels to food samples with missing measurements)	•/• or –/+ (range of opinions)	No consensus discussion took place. The rationale is derived from the individual judgements. a) Same rationale as for CAG-DAC b) Same rationale as for CAG-DAC	Note 24
U24 (unspecific residue definitions)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) The uncertainty related to the assignment of active substances to the occurrence data with unspecific residue definition is covered by the confidence interval around the MOET. The remaining uncertainty is therefore related to the assumptions behind the assignment (i.e. random assignment using equal probabilities). As risk drivers do not involve any substance subject to this source of uncertainty, and as the total contribution of all substances not involved in risk drivers is below 10%, this source of uncertainty has a very limited impact (which can go in both directions) on the MOET at 99.9th percentile. b) No differences are expected between populations	Note 25
U25 (left-censored data: assumption of the authorisation status of pesticide/commodity combinations)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) for substances with specific residue definition, the impact of erroneous assumptions of the authorisation status concerns only the handling of determinations below the LOQ. As the exposure at the 99,9th percentile is mainly driven by the highest quantified residues levels, their impact is minimal, considering in addition that the NOAELs for craniofacial alterations are generally high. For substances with unspecific residue definition, erroneous assumptions also concern the measurements above the LOQ and are therefore more prone to have an impact. For this reason, sensitivity analysis I was conducted assuming that thiram and propineb were authorised (this was the case for a part of the reference period). This sensitivity analysis resulted in a small decrease of the MOET (3%), consistent with the fact that propineb is included in CAG-DAH with a much lower NOAEL than mancozeb. b) Very small differences are expected between populations, as indicated by sensitivity analysis I, but the same range (•/•) is still applicable in all cases	Note 26

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
U26 (left-censored data: assumption about the use frequency)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) The use frequencies in Tier II (based on the assumption that each commodity has been treated by at least one substance included in the CAG) are considered to be conservative. Solving this source of uncertainty would therefore more likely increase than decrease the MOET at the 99.9th percentile, and sensitivity analysis B is in this respect more informative than uncertainty analysis A. The increase of the MOET is expected to be very small (maximum 2% based on sensitivity analysis B). b) No differences are expected between populations	Note 27
U27 (left-censored data: assumption on the residue level)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) Same rationale as for CAG-DAC b) Same rationale as for CAG-DAC	Note 27
U28 (assumption about pesticides in drinking water)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) The assumptions for residues present in drinking water can be considered as conservative in view of the (qualitative) information available from the EC in its synthesis reports on the quality of drinking water. Under these assumptions, drinking water does not appear as a risk driver in Tier II for any of the 14 populations. The largest contribution of drinking water to the exposure above the 99th percentile is seen for Denmark (1.2%). In Germany, this contribution is 0.7% only. Using perfect information about the presence of pesticides and metabolites in drinking water would therefore have a minimal impact (most probably an increase) on the MOET at 99.9th percentile. b) No differences are expected between populations	Note 28
U29 (use of fixed values for the VF)	•/• or –/+ (range of opinions)	No consensus discussion took place. The rationale is derived from the individual judgements. a) As risk drivers are mainly blended processed food commodities, the impact of the unit-to-unit variability on the MOET at 99.9th percentile is expected to be small. This is confirmed by the outcome of sensitivity analysis F which shows that the MOET would be very marginally increased if calculations would be conducted without using any VF. This suggested that using a (parametric) distribution for the VF instead of one single fixed value wouldn't have any effect. One expert, however, considered that the probability for the actual variability to exceed 3.6 in the case of market samples (EFSA PPR Panel, 2005), and to reach values of 5, 6 or 7 was high enough to consider plausible an impact larger than 20% if a distribution of VFs would be used. b) No differences are expected between populations.	Note 29
U30 (use of fixed values for individual unit sizes)	•/• (consensus)	No consensus discussion took place. The rationale is derived from the individual judgements.	Note 30

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
		a) Same rationale as for CAG-DAC b) Same rationale as for CAG-DAC	
U31 (missing PFs)	•/+ (consensus)	a) Solving this source of uncertainty can only increase the MOET. The maximum possible multiplicative factor is 1.8. The actual multiplicative factor will be smaller because the assumption of a full loss of residues is too optimistic. For instance, the water solubility of 2,4-D and thiabendazole will enable a partial transfer of these compounds to orange juice. b) In many other countries, the effect of processing is expected to be in the same range as Germany, with some variation based on sensitivity analysis C (•/•, consensus). In Belgium, Ireland, Finland, Latvia and Netherlands, however, some experts estimated that the impact may exceed a factor 2 (•/+ or •/++, range of opinions), based on sensitivity analysis C.	Note 31
U32 (Use of PFs in the EFSA food classification and description system (FoodEx))	•/• (consensus)	No consensus discussion took place. The rationale is derived from the individual judgements. a) Only one PF was used for substances driving the risk (thiabendazole/oranges and mandarins/peeling). This is a very straightforward processing type, not subject to substantial variations. b) No differences are expected between populations	Note 32
U33 (analytical uncertainty for PFs)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) Same rationale as for CAG-DAC b) Same rationale as for CAG-DAC	–
U34 (accuracy of PFs)	•/• (consensus)	No consensus discussion took place, but all individual judgements were identical. a) Same rationale as for CAG-DAC b) Same rationale as for CAG-DAC	Note 33
U35 (use of fixed values of PFs)	•/• or –/+ (range of opinions)	No consensus discussion took place. The rationale is derived from the individual judgements. a) A limited number of PFs have been used. The observed range of PFs between independent studies can be 2–5 times the median value. Using a distribution of PFs would either increase of decrease the MOET at the percentile of interest. Some experts estimated that the impact would not exceed 20%, but other experts considered that a marginal exceedance cannot be ruled out. b) No differences are expected between populations	Note 34
U36 (effect of peeling of commodities with edible peel and of washing disregarded)	•/• to •/+ (range of opinions)	No consensus discussion took place. The rationale is derived from the individual judgements. a and b) Solving this source of uncertainty can only increase the MOET. Some experts estimated that the impact would be smaller than 20%, and others that it could exceed this threshold. The impact can be larger in some countries than in Germany. The contribution, to the exposures exceeding the 99th percentile, of consumption events of commodities for	Note 35

Source of uncertainty	Consensus judgement	Consensus rationale a) EKE Q1A; b) EKE Q1B	Information notes
		which the processing is not reported (identifiable by the facet '*PROCESS=Unspecified*' in Table C.02 of Annex D2), and therefore not covered by sensitivity analysis C, is variable from one country to the other. This contribution gives insight into the potential impact on the washing and peeling of commodities which are not further process. It is likely that pregnant women wash and peel commodities more frequently than the general population for reason of hygiene. However, the available information indicates that washing and peeling of commodities do not necessarily remove all residue present. The issue caused by the large contribution to exposures above the 99th percentile (8%) of consumption events of wine grapes with the facet 'PROCESS=Unspecified' in the German population was raised during the expert discussion, but not integrated in the consensus judgement. It was rather agreed to considered it under EKE Q2 and EKE Q3.	
U37 (Use of NOAEL to characterise the substances in the CAG)		Assessment not possible. See Section 3.3.2	Note 36
U38 (adequacy of the dose-addition model)	•/• or –/+ (range of opinions)	No consensus discussion took place. The rationale is derived from the individual judgements. a) Even if recently published data show that dose-addition can be applied for different types of phenomenological outcomes irrespective of differences in MIE or KEs, experimental confirmatory data are not available for this type of effect. Synergistic interactions are not expected considering the exposure level, the rarity of scientific papers reporting this type of observation and the absence of biologically plausible hypothesis for the effect under consideration. In addition, the observation of the pattern of exposure indicates that less than 20% consumers at the percentiles of interest are exposed within the same day to at least 2 substances contributing to at least 20% of the cumulative exposure. Most of the experts considered that perfect knowledge about the mode of combination of effects of the substances included in the CAG would not impact the MOET by more than 20%, but one considered that a marginal exceedance of this threshold was plausible. b) No differences are expected between populations.	Note 37
U39 (adequacy of the exposure calculation model)	•/• to –/+ (range of opinions)	a) Same rationale as for CAG-DAC b) Same rationale as for CAG-DAC	Note 38
U40 (adequacy of the combination of occurrence and consumption data)	•/• (consensus)	a) Same rationale as for CAG-DAC b) Same rationale as for CAG-DAC	Note 39
U41 (adequacy of the UF for intraspecies variability)	Not assessed	See Section 3.3.1	Note 40

Appendix H – EKE Q2 toxicology - Record of judgements and reasoning

The EKE Q2 for uncertainties related to toxicology was worded as follows: '*If all the identified sources of uncertainty relating to toxicology were fully resolved (e.g. by obtaining perfect information on the issues involved) and addressed in the modelling, by what multiplicative factor would this change the median estimate for the MOET at the 99.9th percentile of exposure for [craniofacial alterations due to abnormal skeletal development/head soft tissues alterations and brain neural tube defects] in the German population of women in childbearing age at Tier II?*'

As explained in Section 3.3.2, U2 and U37 are not covered by the question above.

The facilitator explained the concept of consensus used in the Sheffield method for EKE (EFSA, 2014a): although their personal opinions may differ, the experts are asked to agree on what it would be reasonable for a RIO to think, having seen the evidence and individual judgements and heard the discussion. To develop such a consensus for EKE Q2 on exposure, the experts discussed the relative magnitudes of the individual uncertainties and how they would combine, taking into account the identified dependencies between them, i.e. positively, negatively dependent or independent uncertainties.

CAG-DAC

General considerations:

The experts agreed that the most impactful uncertainties are U1 (substances causing the effect and not included in the CAG), U4 (uncertainty concerning the assessment methodology) and U5 (uncertainty resulting from the study design of the critical study).

The experts postulated some degree of dependency between U6 (uncertainty concerning from the quality of key studies), on one hand and U4 and U5 on the other hand. If U6 was resolved, i.e. if the study had the perfect quality and was conducted according to the most recent version of the OECD TG 414, this would lower the impact of U5 and U4. The dependency between U4, U5 and U6 was considered to have a low magnitude and it was not concluded whether the dependency was positive or negative. A potential dependency between U3 (uncertainty concerning the data collection) and U4 was also postulated.

Sources of uncertainty with consensus judgements (./.) not influencing the MOET in one direction only, were expected to have a minor impact and cancel one another.

Results and discussion:

The *sources of uncertainty most influencing the distribution towards high values of the multiplicative factor* are U4 and U5. More precisely, it was considered that:

- For 2 substances, including folpet, the NOAEL was set by default, applying an UF of 10 to the LOAEL (U4)
- The use of single staining could have resulted in some instances in a misclassification of delayed ossification as malformations and that the dosing of animals by gavage in developmental toxicity studies tend to lead to conservative NOAELs (U5).

U6 may also further contribute to shifting the distribution towards high values, but to a lesser extent.

Based on these considerations, the experts judged that the combined impact of the exposure uncertainties would increase the MOET up to a maximum factor of 2.0 and suggested a provisional *upper plausible bound of 2.0*.[35]

The *source of uncertainty most influencing the distribution towards low values of the multiplicative factor* is U1 because the acute HQ at percentile 99.9 of certain active substances causing the effect, but not included in CAG-DAC, exceeds 0.1. The experts agreed on a provisional *lower plausible bound of 0.7*.[36]

Further judgements were elicited using the probability method (Oakley and O'Hagan, 2016), which is described in EFSA (2014a) as the fixed interval method. In this method the experts were asked to judge the probability that the quantity of interest lies between a specified value and the lower or upper bound. For this purpose, the facilitator chose three values in different parts of the plausible range, favouring regions where differences between the individual distributions were most marked.

[35] The probability that the actual multiplicative factor is above the upper bound is less than 1%.
[36] The probability that the actual multiplicative factor is below the lower bound is less than 1%.

Specifically, the experts were asked the three questions shown below. For each question a range of answers was discussed, and a provisional consensus was agreed. Distributions were fitted to the provisional consensus probabilities on SHELF tool (MATCH was not performing) and displayed for review by the experts.

- *What is the probability for the true value of the multiplicative factor of the MOET to be lower than 1?*

Provisional consensus: 17%

- *What is the probability for the true value of the multiplicative factor of the MOET to be higher than 1.5?*

Provisional consensus: 35%

- *What is the probability for the true value of the multiplicative factor of the MOET to be lower than 1.25?*

Provisional consensus: 45%

The best-fitting of the distributions available on SHELF for these provisional judgements was the Beta, with a 90% probability interval from 0.82 to 1.86 and a median of 1.33. This distribution (first provisional consensus distribution) is shown in Figure H.1.

The experts were asked whether they considered this distribution appropriate to represent their consensus judgement on EKE Q2, i.e. what it would be reasonable for a RIO to think, having seen the evidence and individual judgements and heard the discussion. There was a general agreement that this distribution was very wide in the middle part, suggesting that the median value is uncertain. Additionally, the experts thought that more weight should be given to the lower end to better reflect their judgements. Thus, the lower plausible bound was raised to 0.8 and the following input values were inserted in the SHELF tool:

- Probability for the true value to be lower than 1: 18%
- Probability for the true value to be higher than 1.5: 35%
- Probability for the true value to be lower than 1.25: 43%

This resulted to the Beta distribution in Figure H.2 (second provisional consensus distribution) with a 90% probability interval from 0.86 to 1.89 and a median of 1.32.

The shape of this alternative distribution was found to not reflect the experts' judgements. The main reason was the too wide range of values with similar plausibility.

A third beta distribution was investigated to increase the probability density between 1 and 1.5 (Figure H.3) with the following parameters:

- Lower bound 0.7
- Upper bound 2.5
- Probability for the true value to be lower than 1: 17%
- Probability for the true value to be higher than 1.5: 31%
- Probability for the true value to be lower than 1.25: 43%

This distribution has a 90% probability interval from 0.86 to 1.94 and a median of 1.31. The experts judged that this distribution reflects better their consensus judgements. Although it exceeds the provisional upper plausible bound and extends to 2.5, the probability for the multiplicative factor of the MOET to be above 2.0 is only 3% and considered acceptable. Furthermore, this distribution (i) reflects adequately the resulting impact of the most influential uncertainties, with a multiplicative factor more likely above 1 and closer to 1 than 2, and (ii) reflects the range of individual judgements, the range of plausible values and their respective probabilities. Therefore, the distribution in Figure 18 was adopted as consensus distribution.

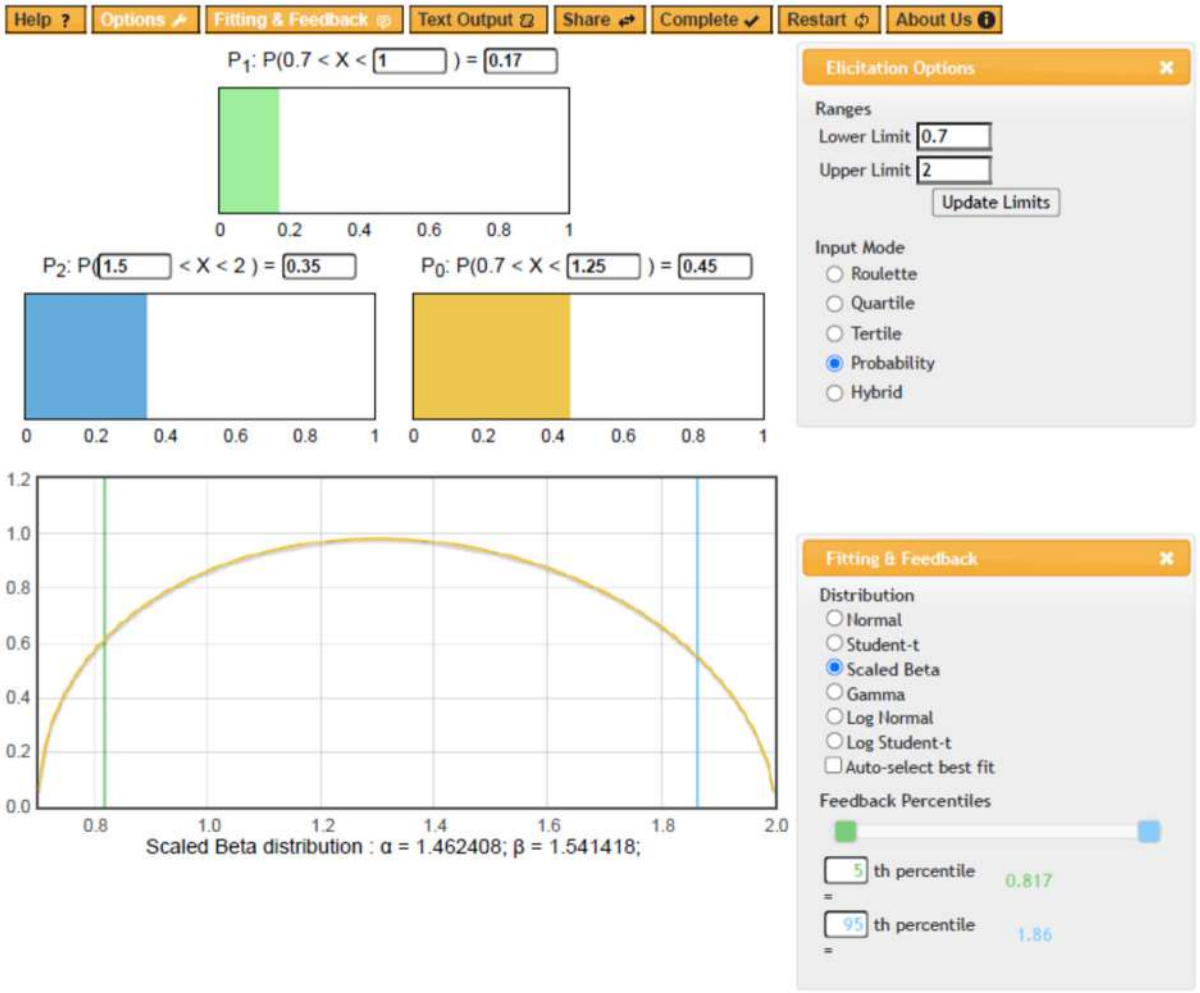


Figure H.1: CAG-DAC – Multiplicative factor for toxicology uncertainties: First provisional consensus distribution. Beta with median of 1.33 and 90% probability interval of 0.82–1.86

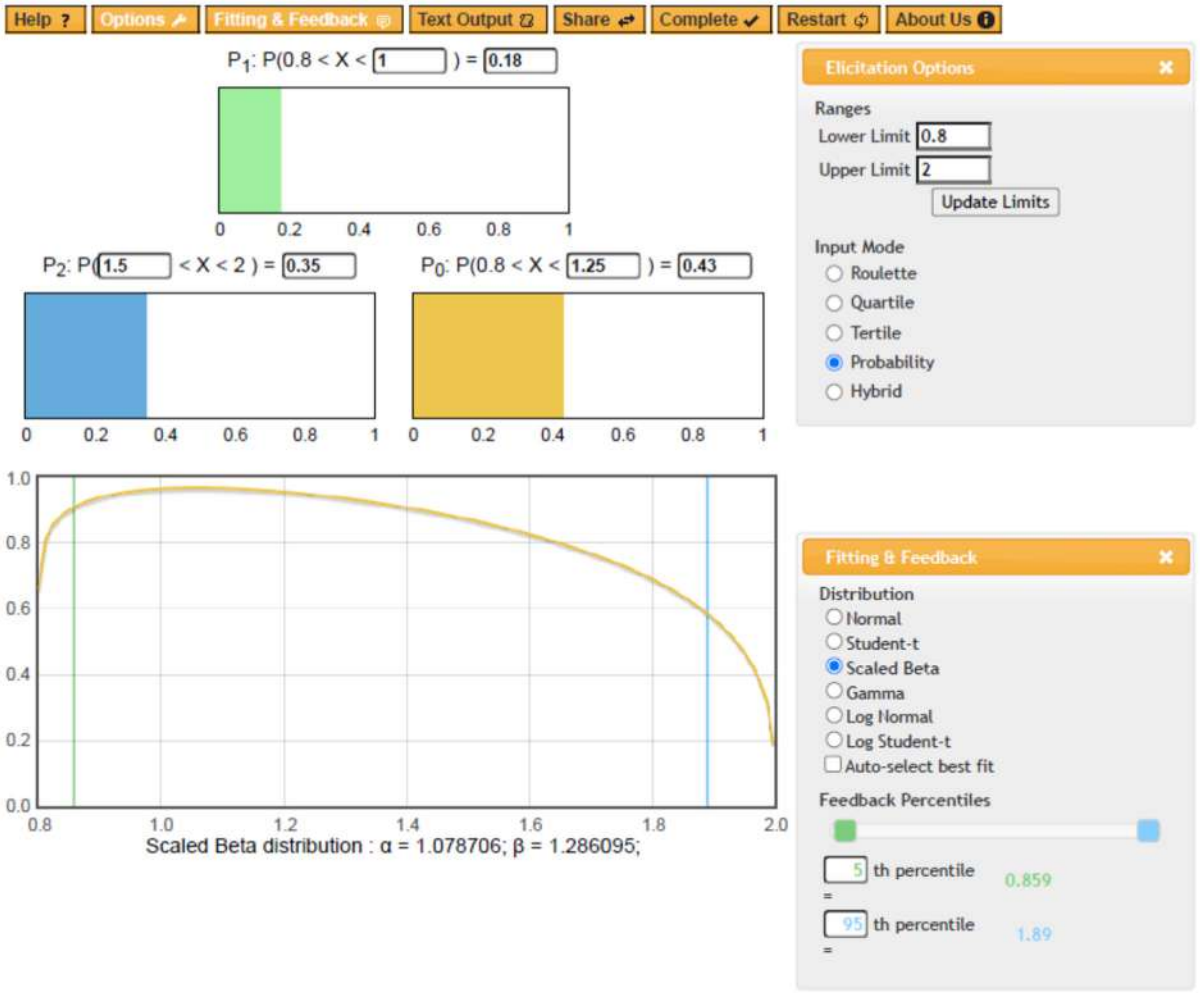


Figure H.2: CAG-DAC – Multiplicative factor for toxicology uncertainties: Second provisional consensus distribution. Beta with median of 1.32 and 90% probability interval of 0.86–1.88

Figure H.3: CAG-DAC – Multiplicative factor for toxicology uncertainties: Consensus distribution. Beta with median of 1.31 and 90% probability interval of 0.86–1.94

CAG-DAH

General considerations:

The experts agreed that the most influential sources of uncertainty are U1 (substances causing the effect and not included in the CAG), U4 (uncertainty concerning the assessment methodology) and U6 (uncertainty associated with the quality of key studies).

The experts postulated some degree of dependency between U6 (uncertainty resulting from the quality of key studies), on one hand and U4 and U5 on the other hand. If U6 was resolved, i.e. if the study had the perfect quality and was conducted according to the most recent version of the OECD TG 414, this would lower the impact of U5 and U4. The dependency between U4, U5 and U6 was considered to have a low magnitude and it was not concluded whether the dependency was positive or negative. A potential dependency between U3 (uncertainty concerning the data collection) and U4 was also postulated.

Sources of uncertainty with consensus judgements (./.) not shown to influence the MOET in one direction only, would be expected to have a minor impact and cancel one another.

Results and discussion:

The *source of uncertainty most influencing the distribution towards high values of the multiplicative factor* is U6. This is explained by the tendency to set NOAELs conservatively in case of studies of suboptimal quality (e.g. not performed according to the most recent version of the OECD TG 414). The experts agreed on a provisional *upper plausible bound of 1.5*.

The *source of uncertainty most influencing the distribution towards low values of the multiplicative factor* are U1 because the acute HQ at percentile 99.9 of certain active substances causing the effect,

but not included in CAG-DAH, exceeds 0.1, and U4 because studies were combined to derive the NOAELs of 2 risk drivers (thiabendazole and deltamethrin). The experts agreed on a provisional *lower plausible bound of 0.5*.

Further judgements were elicited using the probability method (Oakley and O'Hagan, 2016), which is described in EFSA (2014a) as the fixed interval method. In this method the experts were asked to judge the probability that the quantity of interest lies between a specified value and the lower or upper bound. For this purpose, the facilitator chose three values in different parts of the plausible range, favouring regions where differences between the individual distributions were most marked. Specifically, the experts were asked the three questions shown below. For each question a range of answers was discussed, and a provisional consensus was agreed. Distributions were fitted to the provisional consensus probabilities using the MATCH (and SHELF) tools and displayed for review by the experts.

- *What is the probability for the true value of the multiplicative factor of the MOET to be lower than 0.8?*

Provisional consensus: 20%

- *What is the probability for the true value of the multiplicative factor of the MOET to be higher than 1.2?*

Provisional consensus: 25%

- *What is the probability for the true value of the multiplicative factor of the MOET to be lower than 1.0?*

Provisional consensus: 45%

The best-fitting of the distributions available in MATCH for these provisional judgements was the Scaled-Beta, with a 90% probability interval from 0.64 to 1.39 and a median of 1.03. This distribution is shown in Figure H.4.

The experts were asked whether they considered this distribution appropriate to represent their consensus judgement on EKE Q2, i.e. what it would be reasonable for a RIO to think, having seen the evidence and individual judgements and heard the discussion. There was a general agreement that this distribution reflects the experts' judgements and range of opinions. This distribution (i) reflects adequately the expected overall impact resulting from the most influential uncertainties, with a multiplicative factor very close to 1, (ii) reflects the range of individual judgements, the range of plausible values and their respective probabilities and (iii) allows for decreases of the MOET by a larger magnitude than the increases.

Therefore, this distribution was adopted as consensus distribution.

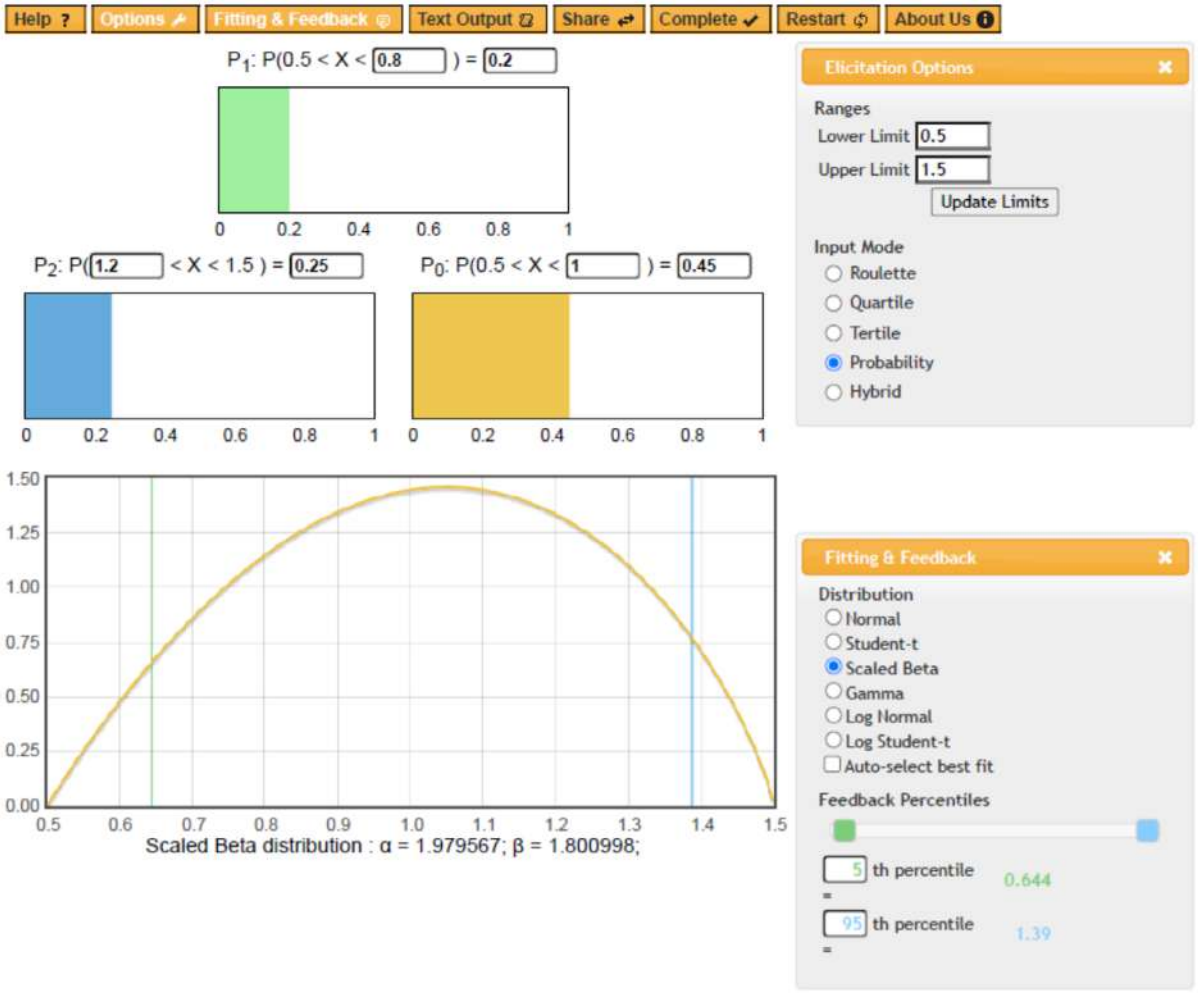


Figure H.4: CAG-DAH – Multiplicative factor for toxicology uncertainties: Provisional and consensus distribution. Scaled-Beta with median of 1.03 and 90% probability interval of 0.64–1.39

Appendix I – EKE Q2 exposure - Record of judgements and reasoning

The EKE Q2 for uncertainties related to exposure was worded as follows: '*If all the identified sources of uncertainty relating to exposure were fully resolved (e.g. by obtaining perfect information on the issues involved) and addressed in the modelling, by what multiplicative factor would this change the median estimate for the MOET at the 99.9th percentile of exposure for [craniofacial alterations due to abnormal skeletal development/head soft tissues alterations and brain neural tube defects] in the German population of women in childbearing age at Tier II?*'

The facilitator explained the concept of consensus used in the Sheffield method for EKE (EFSA, 2014a): although their personal opinions may differ, the experts are asked to agree on what it would be reasonable for a RIO to think, having seen the evidence and individual judgements and heard the discussion. To develop such a consensus for EKE Q2 on exposure, the experts discussed the relative magnitudes of the individual uncertainties and how they would combine, taking into account the identified dependencies between them, i.e. positively, negatively dependent or independent uncertainties.

CAG-DAC

General considerations:

The experts considered that the uncertainty related to the alcohol consumption during pregnancy (U13) has the highest impact on the MOET and the probability distribution of the multiplicative factor. This uncertainty would impact the distribution towards high values of the multiplicative factor.

In contrast, the experts judged that U7 (excluded commodities), and U14/U21 (sampling variability of consumption/occurrence data) affect the distribution of multiplicative factors towards the opposite direction, i.e. towards low values of the multiplicative factor.

Some experts identified a positive dependency between U14 and U21 because they are both affected, presumably in similar intensity, by the sampling bias affecting skewed distributions. If the real multiplicative factor reflecting the impact of sampling bias is close to one or the other edge of the range that could be estimated specifically for consumption data, it can be reasonably anticipated that it would be close to the same edge for occurrence data. Although the impact of U14 and U21 was estimated in a combined assessment under EKE Q1, the possibility of a positive dependency was not considered at that stage. Not all experts shared this view and a range of opinions on the potential dependency between U14 and U21 was recorded.

Sources of uncertainty with consensus judgements (./.) not influencing the MOET in one direction only were expected to have a minor impact and cancel one another.

Results and discussion:

The *source of uncertainty most influencing the distribution towards high values of the multiplicative factor* is U13 (uncertainty on alcohol consumption during pregnancy, expected to decrease during pregnancy). For the German population specifically, the possible misclassification of consumption events reported as consumption of wine grapes with unspecific process further contributes to move the distribution towards high values (see Section 3.3.2).

Based on these considerations, the experts judged that the combined impact of the exposure uncertainties would increase the MOET up to a maximum factor of 3.5 and suggested a *provisional upper plausible bound of 3.5*.[37]

The *sources of uncertainty most influencing the distribution towards low values of the multiplicative factor* were U7 (excluded commodities), U14/U21 (sampling variability of consumption and occurrence data).

U9 (under-reporting of alcohol consumption) may also further contribute to shifting the distribution to lower values, but at a lower extent.

Based on these considerations, the experts agreed on a *provisional lower plausible bound of 0.4*.[38]

Further judgements were elicited using the probability method (Oakley and O'Hagan, 2016), which is described in EFSA (2014a) as the fixed interval method. In this method the experts were asked to judge the probability that the quantity of interest lies between a specified value and the lower or upper bound. For this purpose, the facilitator chose three values in different parts of the plausible range, favouring regions where differences between the individual distributions were most marked.

[37] The probability that the actual multiplicative factor is above the upper plausible bound is less than 1%.
[38] The probability that the actual multiplicative factor is below the lower plausible bound is less than 1%.

Specifically, the experts were asked the three questions shown below. For each question a range of answers was discussed, and a provisional consensus was agreed. Distributions were fitted to the provisional consensus probabilities using the MATCH tool and displayed for review by the experts.

- *What is the probability for the true value of the multiplicative factor of the MOET to be lower than 1?*

Provisional consensus: 10%

- *What is the probability for the true value of the multiplicative factor of the MOET to be higher than 2?*

Provisional consensus: 15%

- *What is the probability for the true value of the multiplicative factor of the MOET to be lower than 1.5?*

Provisional consensus: 40%, with a high variability in the experts' answers.

The best-fitting of the distributions available in MATCH for these provisional judgements was the Scaled Beta, with a 90% probability interval from 0.96 to 2.30 and a median of 1.58. This distribution is shown in Figure I.1.

The experts were asked whether they considered this distribution appropriate to represent their consensus judgement on EKE Q2, i.e. what it would be reasonable for a RIO to think, having seen the evidence and individual judgements and heard the discussion. There was a general agreement that the median and lower bound of this provisional distribution should move to the left in order to balance the impact of U7, U14/21 and U9. Therefore, the following input values were inserted in the MATCH tool:

- Probability for the true value to be lower than 1: 12%
- Probability for the true value to be higher than 2: 15%
- Probability for the true value to be lower than 1.5: 50%

This resulted in several possible distributions, of which a scaled Beta distribution with a 90% probability interval from 0.85 to 2.30 and a median of 1.50 was found to best reflect the views of the group (Figure I.2). It covers the group consensus regarding the probability interval and median values. It is appropriately skewed, and it also considers the range of opinions on the upper end of the distribution which is reflected by an upper limit of 3.5.

An alternative Scaled Beta distribution was proposed, giving a bit more probability between 1.5 and 2 by reducing the upper bound. This distribution had a 90% probability interval from 0.83 to 2.26 and a median of 1.50 (Figure I.3) but was not considered further because it was very similar to the previous one.

The experts retained the distribution of Figure I.2 as final consensus distribution.

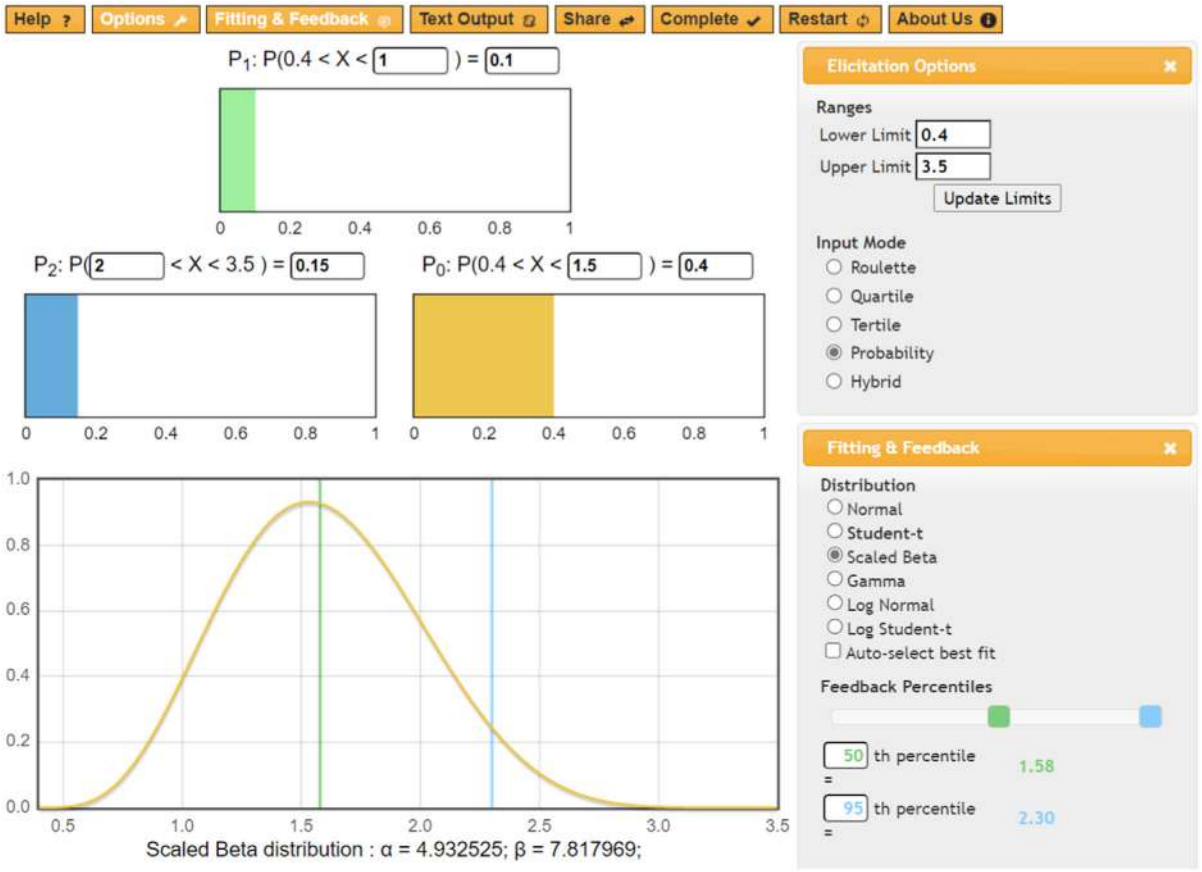


Figure I.1: CAG-DAC – Multiplicative factor for exposure uncertainties: First provisional consensus distribution. Scaled Beta with median of 1.58 and 90% probability interval of 0.96–2.30

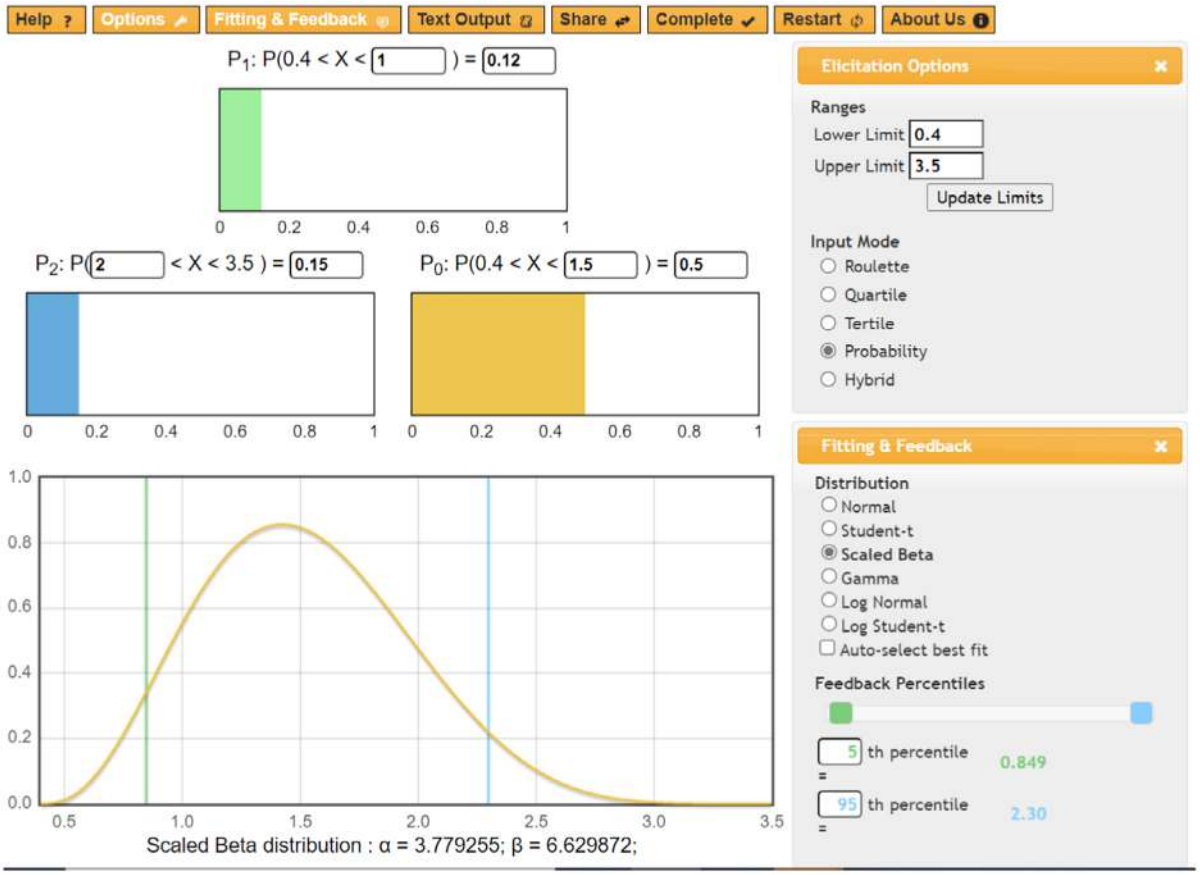


Figure I.2: CAG-DAC – Multiplicative factor for exposure uncertainties: Consensus distribution. Scaled Beta with median of 1.50 and 90% probability interval of 0.85–2.30

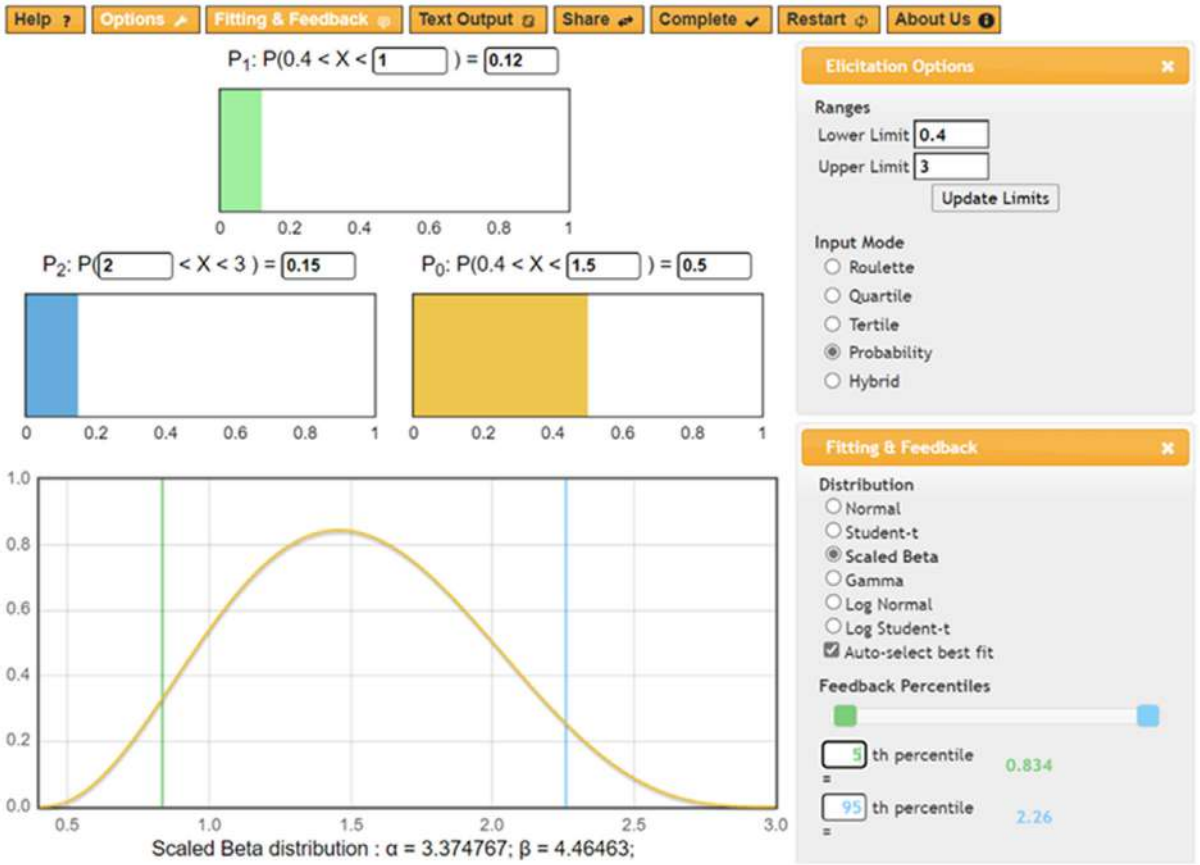


Figure I.3: CAG-DAC – Multiplicative factor for exposure uncertainties: Alternative distribution. Scaled Beta with median of 1.50 and 90% probability interval of 0.83–2.26

CAG-DAH

General considerations:

The experts considered that U31 (missing PFs) has the highest impact on the MOET and the probability distribution of the multiplicative factor. This uncertainty would influence the distribution towards high values of multiplicative factors.

In contrast, the experts judged that U7 (excluded commodities) and U14/U21 (sampling variability of consumption/occurrence data) affect the distribution of multiplicative factors in the opposite direction, i.e. towards low values.

Some experts identified a positive dependency between U14 and U21 because they are both affected, presumably in similar intensity, by the sampling bias affecting skewed distributions. If the real multiplicative factor of sampling bias is close to one or the other edge of the range that could be estimated specifically for consumption data, it can be reasonably anticipated that it would be close to the same edge for occurrence data. Although the impact of U14 and U21 was estimated in a combined assessment under EKE Q1, the possibility of a positive dependency was not considered at that stage. Not all experts shared this view and a range of opinions on the potential dependency between U14 and U21 was recorded.

A potential dependency between U32 (Uncertainty about the assignment of PFs to food items in FoodEx) and U35 (use of fixed values of PFs) was postulated, but it was unclear whether it would be a positive or negative dependency. The experts agreed, however, that the impact of such dependency would be minor, considering that the use of PFs concerned a minority of all possible pesticide/commodity/processing types.

Sources of uncertainty with consensus judgements (./.) not influencing the MOET in one direction only were expected to have a minor impact and cancel one another.

Results and discussion:

The *source of uncertainty most influencing the distribution towards high values of the multiplicative factor* is U31. The impact of this source of uncertainty was discussed and the following points were considered:

a) Sensitivity analysis C (Section 3.2.3) suggests that the MOET would increase by a factor of 1.8 for the German population if residues do not transfer to processed food. A major part of this increase is due to the fact that the contribution of 2,4-D and thiabendazole (in total 45% of the exposures above the 99th percentile – See Annex D2, Table C.02) through the consumption of orange juice is taken out of the calculation.
b) Considering the water-solubility of 2,4-D and thiabendazole, some transfer of residues from the peel to the juice during industrial processes and on-site juice extraction in super-markets, restaurants, etc., is expected. This does not apply when orange juice is extracted manually in household conditions as the contact between the juice and the orange peel is restricted in this case.
c) The Working Group did not have information about the frequency of a washing step prior to the industrial extraction of juice.
d) Thiabendazole and 2,4-D are used for post-harvest treatment of oranges. This is assumed to concern in first instance oranges to be marketed as raw commodities for the final consumer. Data or references from literature were however not available to the Working Group regarding the applicability and frequency of this treatment in case of oranges intended for the juice industry.

The above suggests that this source of uncertainty would increase the MOET by more than 20% but less than a factor of 2. The most plausible value of the multiplicative factor was agreed to be between 1.5 and 1.8.

Based on these considerations, the experts judged that the combined impact of the exposure uncertainties would increase the MOET up to a factor of 2 maximum and concluded for a *provisional upper plausible bound of 2*.

The *sources of uncertainty most influencing the distribution towards low values of the multiplicative factor* were U7 (excluded commodities) and U14/U21 (sampling variability of consumption/occurrence data).

U9 (under-reporting of alcohol consumption) and U17 (contribution of metabolites) might also further contribute to shifting the distribution towards low values, but to a lesser extent.

Based on these considerations, the experts agreed on a *provisional lower plausible bound of 0.4*.

Further judgements were elicited using the probability method (Oakley and O'Hagan, 2016), which is described in EFSA (2014a) as the fixed interval method. In this method the experts were asked to judge the probability that the quantity of interest lies between a specified value and the lower or upper bound. For this purpose, the facilitator chose three values in different parts of the plausible range, favouring regions where differences between the individual distributions were most marked. Specifically, the experts were asked the three questions shown below. For each question a range of answers was discussed, and a provisional consensus was agreed. Distributions were fitted to the provisional consensus probabilities using the MATCH tool and displayed for review by the experts.

- *What is the probability for the true value of the multiplicative factor of the MOET to be lower than 1?*

Provisional consensus: 20%, with high variability in the experts' answers.

- *What is the probability for the true value of the multiplicative factor of the MOET to be higher than 1.5?*

Provisional consensus: 12%

- *What is the probability for the true value of the multiplicative factor of the MOET to be lower than 1.25?*

Provisional consensus: 55%, with high variability in the experts' answers.

The best-fitting of the distributions available in MATCH for these provisional judgements was the Scaled Beta, with a 90% probability interval from 0.81 to 1.58 and a median of 1.22. This distribution is shown in Figure I.4.

The experts were asked whether they considered this distribution appropriate to represent their consensus judgement on EKE Q2, i.e. what it would be reasonable for a RIO to think, having seen the evidence and individual judgements and heard the discussion.

There was a general agreement that the median and lower bounds of this provisional distribution should shift to the left in order to balance the impact of U7, U14/21, U9 and U17. Therefore, the lower plausible bound was set at 0.3 and the following input values were inserted in the MATCH tool:

- Probability for the true value to be lower than 1: 30%
- Probability for the true value to be higher than 2: 20%
- Probability for the true value to be lower than 1.25: 55%

This resulted in several possible distributions, of which a scaled Beta distribution with a 90% probability interval from 0.64 to 1.73 and a median of 1.20 was found to best reflect the views of the group (Figure I.5). This distribution was retained as final consensus distribution. It covers the group consensus regarding the probability interval and median values.

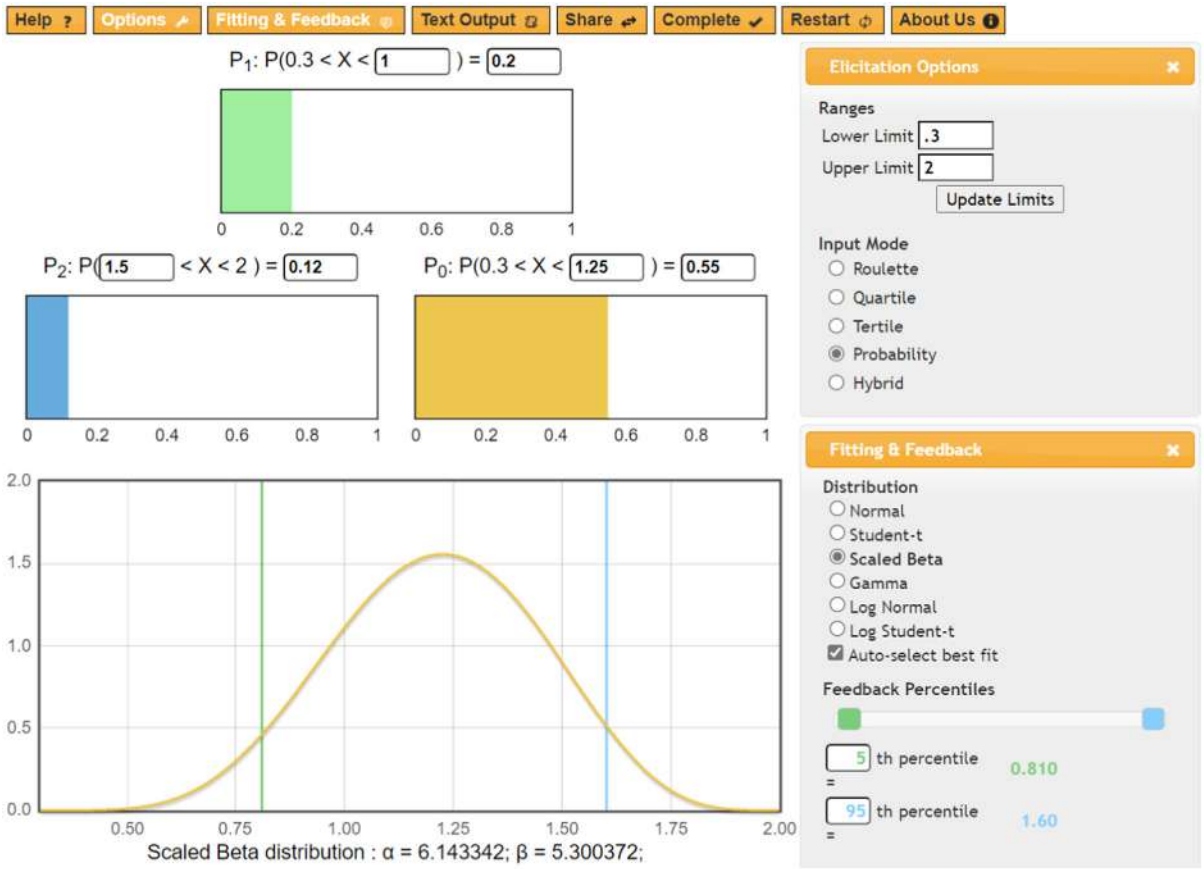


Figure I.4: CAG-DAH – Multiplicative factor for exposure uncertainties: First provisional consensus distribution. Scaled Beta with median of 1.22 and 90% probability interval of 0.81–1.58

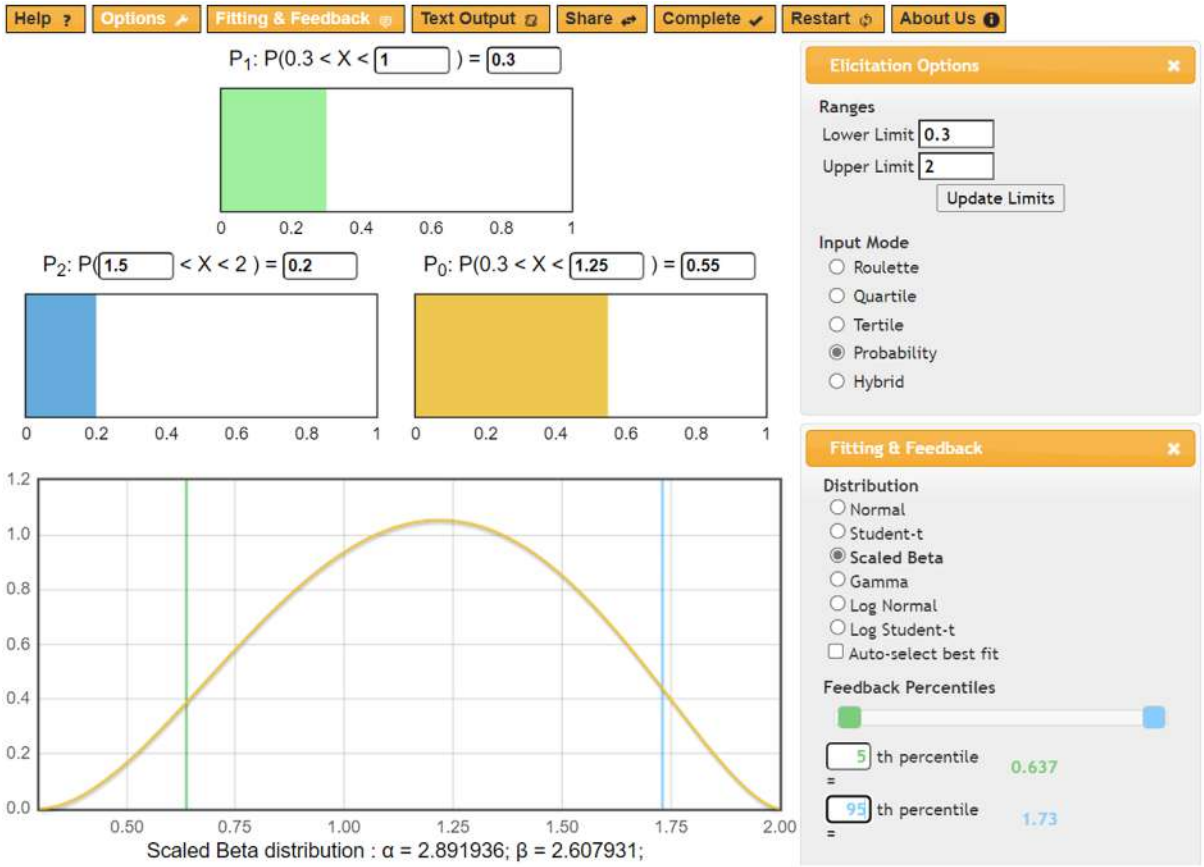


Figure I.5: CAG-DAH – Multiplicative factor for exposure uncertainties: Consensus distribution. Scaled Beta with median of 1.20 and 90% probability interval of 0.64–1.73

Appendix J1 – EKE Q3 CAG-DAC - Record of judgements and reasoning

The EKE Q3 was worded as follows:

For the German population: '*If all the uncertainties in the model, exposure assessment, hazard identification and characterisation and their dependencies were fully resolved (e.g. by obtaining perfect information on the issues involved) and addressed in the modelling, what is your probability that this would result in the MOET for the 99.9th percentile of exposure for the German population in 2017–2019 being below [100/500]?*'

For each of the other 13 populations: '*If all the uncertainties in the model, exposure assessment, hazard identification and characterisation and their dependencies, and differences in these between populations, were fully resolved (e.g. by obtaining perfect information on the issues involved) and addressed in the modelling, what is your probability that this would result in the MOET for the 99.9th percentile of exposure for the [name of the population] in 2017–2019 being below [100/500]?*'

General considerations

In their judgements, the experts considered the following information:

- Boxplots for the MOET distributions at 99.9th percentile of exposure for the 14 populations as calculated by Monte Carlo simulations combining the outputs from the Tier II exposure model with the probability distributions of the multiplicative factor for the exposure and toxicology uncertainties as derived under EKE Q2 for the German population (Figure 9 and Table 28).
- The estimated probability of the MOET at 99.9th percentile of exposure per population being below the regulatory threshold of 100/500 assuming that all exposure and toxicological uncertainties are independent (rho=0) and, in all populations, the same as for the German population (Table 28).
- The estimated probability of the MOET at 99.9th percentile of exposure per population being below 100/500 assuming different degrees of dependency between uncertainties on exposure and toxicology indicated in Tables J.1 and J.2.

Table J.1: CGA-DAC - Effect of dependencies between uncertainties in toxicology and exposure on the probability of the MOET at the 99.9th percentile of exposure being below 100

Country	Q2 probability assuming independence (%) rho = 0	Q2 probability with negative dependency (%) rho =				Q2 probability with positive dependency (%) rho =			
		−1	−0.75	−0.5	−0.25	+0.25	+0.5	+0.75	+1
BE – Belgium	0.19	0.0	0.0	0.0	0.1	0.5	0.8	1.2	1.8
CZ – Czechia	3.2	0.0	0.1	0.8	1.8	4.6	6.1	7.5	9.0
DE -Germany	4.8	0.0	0.2	1.4	3.1	6.6	8.4	10	12
DK -Denmark	1.3	0.0	0.0	0.2	0.7	2.1	3.0	3.9	5.0
ES – Spain	0.1	0.0	0.0	0.0	0.0	0.3	0.6	0.9	1.4
FI – Finland	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
FR – France	0.7	0.0	0.0	0.1	0.3	1.3	2.1	2.9	3.8
HU – Hungary	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2
IE – Ireland	23	5.1	13	17	21	25	27	28	29
IT – Italy	0.1	0.0	0.0	0.0	0.0	0.2	0.3	0.6	0.9
LV – Latvia	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NL – Netherlands	0.3	0.0	0.0	0.0	0.1	0.6	1.1	1.6	2.2
RO – Romania	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SE – Sweden	1.6	0.0	0.0	0.3	0.8	2.5	3.6	4.7	5.9

Table J.2: CGA-DAC - Effect of dependencies between uncertainties in toxicology and exposure on the probability of the MOET at 99.9th percentile of exposure being below 500

Country	Q2 probability assuming independence (%) rho = 0	Q2 probability with negative dependency (%) rho =				Q2 probability with positive dependency (%) rho =			
		−1	−0.75	−0.5	−0.25	+0.25	+0.5	+0.75	+1
BE – Belgium	81	100	93	88	84	78	76	74	72
CZ – Czechia	97	100	100	99	99	96	95	94	92
DE -Germany	99	100	100	100	99	98	97	96	95
DK -Denmark	93	100	99	97	95	91	88	87	85
ES – Spain	76	98	89	84	80	74	72	70	69
FI – Finland	37	16	29	33	35	38	39	39	40
FR – France	91	100	99	97	94	89	86	84	83
HU – Hungary	48	44	47	48	48	48	48	48	48
IE – Ireland	100	100	100	100	100	100	100	100	100
IT – Italy	71	97	85	79	75	69	67	66	65
LV – Latvia	39	20	32	36	37	40	40	41	41
NL – Netherlands	84	100	95	91	87	81	79	77	75
RO – Romania	41	19	35	38	40	42	42	43	43
SE – Sweden	94	100	99	98	96	92	91	89	87

- The elicited CAG-membership probabilities for the 6 risk drivers of CAG-DAC and reported in Note 2 of Appendix F.
- The results from calculations showing how applying the CAG membership probabilities for folpet would change the MOET distributions produced by the Tier II exposure model. The results of these calculations are reported in Information Note 2 in Appendix F.

For the assessment of differences between populations, the following additional information was also considered by the experts:

- The sources of uncertainty identified to have different impact between populations in response to EKE Q1b (Appendix G1).
- The results of the sensitivity analyses (see Table 20). In these sensitivity analyses, the impact in the different populations is reflected by the intensity of change of the median estimate of the MOET. To facilitate the comparison between populations, ratios of the median MOET at 99.9th percentile of exposure obtained in sensitivity analyses C, G and K (sensitivity analyses showing the largest impacts) to the respective median MOET in the Tier II calculation were summarised in Table J.3.

Table J.3: CAG-DAC: Median MOET estimates at 99.9th percentile of exposure in Tier II and most important sensitivity analyses

	BE	CZ	DK	DE	ES	FI	FR	HU	IE	IT	LV	NL	RO	SE
Tier II	179	119	146	107	194	294	148	267	73.5	203	298	173	288	134
SA C	199 *1.1*	123 *1.0*	145 *1.0*	109 *1.0*	232 *1.2*	433 *1.5*	171 *1.2*	288 *1.1*	107 *1.5*	216 *1.1*	378 *1.4*	215 *1.2*	316 *1.1*	156 *1.2*
SA G	402 *2.3*	397 *3.3*	472 *3.3*	140 *1.3*	328 *1.7*	368 *1.3*	373 *2.5*	385 *1.4*	576 *7.8*	405 *2.0*	390 *1.3*	390 *2.3*	341 *1.2*	435 *3.2*
SA K	135 *0.75*	109 *0.92*	133 *0.91*	96.4 *0.90*	132 *0.68*	174 *0.59*	119 *0.80*	148 *0.55*	68.4 *0.93*	159 *0.78*	217 *0.73*	121 *0.70*	134 *0.47*	119 *0.89*

SA C: sensitivity analysis C (assuming no transfer to processed commodities when PFs are not available); SA G: sensitivity analysis G (assuming total alcohol abstinence during pregnancy); SA K: sensitivity analysis K (assuming that propineb and thiram were authorised during the reference period and that dithiocarbamates were completely converted into ETU and PTU during food transformation processes that involve heating).
Ratios between the median MOET observed in the sensitivity analysis and the median Tier II MOET of the respective population are shown in italics.

- About 39% of the exposure in the German population for subjects with exposure exceeding the 99th percentile, as calculated by the model, was resulting from the consumption of wine grapes with the facet '*PROCESS=Unspecified*' (see Section 3.3.2.1.1). This was a source of underestimation of the MOET taken in consideration during the EKE Q2 elicitation for exposure uncertainties and was one of the factors most influencing the distribution of multiplicative factors towards high values. However, this concerned the German population only.

In addition, the experts considered:

- The results from calculations showing how shifting the MOET distributions, as obtained by combining the output of the Tier II exposure model with the probability distributions of the multiplicative factors of the MOET for the exposure and toxicology uncertainties derived under EKE Q2 for the German population, up or down to reflect the impact of CAG-membership probability and differences with the German population would affect the probability of MOET<100/500 for each population assuming different degrees of dependency. They are reported under the paragraphs dealing with each population in Tables J.4–J.31.

Results and discussion:

Impact of U2

Perfect information on U2 can only increase the MOET at the 99.9th percentile. Two perspectives were considered to estimate the magnitude of this increase:

- Based on an overall evaluation of the results of the CAG-membership probabilities for the 6 risk drivers (Note 2 in Appendix F), it is estimated that approx. 65% of compounds included in the CAG actually cause the alterations as a primary effect. Assuming that all substances contribute equally to the risk, the exclusion of the substances that do not cause the effect would result in a shift of the distribution of the MOETs at P99.9 by a factor of about 1.5. In reality, the contribution of substances to the risk is largely variable and it is uncertain which substances are in or out of the CAG. It cannot be excluded that the few substances contributing the most to the risk are all causing the effect as a primary mode of toxicity. Therefore, a large uncertainty around the actual magnitude of the shift needs to be taken into account.
- The simulations testing the effect of the CAG-membership probability of folpet (Note 2 in Appendix F) demonstrate a major impact of the presence or absence of folpet in the CAG on the Tier II MOET distribution. Considering the results using the lower and upper bounds for the CAG-membership probabilities of folpet a decrease by a factor of 2 of the probability of the MOET being below 100/500 would be expected. In reality, folpet, as any other substance, is either in or out of the CAG, and considering the probabilities of the MOET being below 100/500 for a certain CAG-membership probability of a single compound requires high cautiousness. There is an inherent limitation to the use of these simulations because they are not compatible/consistent with the outcome of the EKE Q2 elicitation which is based on the assumption of a CAG-membership probability of 100% for all substances included in the CAG.

The impact of U2 may differ between populations because the contribution of folpet and of the other substances varies between populations. However, these differences are very difficult to quantify, due to the specific nature of U2 and the fact that the hierarchy of risk drivers observed in the Tier II calculations becomes obsolete after their combination with the EKE Q2 distributions of multiplicative factors accounting for toxicology and exposure uncertainties. Therefore, the ranges of probabilities of the MOET at the 99.9th percentile of the exposure distribution being below 100/500 need to be large enough to take this into account.

Dependencies

The following dependencies between U2, uncertainties relating to toxicology and uncertainties relating to exposure were postulated by some experts:

- Negative dependency between uncertainties related to NOAEL setting (U4, U5, U6) and exposure uncertainties: Perfect information on uncertainties U4, U5 and U6 would globally tend to lead to higher NOAELs, lowering the impact of the uncertainties relating to exposure.

- Negative dependency between U2 (CAG-membership probability) and uncertainties relating to exposure and toxicology: Perfect information on U2, would lower the overall impact of toxicological and exposure uncertainties due to the exclusion of substances wrongly assigned to the CAG.

If these or other dependencies turned out to be factual, their magnitude would be low (rho = ±0.25). This applies to all populations.

Differences between populations

There are several factors affecting the validity of the consensus distributions of values of multiplicative factors (Figures 5 and 7), as elicited for the German population, for the other populations:

- The overestimation of the German cumulative exposure related to the consumption events of wine grapes with the facet '*PROCESS=Unspecified*': as explained above, this issue affects the German population only and does not apply to any other population.
- There are differences in the impact of individual sources of uncertainty as identified under EKE Q 1b (see Appendix G1). With respect to toxicology, U4 (principles of the NOAEL-setting) was the main source of uncertainty creating difference with the German population, depending on the contribution of folpet to the risk (documented in figure C.03 of Annex D1). With respect to exposure, the main differences concerned U31 (missing PFs), U13 (degree of alcohol abstinence during pregnancy) and U17 (contribution of metabolites, depending in particular of the rate of degradation of dithiocarbamates into ETU and PTU). For these uncertainties, the magnitude of the difference with the German populations could be estimated by comparing the outcome of sensitivity analyses C, G and K, respectively. The impact of U12 (change of diet during pregnancy) was also considered for possible differences with the German population based on the contribution of citrus fruits (documented in table C.02 of Annex D1). Finally, potential differences in the impact of U36 (effect of peeling of commodities with edible peel and of washing of commodities eaten raw) were also considered, based on the contribution of commodities with edible peel and of commodities which can be eaten raw with facet '*PROCESS=Unspecified*', also documented in table C.02 of Annex D1. The contribution of each of these sources of uncertainty to differences with the German population is variable. Therefore, for each population, they were all considered individually. The difference between populations related to U13 was found to be particularly uncertain because information about the occurrence of binge drinking events during early pregnancy, and how this may differ from country to country, is very limited.

For each population, the overall range of possible up- or downshifts of the MOET distributions reported in Figure 9 and Table 28 resulting from U2 (CAG-membership probability), dependencies between uncertainties and differences in the impact of uncertainties between populations was determined. As explained in Section 3.3.4.1, this was done under a formal EKE process for some populations, and remotely for the other populations.

The outcome is reported in the below sections. For each population, the range of probabilities of the MOET at the 99.9th percentile being below 100/500 resulting from the possible up- or downshifts is indicated in bold in the respective table, and the final consensus judgement is given below the table. The large ranges proposed for some populations result from the uncertainty related to the impact of U2 and of U13 (especially concerning the occurrence of binge drinking).

Germany

Table J.4: CAG-DAC: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the German population as given in Table 28 to take CAG-membership probability into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	**× 0.1**	**× 0.2**	**× 0.33**	**× 0.5**	**× 0.66**	**=**	**× 1.5**	**× 2**	**× 3**	**× 5**	**× 10**
−1	100.0%	100.0%	98.7%	47.3%	2.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	100.0%	93.6%	46.3%	10.9%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	100.0%	99.9%	88.7%	46.6%	16.5%	1.4%	0.0%	0.0%	0.0%	0.0%	0.0%

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−0.25	100.0%	99.5%	84.8%	46.7%	20.1%	**3.1%**	**0.2%**	**0.0%**	0.0%	0.0%	0.0%
0	100.0%	98.9%	81.4%	46.6%	22.7%	**4.8%**	**0.5%**	**0.0%**	0.0%	0.0%	0.0%
+0.25	100.0%	98.1%	78.9%	46.9%	25.2%	**6.6%**	**0.9%**	**0.1%**	0.0%	0.0%	0.0%
+0.5	100.0%	97.2%	76.5%	46.7%	26.6%	8.4%	1.5%	0.3%	0.0%	0.0%	0.0%
+0.75	100.0%	96.3%	74.5%	46.7%	28.1%	10.1%	2.1%	0.4%	0.0%	0.0%	0.0%
+1	100.0%	95.2%	73.0%	46.8%	29.4%	11.7%	3.0%	0.7%	0.0%	0.0%	0.0%

Consensus judgement: 0–7%.

Table J.5: CAG-DAC: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the German population as given in Table 28 to take CAG-membership probability into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	90.1%	8.7%	0.0%	0.0%
−0.75	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	97.4%	78.7%	20.7%	0.2%	0.0%
−0.5	100.0%	100.0%	100.0%	100.0%	100.0%	99.9%	94.0%	73.4%	25.7%	1.4%	0.0%
−0.25	100.0%	100.0%	100.0%	100.0%	100.0%	**99.5%**	**90.8%**	**70.0%**	28.6%	3.1%	0.0%
0	100.0%	100.0%	100.0%	100.0%	100.0%	**98.9%**	**87.8%**	**67.1%**	30.6%	4.8%	0.0%
+0.25	100.0%	100.0%	100.0%	100.0%	100.0%	**98.1%**	**85.3%**	**65.4%**	32.5%	6.6%	0.1%
+0.5	100.0%	100.0%	100.0%	100.0%	99.9%	97.2%	82.9%	63.8%	33.5%	8.4%	0.3%
+0.75	100.0%	100.0%	100.0%	100.0%	99.8%	96.3%	80.8%	62.4%	34.5%	10.1%	0.4%
+1	100.0%	100.0%	100.0%	100.0%	99.7%	95.2%	79.1%	61.4%	35.4%	11.7%	0.7%

Consensus judgement: 66–95%.

Belgium

Table J.6: CAG-DAC: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Belgian population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	16.1%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	93.2%	28.3%	1.8%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	100.0%	88.0%	32.4%	4.7%	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	99.9%	84.0%	34.5%	7.5%	1.5%	**0.1%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
0	99.8%	80.6%	35.9%	10.1%	2.7%	**0.2%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.25	99.5%	78.1%	37.4%	12.5%	4.1%	**0.5%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.5	99.2%	75.7%	38.0%	14.4%	5.5%	0.8%	0.0%	0.0%	0.0%	0.0%	0.0%
+0.75	98.8%	73.7%	38.6%	16.3%	6.9%	1.2%	0.1%	0.0%	0.0%	0.0%	0.0%
+1	98.3%	72.2%	39.3%	18.0%	8.3%	1.8%	0.1%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1%.

Table J.7: CAG-DAC: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Belgian population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	39.3%	3.4%	0.0%	0.0%	0.0%
−0.75	100.0%	100.0%	100.0%	100.0%	100.0%	93.2%	43.7%	10.2%	0.3%	0.0%	0.0%
−0.5	100.0%	100.0%	100.0%	100.0%	99.5%	88.0%	44.8%	15.6%	1.3%	0.0%	0.0%
−0.25	100.0%	100.0%	100.0%	99.9%	98.6%	**84.0%**	**45.3%**	**19.2%**	2.9%	0.1%	0.0%
0	100.0%	100.0%	100.0%	99.8%	97.5%	**80.6%**	**45.3%**	**21.9%**	4.6%	0.2%	0.0%
+0.25	100.0%	100.0%	100.0%	99.5%	96.2%	**78.1%**	**45.8%**	**24.3%**	6.3%	0.5%	0.0%
+0.5	100.0%	100.0%	100.0%	99.2%	94.7%	75.7%	45.8%	25.9%	8.1%	0.8%	0.0%
+0.75	100.0%	100.0%	100.0%	98.8%	93.3%	73.7%	45.8%	27.4%	9.7%	1.2%	0.0%
+1	100.0%	100.0%	100.0%	98.3%	91.9%	72.2%	46.0%	28.7%	11.3%	1.8%	0.0%

Consensus judgement: 33–66% (the interval is narrower than suggested by the data for pragmatic risk communication).

Czechia

Table J.8: CAG-DAC: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Czech population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	94.2%	23.3%	1.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	99.8%	86.5%	31.9%	6.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	100.0%	99.3%	81.0%	35.1%	10.6%	0.8%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	100.0%	98.5%	77.2%	36.8%	14.1%	**1.8%**	**0.1%**	**0.0%**	**0.0%**	0.0%	0.0%
0	100.0%	97.5%	74.0%	37.9%	16.9%	**3.2%**	**0.2%**	**0.0%**	**0.0%**	0.0%	0.0%
+0.25	100.0%	96.3%	71.8%	39.1%	19.5%	**4.6%**	**0.6%**	**0.1%**	**0.0%**	0.0%	0.0%
+0.5	100.0%	94.9%	69.8%	39.6%	21.2%	6.1%	1.0%	0.1%	0.0%	0.0%	0.0%
+0.75	100.0%	93.6%	68.1%	40.1%	22.9%	7.5%	1.4%	0.2%	0.0%	0.0%	0.0%
+1	99.9%	92.3%	66.8%	40.6%	24.4%	9.0%	2.0%	0.4%	0.0%	0.0%	0.0%

Consensus judgement: 0–3%.

Table J.9: CAG-DAC: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Czech population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	96.0%	75.9%	4.1%	0.0%	0.0%
−0.75	100.0%	100.0%	100.0%	100.0%	100.0%	99.8%	93.1%	65.7%	12.1%	0.1%	0.0%
−0.5	100.0%	100.0%	100.0%	100.0%	100.0%	99.3%	88.6%	62.1%	17.5%	0.8%	0.0%
−0.25	100.0%	100.0%	100.0%	100.0%	100.0%	**98.5%**	**84.9%**	**60.0%**	**21.0%**	1.8%	0.0%
0	100.0%	100.0%	100.0%	100.0%	99.9%	**97.5%**	**81.6%**	**58.2%**	**23.5%**	3.2%	0.0%
+0.25	100.0%	100.0%	100.0%	100.0%	99.8%	**96.3%**	**79.2%**	**57.4%**	**25.9%**	4.6%	0.1%
+0.5	100.0%	100.0%	100.0%	100.0%	99.6%	94.9%	76.8%	56.3%	27.3%	6.1%	0.1%
+0.75	100.0%	100.0%	100.0%	100.0%	99.5%	93.6%	74.8%	55.5%	28.7%	7.5%	0.2%
+1	100.0%	100.0%	100.0%	99.9%	99.2%	92.3%	73.3%	55.0%	29.9%	9.0%	0.4%

Consensus judgement: 33–66% (the interval is narrower than suggested by the data for pragmatic risk communication). See comment under Table J.15.

Denmark

Table J.10: CAG-DAC: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Danish population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	65.4%	6.9%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	99.2%	63.3%	13.0%	1.9%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	100.0%	97.3%	60.8%	17.8%	4.2%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	100.0%	95.0%	59.2%	21.1%	6.6%	**0.7%**	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%
0	100.0%	92.7%	57.6%	23.5%	8.9%	**1.3%**	**0.1%**	**0.0%**	**0.0%**	0.0%	0.0%
+0.25	100.0%	90.6%	56.9%	25.8%	11.1%	**2.1%**	**0.2%**	**0.0%**	**0.0%**	0.0%	0.0%
+0.5	99.9%	88.5%	56.0%	27.2%	12.9%	3.0%	0.4%	0.0%	0.0%	0.0%	0.0%
+0.75	99.8%	86.6%	55.2%	28.6%	14.7%	3.9%	0.6%	0.1%	0.0%	0.0%	0.0%
+1	99.7%	84.9%	54.8%	29.8%	16.3%	5.0%	0.8%	0.1%	0.0%	0.0%	0.0%

Consensus judgement: 0–1%.

Table J.11: CAG-DAC: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Danish population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	91.0%	29.9%	1.7%	0.0%	0.0%
−0.75	100.0%	100.0%	100.0%	100.0%	100.0%	99.2%	77.4%	36.6%	4.2%	0.0%	0.0%
−0.5	100.0%	100.0%	100.0%	100.0%	100.0%	97.3%	72.6%	39.2%	7.6%	0.2%	0.0%
−0.25	100.0%	100.0%	100.0%	100.0%	99.8%	**95.0%**	**69.6%**	**40.4%**	**10.6%**	0.7%	0.0%
0	100.0%	100.0%	100.0%	100.0%	99.6%	**92.7%**	**67.0%**	**41.1%**	**13.2%**	1.3%	0.0%
+0.25	100.0%	100.0%	100.0%	100.0%	99.2%	**90.6%**	**65.4%**	**42.1%**	**15.5%**	2.1%	0.0%
+0.5	100.0%	100.0%	100.0%	99.9%	98.6%	88.5%	63.8%	42.3%	17.4%	3.0%	0.0%
+0.75	100.0%	100.0%	100.0%	99.8%	98.1%	86.6%	62.5%	42.6%	19.2%	3.9%	0.1%
+1	100.0%	100.0%	100.0%	99.7%	97.4%	84.9%	61.6%	43.0%	20.8%	5.0%	0.1%

Consensus judgement: 33–66% (the interval is narrower than suggested by the data for pragmatic risk communication). See comment under Table J.15.

Spain

Table J.12: CAG-DAC: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Spanish population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	97.7%	13.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	89.1%	22.3%	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	100.0%	83.6%	26.9%	3.4%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	99.8%	79.7%	29.6%	5.9%	1.1%	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
0	99.6%	76.4%	31.5%	8.2%	2.1%	**0.1%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.25	99.2%	74.1%	33.3%	10.4%	3.2%	**0.3%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
+0.5	98.6%	71.9%	34.2%	12.3%	4.5%	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%
+0.75	98.1%	70.1%	35.1%	14.2%	5.7%	0.9%	0.0%	0.0%	0.0%	0.0%	0.0%
+1	97.4%	68.8%	36.0%	15.8%	7.1%	1.4%	0.1%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1%.

Table J.13: CAG-DAC: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Spanish population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
–1	100.0%	100.0%	100.0%	100.0%	100.0%	97.7%	29.7%	1.4%	0.0%	0.0%	0.0%
–0.75	100.0%	100.0%	100.0%	100.0%	99.8%	89.1%	35.9%	7.3%	0.1%	0.0%	0.0%
–0.5	100.0%	100.0%	100.0%	100.0%	99.0%	83.6%	38.4%	12.3%	0.9%	0.0%	0.0%
–0.25	100.0%	100.0%	100.0%	99.8%	97.7%	**79.7%**	**39.7%**	**15.8%**	2.2%	0.0%	0.0%
0	100.0%	100.0%	100.0%	99.6%	96.3%	**76.4%**	**40.4%**	**18.6%**	3.6%	0.1%	0.0%
+0.25	100.0%	100.0%	100.0%	99.2%	94.6%	**74.1%**	**41.4%**	**21.1%**	5.1%	0.3%	0.0%
+0.5	100.0%	100.0%	100.0%	98.6%	92.9%	71.9%	41.7%	22.8%	6.7%	0.6%	0.0%
+0.75	100.0%	100.0%	100.0%	98.1%	91.3%	70.1%	42.1%	24.4%	8.2%	0.9%	0.0%
+1	100.0%	100.0%	99.9%	97.4%	89.8%	68.8%	42.5%	25.9%	9.8%	1.4%	0.0%

Consensus judgement: 33–66% (the interval is narrower than suggested by the data for pragmatic risk communication). See comment under Table J.15.

Finland

Table J.14: CAG-DAC: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Finnish population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
–1	100.0%	16.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.75	99.2%	29.0%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.5	97.1%	33.2%	2.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.25	94.5%	35.3%	4.3%	0.2%	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%	0.0%
0	91.9%	36.6%	6.5%	0.7%	**0.1%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%	0.0%
+0.25	89.4%	38.1%	8.6%	1.3%	**0.2%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%	0.0%
+0.5	87.1%	38.6%	10.5%	2.1%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+0.75	85.0%	39.3%	12.4%	2.9%	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+1	83.3%	39.9%	14.1%	3.9%	1.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1%.

Table J.15: CAG-DAC: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Finnish population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
–1	100.0%	100.0%	100.0%	100.0%	97.8%	16.0%	0.1%	0.0%	0.0%	0.0%	0.0%
–0.75	100.0%	100.0%	100.0%	99.2%	87.7%	29.0%	1.4%	0.0%	0.0%	0.0%	0.0%
–0.5	100.0%	100.0%	100.0%	97.1%	81.5%	33.2%	4.4%	0.5%	0.0%	0.0%	0.0%

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−0.25	100.0%	100.0%	99.8%	94.5%	**77.3%**	**35.3%**	**7.4%**	1.4%	0.0%	0.0%	0.0%
0	100.0%	100.0%	99.6%	91.9%	**73.9%**	**36.6%**	**10.1%**	2.7%	0.2%	0.0%	0.0%
+0.25	100.0%	100.0%	99.1%	89.4%	**71.6%**	**38.1%**	**12.6%**	4.0%	0.4%	0.0%	0.0%
+0.5	100.0%	100.0%	98.5%	87.1%	69.4%	38.6%	14.6%	5.5%	0.8%	0.0%	0.0%
+0.75	100.0%	100.0%	97.9%	85.0%	67.7%	39.3%	16.5%	6.9%	1.2%	0.0%	0.0%
+1	100.0%	100.0%	97.1%	83.3%	66.4%	39.9%	18.3%	8.4%	1.7%	0.0%	0.0%

Consensus judgement: 33–66%. It is noted that the actual subjective probability range of experts was larger during the formal elicitation process and varied from 10 to 90%. It was however agreed to fit it to the range corresponding to the probability term 'about as likely as not' of the approximate probability scale for harmonised use in EFSA, which reflects well how the risk assessors would wish to communicate the outcome of the risk assessment to risk managers.

France

Table J.16: CAG-DAC: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the French population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	62.5%	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	98.9%	56.7%	7.4%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	100.0%	96.5%	54.9%	12.7%	2.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	100.0%	93.8%	53.8%	16.4%	4.3%	**0.3%**	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%
0	100.0%	91.2%	52.7%	19.3%	6.5%	**0.7%**	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%
+0.25	99.9%	88.8%	52.5%	21.9%	8.5%	**1.3%**	**0.1%**	**0.0%**	**0.0%**	0.0%	0.0%
+0.5	99.9%	86.5%	51.8%	23.5%	10.4%	2.1%	0.2%	0.0%	0.0%	0.0%	0.0%
+0.75	99.8%	84.4%	51.4%	25.1%	12.2%	2.9%	0.3%	0.0%	0.0%	0.0%	0.0%
+1	99.6%	82.7%	51.1%	26.6%	13.9%	3.8%	0.5%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1%.

Table J.17: CAG-DAC: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the French population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	81.4%	17.4%	0.1%	0.0%	0.0%
−0.75	100.0%	100.0%	100.0%	100.0%	100.0%	98.9%	72.4%	28.6%	1.5%	0.0%	0.0%
−0.5	100.0%	100.0%	100.0%	100.0%	100.0%	96.5%	67.8%	32.6%	4.5%	0.1%	0.0%
−0.25	100.0%	100.0%	100.0%	100.0%	99.8%	**93.8%**	**65.0%**	**34.7%**	**7.4%**	0.3%	0.0%
0	100.0%	100.0%	100.0%	100.0%	99.5%	**91.2%**	**62.6%**	**36.0%**	**10.0%**	0.7%	0.0%
+0.25	100.0%	100.0%	100.0%	99.9%	98.9%	**88.8%**	**61.3%**	**37.5%**	**12.4%**	1.3%	0.0%
+0.5	100.0%	100.0%	100.0%	99.9%	98.3%	86.5%	59.9%	38.1%	14.4%	2.1%	0.0%
+0.75	100.0%	100.0%	100.0%	99.8%	97.6%	84.4%	58.8%	38.8%	16.3%	2.9%	0.0%
+1	100.0%	100.0%	100.0%	99.6%	96.7%	82.7%	58.1%	39.4%	18.0%	3.8%	0.0%

Consensus judgement: 33–66% (the interval is narrower than suggested by the data for pragmatic risk communication). See comment under Table J.15.

Hungary

Table J.18: CAG-DAC: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Hungarian population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	43.6%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	99.9%	47.5%	2.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	99.1%	48.0%	5.4%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	97.6%	48.1%	8.4%	0.8%	**0.1%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%	0.0%
0	95.9%	47.8%	11.1%	1.6%	**0.2%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%	0.0%
+0.25	94.0%	48.1%	13.5%	2.6%	**0.5%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%	0.0%
+0.5	92.2%	47.9%	15.5%	3.8%	0.9%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+0.75	90.4%	47.7%	17.4%	4.9%	1.4%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%
+1	88.8%	47.8%	19.1%	6.2%	2.0%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1%.

Table J.19: CAG-DAC: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Hungarian population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	100.0%	100.0%	43.6%	1.1%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	100.0%	100.0%	99.9%	95.6%	47.5%	5.2%	0.4%	0.0%	0.0%	0.0%
−0.5	100.0%	100.0%	100.0%	99.1%	90.5%	48.0%	9.7%	1.6%	0.0%	0.0%	0.0%
−0.25	100.0%	100.0%	100.0%	97.6%	**86.4%**	**48.1%**	**13.3%**	3.3%	0.2%	0.0%	0.0%
0	100.0%	100.0%	99.9%	95.9%	**82.8%**	**47.8%**	**16.2%**	5.1%	0.5%	0.0%	0.0%
+0.25	100.0%	100.0%	99.7%	94.0%	**80.2%**	**48.1%**	**18.8%**	7.0%	1.0%	0.0%	0.0%
+0.5	100.0%	100.0%	99.5%	92.2%	77.7%	47.9%	20.6%	8.8%	1.6%	0.0%	0.0%
+0.75	100.0%	100.0%	99.1%	90.4%	75.6%	47.7%	22.4%	10.5%	2.3%	0.1%	0.0%
+1	100.0%	100.0%	98.7%	88.8%	74.0%	47.8%	24.0%	12.1%	3.1%	0.2%	0.0%

Consensus judgement: 33–66% (the interval is narrower than suggested by the data for pragmatic risk communication). See comment under Table J.15.

Ireland

Table J.20: CAG-DAC: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Irish population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	97.6%	62.9%	5.1%	0.1%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	100.0%	99.9%	91.4%	61.7%	12.6%	0.7%	0.0%	0.0%	0.0%	0.0%
−0.5	100.0%	100.0%	99.2%	86.7%	59.4%	17.3%	1.9%	0.2%	0.0%	0.0%	0.0%
−0.25	100.0%	100.0%	98.2%	83.1%	57.9%	20.5%	**3.6%**	**0.6%**	**0.0%**	**0.0%**	**0.0%**
0	100.0%	100.0%	97.0%	80.0%	56.5%	22.9%	**5.3%**	**1.2%**	**0.1%**	**0.0%**	**0.0%**
+0.25	100.0%	99.9%	95.6%	77.7%	55.9%	25.2%	**7.0%**	**2.0%**	**0.2%**	**0.0%**	**0.0%**
+0.5	100.0%	99.8%	94.2%	75.5%	55.0%	26.6%	8.7%	2.9%	0.3%	0.0%	0.0%

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
+0.75	100.0%	99.7%	92.9%	73.6%	54.3%	28.0%	10.3%	3.8%	0.5%	0.0%	0.0%
+1	100.0%	99.6%	91.5%	72.2%	54.0%	29.2%	11.8%	4.9%	0.8%	0.0%	0.0%

Consensus judgement: 0–10%.

Table J.21: CAG-DAC: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Irish population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	83.7%	5.1%	0.0%
−0.75	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	98.7%	75.3%	12.6%	0.0%
−0.5	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.7%	96.6%	71.1%	17.3%	0.2%
−0.25	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	**99.2%**	**94.2%**	**68.2%**	**20.5%**	**0.6%**
0	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	**98.5%**	**91.9%**	**65.8%**	**22.9%**	**1.2%**
+0.25	100.0%	100.0%	100.0%	100.0%	100.0%	99.9%	**97.6%**	**89.8%**	**64.4%**	**25.2%**	**2.0%**
+0.5	100.0%	100.0%	100.0%	100.0%	100.0%	99.8%	96.6%	87.7%	62.8%	26.6%	2.9%
+0.75	100.0%	100.0%	100.0%	100.0%	100.0%	99.7%	95.6%	85.8%	61.6%	28.0%	3.8%
+1	100.0%	100.0%	100.0%	100.0%	100.0%	99.6%	94.5%	84.2%	60.8%	29.2%	4.9%

Consensus judgement: 33–66% (the interval is narrower than suggested by the data for pragmatic risk communication). See comment under Table J.15.

Italy

Table J.22: CAG-DAC: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Italian population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	96.6%	4.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	84.6%	14.4%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	100.0%	78.6%	20.1%	1.9%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	99.8%	74.7%	23.6%	3.9%	0.6%	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
0	99.4%	71.5%	26.0%	5.9%	1.3%	**0.1%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.25	98.8%	69.4%	28.3%	7.9%	2.2%	**0.2%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.5	98.1%	67.4%	29.6%	9.8%	3.3%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%
+0.75	97.3%	65.8%	30.9%	11.6%	4.3%	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%
+1	96.5%	64.7%	32.1%	13.3%	5.5%	0.9%	0.0%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1%.

Table J.23: CAG-DAC: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Italian population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	100.0%	100.0%	96.6%	12.7%	0.4%	0.0%	0.0%	0.0%
−0.75	100.0%	100.0%	100.0%	100.0%	99.7%	84.6%	26.0%	3.8%	0.0%	0.0%	0.0%

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−0.5	100.0%	100.0%	100.0%	100.0%	98.6%	78.6%	30.5%	8.1%	0.4%	0.0%	0.0%
−0.25	100.0%	100.0%	100.0%	99.8%	96.8%	**74.7%**	**32.9%**	**11.7%**	1.3%	0.0%	0.0%
0	100.0%	100.0%	100.0%	99.4%	94.9%	**71.5%**	**34.5%**	**14.5%**	2.4%	0.1%	0.0%
+0.25	100.0%	100.0%	100.0%	98.8%	92.9%	**69.4%**	**36.1%**	**17.1%**	3.7%	0.2%	0.0%
+0.5	100.0%	100.0%	100.0%	98.1%	90.9%	67.4%	36.8%	19.0%	5.1%	0.3%	0.0%
+0.75	100.0%	100.0%	99.9%	97.3%	89.1%	65.8%	37.6%	20.9%	6.4%	0.6%	0.0%
+1	100.0%	100.0%	99.9%	96.5%	87.4%	64.7%	38.3%	22.5%	7.9%	0.9%	0.0%

Consensus judgement: 20–66%.

Latvia

Table J.24: CAG-DAC: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Latvian population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	20.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	99.6%	31.8%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	97.9%	35.6%	2.4%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	95.4%	37.5%	4.8%	0.3%	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%	0.0%
0	93.0%	38.6%	7.1%	0.8%	**0.1%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%	0.0%
+0.25	90.7%	39.9%	9.3%	1.4%	**0.2%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%	0.0%
+0.5	88.4%	40.3%	11.3%	2.3%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+0.75	86.3%	40.8%	13.2%	3.1%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+1	84.5%	41.3%	14.9%	4.2%	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1%.

Table J.25: CAG-DAC: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Latvian population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	100.0%	100.0%	20.1%	0.1%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	100.0%	100.0%	99.6%	90.4%	31.8%	1.7%	0.0%	0.0%	0.0%	0.0%
−0.5	100.0%	100.0%	100.0%	97.9%	83.9%	35.6%	5.0%	0.6%	0.0%	0.0%	0.0%
−0.25	100.0%	100.0%	99.9%	95.4%	**79.5%**	**37.5%**	**8.2%**	1.6%	0.1%	0.0%	0.0%
0	100.0%	100.0%	99.7%	93.0%	**75.9%**	**38.6%**	**11.0%**	3.0%	0.2%	0.0%	0.0%
+0.25	100.0%	100.0%	99.4%	90.7%	**73.4%**	**39.9%**	**13.5%**	4.4%	0.5%	0.0%	0.0%
+0.5	100.0%	100.0%	98.8%	88.4%	71.2%	40.3%	15.5%	6.0%	0.9%	0.0%	0.0%
+0.75	100.0%	100.0%	98.3%	86.3%	69.3%	40.8%	17.5%	7.4%	1.3%	0.0%	0.0%
+1	100.0%	100.0%	97.6%	84.5%	67.9%	41.3%	19.2%	9.0%	1.9%	0.0%	0.0%

Consensus judgement: 10–66%.

Netherlands

Table J.26: CAG-DAC: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Dutch population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	99.6%	27.3%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	95.3%	35.6%	2.7%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	100.0%	90.9%	38.2%	6.3%	0.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	100.0%	87.2%	39.6%	9.5%	2.1%	**0.1%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
0	99.9%	83.9%	40.3%	12.2%	3.5%	**0.3%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.25	99.7%	81.3%	41.4%	14.7%	5.0%	**0.6%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.5	99.4%	78.9%	41.6%	16.6%	6.6%	1.1%	0.1%	0.0%	0.0%	0.0%	0.0%
+0.75	99.1%	76.8%	42.0%	18.5%	8.1%	1.6%	0.1%	0.0%	0.0%	0.0%	0.0%
+1	98.7%	75.2%	42.4%	20.1%	9.7%	2.2%	0.2%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1%.

Table J.27: CAG-DAC: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Dutch population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	100.0%	100.0%	99.6%	52.8%	4.9%	0.0%	0.0%	0.0%
−0.75	100.0%	100.0%	100.0%	100.0%	100.0%	95.3%	52.0%	13.9%	0.4%	0.0%	0.0%
−0.5	100.0%	100.0%	100.0%	100.0%	99.7%	90.9%	51.2%	19.5%	1.9%	0.0%	0.0%
−0.25	100.0%	100.0%	100.0%	100.0%	99.0%	**87.2%**	**50.7%**	**22.9%**	3.8%	0.1%	0.0%
0	100.0%	100.0%	100.0%	99.9%	98.2%	**83.9%**	**50.0%**	**25.4%**	5.8%	0.3%	0.0%
+0.25	100.0%	100.0%	100.0%	99.7%	97.1%	**81.3%**	**50.0%**	**27.7%**	7.7%	0.6%	0.0%
+0.5	100.0%	100.0%	100.0%	99.4%	95.9%	78.9%	49.6%	29.0%	9.6%	1.1%	0.0%
+0.75	100.0%	100.0%	100.0%	99.1%	94.7%	76.8%	49.3%	30.3%	11.3%	1.6%	0.0%
+1	100.0%	100.0%	100.0%	98.7%	93.4%	75.2%	49.2%	31.5%	13.0%	2.2%	0.0%

Consensus judgement: 33–66% (the interval is narrower than suggested by the data for pragmatic risk communication). See comment under Table J.15.

Romania

Table J.28: CAG-DAC: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Romanian population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	18.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	99.8%	35.1%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	98.6%	38.5%	2.6%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	96.5%	40.0%	5.2%	**0.3%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%	0.0%	0.0%
0	94.3%	40.8%	7.6%	**0.8%**	**0.1%**	**0.0%**	0.0%	0.0%	0.0%	0.0%	0.0%
+0.25	92.0%	41.9%	10.0%	**1.6%**	**0.2%**	**0.0%**	0.0%	0.0%	0.0%	0.0%	0.0%
+0.5	89.8%	42.2%	12.0%	2.5%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+0.75	87.8%	42.5%	14.0%	3.4%	0.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+1	86.0%	42.9%	15.7%	4.5%	1.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1%.

Table J.29: CAG-DAC: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Romanian population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
–1	100.0%	100.0%	100.0%	100.0%	100.0%	18.8%	0.1%	0.0%	0.0%	0.0%	0.0%
–0.75	100.0%	100.0%	100.0%	99.8%	93.3%	35.1%	1.7%	0.0%	0.0%	0.0%	0.0%
–0.5	100.0%	100.0%	100.0%	98.6%	86.8%	38.5%	5.4%	0.6%	0.0%	0.0%	0.0%
–0.25	100.0%	100.0%	100.0%	**96.5%**	**82.2%**	**40.0%**	8.8%	1.7%	0.1%	0.0%	0.0%
0	100.0%	100.0%	99.8%	**94.3%**	**78.3%**	**40.8%**	11.8%	3.2%	0.2%	0.0%	0.0%
+0.25	100.0%	100.0%	99.6%	**92.0%**	**75.6%**	**41.9%**	14.4%	4.7%	0.5%	0.0%	0.0%
+0.5	100.0%	100.0%	99.2%	89.8%	73.2%	42.2%	16.5%	6.4%	0.9%	0.0%	0.0%
+0.75	100.0%	100.0%	98.7%	87.8%	71.2%	42.5%	18.5%	8.0%	1.4%	0.0%	0.0%
+1	100.0%	100.0%	98.1%	86.0%	69.7%	42.9%	20.2%	9.6%	2.1%	0.0%	0.0%

Consensus judgement: 50–90%.

Sweden

Table J.30: CAG-DAC: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Swedish population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
–1	100.0%	100.0%	80.5%	6.9%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.75	100.0%	99.5%	71.0%	16.3%	2.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.5	100.0%	98.1%	66.9%	21.5%	5.2%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.25	100.0%	96.3%	64.4%	24.6%	8.0%	0.8%	**0.0%**	**0.0%**	**0.0%**	**0.0%**	0.0%
0	100.0%	94.4%	62.2%	26.9%	10.5%	1.6%	**0.1%**	**0.0%**	**0.0%**	**0.0%**	0.0%
+0.25	100.0%	92.5%	61.0%	29.0%	12.8%	2.5%	**0.2%**	**0.0%**	**0.0%**	**0.0%**	0.0%
+0.5	99.9%	90.5%	59.7%	30.2%	14.7%	3.6%	0.4%	0.0%	0.0%	0.0%	0.0%
+0.75	99.9%	88.8%	58.6%	31.4%	16.6%	4.7%	0.7%	0.1%	0.0%	0.0%	0.0%
+1	99.8%	87.2%	57.9%	32.5%	18.2%	5.9%	1.0%	0.2%	0.0%	0.0%	0.0%

Consensus judgement: 0–1%.

Table J.31: CAG-DAC: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Swedish population as given in Table 28 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
–1	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	91.0%	41.8%	1.7%	0.0%	0.0%
–0.75	100.0%	100.0%	100.0%	100.0%	100.0%	99.5%	83.1%	44.3%	5.1%	0.0%	0.0%
–0.5	100.0%	100.0%	100.0%	100.0%	100.0%	98.1%	77.8%	45.1%	9.3%	0.3%	0.0%
–0.25	100.0%	100.0%	100.0%	100.0%	99.9%	96.3%	74.3%	45.5%	12.6%	0.8%	0.0%
0	100.0%	100.0%	100.0%	100.0%	99.7%	94.4%	**71.3%**	**45.5%**	**15.3%**	**1.6%**	0.0%
+0.25	100.0%	100.0%	100.0%	100.0%	99.4%	92.5%	**69.3%**	**46.0%**	**17.8%**	**2.5%**	0.0%
+0.5	100.0%	100.0%	100.0%	99.9%	99.0%	90.5%	**67.4%**	**45.9%**	**19.6%**	**3.6%**	0.0%
+0.75	100.0%	100.0%	100.0%	99.9%	98.6%	88.8%	65.9%	45.9%	21.4%	4.7%	0.1%
+1	100.0%	100.0%	100.0%	99.8%	98.0%	87.2%	64.8%	46.1%	22.9%	5.9%	0.2%

Consensus judgement: 20–50%.

Appendix J2 – EKE Q3 CAG-DAH - Record of judgements and reasoning

The EKE Q3 was worded as follows:

For the German population: '*If all the uncertainties in the model, exposure assessment, hazard identification and characterisation and their dependencies were fully resolved (e.g. by obtaining perfect information on the issues involved) and addressed in the modelling, what is your probability that this would result in the MOET for the 99.9th percentile of exposure for the German population in 2017–2019 being below [100/500]?*'

For each of the other 13 populations: '*If all the uncertainties in the model, exposure assessment, hazard identification and characterisation and their dependencies, and differences in these between populations, were fully resolved (e.g. by obtaining perfect information on the issues involved) and addressed in the modelling, what is your probability that this would result in the MOET for the 99.9th percentile of exposure for the [name of the population] in 2017-2019 being below [100/500]?*'

General considerations

In their judgements, the experts considered the following information:

- Boxplots for the MOET distributions at 99.9th percentile of exposure for the 14 populations as calculated by Monte Carlo simulations combining output from the Tier II exposure model with the probability distributions of the multiplicative factor for the exposure and toxicology uncertainties as derived under EKE Q2 for the German population (Figure 10 and Table 29)
- The estimated probability of the MOET at 99.9th percentile of exposure per population being below the regulatory threshold of 100/500 assuming that all exposure and toxicological uncertainties are independent (rho=0) and, in all populations, the same as for the German population (Table 29)
- The estimated probability of the MOET at 99.9th percentile of exposure per population being below 100/500 assuming different degrees of dependency between uncertainties on exposure and toxicology indicated in Tables J.32 and J.33.

Table J.32: CAG-DAH: Effect of dependencies between uncertainties in toxicology and exposure on the probability of the MOET at the 99.9th percentile of exposure being below 100

Country	Q2 probability assuming independence (%) rho = 0	Q2 probability with negative dependency (%) rho =				Q2 probability with positive dependency (%) rho =			
		−1	−0.75	−0.5	−0.25	+0.25	+0.5	+0.75	+1
BE – Belgium	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
CZ – Czechia	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DE -Germany	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DK -Denmark	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ES – Spain	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
FI – Finland	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1
FR – France	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
HU – Hungary	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IE – Ireland	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
IT – Italy	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
LV – Latvia	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NL – Netherlands	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RO – Romania	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SE – Sweden	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table J.33: CAG-DAH: Effect of dependencies between uncertainties in toxicology and exposure on the probability of the MOET at the 99.9th percentile of exposure being below 500

Country	Q2 probability assuming independence (%) rho = 0	Q2 probability with negative dependency (%) rho =				Q2 probability with positive dependency (%) rho =			
		−1	−0.75	−0.5	−0.25	+0.25	+0.5	+0.75	+1
BE – Belgium	23	4.8	11	16	20	24	26	27	28
CZ – Czechia	25	6.4	14	19	22	26	28	29	29
DE -Germany	27	6.7	16	21	25	28	30	31	31
DK -Denmark	10	0.8	1.9	4.6	7.4	12	14	16	17
ES – Spain	14	1.6	4.0	7.9	11	16	18	20	21
FI – Finland	31	15	23	27	29	32	33	34	34
FR – France	16	2.1	5.1	9.3	13	18	20	21	22
HU – Hungary	9	0.7	1.7	4.2	6.8	11	13	15	16
IE – Ireland	28	12	19	23	26	29	30	31	31
IT – Italy	12	1.1	2.8	6.0	9.0	14	16	18	19
LV – Latvia	8	0.7	1.6	3.7	6.1	10	12	14	15
NL – Netherlands	21	4.0	9.7	15	19	23	25	26	27
RO – Romania	3	0.1	0.2	0.8	1.8	4.4	5.9	7.4	8.7
SE – Sweden	14	1.5	3.6	7.4	11	16	18	20	21

- The elicited CAG-membership probabilities for the 6 risk drivers of CAG-DAH and reported in Note 2 of Appendix F.
- The results from calculations showing how applying the CAG membership probabilities for folpet and 2,4-D would change the MOET distributions produced by the Tier II exposure model. The results of these calculations are reported in Information Note 2 in Appendix F.

For the assessment of differences between populations, the following additional information was also considered by the experts:

- The sources of uncertainty identified to have different impact between populations in response to EKE Q1b (Appendix G2)
- The results from the sensitivity analyses (Table 21). In these sensitivity analyses, the impact in the different populations is reflected by the intensity of change of the median estimate of the MOET. To facilitate the comparison between populations, ratios of the median MOET at 99.9th percentile of exposure obtained in sensitivity analyses C, G and K (sensitivity analyses showing the largest impact) to the respective median MOET in the Tier II calculation were summarised in Table J.34.

Table J.34: CAG-DAH: Median MOET estimates at 99.9th percentile of exposure in Tier II and most important sensitivity analyses

	BE	CZ	DK	DE	ES	FI	FR	HU	IE	IT	LV	NL	RO	SE
Tier II	597	573	751	553	674	534	659	775	562	714	812	601	1010	684
SA C	1660 *2.8*	1120 *2.0*	1200 *1.6*	1000 *1.8*	1470 *2.2*	2690 *5.0*	1440 *2.2*	2020 *2.6*	999 *1.8*	1560 *2.2*	2440 *3.0*	1710 *2.8*	1570 *1.6*	1330 *1.9*
SA G	607 *1.0*	628 *1.1*	835 *1.1*	572 *1.0*	713 *1.1*	530 *1.0*	713 *1.1*	800 *1.0*	933 *1.7*	729 *1.0*	794 *1.0*	626 *1.0*	1090 *1.1*	761 *1.1*
SA K	487 *0.82*	485 *0.85*	602 *0.80*	381 *0.69*	535 *0.79*	436 *0.82*	519 *0.79*	565 *0.73*	458 *0.81*	574 *0.80*	603 *0.74*	471 *0.78*	567 *0.56*	552 *0.81*

SA C: sensitivity analysis C (assuming no transfer to processed commodities when PFs are not available); SA G: sensitivity analysis G (assuming total alcohol abstinence during pregnancy); SA K: sensitivity analysis K (assuming that propineb and thiram were authorised during the reference period and that dithiocarbamates were completely converted into ETU and PTU during food transformation processes that involve heating).
Ratios between the median MOET observed in the sensitivity analysis and the median Tier II MOET of the respective population are shown in italics.

- About 7.5% of the exposure of the German population for subjects with exposure exceeding the 99th percentile, as calculated by the model, was resulting from the consumption of wine grapes with the facet 'PROCESS=Unspecified'. This was a source of underestimation of the MOET calculated by the model concerning the German population only, which could not be properly addressed under EKE Q1a. Therefore, this issue was taken in consideration during the EKE Q2 elicitation for exposure uncertainties.

In addition, the experts considered:

- The results from calculations showing how shifting the MOET distributions, as obtained by combining the output of the Tier II exposure model with the probability distributions of the multiplicative factors of the MOET for the exposure and toxicology uncertainties derived under EKE Q2 for the German population, up or down to reflect the impact of CAG-membership probability and differences with the German population would affect the probability of MOET being below 100/500 for each population, assuming different degrees of dependency. They are reported under the paragraphs dealing with each population in Tables J.35–J.62.

Results and discussion:

Impact of U2

Perfect information on U2 can only increase the MOET at the 99.9th percentile. Two perspectives were considered to estimate the magnitude of this increase:

- Based on the overall results of the CAG-membership probabilities for the 6 risk drivers (Note 2 in Appendix F), it is estimated that approx. 65% of compounds included in the CAG actually cause the alterations as a primary effect. Assuming that all substances contribute equally to the risk, the exclusion of the substances that do not cause the effect would result in a shift of the distribution of the MOETs at P99.9 by a factor of about 1.5. In reality, the contribution of substances to the risk is largely variable and it is uncertain which substances are in or out of the CAG. It cannot be excluded that the few substances contributing the most to the risk are all causing the effect as a primary mode of toxicity. Therefore, a large uncertainty around the actual magnitude of the shift needs to be taken into account.
- The simulations testing the effect of the CAG-membership probability of 2,4-D and folpet (Note 2 in Appendix F) demonstrate varying impacts of their presence or absence in the CAG on the Tier II MOET distribution. Considering the results for the lower and upper bounds for the CAG-membership probabilities of folpet and 2,4-D, a decrease by a factor smaller than 2 of the probability of the MOET being below 500 would be expected, while the probability of the MOET being below 100 would not be affected as it is already quasi nil with all substances included in the CAG. In reality, 2,4-D and folpet are either in or out of the CAG and considering the probabilities of the MOET being below 100/500 for a certain CAG-membership probability of a single compound requires high cautiousness. There is an inherent limitation to the use of these simulations because they are not compatible/consistent with the outcome of the EKE Q2 elicitation which assumes of a CAG-membership probability of 100% for all substances included in the CAG.

The impact of U2 may differ between populations because the contribution of folpet, 2,4-D and the other substances varies between populations. However, these differences are very difficult to quantify, due to the specific nature of U2 and the fact that the hierarchy of risk drivers observed in the Tier II calculations becomes obsolete after their combination with the EKE Q2 distributions of multiplicative factors accounting for toxicology and exposure uncertainties. Therefore, the ranges of probabilities of the MOET at the 99.9th percentile of the distribution being below 100/500 need to be large enough to take this into account.

Dependencies

The following dependencies between U2, uncertainties relating to toxicology and uncertainties relating to exposure were postulated by some experts:

- Negative dependency between uncertainties related to NOAEL setting (U4, U5, U6) and exposure uncertainties: Perfect information on uncertainties U4, U5 and U6 would tend to lead to higher NOAELs, lowering the impact of the uncertainties relating to exposure.
- Negative dependency between U2 (CAG-membership probability) and uncertainties relating to exposure and toxicology: Perfect information on U2, would lower the overall impact of toxicological and exposure uncertainties due to the exclusion of substances wrongly assigned to the CAG.

If these or other dependencies turned out to be factual, their magnitude would be low (rho = ±0.25). This applies to all populations.

Differences between populations

There are several factors affecting the validity of the consensus distributions of values of multiplicative factors (Figures 6 and 8), as elicited for the German population, for the other populations:

- The overestimation of the German cumulative exposure related to the consumption events of wine grapes with the facet '*PROCESS=Unspecified*': as explained above, this issue affects the German population only and does not apply to any other population.
- There are differences in the impact of individual sources of uncertainty as identified under EKE Q 1b (see Appendix G2). With respect to toxicology, U4 (principles of the NOAEL-setting) was the main source of uncertainty creating difference with the German population. Differences are indeed expected depending, on one hand, on the contribution to the risk of thiabendazole and deltamethrin (substances for which toxicological studies were combined to set the NOAEL), and, on the other hand, on the contribution of cyproconazole (substance for which the NOAEL was set by applying an UF of 10 to the LOAEL), as documented in figure C.03 of Annex D2. With respect to exposure, the main differences concerned U31 (missing PFs), U13 (degree of alcohol abstinence during pregnancy) and U17 (contribution of metabolites, depending in particular of the rate of degradation of dithiocarbamates into ETU and PTU). For these uncertainties, the magnitude of the difference with the German populations was estimated by comparing the outcome of sensitivity analyses C, G and K, respectively. The impact of U12 (change of diet during pregnancy) was also considered for possible differences with the German population regarding the contribution of citrus fruits and cereals (documented in table C.02 of Annex D2). Finally, potential differences in the impact of U36 (effect of peeling of commodities with edible peel and of washing of commodities eaten raw) were also considered, based on the contribution of commodities with edible peel and of commodities which can be eaten raw with facet 'PROCESS=Unspecified', also documented in table C.02 of Annex D2. The contribution of each of these sources of uncertainty to the difference with the German population is variable. Therefore, for each population, they were all considered individually.

For each population, the overall range of possible up- or downshifts of the MOET distributions reported in Figure 10 and Table 29 resulting from U2 (CAG-membership probability), dependencies between uncertainties and differences in the impact of uncertainties between populations was determined. As explained in Section 3.3.4.1, this was done under a formal EKE process for some populations, and remotely for the other populations.

The outcome is reported in the below sections. For each population, the range of probabilities of the MOET at the 99.9th percentile being below 100/500 resulting from the possible up- or downshifts is indicated in bold in the respective table, and the final consensus judgement is given below the table. The large ranges proposed for some populations reflects the uncertainty related to the impact of U2.

Germany

Table J.35: CAG-DAH: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the German population as given in Table 29 to take CAG-membership probability into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	6.7%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	98.5%	15.7%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	95.2%	21.1%	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	91.6%	24.6%	2.6%	0.2%	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%	0.0%
0	88.5%	26.8%	4.3%	0.5%	**0.1%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%	0.0%
+0.25	85.5%	28.3%	6.0%	1.0%	**0.2%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%	0.0%
+0.5	82.6%	29.7%	7.9%	1.7%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+0.75	80.2%	30.7%	9.5%	2.5%	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+1	77.6%	31.1%	10.9%	3.4%	1.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1% (0%).

Table J.36: CAG-DAH: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the German population as given in Table 29 to take CAG-membership probability into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	100.0%	94.6%	6.7%	0.3%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	100.0%	100.0%	98.5%	77.1%	15.7%	0.7%	0.0%	0.0%	0.0%	0.0%
−0.5	100.0%	100.0%	100.0%	95.2%	70.9%	21.1%	2.4%	0.2%	0.0%	0.0%	0.0%
−0.25	100.0%	100.0%	99.9%	91.6%	**67.0%**	**24.6%**	**4.6%**	0.9%	0.0%	0.0%	0.0%
0	100.0%	100.0%	99.8%	88.5%	**64.3%**	**26.8%**	**6.8%**	1.8%	0.2%	0.0%	0.0%
+0.25	100.0%	100.0%	99.6%	85.5%	**61.9%**	**28.3%**	**8.7%**	2.9%	0.4%	0.0%	0.0%
+0.5	100.0%	100.0%	99.3%	82.6%	59.9%	29.7%	10.8%	4.2%	0.7%	0.0%	0.0%
+0.75	100.0%	100.0%	98.9%	80.2%	58.5%	30.7%	12.6%	5.5%	1.1%	0.0%	0.0%
+1	100.0%	100.0%	98.4%	77.6%	56.8%	31.1%	14.0%	6.8%	1.7%	0.0%	0.0%

Consensus judgement: 5–33%.

Belgium

Table J.37: CAG-DAH: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Belgian population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	4.8%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	96.0%	11.4%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	91.2%	16.5%	0.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	87.0%	20.1%	2.0%	0.1%	0.0%	0.0%	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%
0	83.7%	22.6%	3.3%	0.4%	0.0%	0.0%	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%
+0.25	80.6%	24.4%	4.8%	0.8%	0.1%	0.0%	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%
+0.5	77.7%	26.0%	6.5%	1.3%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+0.75	75.4%	27.2%	8.0%	2.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+1	73.0%	27.9%	9.4%	2.8%	0.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1% (0%).

Table J.38: CAG-DAH: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Belgian population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
–1	100.0%	100.0%	100.0%	100.0%	75.9%	4.8%	0.2%	0.0%	0.0%	0.0%	0.0%
–0.75	100.0%	100.0%	100.0%	96.0%	66.6%	11.4%	0.5%	0.0%	0.0%	0.0%	0.0%
–0.5	100.0%	100.0%	99.9%	91.2%	62.5%	16.5%	1.7%	0.2%	0.0%	0.0%	0.0%
–0.25	100.0%	100.0%	99.7%	87.0%	59.8%	20.1%	**3.5%**	**0.6%**	**0.0%**	0.0%	0.0%
0	100.0%	100.0%	99.4%	83.7%	57.9%	22.6%	**5.3%**	**1.4%**	**0.1%**	0.0%	0.0%
+0.25	100.0%	100.0%	98.8%	80.6%	56.1%	24.4%	**7.1%**	**2.3%**	**0.3%**	0.0%	0.0%
+0.5	100.0%	100.0%	98.0%	77.7%	54.7%	26.0%	9.1%	3.4%	0.5%	0.0%	0.0%
+0.75	100.0%	100.0%	97.3%	75.4%	53.7%	27.2%	10.8%	4.5%	0.8%	0.0%	0.0%
+1	100.0%	100.0%	96.2%	73.0%	52.4%	27.9%	12.2%	5.7%	1.3%	0.0%	0.0%

Consensus judgement: 0–5%.

Czechia

Table J.39: CAG-DAH: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Czech population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
–1	100.0%	6.4%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.75	96.5%	14.2%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.5	92.3%	19.1%	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.25	88.6%	22.5%	2.4%	0.2%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
0	85.4%	24.7%	3.9%	0.5%	0.1%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.25	82.5%	26.4%	5.5%	0.9%	0.2%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.5	79.7%	27.9%	7.3%	1.6%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+0.75	77.4%	28.9%	8.8%	2.3%	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+1	74.9%	29.4%	10.2%	3.1%	0.9%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1% (0%).

Table J.40: CAG-DAH: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Czech population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
–1	100.0%	100.0%	100.0%	100.0%	80.4%	6.4%	0.3%	0.0%	0.0%	0.0%	0.0%
–0.75	100.0%	100.0%	100.0%	96.5%	70.4%	14.2%	0.7%	0.0%	0.0%	0.0%	0.0%
–0.5	100.0%	100.0%	99.9%	92.3%	65.9%	19.1%	2.2%	0.2%	0.0%	0.0%	0.0%
–0.25	100.0%	100.0%	99.8%	88.6%	62.8%	22.5%	**4.2%**	**0.8%**	0.0%	0.0%	0.0%
0	100.0%	100.0%	99.4%	85.4%	60.7%	24.7%	**6.1%**	**1.6%**	0.1%	0.0%	0.0%
+0.25	100.0%	100.0%	99.0%	82.5%	58.7%	26.4%	**8.0%**	**2.7%**	0.3%	0.0%	0.0%
+0.5	100.0%	100.0%	98.3%	79.7%	57.0%	27.9%	10.0%	3.9%	0.6%	0.0%	0.0%
+0.75	100.0%	100.0%	97.7%	77.4%	55.8%	28.9%	11.7%	5.1%	1.0%	0.0%	0.0%
+1	100.0%	100.0%	96.8%	74.9%	54.4%	29.4%	13.1%	6.3%	1.5%	0.0%	0.0%

Consensus judgement: 1–10%.

Denmark

Table J.41: CAG-DAH: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Danish population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	88.3%	0.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	73.8%	1.9%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	68.3%	4.6%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	64.7%	7.4%	0.4%	0.0%	0.0%	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
0	62.3%	10.0%	0.9%	0.1%	0.0%	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.25	60.1%	12.1%	1.7%	0.2%	0.0%	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.5	58.3%	14.3%	2.6%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+0.75	57.0%	16.1%	3.6%	0.6%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+1	55.5%	17.3%	4.7%	1.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1% (0%).

Table J.42: CAG-DAH: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Danish population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	88.3%	14.9%	0.8%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	100.0%	99.6%	73.8%	27.4%	1.9%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	100.0%	100.0%	98.0%	68.3%	31.4%	4.6%	0.2%	0.0%	0.0%	0.0%	0.0%
−0.25	100.0%	100.0%	95.8%	64.7%	33.6%	**7.4%**	**0.8%**	**0.1%**	0.0%	0.0%	0.0%
0	100.0%	100.0%	93.6%	62.3%	34.8%	**10.0%**	**1.6%**	**0.3%**	0.0%	0.0%	0.0%
+0.25	100.0%	100.0%	91.3%	60.1%	35.5%	**12.1%**	**2.7%**	**0.7%**	0.0%	0.0%	0.0%
+0.5	100.0%	100.0%	88.7%	58.3%	36.3%	14.3%	4.0%	1.2%	0.1%	0.0%	0.0%
+0.75	100.0%	100.0%	86.6%	57.0%	36.7%	16.1%	5.2%	1.8%	0.2%	0.0%	0.0%
+1	100.0%	100.0%	84.1%	55.5%	36.7%	17.3%	6.5%	2.5%	0.3%	0.0%	0.0%

Consensus judgement: 0–10%.

Spain

Table J.43: CAG-DAH: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Spanish population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	97.8%	1.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	86.0%	4.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	79.4%	7.9%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	74.8%	11.3%	0.8%	0.0%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
0	71.6%	14.1%	1.6%	0.1%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.25	68.6%	16.3%	2.6%	0.3%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.5	66.2%	18.3%	3.9%	0.6%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
+0.75	64.4%	20.0%	5.1%	1.0%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+1	62.4%	21.1%	6.3%	1.5%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1% (0%).

Table J.44: CAG-DAH: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Spanish population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	97.8%	33.6%	1.6%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	100.0%	99.9%	86.0%	42.2%	4.0%	0.1%	0.0%	0.0%	0.0%	0.0%
−0.5	100.0%	100.0%	99.4%	79.4%	43.3%	7.9%	0.5%	0.0%	0.0%	0.0%	0.0%
−0.25	100.0%	100.0%	98.3%	74.8%	43.5%	11.3%	**1.5%**	**0.2%**	0.0%	0.0%	0.0%
0	100.0%	100.0%	97.0%	71.6%	43.6%	14.1%	**2.7%**	**0.6%**	0.0%	0.0%	0.0%
+0.25	100.0%	100.0%	95.5%	68.6%	43.3%	16.3%	**4.0%**	**1.1%**	0.1%	0.0%	0.0%
+0.5	100.0%	100.0%	93.6%	66.2%	43.2%	18.3%	5.6%	1.8%	0.2%	0.0%	0.0%
+0.75	100.0%	100.0%	92.0%	64.4%	43.1%	20.0%	7.1%	2.6%	0.3%	0.0%	0.0%
+1	100.0%	100.0%	89.9%	62.4%	42.6%	21.1%	8.4%	3.6%	0.6%	0.0%	0.0%

Consensus judgement: 0–5%.

Finland

Table J.45: CAG-DAH: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Finnish population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	15.3%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	97.6%	23.0%	0.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	94.7%	26.8%	2.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	91.8%	29.3%	3.9%	0.4%	0.0%	0.0%	0.0%	**0.0%**	**0.0%**	**0.0%**	0.0%
0	89.3%	30.8%	5.8%	0.8%	0.1%	0.0%	0.0%	**0.0%**	**0.0%**	**0.0%**	0.0%
+0.25	86.7%	31.9%	7.5%	1.5%	0.3%	0.0%	0.0%	**0.0%**	**0.0%**	**0.0%**	0.0%
+0.5	84.2%	32.8%	9.4%	2.3%	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+0.75	82.1%	33.5%	11.1%	3.2%	0.9%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%
+1	79.8%	33.7%	12.4%	4.1%	1.4%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1% (0%).

Table J.46: CAG-DAH: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Finnish population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	100.0%	88.8%	15.3%	0.7%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	100.0%	100.0%	97.6%	78.8%	23.0%	1.8%	0.1%	0.0%	0.0%	0.0%
−0.5	100.0%	100.0%	99.9%	94.7%	73.7%	26.8%	4.1%	0.6%	0.0%	0.0%	0.0%
−0.25	100.0%	100.0%	99.8%	91.8%	70.1%	29.3%	6.5%	**1.5%**	**0.1%**	**0.0%**	0.0%

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
0	100.0%	100.0%	99.6%	89.3%	67.5%	30.8%	8.7%	**2.6%**	**0.3%**	**0.0%**	0.0%
+0.25	100.0%	100.0%	99.3%	86.7%	65.1%	31.9%	10.7%	**3.8%**	**0.6%**	**0.0%**	0.0%
+0.5	100.0%	100.0%	98.9%	84.2%	63.1%	32.8%	12.7%	5.3%	1.0%	0.0%	0.0%
+0.75	100.0%	100.0%	98.5%	82.1%	61.5%	33.5%	14.4%	6.6%	1.5%	0.1%	0.0%
+1	100.0%	100.0%	97.9%	79.8%	59.8%	33.7%	15.7%	7.9%	2.2%	0.1%	0.0%

Consensus judgement: 0–5%.

France

Table J.47: CAG-DAH: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the French population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	99.6%	2.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	88.9%	5.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	82.3%	9.3%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	77.6%	12.8%	0.9%	0.0%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
0	74.3%	15.6%	1.9%	0.2%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.25	71.2%	17.8%	3.0%	0.4%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.5	68.6%	19.8%	4.3%	0.7%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+0.75	66.7%	21.4%	5.6%	1.1%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+1	64.5%	22.4%	6.9%	1.7%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1% (0%).

Table J.48: CAG-DAH: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the French population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	99.6%	41.4%	2.1%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	100.0%	100.0%	88.9%	47.1%	5.1%	0.1%	0.0%	0.0%	0.0%	0.0%
−0.5	100.0%	100.0%	99.6%	82.3%	47.1%	9.3%	0.7%	0.1%	0.0%	0.0%	0.0%
−0.25	100.0%	100.0%	98.8%	77.6%	46.8%	12.8%	**1.8%**	**0.3%**	0.0%	0.0%	0.0%
0	100.0%	100.0%	97.8%	74.3%	46.4%	15.6%	**3.1%**	**0.7%**	0.0%	0.0%	0.0%
+0.25	100.0%	100.0%	96.5%	71.2%	45.9%	17.8%	**4.6%**	**1.3%**	0.1%	0.0%	0.0%
+0.5	100.0%	100.0%	94.8%	68.6%	45.5%	19.8%	6.2%	2.1%	0.2%	0.0%	0.0%
+0.75	100.0%	100.0%	93.3%	66.7%	45.2%	21.4%	7.7%	3.0%	0.4%	0.0%	0.0%
+1	100.0%	100.0%	91.5%	64.5%	44.5%	22.4%	9.1%	4.0%	0.7%	0.0%	0.0%

Consensus judgement: 0–5%.

Hungary

Table J.49: CAG-DAH: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Hungarian population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
–1	78.8%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.75	68.8%	1.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.5	64.4%	4.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.25	61.5%	6.8%	0.3%	0.0%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
0	59.5%	9.2%	0.9%	0.1%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.25	57.6%	11.3%	1.5%	0.1%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.5	56.0%	13.4%	2.4%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+0.75	54.9%	15.2%	3.3%	0.5%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+1	53.6%	16.5%	4.4%	0.9%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1% (0%).

Table J.50: CAG-DAH: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Hungarian population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
–1	100.0%	100.0%	100.0%	78.8%	13.9%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.75	100.0%	100.0%	99.1%	68.8%	24.7%	1.7%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.5	100.0%	100.0%	96.9%	64.4%	28.8%	4.2%	0.2%	0.0%	0.0%	0.0%	0.0%
–0.25	100.0%	100.0%	94.3%	61.5%	31.2%	6.8%	**0.7%**	**0.1%**	0.0%	0.0%	0.0%
0	100.0%	100.0%	91.8%	59.5%	32.7%	9.2%	**1.5%**	**0.3%**	0.0%	0.0%	0.0%
+0.25	100.0%	100.0%	89.3%	57.6%	33.6%	11.3%	**2.5%**	**0.6%**	0.0%	0.0%	0.0%
+0.5	100.0%	99.9%	86.8%	56.0%	34.5%	13.4%	3.7%	1.1%	0.1%	0.0%	0.0%
+0.75	100.0%	99.9%	84.6%	54.9%	35.1%	15.2%	4.8%	1.6%	0.2%	0.0%	0.0%
+1	100.0%	99.8%	82.1%	53.6%	35.2%	16.5%	6.0%	2.3%	0.3%	0.0%	0.0%

Consensus judgement: 0–5%.

Ireland

Table J.51: CAG-DAH: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Irish population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
–1	100.0%	12.2%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.75	96.6%	18.7%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
-0.5	92.9%	22.9%	1.6%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.25	89.6%	25.7%	3.2%	0.3%	0.0%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%
0	86.7%	27.5%	4.8%	0.7%	0.1%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%
+0.25	84.0%	28.9%	6.5%	1.2%	0.2%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%
+0.5	81.4%	30.1%	8.3%	1.9%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+0.75	79.3%	31.0%	9.9%	2.7%	0.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
+1	76.9%	31.4%	11.2%	3.6%	1.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1% (0%).

Table J.52: CAG-DAH: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Irish population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	100.0%	81.1%	12.2%	0.5%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	100.0%	100.0%	96.6%	73.2%	18.7%	1.3%	0.1%	0.0%	0.0%	0.0%
−0.5	100.0%	100.0%	99.9%	92.9%	68.8%	22.9%	3.2%	0.4%	0.0%	0.0%	0.0%
−0.25	100.0%	100.0%	99.7%	89.6%	65.7%	25.7%	5.3%	**1.2%**	**0.1%**	0.0%	0.0%
0	100.0%	100.0%	99.4%	86.7%	63.5%	27.5%	7.4%	**2.1%**	**0.2%**	0.0%	0.0%
+0.25	100.0%	100.0%	99.0%	84.0%	61.4%	28.9%	9.3%	**3.2%**	**0.5%**	0.0%	0.0%
+0.5	100.0%	100.0%	98.4%	81.4%	59.6%	30.1%	11.3%	4.6%	0.8%	0.0%	0.0%
+0.75	100.0%	100.0%	97.8%	79.3%	58.3%	31.0%	13.0%	5.8%	1.3%	0.0%	0.0%
+1	100.0%	100.0%	97.0%	76.9%	56.8%	31.4%	14.3%	7.0%	1.9%	0.1%	0.0%

Consensus judgement: 0–5%.

Italy

Table J.53: CAG-DAH: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Italian population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	88.8%	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	77.8%	2.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	72.1%	6.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	68.3%	9.0%	0.5%	0.0%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
0	65.7%	11.6%	1.2%	0.1%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.25	63.2%	13.8%	2.1%	0.2%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.5	61.2%	15.9%	3.1%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+0.75	59.7%	17.6%	4.2%	0.7%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+1	58.0%	18.8%	5.3%	1.2%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1% (0%).

Table J.54: CAG-DAH: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Italian population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	88.8%	23.9%	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	100.0%	99.6%	77.8%	33.4%	2.8%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	100.0%	100.0%	98.2%	72.1%	36.1%	6.0%	0.3%	0.0%	0.0%	0.0%	0.0%
−0.25	100.0%	100.0%	96.4%	68.3%	37.4%	9.0%	**1.1%**	**0.1%**	0.0%	0.0%	0.0%
0	100.0%	100.0%	94.6%	65.7%	38.1%	11.6%	**2.1%**	**0.4%**	0.0%	0.0%	0.0%

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
+0.25	100.0%	100.0%	92.6%	63.2%	38.5%	13.8%	**3.3%**	**0.9%**	0.1%	0.0%	0.0%
+0.5	100.0%	100.0%	90.3%	61.2%	38.9%	15.9%	4.6%	1.4%	0.1%	0.0%	0.0%
+0.75	100.0%	100.0%	88.4%	59.7%	39.1%	17.6%	5.9%	2.1%	0.2%	0.0%	0.0%
+1	100.0%	99.9%	86.1%	58.0%	38.9%	18.8%	7.2%	2.9%	0.4%	0.0%	0.0%

Consensus judgement: 0–5%.

Latvia

Table J.55: CAG-DAH: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Latvian population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
–1	66.9%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.75	62.7%	1.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.5	59.7%	3.7%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.25	57.5%	6.1%	0.3%	0.0%	0.0%	0.0%	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%
0	56.0%	8.3%	0.8%	0.1%	0.0%	0.0%	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%
+0.25	54.5%	10.3%	1.4%	0.1%	0.0%	0.0%	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%
+0.5	53.3%	12.4%	2.2%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+0.75	52.4%	14.1%	3.0%	0.5%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+1	51.2%	15.4%	4.0%	0.8%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1% (0%).

Table J.56: CAG-DAH: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Latvian population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
–1	100.0%	100.0%	100.0%	66.9%	12.6%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.75	100.0%	100.0%	98.3%	62.7%	21.4%	1.6%	0.0%	0.0%	0.0%	0.0%	0.0%
–0.5	100.0%	100.0%	95.3%	59.7%	25.7%	3.7%	0.2%	0.0%	0.0%	0.0%	0.0%
–0.25	100.0%	100.0%	92.3%	57.5%	28.4%	6.1%	**0.7%**	**0.1%**	**0.0%**	0.0%	0.0%
0	100.0%	100.0%	89.6%	56.0%	30.1%	8.3%	**1.4%**	**0.3%**	**0.0%**	0.0%	0.0%
+0.25	100.0%	99.9%	86.9%	54.5%	31.3%	10.3%	**2.2%**	**0.5%**	**0.0%**	0.0%	0.0%
+0.5	100.0%	99.8%	84.3%	53.3%	32.4%	12.4%	3.3%	1.0%	0.1%	0.0%	0.0%
+0.75	100.0%	99.7%	82.1%	52.4%	33.1%	14.1%	4.4%	1.4%	0.1%	0.0%	0.0%
+1	100.0%	99.6%	79.6%	51.2%	33.3%	15.4%	5.6%	2.1%	0.2%	0.0%	0.0%

Consensus judgement: 0–5%.

Netherlands

Table J.57: CAG-DAH: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Dutch population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	4.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	95.5%	9.7%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	90.3%	14.8%	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	85.9%	18.6%	1.7%	0.1%	0.0%	0.0%	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%
0	82.5%	21.2%	3.0%	0.3%	0.0%	0.0%	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%
+0.25	79.2%	23.1%	4.4%	0.7%	0.1%	0.0%	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%
+0.5	76.3%	24.9%	6.1%	1.2%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+0.75	74.1%	26.2%	7.5%	1.8%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+1	71.6%	26.9%	8.9%	2.5%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1% (0%).

Table J.58: CAG-DAH: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Dutch population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	100.0%	72.1%	4.0%	0.1%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	100.0%	100.0%	95.5%	63.8%	9.7%	0.4%	0.0%	0.0%	0.0%	0.0%
−0.5	100.0%	100.0%	99.9%	90.3%	60.1%	14.8%	1.4%	0.1%	0.0%	0.0%	0.0%
−0.25	100.0%	100.0%	99.7%	85.9%	57.7%	18.6%	**3.1%**	**0.5%**	**0.0%**	0.0%	0.0%
0	100.0%	100.0%	99.3%	82.5%	56.0%	21.2%	**4.8%**	**1.2%**	**0.1%**	0.0%	0.0%
+0.25	100.0%	100.0%	98.7%	79.2%	54.4%	23.1%	**6.6%**	**2.1%**	**0.2%**	0.0%	0.0%
+0.5	100.0%	100.0%	97.8%	76.3%	53.2%	24.9%	8.5%	3.1%	0.4%	0.0%	0.0%
+0.75	100.0%	100.0%	96.9%	74.1%	52.2%	26.2%	10.2%	4.2%	0.7%	0.0%	0.0%
+1	100.0%	100.0%	95.8%	71.6%	51.1%	26.9%	11.6%	5.4%	1.2%	0.0%	0.0%

Consensus judgement: 0–5%.

Romania

Table J.59: CAG-DAH: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Romanian population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	18.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	26.8%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	30.3%	0.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	32.4%	1.8%	0.0%	0.0%	**0.0%**	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
0	33.6%	3.0%	0.2%	0.0%	**0.0%**	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.25	34.5%	4.4%	0.4%	0.0%	**0.0%**	**0.0%**	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.5	35.2%	5.9%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
+0.75	35.7%	7.4%	1.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+1	35.8%	8.7%	1.7%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1% (0%).

Table J.60: CAG-DAH: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Romanian population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	94.8%	18.0%	2.3%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	100.0%	83.3%	26.8%	5.4%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	100.0%	99.7%	77.8%	30.3%	9.1%	0.8%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	100.0%	99.2%	73.8%	32.4%	**12.3%**	**1.8%**	**0.1%**	**0.0%**	0.0%	0.0%	0.0%
0	100.0%	98.4%	71.0%	33.6%	**14.8%**	**3.0%**	**0.4%**	**0.0%**	0.0%	0.0%	0.0%
+0.25	100.0%	97.6%	68.3%	34.5%	**16.9%**	**4.4%**	**0.7%**	**0.1%**	0.0%	0.0%	0.0%
+0.5	100.0%	96.4%	66.1%	35.2%	18.9%	5.9%	1.2%	0.2%	0.0%	0.0%	0.0%
+0.75	100.0%	95.3%	64.3%	35.7%	20.4%	7.4%	1.8%	0.4%	0.0%	0.0%	0.0%
+1	100.0%	94.0%	62.4%	35.8%	21.5%	8.7%	2.5%	0.7%	0.0%	0.0%	0.0%

Consensus judgement: 0–10%.

Sweden

Table J.61: CAG-DAH: Probability of the MOET at 99.9th percentile being below 100: effect of downshift/upshift of the MOET distribution for the Swedish population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	98.1%	1.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	85.3%	3.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.5	78.5%	7.4%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.25	73.9%	10.8%	0.7%	0.0%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
0	70.7%	13.5%	1.5%	0.1%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.25	67.8%	15.8%	2.5%	0.3%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	0.0%
+0.5	65.4%	17.8%	3.7%	0.6%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+0.75	63.6%	19.6%	4.9%	0.9%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
+1	61.7%	20.7%	6.1%	1.4%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Consensus judgement: 0–1% (0%).

Table J.62: CAG-DAH: Probability of the MOET at 99.9th percentile being below 500: effect of downshift/upshift of the MOET distribution for the Swedish population as given in Table 29 to take CAG-membership probability and differences with the German population into account, and for different degrees of dependency between exposure and toxicology uncertainties

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
−1	100.0%	100.0%	100.0%	98.1%	28.9%	1.5%	0.0%	0.0%	0.0%	0.0%	0.0%
−0.75	100.0%	100.0%	99.9%	85.3%	40.4%	3.6%	0.1%	0.0%	0.0%	0.0%	0.0%
−0.5	100.0%	100.0%	99.3%	78.5%	41.9%	7.4%	0.5%	0.0%	0.0%	0.0%	0.0%
−0.25	100.0%	100.0%	98.2%	73.9%	42.4%	10.8%	**1.4%**	**0.2%**	0.0%	0.0%	0.0%

rho	× 0.1	× 0.2	× 0.33	× 0.5	× 0.66	=	× 1.5	× 2	× 3	× 5	× 10
0	100.0%	100.0%	96.9%	70.7%	42.6%	13.5%	**2.5%**	**0.5%**	0.0%	0.0%	0.0%
+0.25	100.0%	100.0%	95.3%	67.8%	42.5%	15.8%	**3.9%**	**1.0%**	0.1%	0.0%	0.0%
+0.5	100.0%	100.0%	93.3%	65.4%	42.5%	17.8%	5.4%	1.7%	0.2%	0.0%	0.0%
+0.75	100.0%	100.0%	91.6%	63.6%	42.4%	19.6%	6.8%	2.5%	0.3%	0.0%	0.0%
+1	100.0%	100.0%	89.4%	61.7%	42.0%	20.7%	8.2%	3.4%	0.6%	0.0%	0.0%

Consensus judgement: 0–5%.

Annexes

The following annexes can be found in the online version of this output ('Supporting information' section): https://doi.org/10.5281/zenodo.7143238:

- Annex A – Indicators of craniofacial alterations collected for 85 selected active substances;
- Annex B1 – Input data for the exposure assessment of CAG-DACL;
- Annex B2 – Input data for the exposure assessment of CAG-DAH;
- Annex C1 – Output data for the Tier I exposure assessment of CAG-DAC;
- Annex C2 – Output data for the Tier I exposure assessment of CAG-DAH;
- Annex D1 – Output data for the Tier II exposure assessment of CAG-DAC;
- Annex D2 – Output data for the Tier II exposure assessment of CAG-DAH.