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## Cumulative dietary risk characterisation of pesticides that have acute effects on the nervous system

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### Abstract

A retrospective acute cumulative risk assessment of dietary exposure to pesticide residues, supported by an uncertainty analysis based on expert knowledge elicitation, was conducted for two effects on the nervous system: brain and/or erythrocyte acetylcholinesterase inhibition, and functional alterations of the motor division. The pesticides considered in this assessment were identified and characterised in the scientific report on the establishment of cumulative assessment groups of pesticides for their effects on the nervous system. Cumulative exposure assessments were conducted through probabilistic modelling by EFSA and the Dutch National Institute for Public Health and the Environment (RIVM) using two different software tools and reported separately. These exposure assessments used monitoring data collected by Member States under their official pesticide monitoring programmes in 2014, 2015 and 2016 and individual consumption data from 10 populations of consumers from different countries and different age groups. This report completes the characterisation of cumulative risk, taking account of the available data and the uncertainties involved. For each of the 10 populations, it is concluded with varying degrees of certainty that cumulative exposure to pesticides that have the acute effects on the nervous system mentioned above does not exceed the threshold for regulatory consideration established by risk managers.

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## Summary

A retrospective acute cumulative risk assessment (CRA) of dietary exposure to pesticide residues in 2014, 2015 and 2016 was conducted for two effects on the nervous system: brain and/or erythrocyte acetylcholinesterase (AChE) inhibition, and functional alterations of the motor division.

The **first step of the process was to establish cumulative assessment groups (CAGs)** of pesticides for the effects of relevance so as to assess their combined toxicity on the nervous system. This step is reported in the EFSA scientific report on the establishment of CAGs for their effects on the nervous system (EFSA, 2019a). In that report, all effects of pesticides on the nervous system were reviewed and five were found to meet the criteria established by the EFSA Panel on Plant Protection Products and their Residues (PPR Panel) and to be specific for consideration in CRA (brain and/or AChE inhibition, functional alterations of three divisions of the nervous system – motor, sensory and autonomic divisions – and histological neuropathological changes in neural tissues).

A CAG was established for each of the five specific effects and more than 400 active substances were screened for potential inclusion in these CAGs. Any active substance possessing a chemical structure associated with a mode of action (MoA) of direct relevance for the effects or exhibiting selected indicators (toxicological endpoints) reflecting the specific effect in regulatory toxicological studies was included in the respective CAG.

In total, 47 active substances were included in the CAG for brain and/or erythrocyte AChE inhibition; 119 were included in the CAG for functional alterations of the motor division; and the CAGs for functional alterations of the sensory and autonomic divisions each contained 101 active substances. The CAG for histological neuropathological changes in neural tissues contained 19 active substances only. All active substances included in the CAGs were characterised by no observed adverse effect levels (NOAELs) for short- and long-term cumulative exposure/risk assessment, derived from the most sensitive indicator, using all available information across studies, species and sexes.

The number and the identity of the active substances included in the CAGs, as well as the allocated NOAELs, are subject to uncertainties. Sources of uncertainty resulting from the methods used to collect and assess toxicological data and from the limitations in the available data and scientific knowledge were therefore identified for appropriate consideration during the CRA conducted with these CAGs. The sources of uncertainty were related to the composition of the CAGs, the toxicological characterisation of the active substances, the slope and shape of the dose–response relationship, the contribution of metabolites and degradation products, the adequacy of the dose-addition model and the inter- and intraspecies differences in toxicological sensitivity.

With respect to the composition of the CAGs, the EFSA scientific report used weight of evidence and expert knowledge elicitation (EKE) techniques to address the uncertainty about the total number of active substances in the CAG for functional alterations of the motor division that actually cause the effect. In this process, active substances were allocated in subgroups of varying levels of evidence and a median estimate of 104 was derived for the number of active substances actually causing functional alteration of the motor division. A similar exercise was not conducted with the CAG for brain and/or erythrocyte AChE inhibition because the association between the chemical structure and the MoA is obvious for organophosphorus and N-methyl carbamate insecticides.

Based on the number and NOAELs of active substances included in each CAG, two of them (for brain and/or erythrocyte AChE inhibition and for functional alterations of the motor division) were considered sufficient to cover the cumulative risks associated with all five specific effects.

In a **second step, cumulative exposure assessments** were conducted of all pesticides with short term toxicity potential included in the CAGs for brain and/or erythrocyte AChE inhibition (47 active substances) and for functional alterations of the motor division (100 active substances). These were carried out by EFSA and the Dutch National Institute for Public Health and Environment (RIVM) using probabilistic modelling and with different software tools. The results are reported in the EFSA scientific report on cumulative dietary exposure assessment of pesticides that have acute effects on the nervous system using SAS<sup>®</sup> software (EFSA 2019b) and in the external scientific report on cumulative dietary exposure assessment of pesticides that have acute effects on the nervous system using MCRA software. The two tools produced nearly identical results and any observed differences are mainly attributed to the random effect of probabilistic modelling. These minor differences do not impact on the outcome of the exposure assessment.

The exposure calculations used monitoring data collected by EU Member States (MSs) under their official monitoring programmes in 2014, 2015 and 2016 and individual food consumption data from 10 populations of consumers from different countries and from different age groups, including vulnerable

ones: four populations of adults, three populations of children (3–9 years) and three populations of toddlers (1–3 years).

As agreed by risk managers in the Standing Committee on Plants, Animals, Food and Feed (SC PAFF), the exposure estimates were conducted in a tiered approach. The first-tier calculations (tier I) use very conservative assumptions for an efficient screening of the exposure with low risk for underestimation; the second-tier assessment (tier II) includes assumptions that are more refined but still intended to be conservative and therefore likely to overestimate the actual exposure.

For each scenario, exposure estimates relied on the principle of dose-addition. They were obtained for different percentiles of the exposure distribution and the combined margin of exposure (MOET) was calculated at each percentile. In accordance with the threshold agreed at the SC PAFF, further regulatory consideration would be required when the MOET calculated at the 99.9th percentile of the exposure distribution is below 100.

The lowest MOET estimates were obtained with the CAG for brain and/or erythrocyte AChE inhibition. In tier II, estimates at the 50th, 95th and 99th percentile of the exposure distribution were all well above 100. At the 99.9th percentile of the exposure distribution, estimates were mostly below 100, ranging from 40 to 59 in toddlers and other children. For adults, the MOETs ranged from 92 to 124. The exposure to this group of pesticides was predominantly driven by the occurrence of chlorpyrifos, triazophos and omethoate. Other important contributors included dichlorvos, formetanate and carbofuran.

For pesticides included in the CAG for functional alterations of the motor division, MOETs calculated at the 99.9th percentile of the exposure distribution were higher, ranging from 63 to 89 in toddlers and other children and from 141 to 176 in adults. In this case, the main drivers for the exposure were identified as triazophos and deltamethrin. Other important contributions came from beta-cypermethrin, omethoate, thiram, chlormequat and acrinathrin.

The **third and last step of the exercise was a cumulative risk characterisation** which is documented in detail in this report. This was based on the outcome of the first two steps and included an uncertainty analysis, performed following the guidance of the EFSA Scientific Committee in order to take account of the limitations in scientific knowledge and data and of the assumptions used in all steps of the assessment.

Thirty-four sources of uncertainty affecting the input data, model assumptions and the assessment methodology were identified. The impact of each source of uncertainty on the MOETs at the 99.9th percentile of exposure was quantified. This showed that uncertainties had variable effects, with some tending to overestimate the MOET (e.g. the metabolites were not considered in the assessment) and others tending to underestimate it (e.g. limited availability of processing factors; when such data are missing, it is assumed that all pesticide residues in the raw primary commodity (RPC) will reach the end consumer without any loss during household or industrial processing). The combined impact of the uncertainties, and their dependencies, on the assessment was then quantified in a sequential approach using EKE techniques and 1-D Monte Carlo simulations.

As a result of this process, the MOETs at the 99.9th percentile and their confidence intervals were adjusted to take account of the identified uncertainties. For both CAGs, the adjusted MOETs were around four to five times higher compared to those calculated in tier II by the probabilistic tools. This is consistent with the intention of MSs, when selecting the parameters and assumptions to be used, to ensure that the tier II calculations are sufficiently conservative.

Analysis of the factors influencing the upper part of the exposure distribution also revealed that most of the highest acute exposures do not result from cumulative exposure to multiple compounds. For toddlers and children, around 75% of the high exposure estimates were driven by a single substance in a specific commodity. For pesticides associated with brain and/or erythrocyte AChE inhibition, around 95% of these combinations were found to exceed the maximum residue level (MRL) that was in place at the end of the reference period. It should be noted, however, that MRLs for some of these combinations were lowered shortly before the end of the reference period, which should tend to decrease their contribution in the future (e.g. MRLs for chlorpyrifos in apples and pears were lowered in August 2016). A sensitivity analysis showed that when commodity samples with residue concentrations exceeding the MRL are excluded from the calculations, the MOET estimates with the CAG for brain and/or erythrocyte AChE inhibition increased by a factor 3–5, resulting in values above 100 for all populations. For the CAG on functional alterations of the motor division, an increase by a factor of about 1.5 was observed.

Taking account of all uncertainties identified by experts, for brain and/or erythrocyte AChE inhibition, it was concluded that, with varying degrees of certainty, cumulative exposure does not reach the threshold for regulatory consideration for all the population groups considered. This certainty



exceeds 99% for all four adult populations, 95% for two children populations and one toddler population, 90% for one children population and one toddler population and 80% for the remaining toddler population. For functional alterations of the nervous system, the same conclusion was drawn with a certainty exceeding 99% for all adult populations and one children population, and 95% for two populations of children and all toddler populations.

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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 (US EPA, 2003). It differs from most assessments which consider the effects of one agent or stressor in isolation.

Regulation (EC) No. 396/2005 on Maximum Residue Levels (MRLs) of pesticides in or on food and feed states that cumulative and synergistic effects of pesticides should be taken into account for dietary risk assessment, when appropriate methodologies are available. Regulation (EC) No. 1107/2009 concerning the placing of plant protection products on the market also states that the residues of the plant protection products shall not have any harmful effects on human health, taking into account known cumulative and synergistic effects where the scientific methods accepted by EFSA to assess such effects are available.

For this reason, 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 (CAGs) of pesticides on the basis of their toxicological profile (EFSA PPR Panel, 2013a).

### 1.1. Background and Terms of Reference

In 2014, EFSA started a pilot programme of activities aiming at implementing the CRA of pesticides, using the methodologies developed by the PPR Panel. The objectives of this pilot programme were to evaluate the cumulative effects of pesticide residues on two organs which are known to be sensitive to pesticides (the nervous system and the thyroid), and to test the methodologies over the entire risk assessment process (hazard identification and characterisation, exposure assessment and risk characterisation) for acute and chronic effects.

As part of this program, the Pesticides Unit (nowadays Pesticides Residues and Pesticides Peer Review units) has been requested by EFSA to prepare a scientific report on the CRA of pesticides residues regarding two acute effects on the nervous system.

In accordance with article 32 of Regulation (EC) No 396/2005, EFSA has to draw up annual reports on pesticide residues taking into account the results of official control of pesticide residues in food and feed commodities carried out by Member States (MSs), and including an analysis of the acute and chronic risks to the health of consumers from pesticide residues. The present report falls under this article and investigates cumulative risks resulting from the actual exposure to multiple residues.

Based on methodologies adopted by the PPR Panel (EFSA PPR Panel, 2013a,b), EFSA has identified five effects of pesticides on the nervous system which are relevant for CRA. The most critical of these effects are expected to be brain and/or erythrocyte acetylcholinesterase (AChE) inhibition and functional alterations of the motor division, considering the number of active substances included in these CAGs and the no observed adverse effect levels (NOAELs) allocated to these active substances (EFSA, 2019a).

Therefore, the assessment questions to be addressed by the present report were defined as follows:

- What was the acute cumulative risk of brain and/or erythrocyte AChE inhibition for European consumers resulting from dietary exposure to pesticide residues from 2014 to 2016?
- What was the acute cumulative risk of functional alterations of the motor division (e.g. locomotor activity, muscle strength, coordination and equilibrium) for European consumers resulting from dietary exposure to pesticide residues from 2014 to 2016?

These retrospective assessments were conducted based on official monitoring data collected in 2014, 2015 and 2016, and reported in the respective EFSA annual monitoring reports (EFSA 2016a, 2017a, 2018a). This corresponds to the latest cycle of 3 years of the European coordinated programme (EUCP) for which data were available when the assessments started.

Thirty plant commodities were selected by EFSA, based on their importance in the diet (EFSA, 2015a), to perform the assessments. Ten populations of consumers, from various MSs and various age groups were selected from the EFSA comprehensive food consumption database: Belgian adults (18–64 years), Czech Republic adults (18–64 years), German adults (18–64 years), Italian adults (18–65 years), Bulgarian children (3–5 years), Dutch children (3–6 years), French children (3–9 years), Danish toddlers (1–3 years), Dutch toddlers (2 years) and United Kingdom toddlers (1–2 years).

It should be noted that:

- Non-dietary routes of exposure are not included in the assessments.
- Only pesticide residues are considered in the assessments.
- Chronic cumulative effects of pesticide residues are not included in the assessments.
- Due the lack of sufficient data in current regulatory dossiers, developmental neurotoxicity and neurodegenerative diseases were not considered when CAGs were established, and therefore, are not covered by the assessments.
- For prospective cumulative assessments (e.g. assessments which would be conducted in the context of applications for MRLs), an approach is currently under development.

As explained in the EFSA Scientific Report on the establishment of CAGs of pesticides for their effects on the nervous system, the acute cumulative effects of pesticide residues on the sensory and autonomic divisions can be considered as covered by the assessment of the risk of functional alterations of the motor division.

## 1.2. Input from Risk Managers and threshold for regulatory consideration

During the Standing Committee on Plants, Animals, Food and Feed of 11–12 June 2015 (European Commission, 2015), MSs 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 Standing Committee on Plants, Animals, Food and Feed of 18–19 September 2018 (European Commission, 2018), MSs agreed on an MOET of 100 at 99.9th percentile of exposure in whole populations as the threshold for regulatory consideration, as an indicative target of safety by analogy to the safety margin currently used for establishing the toxicological reference values (a factor 10 for inter-species variability and a factor of 10 for intra-species variability).

The uniform principles for evaluation and authorisation of plant protection products further specify that in interpreting the results of evaluations, MSs 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, and Article 1 of Regulation (EC) No 1107/2009 states that MSs shall not be prevented from applying the precautionary principle where there is scientific uncertainty. Estimates of cumulative risk are necessarily subject to a degree of scientific uncertainty, due to limitations in the data and to assumptions used to address those limitations. In this context, the Standing Committee on Plants, Animals, Food and Feed stated (European Commission, 2018) that the MOET of 100 at 99.9th percentile of exposure would be acceptable provided that the assumptions are sufficiently conservative. This 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 above 100. This provides a measure of the degree to which the assumptions in the assessment are conservative.

## 2. Methodology, data and uncertainty analysis

### 2.1. Methodology

The CRAs conducted in this report were carried out under the assumption of dose addition as recommended by the PPR Panel (EFSA PPR panel, 2008, 2013b) and the Scientific Committee of EFSA (EFSA Scientific Committee, 2019).

The threshold for regulatory consideration specified by the MSs is expressed in terms of the MOET. Two options are possible to calculate MOET:

Directly, by calculating the reciprocal of the sum of the reciprocals of individual MOEs to each chemical<sup>1</sup> contributing to the risk (EFSA PPR Panel, 2008):

$$\frac{1}{\text{MOET}} = \sum_i \frac{1}{\text{MOE}_i} = \frac{1}{\text{MOE}_1} + \frac{1}{\text{MOE}_2} + \frac{1}{\text{MOE}_3} \dots + \frac{1}{\text{MOE}_n}$$
 where  $\text{MOE}_i$  is the margin of exposure for the  $i$  th chemical,

<sup>1</sup> In EFSA (2019b),  $1/\text{MOET}$  is referred to as the total normalised exposure, reflecting that the exposures are normalised relative to the potency of each substance.

$MOE_i = \frac{RfP_i}{E_i}$  and  $RfP_i$  is the toxicological reference point (NOAEL in the present report) for chemical  $i$  and  $E_i$  its exposure. The MOET is then obtained by taking the reciprocal of  $1/MOET$ .

Indirectly, by determining the sum of potency-normalised individual exposures as total Index Compound (IC) equivalents and translating the IC equivalents into the MOET to the  $RfP$  of the IC. This approach, however, requires additional work to select an IC and calculate a Relative Potency Factor ( $RPF_i$ ) for each chemical.

$RPF_i = \frac{RfP_{IC}}{RfP_i}$  where  $RfP_{IC}$  and  $RfP_i$  are the reference points for the IC and chemical  $i$ ,

$MOET = \frac{RfP_{IC}}{\sum_i E_i \times RPF_i}$  where the denominator sums over all chemicals including the IC.

It should be noted that direct or indirect calculations lead exactly to the same results. This is demonstrated as follows:

$\frac{1}{MOET} = \frac{\sum_i E_i \times \frac{RfP_{IC}}{RfP_i}}{RfP_{IC}}$  inverting the previous equation and substituting for  $RPF_i$

$\frac{1}{MOET} = \frac{\sum_i E_i \times \frac{RfP_{IC}}{RfP_i}}{RfP_{IC}}$  cancelling out  $RfP_{IC}$  in numerator and denominator

So:  $\frac{1}{MOET} = \sum_i \frac{E_i}{RfP_i} = \frac{1}{MOE_1} + \frac{1}{MOE_2} + \frac{1}{MOE_3} \dots + \frac{1}{MOE_n}$  as in the direct calculation above.

An important consequence of this is that the choice of the IC has no influence at all on the result of the assessment, nor on the uncertainties affecting the MOET. This is because any change in  $RfP_{IC}$ , e.g. through choosing a different IC or errors in the  $RfP$  of the IC, affects both the numerator and denominator of the equation and cancels out, as shown above.

To perform the cumulative exposure assessments for CAG-NAN and CAG-NAM, EFSA used the direct calculation method (EFSA, 2019b) and the Dutch National Institute for Public Health and the Environment (RIVM) used the method based on ICs (van Klaveren et al., 2019).

## 2.2. Data

The outcome of the hazard assessment (CAGs) and exposure assessment supporting the CRAs of the effects of pesticides on the nervous system are presented in the respective EFSA and RIVM reports (EFSA 2019b, EFSA, 2019a, van Klaveren et al., 2019). They represent the input to the uncertainty analyses and risk characterisations performed in the present report.

### 2.2.1. Cumulative assessment groups (CAGs)

Two CAGs were used to perform the acute CRA of dietary exposure to pesticides for the nervous system.

The CAG for brain and/or erythrocyte AChE inhibition (CAG-NAN<sup>2</sup>) includes 47 active substances. All included active substances are either N-methyl carbamate insecticides or organophosphorus pesticides, and therefore AChE inhibitors. In this CAG, the probability of including an active substance not contributing to the effect is virtually non-existent.

One hundred out of the 119 active substances included in the CAG for functional alterations of the motor division (CAG-NAM<sup>3</sup>) are characterised for acute exposure/risk assessment. A significant proportion of these substances (85) act via one of 11 modes of action (MoAs) considered to be of direct relevance for the effect. The other substances (15) act via either a presumed or an unknown neurotoxic MoA in mammals. There is therefore a probability that some of the active substances in this CAG do not produce functional alterations of the motor division as a primary effect, which was assessed by expert knowledge elicitation (EKE) and Monte Carlo simulations<sup>4</sup> (EFSA, 2019a). This uncertainty on whether the CAG contains only active substances causing the effect was taken into account in the uncertainty analysis (see Section 3.1 and note 28) as all active substances were kept in the CAG to perform the cumulative exposure assessments described in the following section.

<sup>2</sup> CAG-NAN stands for 'Cumulative Assessment Group - Nervous system/Acute/Neurochemical effects'.

<sup>3</sup> CAG-NAM stands for 'Cumulative Assessment Group - Nervous system/Acute/Motor division effects'.

<sup>4</sup> Monte Carlo analysis is a computer-based method of analysis developed in the 1940s that uses statistical sampling techniques in obtaining a probabilistic approximation to the solution of a mathematical equation or model (US EPA, 1997).

## 2.2.2. Cumulative exposure assessments

Cumulative exposure assessments for CAG-NAN (47 active substances) and CAG-NAM (100 active substances) have been conducted probabilistically, on whole population basis, by EFSA using SAS<sup>®</sup> software and by RIVM, using the Monte Carlo Risk Assessment (MCRA) software (van Klaveren et al., 2019). The acute dietary exposures were modelled for 24-hour time intervals, corresponding to the recorded individual consumption days by means of empirical Monte Carlo simulation. Very similar results were obtained, despite minor methodological differences between the two software tools, identified and commented in Section 3.3 of EFSA (2019b) and in Section 5.3 of van Klaveren et al. (2019).

The assessments included two tiers<sup>5</sup> and were based on all parameters and assumptions agreed by MSs for the assessment of cumulative exposure to pesticide residues (European Commission, 2018). While the first-tier calculations (Tier I) used very conservative assumptions, the second-tier assessment (Tier II) included assumptions that are more refined but still intended to be conservative. They produced distributions of MOET estimates, from which the one corresponding to the 99.9th percentile of the cumulative exposure, e.g. the threshold for regulatory consideration established by the European Commission and MSs, was specially considered. At that percentile, an MOET of at least 100 is of interest as explained in Section 1.2.

The calculation model and input data, including sample size and statistics, are included in EFSA (2019b) and van Klaveren et al. (2019). Confidence intervals (95%) were generated by outer loop execution<sup>6</sup> addressing the sampling variability of the consumption and occurrence data as well as some uncertainties associated with probabilities applied in the model.

The MOET estimates at various percentiles of the exposure distribution, and their respective confidence intervals are reported in Tables 1A and 2A.

### 2.2.2.1. Cumulative exposure assessment for CAG-NAN

The results of the cumulative exposure assessment at Tier II to pesticides associated with brain and/or erythrocyte AChE inhibition are presented in Table 1A.

**Table 1A:** CAG-NAN: Estimates of the MOET and their corresponding 95% confidence intervals at the 50th, 99th and 99.9th percentiles<sup>7</sup> of the exposure at Tier II for 10 European populations in 2014–2016

Country	Population class (No. of individuals)	50th Percentile SAS <sup>®(a)</sup>	99th Percentile SAS <sup>®(a)</sup>	99.9th Percentile SAS <sup>®(a)</sup>	99.9th Percentile MCRA <sup>(b)</sup>
Belgium (BE)	Adults (1356)	2960 [2880–3030]	552 [432–618]	106 [72.1–153]	102 [72–162]
Czech Republic (CZ)	Adults (1666)	2870 [2790–2930]	584 [509–655]	121 [85.7–166]	120 [87–176]
Germany (DE)	Adults (10419)	2330 [2300–2350]	414 [361–452]	92.4 [72.9–116]	95 [73–120]
Italy (IT)	Adults (2313)	3820 [3540–4030]	390 [266–545]	96.5 [70.9–131]	96 [75–149]
Bulgaria (BG)	Other children (434)	1970 [1890–2070]	236 [203–269]	48.6 [36.5–63.4]	49 [36–63]
France (FR)	Other children (482)	2570 [2490–2660]	287 [253–321]	59.1 [43–72.7]	59 [46–74]
Netherlands (NL)	Other children (957)	2170 [2110–2220]	229 [200–254]	52 [41.9–62]	52 [45–62]
Denmark (DK)	Toddlers (917)	1630 [1600–1660]	211 [193–229]	58.9 [45.3–72.8]	60 [50–69]

<sup>5</sup> The cumulative exposure assessments were conducted in two steps. The most refined, TIER II, is underlying the risk characterisation performed in the present report.

<sup>6</sup> Outer loop execution, bootstrapping: Sampling variability of consumption and occurrence data was addressed by repeating the inner loop (nominal modelling run) 100 times, each time replacing the original consumption and occurrence data sets with bootstrap data sets, obtained by resampling, with replacement, the same number of observations from the original datasets.

<sup>7</sup> Results at 50th and 99th percentiles of the exposure distribution are given for the SAS<sup>®</sup> model only, for reason of space.



Country	Population class (No. of individuals)	50th Percentile SAS <sup>®(a)</sup>	99th Percentile SAS <sup>®(a)</sup>	99.9th Percentile SAS <sup>®(a)</sup>	99.9th Percentile MCRA <sup>(b)</sup>
Netherlands (NL)	Toddlers (322)	1670 [1580–1760]	173 [154–187]	40.2 [32.7–47]	40 [33–50]
United Kingdom (UK)	Toddlers (1314)	1660 [1610–1700]	261 [231–285]	61.7 [44.7–74]	61 [47–76]

(a): Results obtained by EFSA with SAS<sup>®</sup> software.

(b): Results obtained by RIVM with MCRA.

Median estimates of the MOET below 100 at Tier II were observed in eight populations at the 99.9th percentile of exposure.

Pesticide/commodity combinations contributing significantly to the cumulative risk were identified. Risk drivers were defined as the pesticide/commodity combinations, which, under the precise modelling conditions and assumptions at Tier II, contribute on average, in at least one out of the 10 populations, at least 5% of the cumulative exposures exceeding the 99th percentile estimate. To identify these combinations, the cumulative exposure assessments conducted by both EFSA and RIVM were considered (EFSA, 2019b; van Klaveren et al., 2019).

The risk drivers identified in the 10 populations are reported in Table 1B and ordered according to their contribution level to the cumulative exposure.

**Table 1B:** CAG-NAN: Risk drivers identified in the 10 populations of consumers

Risk drivers	Contribution to the cumulative exposure per population		
	From 5 to 10%	From 10 to 20%	Exceeding 20%
Triazophos/beans with pods	Toddlers: DK	Adults: BE, IT Toddlers: UK	Adults: DE Other children: FR, NL Toddlers: NL
Triazophos/sweet peppers	Adults: CZ		
Triazophos/rice	Adults: CZ, IT Other children: BG	Toddlers: UK	
Chlorpyrifos/apples	Adults: BE, IT	Adults: CZ Other children: BG, FR Toddlers: UK	Adults: DE Children: NL Toddlers: DK, NL
Chlorpyrifos/wine grapes		Adults: BE, CZ, DE, IT	
Chlorpyrifos/peaches	Other children: BG		
Chlorpyrifos/table grapes	Toddlers: UK		
Chlorpyrifos/pears	Toddlers: UK		
Formetanate/table grapes	Toddlers: DK		
Omethoate/olives for oil production	Adults: CZ	Adults: IT	
Omethoate/wine grapes	Adults: BE, CZ, DE, IT		
Omethoate/tomatoes	Other children: BG		
Dichlorvos/wheat	Adults: CZ, IT, BE Other children: BG, NL Toddlers: DK, UK		
Carbofuran/tomatoes	Other children: BG		

This table shows that the main risk drivers involve chlorpyrifos and triazophos, as their residues in eight commodities contribute five to more than 20% of the cumulative exposure in one or several populations. Triazophos in beans with pods and chlorpyrifos in apples show the highest contributions to the cumulative risks.

### 2.2.2.2. Cumulative exposure assessment for CAG-NAM

The results of the cumulative exposure assessment at Tier II to pesticides associated with functional alterations of the motor division are presented in Table 2A.

**Table 2A:** CAG-NAM: Estimates of the MOET and their corresponding 95% confidence intervals at the 50th, 99th and 99.9th percentiles<sup>7</sup> of the exposure at Tier II for 10 European populations in 2014–2016

Country	Population class (No. of individuals)	50th Percentile SAS <sup>®(a)</sup>	99th Percentile SAS <sup>®(a)</sup>	99.9th Percentile SAS <sup>®(a)</sup>	99.9th Percentile MCRA <sup>(b)</sup>
Belgium (BE)	Adults (1356)	3380 [3290–3460]	651 [523–744]	180 [122–259]	176 [115–228]
Czech Republic (CZ)	Adults (1666)	3180 [3100–3240]	635 [551–733]	181 [133–243]	172 [131–236]
Germany (DE)	Adults (10419)	2630 [2600–2670]	574 [502–643]	170 [128–216]	171 [127–211]
Italy (IT)	Adults (2313)	4330 [4060–4610]	475 [379–638]	145 [102–190]	141 [109–185]
Bulgaria (BG)	Other children (434)	2120 [2030–2240]	249 [196–285]	66.3 [51.4–93.5]	63 [53–81]
France (FR)	Other children (482)	2750 [2680–2840]	318 [271–362]	84.3 [65.6–111]	84 [65–102]
Netherlands (NL)	Other children (957)	2340 [2280–2410]	305 [240–349]	89.5 [71.7–113]	89 [75–111]
Denmark (DK)	Toddlers (917)	1640 [1570–1710]	212 [179–257]	80.7 [64.1–101]	80 [63–100]
Netherlands (NL)	Toddlers (322)	1850 [1770–1940]	243 [206–274]	69.5 [56–88.4]	68 [56–85]
United Kingdom (UK)	Toddlers (1314)	1790 [1740–1830]	244 [208–277]	74.4 [59.4–90.9]	73 [61–89]

(a): Results obtained by EFSA with SAS<sup>®</sup> software.

(b): Results obtained by RIVM with MCRA.

Median estimates of the MOET below 100 in Tier II were observed in all populations of children and toddlers at the 99.9th percentile of exposure.

Risk drivers were identified as described in previous section, and are reported in Table 2B, ordered according to their contribution level to the cumulative exposure:

**Table 2B:** CAG-NAM: Risk drivers identified in the 10 populations of consumers

Risk drivers	Contribution to the cumulative exposure per population		
	From 5 to 10%	From 10 to 20%	Exceeding 20%
Triazophos/beans with pods	Adults: DE Other children: BG Toddlers: DK	Adults: CZ, IT Toddlers: UK	Adults: BE Other children: FR, NL Toddlers: NL
Triazophos/rice	Adults: CZ, IT Other children: BG, FR, NL Toddlers: NL	Toddlers: UK	
Triazophos/sweet peppers	Adults: CZ		
Chlormequat/wheat	Adults: BE, CZ, IT Other children: BG, NL		
Chlormequat/oats		Toddlers: DK, UK	
Beta-cypermethrin/wheat	Adults: BE, DE Other children: NL Toddlers: DK, NL, UK	Adults: CZ, IT Other children: BG	

Risk drivers	Contribution to the cumulative exposure per population		
	From 5 to 10%	From 10 to 20%	Exceeding 20%
Deltamethrin/wheat	Adults: DE Other children: FR Toddlers: DK, NL, UK	Adults: BE, CZ, IT Other children: BG, NL	
Deltamethrin/oats	Toddlers: DK		
Omethoate/wine grapes	Adults: BE, CZ, DE, IT		
Omethoate/olives for oil production		Adults: IT	
Thiram/wine grapes	Adults: BE, DE		
Thiram/lettuce	Adults: DE		
Thiram/apples	Adults: DE		
Acrinathrin/bananas	Toddlers: DK, NL, UK		

This table shows that the main risk drivers involve triazophos, chlormequat, beta-cypermethrin, deltamethrin and omethoate, through their residue levels in various commodities. Triazophos in beans with pods show the highest contributions to the cumulative risks.

### 2.2.2.3. Sensitivity analyses

In addition, for both CAG-NAN and CAG-NAM, sensitivity analyses<sup>8</sup> were conducted to test the impact of assumptions applied to the left-censored data<sup>9</sup> and of missing information on the effect of processing. For a complete understanding of the modalities of these sensitivity analyses, EFSA (2019b) or van Klaveren et al. (2019) should be consulted.

In the case of CAG-NAN, the imputation of left-censored data with 1/2 of the limit of quantification (LOQ) assuming 100% of use in case of authorisation, has a limited impact on the outcome of the assessment. The MOETs at the 99.9th percentile of the exposure distribution dropped by a factor of 1.1–1.4 only. This finding is consistent with the expectation that, for acute risks, the MOETs at the 99.9th percentile of the exposure are primarily driven by samples with measurable findings. The impact of missing processing factors was higher. Assuming that no residue would be transferred to any processed food when a processing factor is missing, the MOETs increased by a factor of 1.6–2.5.

In the case of CAG-NAM, when left-censored data were imputed with 1/2 LOQ assuming 100% of use in case of authorisation, the MOETs dropped by a factor of 1.3–1.7. When no residues were assumed to be present in processed foods when no processing factor was available, the MOETs increased by a factor of 1.9–3.5.

It must be noted that sensitivity analyses related to missing processing factors do not consider the effect of washing and/or peeling of commodities with edible peel consumed without further processing.

### 2.2.2.4. Contribution of food commodities with residues exceeding the MRLs

Analysis of factors influencing the upper part of the exposure distribution suggested a significant contribution from substance/commodity combinations which exceeded the MRLs, especially in the case of CAG-NAN (EFSA, 2019b). Therefore, as an additional sensitivity analysis, cumulative exposure assessments were repeated after exclusion of all commodity samples with residues exceeding the MRL in place at the end of the reference period by more than 50%, considered as a default measurement uncertainty (European Commission, 2017a). The results are given in Table 3.

**Table 3:** CAG-NAN and CAG-NAM: Estimates of the MOET at 99.9th percentile of the exposure and corresponding 95% confidence intervals at Tier II and sensitivity to MRL non-compliance

Country	Population class	CAG-NAN 99.9th Percentile SAS <sup>®</sup>	CAG-NAN non-compliant samples excluded SAS <sup>®(a)</sup>	CAG-NAM 99.9th Percentile SAS <sup>®</sup>	CAG-NA Mnon-compliant samples excluded SAS <sup>®(a)</sup>
Belgium	Adults	106 [72.1–153]	313 [177–450]	180 [122–259]	301 [196–386]

<sup>8</sup> Additional model runs with different combinations of assumptions from the basic simulations.

<sup>9</sup> Low measured levels of pesticide residues for which an accurate value is not available, because these levels have been reported as being below a Limit of Reporting.

Country	Population class	CAG-NAN 99.9th Percentile SAS <sup>®</sup>	CAG-NAN non-compliant samples excluded SAS <sup>®(a)</sup>	CAG-NAM 99.9th Percentile SAS <sup>®</sup>	CAG-NA Mnon-compliant samples excluded SAS <sup>®(a)</sup>
Czech Republic	Adults	121 [85.7–166]	360 [268–444]	181 [133–243]	264 [171–324]
Germany	Adults	92.4 [72.9–116]	280 [191–377]	170 [128–216]	257 [197–303]
Italy	Adults	96.5 [70.9–131]	226 [173–388]	145 [102–190]	234 [157–292]
Bulgaria	Other children	48.6 [36.5–63.4]	211 [185–255]	66.3 [51.4–93.5]	103 [63.7–129]
France	Other children	59.1 [43–72.7]	261 [196–312]	84.3 [65.6–111]	154 [105–174]
Netherlands	Other children	52 [41.9–62]	268 [227–303]	89.5 [71.7–113]	137 [99.4–163]
Denmark	Toddlers	58.9 [45.3–72.8]	196 [182–216]	80.7 [64.1–101]	106 [82.6–129]
Netherlands	Toddlers	40.2[32.7–47]	172[150–193]	69.5[56–88.4]	108 [82.3–136]
United Kingdom	Toddlers	61.7[44.7–74]	211[178–237]	74.4[59.4–90.9]	0.9–123]

(a): Sensitivity analysis after exclusion of samples non-compliant to the MRL legislation.

As can be seen from this table, for CGA-NAN, when commodity samples with residue concentrations exceeding the MRL are excluded from the calculations, the MOET estimates increased by a factor 3–5, resulting in values, including confidence intervals, above 100. For CAG-NAM, a significant increase is also observed, although less intense and corresponding to a factor of about 1.5. The resulting MOET estimates are all above 100, but the confidence intervals still extend to values below 100 in five cases.

This sensitivity analysis shows the critical impact of non-compliant samples on the probability of reaching the threshold for regulatory consideration for the two effects considered in the present assessments.

### 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 questions mentioned in Section 1.

Therefore, an uncertainty analysis was conducted for each assessment question in order to provide an answer to the following:

*If all the uncertainties in the model,<sup>10</sup> 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 2014–2016 is below 100?*

This question was considered separately for each of the 10 consumer populations addressed in the probabilistic modelling (EFSA, 2019b, van Klaveren et al., 2019).

This 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). Specifically, it followed an approach based on the guidance and flow charts for case-specific assessments, in the sequence summarised below:

- When planning the assessment and uncertainty analysis, it was decided to quantify some sources of uncertainty within the probabilistic models for cumulative exposure, rather than assess all sources of uncertainty collectively outside the models. This choice is part of the first phase of uncertainty analysis, depicted in Figure 5 of the Guidance on Uncertainty Analysis in Scientific Assessments (EFSA Scientific Committee et al., 2018a). Specifically, it was decided to quantify sampling variability of occurrence and consumption data in the probabilistic models,

<sup>10</sup> Conceptual mathematical model on which probabilistic modelling is based.

since methods for this are included in the guidance on the use of probabilistic methodology for modelling dietary exposure to pesticide residues (EFSA PPR Panel, 2012).

- Since the cumulative assessment involves quantities that are variable as well as uncertain, the probabilistic modelling of uncertainty involved the choices summarised in Figure 10 of EFSA Scientific Committee (2018a). It was decided to model variability and uncertainty using distributions, rather than probability bounds, because methods for this were already established (EFSA PPR Panel, 2012) and implemented in existing software (van Klaveren et al., 2019). Specifically, variability and sampling variability for some of the model inputs (consumption and occurrence) was quantified by bootstrapping<sup>6</sup> as described by EFSA (2019b) and RIVM (van Klaveren et al., 2019).
- The final phase is characterisation of overall uncertainty, summarised in Figures 15–17 of EFSA Scientific Committee (2018a). First, following Figure 15 (ibid.), it was decided to make separate probability judgements for the additional uncertainties and then combine them by calculation with those quantified in the probabilistic models. This process is summarised briefly in Figure 17 (ibid.) and requires defining and implementing an appropriate model to combine the probability distribution from the probabilistic modelling with another one for the collective contribution of the additional uncertainties. The model developed for this process and the methods used to implement it are described in the following sections, after first describing the approach taken to identify sources of uncertainty.

### 2.3.1. Identification of sources of uncertainty affecting the assessment

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

The sources of uncertainty were first identified by expert discussion using a systematic approach, reviewing each part of the assessment for potential sources of uncertainty. Specifically, the Working Group experts examined each input data (e.g. occurrence date, processing factors...) and each part of the assessment model (e.g. Dose-Addition model, short-term exposure calculation model...) and considered whether it was affected by any of the types of uncertainty listed in Tables 1 the EFSA Scientific Committee (2018a,b) (ambiguity, accuracy, sampling uncertainty, missing data, missing studies, assumptions, excluded factors, use of fixed values...).

Afterwards, the identified uncertainties were further discussed and precisely defined/described in such a way that they were unambiguously understood by the experts participating to the uncertainty analysis and not overlapping with each other. For instance, three distinct sources of uncertainty were identified regarding the handling of left-censored occurrence data, corresponding to three associated 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 a use is assumed.

The sources of uncertainty included those related to the identification of substances to be included in each CAG, which had already been described and assessed in the EFSA Scientific report on the establishment of CAGs of pesticides for their effects on the nervous system (EFSA, 2019a).

All the identified sources of uncertainty were listed in tables, which are presented in Section 3.1 and Appendix A. The Working Group experts then collected and discussed further information that would be helpful to evaluate their impact on the assessment. The results of these discussions and investigations were then summarised in a series of notes, which are included in Appendix B 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 (hazard identification and characterisation). In subsequent steps of the uncertainty analysis (EKE Questions 1 and 2, see next Section 2.3.2), the uncertainties relating to exposure were evaluated by the exposure experts in the Working Group and the uncertainties relating to toxicology were evaluated by the toxicology experts.

### 2.3.2. Model and process for characterising overall uncertainty

The approach developed for characterising overall uncertainty in this assessment is summarised graphically in Figure 1. 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 1 – as the



starting point for the rest of the uncertainty analysis. The rest of the analysis comprised five key steps, listed on the right-hand side of Figure 1, as follows:

*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 experts to consider each source of uncertainty separately, 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 adult population 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 on a single population avoided repeating the assessment for each population, which would take 10 times as long and be more vulnerable to biases in judgement due to progressive expert fatigue; German adults were chosen because the consumption survey used in the modelling for this population is larger than that for other populations, and therefore, the model estimates are less affected by sampling variability. The experts expressed their judgements as multiplicative factors, e.g. a factor of 1 would represent no change in the MOET at the 99.9th percentile of exposure, factors greater than 1 represent an increase, factors less than 1 represent a decrease. The scale and methods used for this step are described in Section 2.3.4 and the results are reported in the tables in Appendix A.

*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 adult population would change if all those sources of uncertainty were resolved. This focussed on German adults for the same reason as EKE Q1 (see above) and the degree of change was again expressed as a multiplicative 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 2.3.5 and the results are reported in Section 3.3.

*Combine 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 10 modelled populations (see Section 2.3.6).

*EKE Question 3 (EKE Q3):* For reasons of practicality, the preceding steps involved two important simplifications. In EKE Q2, the uncertainties were assessed with reference to only one of the 10 modelled populations (German adults). Then, in the Monte Carlo simulations, the distributions elicited for German adults were applied to all 10 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 German adults and each of the other populations and also for any other remaining uncertainties (including differences between the MCRA and EFSA probabilistic models, see following section). 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.

*Extrapolation to EFSA PRIMo populations:* The recommendation of European Commission and MSs that the MOET at the 99.9th percentile of exposure should be assessed for each of the consumer populations included in the EFSA PRIMo model is addressed in Section 4.3, where the implications of the results for the PRIMo populations are discussed.

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,

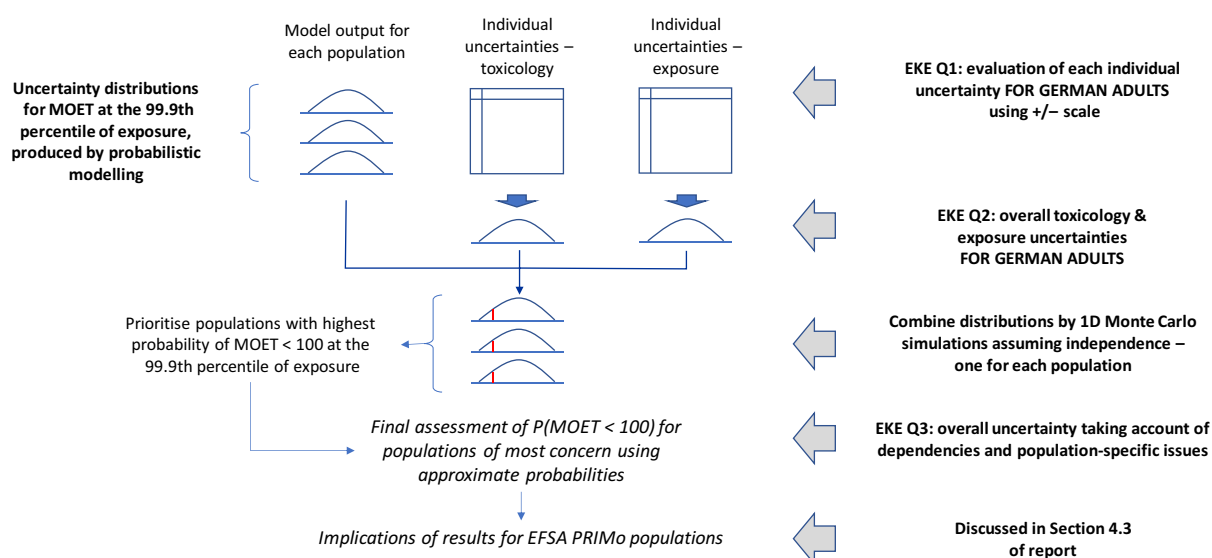


which would have required eliciting distributions for each of them in EKE Q1 and specification of a suitable model to combine them. It was also considered more rigorous and reliable than combining all the uncertainties in a single expert judgement, since that would have required simultaneous consideration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

The experts addressing the EKE Questions were the following:

- Toxicology uncertainties: Antonio Hernández-Jerez, Susanne Hougaard Bennekou, Carsten Kneuer (EKE Q2 and EKE Q3 only) and Gerrit Wolterink (EKE Q2 and EKE Q3 only);
- Exposure uncertainties: Bruno Dujardin, Luc Mohimont and Bernadette Ossendorp.

All experts involved in the exercise had thorough knowledge of CRA methodologies and of uncertainty analysis. Experts in exposure were furthermore very familiar with probabilistic methodology and all were trained to the practice of the EKE technique.



**Figure 1:** Overview of the approach to characterise overall uncertainty in the CRA, which was conducted separately for each CAG

### 2.3.3. Choice of probabilistic model output for use in the uncertainty analysis

It was decided that EKE Q1 and Q2 would elicit judgements expressed as adjustments to the results from one of the two implementations of the probabilistic model (MCRA or SAS<sup>®</sup>). The two implementations used the same inputs and were designed to implement the same model, but in practice there were minor differences between their results. These differences are reported and discussed in detail in EFSA (2019b) and van Klaveren et al. (2019). Part of the difference was attributed to not being able to implement the handling of unspecific residue definitions as intended in the EFSA model (see Section 3.3 of EFSA (2019b)). For EKE Q1 and for the individual judgements on EKE Q2 (see below), the elicitation was based on the results of the EFSA model, since at that time the sample data needed for combining with the elicited distributions were not available from MCRA. However, when those data became available, it was decided to use the MCRA results for the subsequent steps of the process, starting with the consensus judgements on EKE Q2 (see Section 2.3.5). The MCRA model was preferred at that stage because it implemented the unspecific residue definitions as intended. To take account of the uncertainty implied by the differences between the two models, the experts were asked to consider this when making their judgements on EKE Q3 (Section 2.3.7).

### 2.3.4. Evaluation of individual uncertainties (EKE Question 1)

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

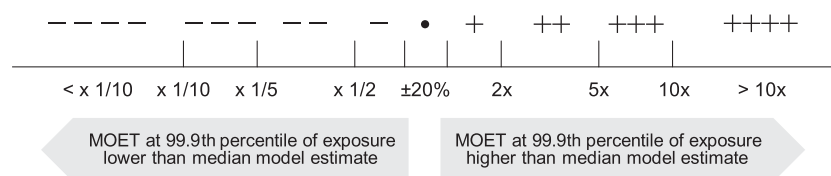
EKE Q1A: *If this source of uncertainty was fully resolved (e.g. by obtaining perfect information on the issue involved) and addressed in the modelling, by what multiplicative factor would this change the*

median estimate of the MOET for [CAG name] at the 99.9<sup>th</sup> percentile of exposure of the German adult 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 (depicted in Figure 1) and the detailed wording of the questions was 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': e.g., if the cause of a source of uncertainty is that there are very few data available for one of the model inputs, or that the data are biased or unreliable, then EKE Q1A asks the experts to consider how the estimated MOET would change if the current data were replaced with a very large sample of perfectly reliable data, such that this source of uncertainty was 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' (i.e. the magnitude of their contribution to the estimated MOET).

The meaning of 'multiplicative factor' was carefully explained to the experts, and they were asked to assess the factor using the scale shown in Figure 2. 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  $\times 1/10$  and  $+ 20\%$ ; '+ + / + + +' means  $\geq 90\%$  chance between  $2\times$  and  $5\times$ , etc. The scaling was proportionate to the size of the uncertainties to be considered.



**Figure 2:** Scale used by the experts when assessing EKE Question 1

It was explained 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. It was decided not to further consider them under EKE Q1, and it was agreed to consider that the magnitude of the 95% confidence interval obtained by bootstrapping was sufficiently representative of the sampling variability of occurrence and consumption data (see also note 7 in Appendix B.2).

When making their assessments, the experts were provided with the agreed description/definition of each of the uncertainties (Appendix A), the detailed notes summarising the information collected to support the assessment (Appendix B.2) and the list of risk drivers for the CAG under assessment.

Five experts participated in answering EKE Q1: three exposure experts and two toxicology experts. The questions were first addressed separately by each expert, working individually. Each expert was asked to answer both questions for each of the uncertainties that related to their area of expertise (exposure or toxicology), for each of the two CAGs addressed in this report. The answers provided by the experts were then collated and, where there were differences between the assessment of the same uncertainty by different experts, these were resolved remotely to arrive at a consensus judgement. The final judgements for EKE Q1A and Q1B for each source of uncertainty are reported in Appendix A.

### 2.3.5. Evaluation of combined 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 99.9<sup>th</sup> percentile of exposure for [name of CAG] in the German adult population at Tier II?*

This question was addressed twice for each CAG: 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 German adults.

The elicitation was conducted in two stages. In the first stage, six experts (the same experts as for EKE Q1 plus one additional toxicology expert) worked separately to make individual judgements. In the second stage, the same experts, plus a further toxicologist, worked together to develop consensus judgements. The meaning of 'perfect information' in the EKE question was discussed and defined during the second stage (see below). For the reasons explained in Section 2.3.3, the individual judgements were made relative to the MOET estimates from the EFSA model, but the consensus judgements were made relative to MCRA estimates.

The experts' uncertainty about the multiplicative factor required by the question was elicited in the form of a probability distribution using the 'Sheffield' protocol<sup>11</sup> described in EFSA's guidance document on EKE (EFSA, 2014a). 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. 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.

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,<sup>12</sup> 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 (Appendix A) and detailed supporting notes on them (Appendix B.2); the lists of risk drivers and supporting information on them (Appendix B.1); the draft reports of RIVM and EFSA modelling and sensitivity analyses for CAG-NAN and CAG-NAM (EFSA, 2019b; van Klaveren et al., 2019); detailed graphics and tables on the model outputs and contributions of risk drivers; 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; and the draft of the EFSA Scientific report on the establishment of CAGs of pesticides for their effects on the nervous system (EFSA, 2019a).

The experts were provided with a template document in which to record their judgements and reasoning. These were then used by the facilitator to produce graphs<sup>13</sup> in which the best-fitting distributions obtained from the judgements of different experts for the same question were plotted together.

While the experts were making their individual judgements, the results of the EFSA probabilistic model were subjected to further analysis. This was designed to provide additional information on a source of uncertainty identified in EKE Q1: the effect of limitations in sample size (for the consumption and occurrence data) on the performance of the bootstrap method for quantifying uncertainty of the MOET at the 99.9th percentile of exposure.

The consensus judgements were elicited during a face-to-face meeting attended by all seven experts, following the guidance for facilitation of consensus judgements in the Sheffield protocol provided by EFSA (2014a) and in the SHELF framework.<sup>14</sup> EFSA (2014a) recommends no more than six to eight experts for the Sheffield protocol. The first half day of the meeting was used to provide the experts with additional information relevant to their judgements: a presentation reviewing recent research (including the Euromix project, <https://www.euromixproject.eu/>) on the applicability of the dose addition model, a detailed presentation of the final results of the EFSA model and comparison with the MCRA results and the analysis of the performance of the bootstrap method. The facilitator then 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 would judge ("RIO" Concept), having seen the evidence, the list of uncertainties and the individual judgements and having heard the experts' discussion (EFSA, 2014a;

<sup>11</sup> Sheffield method: 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.

<sup>12</sup> Available online at <http://optics.eee.nottingham.ac.uk/match/uncertainty.php>

<sup>13</sup> Using the SHELF Shiny app available at <https://jeremy-oakley.shinyapps.io/SHELF-multiple/>. This fits a selection of parametric distributions (normal, lognormal, student t, log student t, gamma, beta or the best-fitting of these) to the judgements of each expert using least squares on the cumulative distribution function.

<sup>14</sup> <http://www.tonyohagan.co.uk/shelf/>

Oakley and O'Hagan, 2016). The experts reviewed the wording of EKE Q2 and agreed to define 'perfect information' for exposure assessment as 'actual consumption, occurrence, processing methods, processing factors etc.' and for toxicology as 'the lowest BMDL20 (for CAG-NAN) or BMDL10 (for CAG-NAM)<sup>15,16</sup> from a perfect set of toxicity studies and perfect knowledge of CAG membership, the toxicity-exposure relationship and how substances combine'.

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 in the sense defined by 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,b) as the fixed interval method), the experts are 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<sup>17</sup> and the best-fitting distribution provided by the app was displayed for review by the experts.

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.

### 2.3.6. 1-D Monte Carlo simulations to combine uncertainties related to exposure and toxicology

In this step, the two distributions elicited to quantify uncertainties relating to exposure and toxicology, respectively, were combined by Monte Carlo simulation with an uncertainty distribution for the MOET at the 99.9th percentile of exposure generated by MCRA model. The latter distribution comprised, for each modelled population, the 100 estimates of the MOET at the 99.9th percentile of exposure generated in the 100 outer loops of the MCRA Tier II model. A computer programme to carry out this calculation was prepared in advance using the R software, assuming independence between the three distributions, and this programme was then run for each combination of the two CAGs and 10 consumer populations as the consensus EKE Q2 distributions became available. This was done during the 3-day meeting referred to in the preceding section, so that the results could be used as the starting point for EKE Q3 which was addressed in the same meeting.

Specifically, for each CAG, the same 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 consumer group:
  - Multiply each of the 100 values for the estimates of the MOET at 99.9th percentile of exposure generated by the MCRA 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' in Tables 14 and 15).

<sup>15</sup> 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 RfP to derive an acceptable daily intake (ADI) or an acute reference dose (ARfD).

<sup>16</sup> In the case of CAG-NAN (AChE inhibition), the BMDL20 is already established as the appropriate adverse effect size. For CAG-NAM, the critical response level should normally be defined by Risk managers, because it relates to protection goals. However, this was not available, and therefore, the 10% response level was chosen by the Working Group as suggested by the guidance on the use of the benchmark dose approach in risk assessment (EFSA Scientific Committee, 2017) for quantal data.

<sup>17</sup> <https://jeremy-oakley.shinyapps.io/SHELF-single/>. This offers the same choice of distributions as the SHELF-multiple app (see footnote 13).



- 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 5 and 8, Tables 8 and 11).

The Working Group was provided with output from the Monte Carlo simulations 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 10 consumer populations in each CAG; and second, tables containing the numerical values used in the boxplots plus, for each CAG and population, the calculated probability of the MOET at the 99.9th percentile of exposure being less than 100. The latter probabilities were then used as the starting point for judgements on EKE Q3 (see below).

### 2.3.7. Overall uncertainty analysis (EKE Question 3)

Two versions of EKE Question 3 were defined, one for the German adults 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, this comprised mainly 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 included the uncertainty of extrapolating the results of those simulations for German adults to the other nine consumer populations.

For German adults, 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 adult population in 2014-2016 being below 100?*

For the other nine 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 2014-2016 being below 100?*

For both versions of the question, it was agreed that 'perfect information' had the same meaning as that defined for EKE Q2 (Section 2.3.5, combining the definitions for the exposure and toxicology versions of Q2).

Elicitation for EKE Q3 was conducted in two stages: partly during the same 3-day meeting as the consensus judgements for EKE Q2 and partly after the meeting, by email correspondence. This was necessary because Q3 was not completed within the scheduled meeting time; however, this also provided the opportunity for additional simulations to help inform judgements on Q3, as described below.

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. The experts considered that 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 CAG and population, the calculated probability of the MOET at the 99.9th percentile of exposure being less than 100 provided by the Monte Carlo simulations in the preceding step. In addition, the experts were advised to consider the following evidence: other quantiles of the calculated MOET distribution for each population (as shown in the tables and graphics described in the preceding section), considerations identified in the group discussion of dependencies and population differences, notes from EKE Q1B (see Section 2.3.4) on country differences for individual sources of uncertainty (included in the tables in Appendix A) and their personal knowledge and reasoning about the issues involved.

Judgements for EKE Q3 were elicited using the Approximate Probability Scale (APS, Figure 2), 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 combination of CAG and population. First, the experts were asked to work separately and record their individual judgements in spreadsheet templates provided by the facilitator. The completed templates were collected, and the judgements were collated in a table for each CAG, showing the number of experts who selected each probability range for each population, which was displayed on screen for review by the group. The facilitator then led a discussion to develop consensus judgements (applying the RIO concept, see Section 2.3.5).

The steps described above were not all completed during the 3-day meeting. All seven experts completed their judgements for CAG-NAN (brain and/or erythrocyte AChE inhibition), but only two experts did so for CAG-NAM (alterations of the motor division of the nervous system). In view of the limited time remaining, the facilitator focussed discussion on seeking consensus for the upper bound of probability for those populations where the individual probability judgements were highest (infants and other children). The process was completed remotely.

During the meeting, the experts found it difficult to assess the potential impact of dependencies between the uncertainties relating to exposure and toxicology. Therefore, before continuing the EKE Q3 assessment after the meeting, the opportunity was taken to extend the Monte Carlo simulations described in Section 2.3.6, to explore the impact of different degrees of dependence between the uncertainties relating to exposure and toxicology (specifically, rank correlations of  $-1$ ,  $-0.75$ ,  $-0.5$ ,  $-0.25$ ,  $0.25$ ,  $0.5$ ,  $0.75$  and  $1$ ). The results of these simulations, together with the individual judgements, discussions and evidence considered in the meeting, were used to develop proposed consensus judgements on EKE Q3 for all of populations for each CAG. This was done by one of the exposure experts, who also had a good knowledge of the toxicological evidence. The other experts were then given the opportunity to review, comment on and revise the proposed judgements by email until a consensus judgement was achieved.

### 3. Results of uncertainty analyses

#### 3.1. Sources of uncertainty

Thirty sources of uncertainty related to the assessment inputs were identified as affecting the CRAs for CAG-NAN and CAG-NAM. They are listed in Table 4. In this table, each source of uncertainty is associated with a group number. This refers to the area of expertise they relate to (exposure or toxicology), as explained in Section 2.3.1.

**Table 4:** Sources of uncertainty concerning the input data and affecting the CRA of brain and/or erythrocyte AChE inhibition (CAG-NAN) and of functional alterations of the motor division (CAG-NAM). Uncertainties relating to exposure were included in group 1 and uncertainties relating to toxicology were included in group 2

Assessment input	Type of uncertainty	Description of the uncertainty
Consumption data (all group 1)	Excluded data	Consumption data of animal commodities and plant commodities not in the list of the 30 selected commodities and their processed derivatives have not been used
	Ambiguity	The consumption data do not always discriminate between different commodities of a same group (e.g. tomatoes and cherry tomatoes are considered as tomatoes)
	Accuracy	The accuracy of the reported amount of food consumed in surveys may be affected by methodological limitations or psychological factors
	Sampling variability	Sample size (number of consumers in the 10 populations). A small number of consumers may affect the reliability of risk estimates at the 99.9th percentile of exposure.
	Sampling bias	Representativeness of the consumption data (selection bias) for the whole population
	Use of fixed values	One invariable recipe and conversion factor are used to convert the amount of food consumed into the respective amount of raw primary commodity (RPC)



Assessment input	Type of uncertainty	Description of the uncertainty
Occurrence data (all group 1)	Missing data	Active substance/commodity combinations, for which occurrence data are missing and extrapolation from another commodity is not possible, were excluded
	Excluded data	The contribution of all metabolites and degradation products to the effect has not been considered
	Ambiguity	The occurrence data do not always discriminate between different commodities of a same group (e.g. tomatoes and cherry tomatoes are considered as tomatoes)
	Accuracy	Laboratory analytical uncertainty
	Sampling variability	Sample size (number of occurrence data). A small number of occurrence data may affect the reliability of risk estimates at the 99.9th percentile of exposure. This number varies from one pesticide/commodity combination to the other
	Sampling bias	Representativeness of the monitoring data (selection bias)
	Extrapolation uncertainty	Extrapolation of occurrence data between crops
	Extrapolation uncertainty	Extrapolation of occurrence data between countries
	Imputed data	Imputation of unmeasured residues in food samples
	Assumption	Assumption of the active substance present on the commodity in case of unspecific residue definition for monitoring
	Assumption	Left-censored data: Assumption of the authorisation status of all pesticide/commodity combinations
	Assumption	Left-censored data: Assumption of the use frequency for authorised pesticide/commodity combinations
	Assumption	Left-censored data: Assumption on the residue level ( $\frac{1}{2}$ LOQ as imputed value) when an active substance is used, and its residues are below the LOQ
Assumption	Occurrence of residues in drinking water	
Processing factors (all group 1)	Assumption	Pesticide residues are transferred without any loss to processed commodities when processing factors are not available
	Ambiguity	Application of processing factors, derived from a limited number of standardised studies, to the EFSA food classification and description system (FoodEx)
	Accuracy	Laboratory analytical uncertainty
	Accuracy	Calculation of processing factors is affected by residue levels below the LOQ
	Use of fixed values	The value of processing factors used in the calculations is the mean or median value of a limited number of independent trials
	Excluded data	Some processing factors are not considered (e.g. peeling and washing of commodities with edible peel)
Variability factors (group 1)	Use of fixed values	The variability factor used in the calculations is 3.6 for all commodities above 25 g
NOAELs (all group 2)	Adequacy of the CAG	Uncertainty on whether the CAG contains all the active substances causing the effect
	Adequacy of the CAG	Uncertainty on whether the CAG contains only the active substances causing the effect
	Accuracy	Uncertainties affecting the characterisation of active substances included in the CAG (quality of data and NOAEL setting process). This includes uncertainties affecting: <ul style="list-style-type: none"> <li>a) The choice of the indicators of the effect</li> <li>b) The hazard characterisation principles applied to the effect</li> <li>c) The data collection methodology</li> <li>d) The data assessment methodology</li> </ul>

Four additional sources of uncertainty were found to be associated with the assessment methodology and are listed in Table 5. One of these sources is related to exposure (group 1) and the other three are related to toxicology (group 2).

**Table 5:** Sources of uncertainty concerning the assessment methodology and affecting the CRA of brain and/or erythrocyte AChE inhibition (CAG-NAN) and of functional alterations of the motor division (CAG-NAM)

Element of the assessment methodology	Description of the uncertainty
Dose addition (group 2)	Uncertainty about the actual mode of combined toxicity
Dose–response relationship (group 2)	Uncertainty about the slope and the shape of the dose–response, and consequently about the effect size of individual active substances at the actual exposure levels
Combination of occurrence and consumption data (group 1)	Uncertainty regarding the combination of occurrence and consumption data
Adequacy of the acute exposure calculation model (group 2)	Uncertainty about the fitness of the acute exposure calculation model to human toxicokinetic and toxicodynamic processes involved in the effect

Extensive information describing the sources of uncertainty listed in Tables 4 and 5 is given as technical notes in Appendix B, Section B.2.

### 3.2. Evaluation of individual uncertainties (EKE Question 1)

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 [brain and/or erythrocyte AChE inhibition/functional alterations of the motor division] for the 99.9th percentile of exposure of the German adult 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 34 sources of uncertainty were divided into two groups as indicated in Tables 4 and 5. Group 1 included sources of uncertainty pertaining to the exposure assessment step of CRA and were evaluated by three exposure experts as described in Section 2.3.4. Group 2 included sources of uncertainty pertaining to the hazard identification and characterisation step of CRA and were evaluated by two toxicology experts.

EKE Q1A was addressed using the notes compiled in Appendix B.2 and the resulting assessments (ranges of multiplicative factors of MOET at 99.9th percentile of exposure distribution at Tier II) are reported in Tables A.1 and A.2 of Appendix A for CAG-NAN and CAG-NAM.

The experts judged that resolving uncertainty would lead to similar multiplicative factors applicable to AChE inhibition and functional alterations of the motor division for most sources of uncertainty.

Multiplicative factors above 1 (increasing MOET estimates) are expected if perfect information was available resolving the ambiguity of consumption data, the representativeness of monitoring data, lack of knowledge on the effect of food processing and of washing and peeling of commodities consumed without further processing, the contribution of pesticides included in the CAG but not actually causing the effect (CAG-NAM only), uncertainties in NOAEL-setting, uncertainty about the relevance of dose addition (CAG-NAM only) and the combination of occurrence and consumption data.

Multiplicative factors below 1 (decreasing MOET estimates) are expected if perfect information was available to take account of the excluded commodities and all metabolites relevant for the effect, and to ensure an appropriate combination of the exposure and hazard assessments (CAG-NAN only). Resolving uncertainty due to not taking into account exposure to non-approved pesticides present in consumer diet would lead to lower MOETs, but the magnitude of the decrease was difficult to assess.

Multiplicative factors either above or below 1 (higher or lower MOETs) might result from perfect information solving the analytical uncertainties of laboratories, the uncertainty about the dose–response relationship at the actual levels of exposure (CAG-NAM only) and allowing an appropriate combination of the exposure and hazard assessments (CAG-NAM only).

EKE Q1B was found to be particularly difficult to address for individual sources of uncertainty, because any difference would result from their combination (e.g. differences in consumption of some commodities have significant impact if this is accompanied by exposure to different pesticides, different residues levels or different behaviour in food processing). Only one source of uncertainty (excluded commodities) was noted as a source of possible difference between populations on its own (Appendix A).

### 3.3. Combined impact of uncertainties (EKE Question 2)

The combined impact of individual uncertainties was evaluated as described in Section 2.3.5, addressing the following elicitation question:

*'If all the identified sources of uncertainty in [first/second] group 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 of the MOET for the 99.9th percentile of exposure for [brain and/or erythrocyte AChE inhibition/functional alterations of the motor division] in the German adult population at Tier II?'*

#### 3.3.1. Impact of uncertainties on the MOET estimates at the 99.9th percentile of exposure in the German adult population for CAG-NAN

##### a) Combined impact of uncertainties related to exposure

Following discussion, the experts identified the most important contributors to the combined uncertainty as follows<sup>18</sup>:

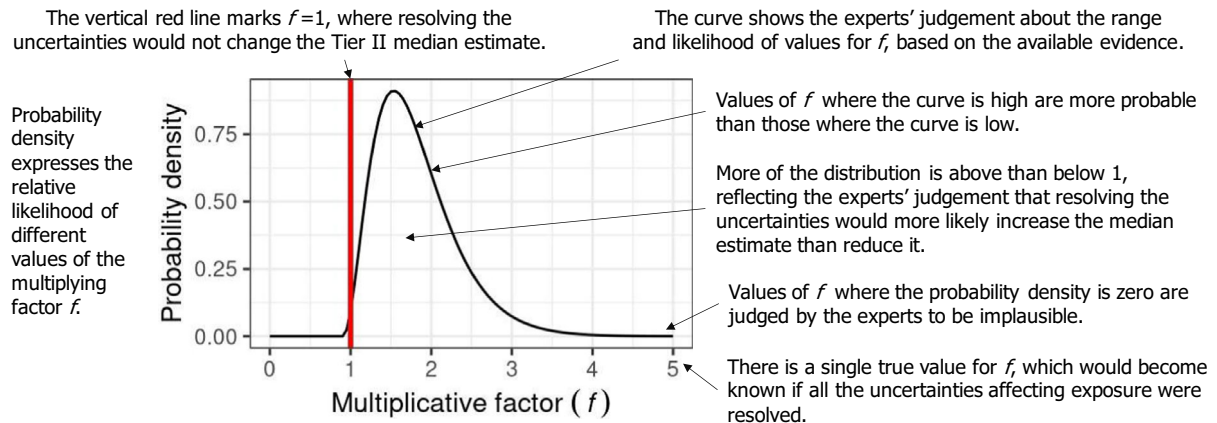
- Lack of data on the effect of processing for many substance/commodity combinations and lack of information about processing type in consumption data (+, see note 21)
- Non-consideration of the effect of peeling and washing on the residue levels for commodities consumed without further processing (+, see note 25)
- Biases in occurrence data due to selective sampling (+, see note 13)
- Analytical error in measurement of pesticide residues (+/–, see note 12)
- Use of a fixed value by the RPC model to convert the amount of food as consumed to the respective amount of RPC (–, see note 9)
- Missing contribution of commodities not included in modelling (–, see notes 1, 2, 3)

Overall, the experts judged it most likely that the MOET at the 99.9th percentile of exposure in the German adult population would increase if all the uncertainties affecting exposure were resolved, although a small decrease was also plausible. Their consensus judgements are shown in Table 6 together with the parameters for their final consensus distribution, which is also presented in Figure 3.

**Table 6:** CAG-NAN: Consensus judgements and distribution of the experts for the combined impact of the quantified uncertainties affecting exposure (if resolved) on the MOET at the 99.9th percentile of exposure for the German adult population in 2014–2016. The impact is expressed as a multiplicative factor  $f$  to be applied to the Tier II median estimate (shown in Table 1A). The bottom row of the table gives the parameters for the consensus distribution, which is shown graphically in Figure 3

	Experts' exposure multiplicative factor ( $f$ )
Lower plausible bound	$f = 0.9$ (experts judged there to be < 1% probability that $f$ would be < 0.9)
Upper plausible bound	$f = 3$ (experts judged there to be < 1% probability that $f$ would be > 3)
Probability 1	$p(f < 1) = 1\%$ (experts' probability that $f$ would be less than 1)
Probability 2	$p(f > 2) = 30\%$ (experts' probability that $f$ would be more than 2)
Probability 3	$p(f > 1.5) = 65\%$ (experts' probability that $f$ would be more than 1.5)
Consensus distribution	Gamma distribution with shape 3.26 and rate 3.56, offset to start from 0.9 (the experts' lower plausible bound) instead of 0.0

<sup>18</sup> Symbols indicate those uncertainties which, if resolved (e.g. by obtaining perfect information), would tend predominantly to increase (+) or decrease (–) the modelled estimate of the MOET at the 99.9th percentile of exposure for the German adult population, and those which could change it in either direction (+/–). The notes cited for each source of uncertainty are presented in Appendix B.2.



**Figure 3:** CAG-NAN: Consensus distribution of the experts for the combined impact of the quantified uncertainties affecting exposure (if resolved) on the MOET at the 99.9th percentile of exposure for the German adult population in 2014–2016, expressed as a multiplicative factor  $f$  to be applied to the Tier II median estimate shown in Table 1A. 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 6.

b) Combined impact of uncertainties related to toxicology

Following discussion, the experts identified the most important contributors to the combined uncertainty as follows<sup>19</sup>:

- NOAEL-setting:
  - Tendency of the NOAEL to underestimate the BMDL20 (the critical effect level for AChE inhibition) due to the wide dose interval between the NOAEL and LOAEL in the critical studies. This concerns especially the risk drivers triazophos and dichlorvos (+, see EFSA, 2019a).
  - Derivation of NOBELs from studies using the gavage method of dosing for about 60% of the active substances included in the CAG. This is expected to overestimate toxicity compared to the dietary route (+, see note 29 and EFSA, 2019a).
  - Use of NOAELs from repeated dose studies, which are known to underestimate NOAELs relevant for acute effects which are not quickly reversible, for about 45% of the active substances included in the CAG, of which two are risk drivers (dichlorvos and triazophos) (+, see note 29 and EFSA, 2019a).
- Inadequacy of the acute exposure calculation model (summing up all intakes over a 24-hour period) to encompass human toxicokinetic and toxicodynamic processes related to AChE inhibition: The model used for acute risk does not account for the possible cumulative effect resulting from exposure on consecutive days, which is expected given that the risk drivers are organophosphates rather than N-methyl carbamates, and the irreversible AChE inhibition induced by the former compounds may accumulate over time (–, see note 33).
- First-pass metabolism of organophosphorus (OP) insecticides at low doses: The intestinal and liver metabolism play a relevant role for risk assessment of the intake of low doses of OP residues on food. The balance between bioactivation and detoxification will drive the toxicity of these compounds. A number of *in vivo* animal and human studies suggest a low oral bioavailability of OP insecticides as a result of rapid first-pass metabolism. At low oral dose exposures, most active metabolites (i.e. oxon metabolites) generated in the gut and/or liver by CYP450s isoforms are rapidly detoxified, either catalytically (paraoxonase-1 and CYP450) or stoichiometrically (carboxylesterase and butyrylcholinesterase). As a result, the systemic distribution and target organ impact of the active moiety is reduced. Even if a small fraction of oxon metabolites leaks

<sup>19</sup> Symbols indicate those uncertainties which, if resolved (e.g. by obtaining perfect information), would tend predominantly to increase (+) or decrease (–) the modelled estimate of the MOET at 99.9th percentile of exposure for the German adult population, and those which could change it in either direction (+/–).

from the liver without being detoxified, it is rapidly bound and inactivated by serum butyrylcholinesterase and albumin. Besides, as oxon metabolites are highly reactive, they undergo spontaneous hydrolysis (their half-life is less than one minute in blood), so even if these metabolites escape from the liver detoxification to the systemic circulation, there would not be enough time to reach the brain intact (+, Poet et al., 2003; US EPA, 2008)

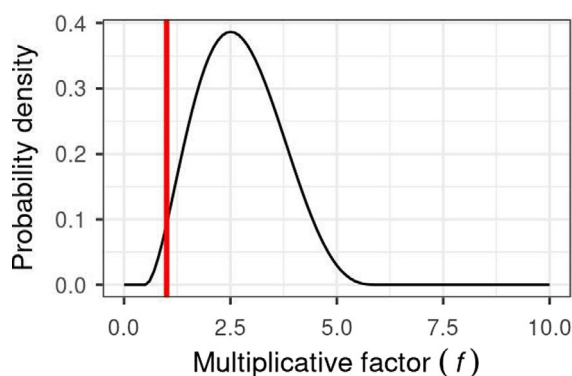
Another contributor to the combined uncertainty has a limited effect

- It was noted that monitoring data occasionally show quantifiable residues of non-approved organophosphorus and N-methyl carbamate pesticides that are not included in CAG-NAN. The impact of this source of uncertainty leads to an overestimation of the MOET but was difficult to quantify during the face-to-face meeting. Therefore, monitoring data of the reference period (2014, 2015 and 2016) were consulted after the meeting to extract all individual findings above the LOQ of active substances of these chemical classes non-included in CAG-NAN. This information was collected in Table 8 in note 27 of Appendix B and circulated to the experts. On that basis, they considered the low frequency of these findings and did not observe any high residue level (above 1 mg/kg) on a commodity with both frequent and high short-term consumption. Therefore, it was concluded that this source of uncertainty has only a limited impact on the magnitude of the MOET at the 99.9th percentile of the exposure (limited –, see note 27).

Overall, the experts judged it most likely that the MOET at the 99.9th percentile of exposure in the German adult population would increase if all the uncertainties affecting toxicology were resolved, although a smaller decrease was also plausible. Their consensus judgements are shown in Table 7 together with the parameters for their final consensus distribution, which is also presented in Figure 4.

**Table 7:** CAG-NAN: Consensus judgements and 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 adult population in 2014–2016. The impact is expressed as a multiplicative factor  $f$  to be applied to the Tier II median estimate (shown in Table 1A). For more explanation, see Table 6

	<b>Experts' toxicology multiplicative factor (<math>f</math>)</b>
Lower plausible bound	0.5
Upper plausible bound	6
Probability 1	$p(f < 1) = 2.5\%$
Probability 2	$p(f > 4) = 10\%$
Probability 3	$p(f > 2) = 75\%$
Consensus distribution (see Figure 4)	Beta distribution with shape parameters 2.87 and 4.26, scaled to the interval from 0.5 to 6



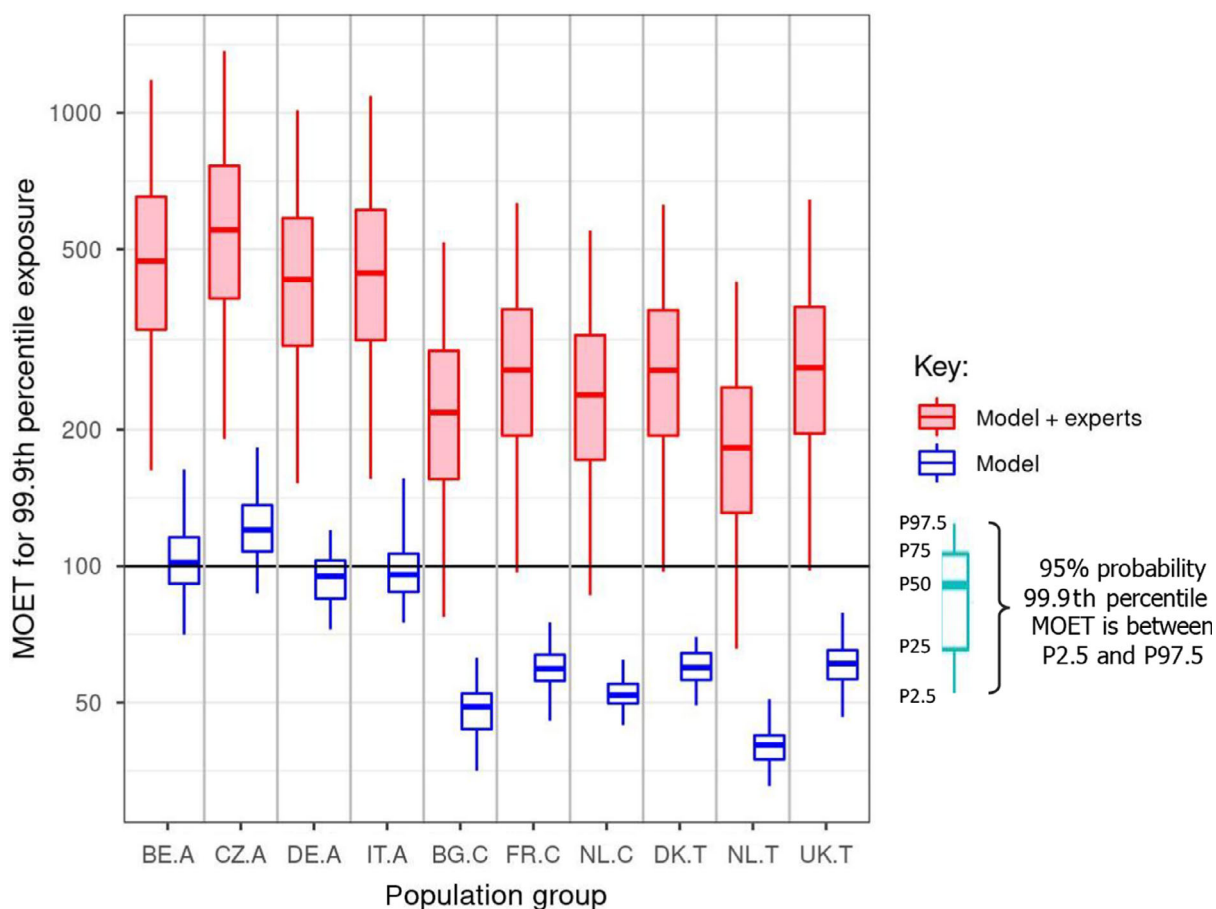
**Figure 4:** CAG-NAN: Consensus distribution of the experts for the combined impact of the quantified uncertainties affecting toxicology (if resolved) on the MOET at the 99.9th percentile of exposure for the German adult population in 2014–2016, expressed as a multiplicative factor  $f$  to be applied to the Tier II median estimate shown in Table 1A. Distribution parameters are shown in Table 7. Graph content is explained in Figure 3

### c) Combined impact of uncertainties related to exposure and toxicology

The elicited distributions for the uncertainties related to toxicology and exposure were combined with the output of the MCRA Tier II model for the MOET at the 99.9th percentile of exposure in each consumer population (see Section 2.2.2.1), using the Monte Carlo calculation described in Section 2.3.6. The elicited distributions were combined with the median 99.9th percentile and uncertainty due to sampling variability (mainly on the occurrence data and consumption data) quantified in the Tier II model and reflected in confidence intervals calculated by outer loop execution (referred to as 'model' in Figure 5). These calculations were conducted assuming perfect independence



between the elicited distributions for uncertainties affecting exposure and toxicology. The results of combining distributions are shown as 'model+experts' in Figure 5.



Keys: Population groups: BE.A (Belgian adults), CZ.A (Czech Republic adults), DE.A (German adults), IT.A (Italian adults), BG.C (Bulgarian children), FR.C (French children), NL.C (Dutch children), DK.T (Danish toddlers), NL.T (Dutch toddlers), UK.T (United Kingdom toddlers). 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 5:** CAG-NAN: 'Model' boxplots show the unadjusted output of the MCRA Tier II model for the MOET at the 99.9th percentile of exposure in each consumer population in 2014–2016. 'Model + experts' boxplots show the result of combining the output of the Tier II model with the elicited distributions quantifying additional sources of uncertainty. Note that the vertical axis is plotted on a logarithmic scale; the values plotted for 'model + experts' are shown numerically in Table 7. A key to the populations and explanation of the boxplots are provided in the footnote below the graph

The boxplots for 'model + experts' in Figure 5 are much wider than those for 'model'. This shows that the combined impact of the sources of uncertainty quantified by elicitation is much larger than the sampling variability that was quantified within the model.

It can also be seen in Figure 5 that the median estimates for 'model + experts' are markedly higher than those for 'model' (Figure 5). This is to be expected, because the uncertainties quantified in the expert elicitation include the impact of assumptions in the model that were intentionally conservative (overestimating exposure and hence underestimating MOETs). However, the much larger magnitude of the additional uncertainties leads to the 95% probability intervals for the MOET at the 99.9th percentile of exposure extending below 100 for all six populations of toddlers and other children.

These results emphasise the importance of considering uncertainties that are not quantified in the MCRA and EFSA probabilistic models. Calculated probabilities for the MOET at the 99.9th percentile of



exposure being below 100 in each population group are shown in Table 8. Note that they do not take account of dependencies and population differences in uncertainty, which are addressed in EKE Q3 (see below).

**Table 8:** CAG-NAN: Statistics for the MOET at the 99.9th percentile of exposure in each consumer population in 2014–2016, calculated by combining the elicited distributions for uncertainties related to exposure and toxicology with the output of the MCRA Tier II model. P2.5, P25 etc. refer to the percentiles plotted in the 'model + experts' boxplots in Figure 5

Population group	MOET at the 99.9th percentile of exposure distribution combining model and elicited uncertainties (from 'model + expert' boxplots in figure 5)					
	P2.5	P25	P50	P75	P97.5	Probability of 99.9th percentile MOET < 100 (%)
Belgian adults	163	333	471	653	1,182	0.2
Czech Rep. adults	191	390	552	764	1,369	0.1
German adults	152	306	429	586	1,013	0.3
Italian adults	156	315	443	611	1,091	0.3
Bulgarian children	77	156	218	299	518	6.8
French children	97	194	271	368	633	2.9
Dutch children	86	172	239	323	550	4.5
Danish toddlers	97	194	270	367	627	2.8
Dutch toddlers	66	131	183	248	424	11.7
United Kingdom toddlers	98	196	274	373	643	2.8

### 3.3.2. Impact of uncertainties on the MOET estimates at 99.9th percentile of exposure in the German adult population for CAG-NAM

#### a) Combined impact of uncertainties related to exposure

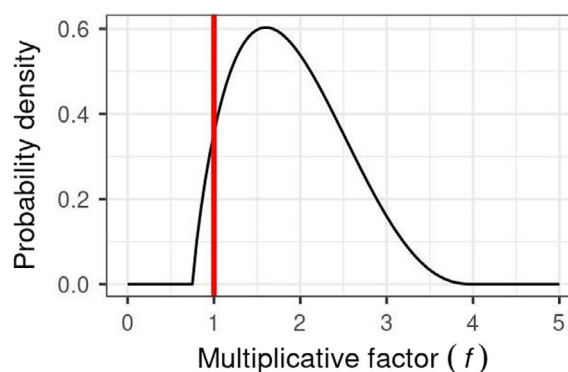
Following discussion, the experts identified the most important contributors to the combined uncertainty as follows<sup>19</sup>:

- Lack of data on the effect of processing for many substance/commodity combinations and lack of information about processing type in consumption data (+, see note 21).
- Biases in occurrence data due to selective sampling (+, see note 13).
- Unspecific residue definition for residues of dithiocarbamates and assumption about the agricultural use of omethoate and thiram, which are expected to be used less frequently in practice than dimethoate and other dithiocarbamates, respectively (+, see note 17).
- Missing contribution of commodities not included in modelling (–, see notes 1, 2, 3).
- Use of a fixed value by the RPC model to convert the amount of food as consumed to the respective amount of RPC (–, see note 9).
- Missing contribution of metabolites for some of these substances, not included in modelling (–, see note 11).

Overall, the experts judged it most likely that the MOET at the 99.9th percentile of exposure in the German adult population would increase if all the uncertainties affecting exposure were resolved, although a small decrease was also plausible. Their consensus judgements are shown in Table 9 together with the parameters for their final consensus distribution, which is also presented in Figure 6. The distribution is a little wider than that for exposure uncertainties in CAG-NAN, reflecting the different uncertainties involved.

**Table 9:** CAG-NAM: Consensus judgements and distribution of the experts for the combined impact of the quantified uncertainties affecting exposure (if resolved) on the MOET at the 99.9th percentile of exposure for the German adult population in 2014–2016. The impact is expressed as a multiplicative factor  $f$  to be applied to the Tier II median estimate (shown in Table 2A). For more explanation, see Table 6.

	<b>Experts' exposure multiplicative factor (<math>f</math>)</b>
Lower plausible bound	0.75
Upper plausible bound	4
Probability 1	$p(f < 1) = 5\%$
Probability 2	$p(f > 3) = 5\%$
Probability 3	$p(f > 2) = 40\%$
Consensus distribution (see Figure 6)	Beta distribution with shape parameters 1.89 and 3.51 scaled to the interval from 0.75 to 4



**Figure 6:** CAG-NAM: Consensus distribution of the experts for the combined impact of the quantified uncertainties affecting exposure (if resolved) on the MOET at the 99.9th percentile of exposure for the German adult population in 2014–2016, expressed as a multiplicative factor  $f$  to be applied to the Tier II median estimate shown in Table 2A. Distribution parameters are shown in Table 9. Graph content is explained in Figure 3

#### b) Combined impact of uncertainties related to toxicology

Following discussion, the experts identified the most important contributors to the combined uncertainty as follows<sup>19</sup>:

- NOAEL-setting:
  - Uncertainties affecting the toxicological characterisation of the active substances included in the CAG could cause either overestimation or underestimation of MOET overall but more likely the former because the specific indicators of functional effects on the motor division are not objectively assessed and thus, they may lack sensitivity (+/–, see note 31).
  - The use of cholinesterase inhibition (which is more sensitive) as a surrogate for a motor division endpoint in the case of triazophos, which is one of the risk drivers (+, see EFSA, 2019a and note 29).
  - Derivation of NOAELs from studies using the gavage method of dosing for about 60% of the active substance included in the CAG. This is expected to overestimate their toxicity compared to the dietary route (+, see EFSA, 2019a).
  - Use of NOAELs from repeated dose studies, for about 25% of the active substances included in the CAG. This may lead to underestimated NOAELs (and underestimated MOETs) for substances with irreversible or slowly reversible effects which can be accumulated over time. This is e.g. the case of triazophos, one of the two main risk drivers (+, see EFSA, 2019a).
  - Lack of neurotoxicity studies for some substances, although Commission Regulation (EU) No 283/2013 setting out the data requirements for active substances provides that such studies should be performed for active substances with structures that are similar or close to those capable of inducing neurotoxicity. The absence of neurotoxicity studies, including the battery of functional and clinical tests, may result in overestimated NOAELs. This is the case for chlormequat (one of the risk drivers) (–, see EFSA, 2019a and note 29).
- Inadequacy of the acute exposure calculation model (summing up all intakes over a 24-hour period) to encompass human toxicokinetic and toxicodynamic processes related to the effect: Uncertainties affecting the relation between toxicology and exposure, could cause either overestimation or underestimation of MOET overall but more likely the former because the model used for acute risk might not account for the contribution from exposure on consecutive days as expected from organophosphorus insecticides (+/–, see note 33).

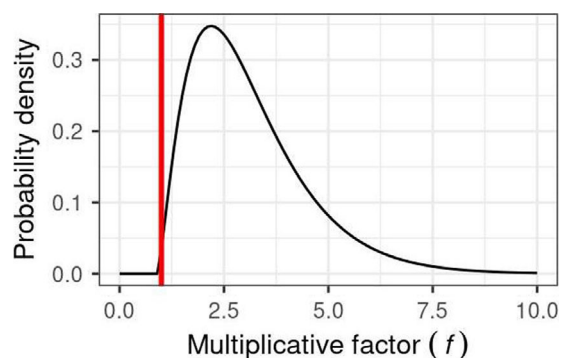
Other contributors to the combined uncertainty have a limited effect:

- Uncertainty about whether combined toxicity of active substances in this CAG might be less than dose additive, due to the inclusion of substances with differing MoAs and adverse outcome pathways (AOPs) (e.g. thiram acting on peripheral nervous system, rather than central nervous system); however, the impact of this would be limited as most upper tail exposures (> 80%) were due to single substances (limited +, see note 30 and EFSA, 2019b).
- With respect to CAG membership, EFSA concluded that, for many substances in this CAG, there was high uncertainty about whether they actually cause functional alterations of the motor division. Resolving this uncertainty would tend to increase the MOET; however, it would have limited impact because the risk drivers were all assessed to have a high probability of causing functional alterations of the motor division (limited +, see note 28 and EFSA, 2019a).
- There is a possibility that some of the substances that were considered for inclusion in this CAG might have been wrongly excluded due to failure of the available studies to detect effects on the motor division. However, the chance of this happening is limited because each substance has multiple studies in which these effects could be detected (limited –, see note 27).
- It was noted that monitoring data occasionally show quantifiable residues of non-approved organophosphorus, N-methyl carbamate, pyrethroid and neonicotinoid pesticides that are not included in CAG-NAM. The impact of this source of uncertainty leads to an overestimation of the MOET but was difficult to quantify during the face-to-face meeting. Therefore, monitoring data of the reference period (2014, 2015 and 2016) were consulted after the meeting to extract all individual findings above the LOQ of active substances of these chemical classes non-included in CAG-NAM. This information was collected in Table B.8 in note 27 of Appendix B and circulated to the experts. On that basis, they considered the low frequency of these findings and did not observe any high residue level (above 1 mg/kg) on a commodity with both frequent and high short-term consumption. Therefore, it was concluded that this source of uncertainty has only a limited impact on the magnitude of the MOET at the 99.9th percentile of the exposure (limited –, see note 27).

Overall, the experts judged it most likely that the MOET at the 99.9th percentile of exposure in the German adult population would increase if all the uncertainties affecting toxicology were resolved, although a small decrease was also plausible. Their consensus judgements are shown in Table 10 together with the parameters for the final consensus distributions, which are also presented in Figure 7.

**Table 10:** CAG-NAM: Consensus judgements and 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 adult population in 2014–2016. The impact is expressed as a multiplicative factor  $f$  to be applied to the Tier II median estimate (shown in Table 2A). For more explanation, see Table 5

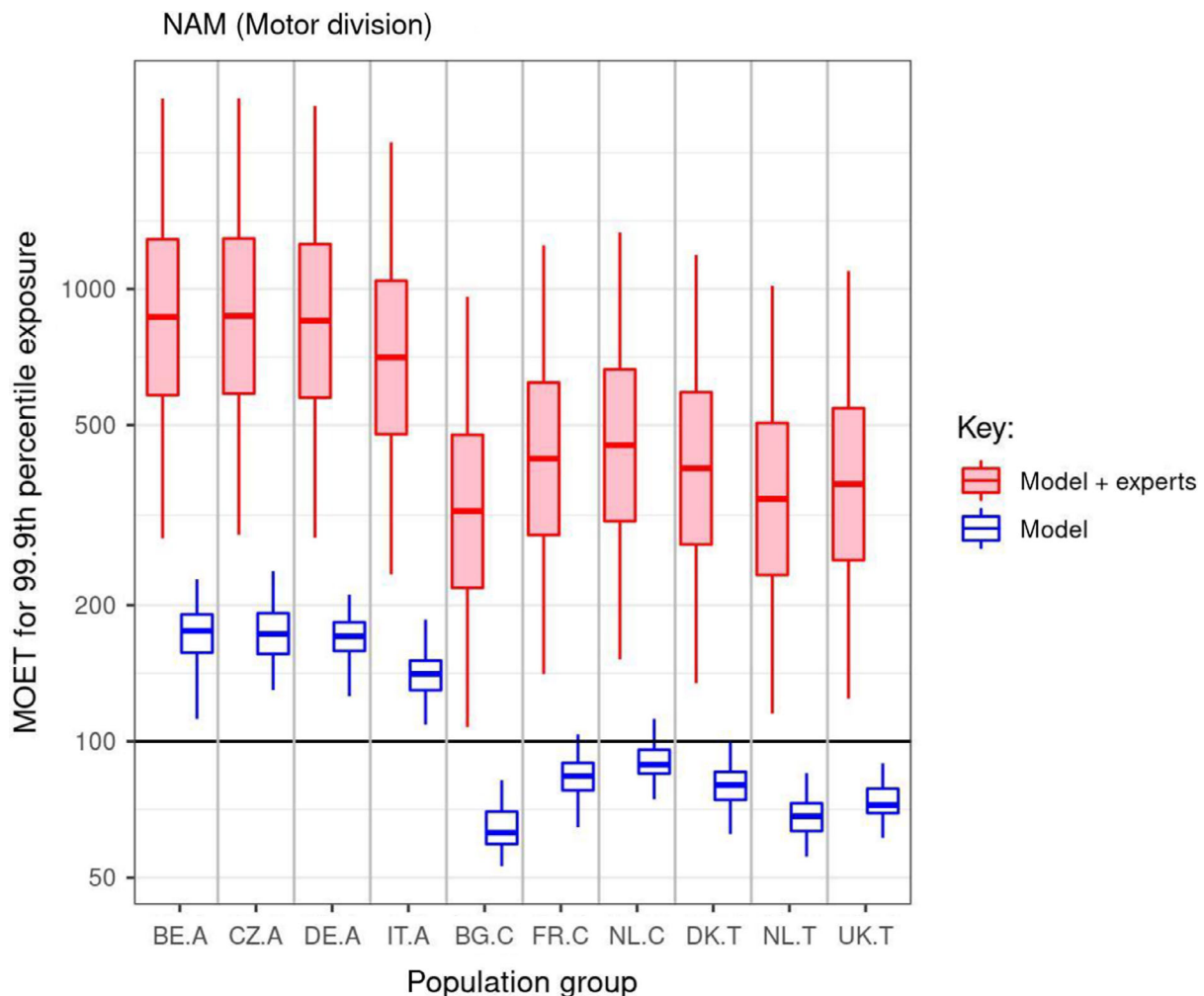
	Experts' toxicology multiplicative factor ( $f$ )
Lower plausible bound	0.9
Upper plausible bound	7
Probability 1	$p(f < 1) = 1\%$
Probability 2	$p(f > 5) = 10\%$
Probability 3	$p(f > 2.5) = 60\%$
Consensus distribution	Gamma distribution with shape 2.42 and rate 1.1, offset to start from 0.9



**Figure 7:** CAG-NAM: 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 adult population in 2014–2016. The impact is expressed as a multiplicative factor  $f$  to be applied to the Tier II median estimate shown in Table 2A. Distribution parameters are shown in Table 10. Graph content is explained in Figure 3

## c) Combined impact of uncertainties related to exposure and toxicology

The elicited distributions for the uncertainties related to toxicology and exposure were combined with the output of the MCRA Tier II model for the MOET at the 99.9th percentile of exposure in each consumer population (see Section 2.2.2.2), using the Monte Carlo calculation described in Section 2.3.6. The elicited distributions were combined with the median 99.9th percentile and uncertainty due to sampling variability (mainly on the occurrence data and consumption data) quantified in the Tier II model and reflected in confidence intervals calculated by outer loop execution (referred to as 'model' in Figure 8). These calculations were conducted assuming perfect independence between the elicited distributions for uncertainties affecting exposure and toxicology. The results of combining distributions are shown as 'model+experts' in Figure 8.



**Figure 8:** 'Model' boxplots show the unadjusted output of the MCRA Tier II model for the MOET at the 99.9th percentile of exposure in each consumer population in 2014–2016. 'Model + experts' boxplots show the result of combining the output of the Tier II model with the elicited distributions quantifying additional sources of uncertainty. Note that the vertical axis is plotted on a logarithmic scale; the values plotted for 'model + experts' are shown numerically in Table 10. A key to the populations and explanation of the boxplots are provided in the footnote below Figure 5

Similar to the results for CAG-NAN, the boxplots for 'model + experts' in Figure 8 are much wider than those for 'model'. This shows that the combined impact of the sources of uncertainty quantified by elicitation is again much larger than the sampling variability that was quantified within the model.

As for CAG-NAN, the median estimates for 'model+experts' are markedly higher than those for 'model' (Figure 5), because the uncertainties quantified in the expert elicitation include model assumptions that were intentionally conservative. The 95% probability intervals for CAG-NAM do not

extend below 100 for any of the assessed populations. Accordingly, calculated probabilities for the MOET at the 99.9th percentile of exposure being below 100 were lower than for CAG-NAN all were below 2%, as shown in Table 11. Note that these results do not take account of dependencies and population differences in uncertainty, which are addressed in EKE Q3 (see below).

**Table 11:** CAG-NAM: Statistics for the MOET at the 99.9th percentile of exposure in each consumer population in 2014–2016, calculated by combining the elicited distributions for uncertainties related to exposure and toxicology with the output of the MCRA Tier II model. P2.5, P25 etc. refer to the percentiles plotted in the 'model + experts' boxplots in Figure 8

Population group	MOET at the 99.9th percentile of exposure distribution combining model and elicited uncertainties (from 'model + experts' boxplots in Figure 8)					
	P2.5	P25	P50	P75	P97.5	Probability of 99%ile MOET < 100 (%)
Belgian adults	281	582	867	1,288	2,635	< 0.01
Czech Rep. adults	286	587	872	1,292	2,638	< 0.01
German adults	282	575	851	1,256	2,539	< 0.01
Italian adults	234	477	706	1,043	2,110	< 0.01
Bulgarian children	108	219	323	476	962	1.8
French children	141	286	422	621	1,249	0.4
Dutch children	152	307	452	664	1,333	0.2
Danish toddlers	134	272	402	591	1,189	0.5
Dutch toddlers	115	233	344	506	1,016	1.2
United Kingdom toddlers	124	251	371	545	1,095	0.8

### 3.4. Accounting for dependencies, population differences and additional uncertainties (EKE Question 3)

EKE was used to evaluate how much the calculated probabilities for the MOETs at the 99.9th percentile of exposures should be adjusted to take account of (a) 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), (b) differences between the uncertainties affecting exposure and toxicology for the German adults population (which were quantified by the elicited distributions) and the uncertainties for other population groups (which were assumed in the 'model+experts' calculation to be the same as for German adults) and (c) any other uncertainties which were not yet accounted for.

These factors were addressed by considering the following elicitation questions, repeated for each CAG:

For the German adults 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, and also the differences between the EFSA and RIVM models, what is your probability that this would result in the MOET for the 99.9th percentile of exposure for the German adult population in 2014-2016 being below 100?'*

For each of the other nine modelled populations: *'If all the uncertainties in the model, exposure assessment, hazard identification and characterisation and their dependencies, the differences between the EFSA and RIVM models, 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 2014-2016 being below 100?'*

Seven experts participated to these assessments and provided independent replies to the elicitation questions for each CAG. Later, they considered differences in their judgements and developed a consensus assessment of the probability of the MOET for the 99.9th percentile of exposure in 2014–2016 being below 100 in each of the 10 populations under consideration. The consensus process was conducted partly during a physical meeting and completed remotely as described in Section 2.3.7.



It was very difficult to assess the impact of the dependencies referred to in the EKE 3 elicitation questions by expert judgement. Therefore, it was decided to facilitate this assessment by repeating the 1-D Monte Carlo simulations described in Section 2.3.6 with the addition of varying levels of dependency between the EKE Q2 distributions for uncertainties affecting exposure and toxicology for the same CAG. This quantified the range of possible effects resulting from dependencies. The worst-case simulation, assuming perfect positive dependency, was used to define a maximum upper bound for the impact of this dependency on the probability that the MOET is below 100. Conversely, the best-case simulation, assuming perfect negative dependency, was used to define the minimum lower bound for the impact of this dependency on the probability that the MOET is below 100. In practice, the real level of dependency would be between these two extremes. The maximum effect of dependency was found to differ significantly depending on the nominal probability calculated from the EKE Question 2 process. Under the assumption of perfect positive dependency, the increase in probability exceeds a factor 7 for initial probabilities below 0.25 % but does not exceed a factor 2 for initial probabilities above 5 %, as can be seen in Tables 12 and 13.

For the German adult population, only the dependencies and differences between the EFSA and RIVM probabilistic models need to be considered when addressing EKE Question 3, since EKE Question 2 refers specifically to the German adult population. For the other nine consumer populations, EKE Question 3 requires considering, in addition, how the uncertainties relating to exposure and toxicology differ between them and the German adult population. This was done by expert judgement, taking into account the probabilities calculated for each population from EKE Question 2, the results of the calculations for the impact of dependencies, and differences in uncertainties between the populations which are summarised in the following sections.

By capturing these residual uncertainties and combining them to those previously evaluated, the EKE 3 elicitation questions conclude the uncertainty analysis process and allow the assessment of the overall uncertainty affecting CAG-NAN and CAG-NAM.

#### 3.4.1. Overall uncertainty affecting the cumulative risk assessment of brain and/or erythrocyte AChE inhibition

The experts first discussed their individual judgements for Question 3 for the German adult population. The key considerations were as follows:

- EKE 2 was considered with high emphasis to risk drivers. This is introducing a systematic methodological uncertainty which was taken into consideration in EKE 3. If resolving toxicology uncertainties might cause the risk drivers to be different, then the exposure uncertainty judgement might change and the resulting overall probability interval combining all uncertainties be impacted. Similarly, if resolving exposure uncertainties change the risk drivers, then the toxicology uncertainty might change. This is a form of dependency between the exposure and toxicology uncertainties. The experts considered that this might increase the probability that the MOET at 99.9th percentile of the exposure distribution was below 100 by a factor less than 3, which would correspond to a rank correlation of about 0.5 or less (see Table 12).
- No obvious cause or risk of any other dependency between the exposure and toxicology judgements was identified.
- The contribution of uncertainty due to differences between results from the RIVM and EFSA probabilistic models is negligible, given the much larger magnitude of the uncertainties quantified in EKE 2 and 3.

Based on these considerations, the experts agreed on a consensus upper bound of 1% for their probability that the MOET for the 99.9th percentile of exposure for the German adult population in 2014–2016 is less than 100 (see right-hand column of Table 12).

The experts next discussed their individual judgements for the other populations, and identified the following key considerations:

- The degree of dependency between uncertainties in the other populations was considered to be similar to that for German adults. Therefore, similar to German population, the increased probabilities calculated for a rank correlation of 0.5 were considered as an upper bound for the contribution of dependencies in the other populations.
- The differences between populations are essentially induced by differences in food consumption. In this respect, it was assumed that the effect of washing and peeling of commodities with edible peel and eaten raw may be more pronounced for toddlers and

children than for adults. This is especially the case for Dutch toddlers where apples and table grapes contribute more than 40% of total exposure above the 99th percentile. This would tend to shift the overall distribution of the multiplicative factor of the MOET towards higher values. It was judged that the estimated MOET at 99.9th percentile of exposure would increase by at least 10% in toddlers and children populations.

- The difference in occurrence of pesticide residues in food commodities between populations and countries are expected to have a low impact, due to the common market.
- For CAG-NAN, no element related to the hazard characterisation process was identified as source of difference between populations in different countries or different age ranges.
- The vast majority of sources of uncertainty were considered during the EKE Q1 process as impacting the multiplicative factor in the same way for all populations.
- It was also considered that the impact of differences between populations, summarised in the preceding bullets, did not contribute to further increase the probability of the MOET for the 99.9th percentile of exposure in 2014–2016 being below 100.

Based on these considerations, the experts agreed on consensus upper bounds for their probabilities for each of the nine other populations and, in addition, a lower bound probability for three populations (see right-hand column of Table 12). In making these judgements, the experts considered that the probability calculated for a rank correlation of 0.5 was their upper bound for the impact of dependency, and therefore could be regarded as also allowing for part of the impact of differences between populations, and that for some populations the uncertainty was expected to be less than for German adults (see above). For example, in the case of Dutch toddlers, combining the uncertainty distributions from Q2 with a rank correlation of 0.5 gives a probability of 16% for MOET < 100 (Table 12). However, the differences in exposure uncertainties compared to German adults (especially regarding processing effects, see above) tend to increase the MOETs for Dutch toddlers and therefore reduce the calculated probabilities. Therefore, even allowing for dependency, the probability that the MOET at the 99.9th percentile of exposure for Dutch toddlers in 2014–2016 is below 100 was judged to be less than 20%, but more than 5% (right-hand column in Table 12). The width of the final probability ranges in Table 12 reflects the difficulty of assessing the issues addressed in EKE Question 3.

**Table 12:** CAG-NAN: Results of EKE Q3. The central five columns give the calculated % probability that the MOET for the 99th percentile of exposure for each population in 2014–2016 is below 100 assuming perfect independence (column 2) or varying degrees of dependence (columns 3–6) between the experts' assessments of uncertainties relating to exposure and toxicology, i.e. between the distributions in Figures 3 and 4 above. The degree of dependency is shown as a correlation coefficient (Corr.). The right-hand column shows the consensus judgement of the experts for the probability that the MOET for the 99th percentile of exposure for each population in 2014–2016 is below 100, taking into account both dependencies and differences in uncertainties between populations

Population	Q2 probability assuming independence (%)	Q2 probability with negative dependency		Q2 probability with positive dependency		Consensus probability for Q3, including dependency and population differences
		Corr. -1	Corr. -0.5	Corr. +1	Corr. +0.5	
Belgian adults	0.20*	0.00	0.01	1.4	0.68	< 1%
Czech Rep. adults	0.07	0.00	0.00	0.69	0.3	< 1%
German adults	0.28	0.00	0.02	1.89	0.92	< 1%
Italian adults	0.25	0.00	0.01	1.7	0.83	< 1%
Bulgarian children	6.8	0.02	2.8	13.4	10	1–10%
French children	2.8	0.00	0.71	7.8	5.3	< 5%
Dutch children	4.6	0.00	1.4	10.6	7.7	1–10%
Danish toddlers	2.8	0.00	0.69	7.8	5.3	< 5%
Dutch toddlers	12	0.08	6.2	19.3	16	5–20%

Population	Q2 probability assuming independence (%)	Q2 probability with negative dependency		Q2 probability with positive dependency		Consensus probability for Q3, including dependency and population differences
		Corr. -1	Corr. -0.5	Corr. +1	Corr. +0.5	
United Kingdom toddlers	2.7	0.00	0.69	7.6	5.2	< 5%

\*: The probabilities in this column differ slightly from those shown in Table 8 because they were obtained after repeating the Monte Carlo calculations. This commonly occurs in Monte Carlo calculations unless the number of Monte Carlo samples is very large. In the present case, the overall relative error in a calculated probability is very unlikely to be more than 10% (e.g.  $\pm 0.46$  for Dutch children) except for probabilities calculated to be less than 1% where the relative error may be as much as 50% in some cases and probabilities calculated to be less than 0.1% where it is unlikely that the probability actually exceeds 0.2%.

### 3.4.2. Overall uncertainty affecting the cumulative risk assessment of functional alterations of the motor division of the nervous system

Due to limitations of time, a detailed discussion of individual assessments did not take place for CAG-NAM. As for CAG-NAN, the experts agreed to consider the outcome of the 1-D Monte Carlo simulations with intermediate levels of correlations ( $-0.5$  and  $+0.5$  for negative and positive correlations, respectively, shown in Table 13) as representing reasonably the maximum effect of dependency.

The experts further agreed that the most important differences in uncertainty between populations for the EKE Q3 elicitation identified above for CAG-NAN apply also here, with the exception of the effect of peeling and washing which does not play a significant role in case of CAG-NAM because the specific risk drivers are different, and much less sensitive to this source of uncertainty.

Taking these considerations into account and following similar reasoning to that for CAG-NAN, the experts agreed on consensus upper bounds for their probabilities for each of the 10 populations shown in the right-hand column of Table 13.

**Table 13:** CAG-NAM: Results of EKE Question 3 for CAG NAM. The central five columns give the calculated % probability that the MOET for the 99th percentile of exposure for each population in 2014–2016 is below 100 assuming no dependence (column 2) or varying degrees of dependence between the experts' assessments of uncertainties relating to exposure and toxicology, i.e. between the distributions in Figures 6 and 7 above. The degree of dependency is shown as a correlation coefficient (Corr.). The right-hand column shows the consensus judgement of the experts for the probability that the MOET for the 99th percentile of exposure for each population in 2014–2016 is below 100, taking into account both dependencies and differences in uncertainties between populations

Population	Q2 probability assuming independence (%)	Q2 probability with negative dependency		Q2 probability with positive dependency		Consensus probability for Q3, including dependency and population differences
		Corr. -1	Corr. -0.5	Corr. +1	Corr. +0.5	
Belgian adults	0.00*	0.00	0.00	0.03	0.01	< 1%
Czech Rep. adults	0.00	0.00	0.00	0.01	0.00	< 1%
German adults	0.00	0.00	0.00	0.01	0.00	< 1%
Italian adults	0.00	0.00	0.00	0.11	0.03	< 1%
Bulgarian children	1.75	0.00	0.15	7.39	4.3	< 5%
French children	0.34	0.00	0.01	3.12	1.4	< 5%
Dutch children	0.18	0.00	0.00	2.32	0.94	< 1%
Danish toddlers	0.47	0.00	0.02	3.73	1.8	< 5%
Dutch toddlers	1.22	0.00	0.08	6.16	3.4	< 5%
United Kingdom toddlers	0.78	0.00	0.04	4.89	2.5	< 5%

\*: The probabilities in this column differ slightly from those shown in Table 11. See footnote to Table 12 for explanation.

## 4. Cumulative risk characterisation

### 4.1. Brain and/or erythrocyte AChE inhibition

Based on the above findings and analyses, the cumulative risks for brain and/or erythrocyte AChE inhibition can be summarised as follows:

- 1) Very similar results in probabilistic modelling of cumulative exposure were obtained by EFSA and RIVM and showed eight populations with median estimate of the MOET below 100 at the 99.9th percentile of the exposure (Table 1A, second column of Table 14), which has been identified by the European Commission and MSs as a threshold for regulatory consideration. At 99th percentile of the exposure, the MOET was above 100 in all cases (table 1). Toddlers and children had similar levels of exposure, which were higher than the exposure levels observed for adults.
- 2) Uncertainties in the assessment of toxicology and exposure were quantified by a formal process of expert judgement and combined with the MCRA model results by calculation. For all population groups, this increased the median estimate of the MOET at the 99.9th percentile of exposure by about a factor of 4–5 (Table 8, third column of Table 14), reflecting the effect of purposely conservative assumptions in the assessment, as called for by the legislation (see Section 1.2).
- 3) The 95% probability intervals for the adjusted results are much wider than those calculated by the models, because only a small proportion of the uncertainties is quantified in the MCRA and EFSA models. Calculated probabilities for the MOET at the 99.9th percentile of exposure being below the threshold for regulatory consideration were less than 1% for the four adult populations and 3–7% for the children and toddlers, except for Dutch toddlers (12%) (right-hand column of Table 8).
- 4) Finally, the experts considered the impact of dependencies between the toxicology and exposure uncertainties, differences between populations and additional uncertainties not considered earlier. This results in their overall assessment (fourth column of Table 14). For all four adult populations (BE, CZ, DE and IT), the probability of the MOET at the 99.9th percentile of exposure being below the threshold for regulatory consideration was assessed to remain below 1%. For French children, Danish and UK toddlers, the probability was assessed to be less than 5%. For Bulgarian and Dutch children, the probability was assessed to be between 1% and 10%. For Dutch toddlers, it was assessed to be between 5% and 20%. The width of these probability ranges reflects the difficulty of assessing the impacts of dependencies and population differences on overall uncertainty.
- 5) EFSA's guidance on communicating uncertainty (EFSA, 2019c) recommends that for the purpose of communication, probabilities quantifying uncertainty should be expressed as 'percentage certainty' of the more probable outcome (in this case, that the MOET at the 99.9th percentile of exposure in 2014–2016 is equal or greater than 100, rather than less). This advice is applied in the right-hand column of Table 14. Also shown in the same column are verbal probability terms associated with the assessed range of percent certainty, based on the APS recommended for harmonised use in EFSA assessments.

**Table 14:** CAG-NAN: Outcome of the CRA of brain and/or erythrocyte AChE inhibition resulting from dietary exposure to pesticides for each population in 2014–2016

Population	MOET at the 99.9th percentile of exposure			
	Median and 95% confidence interval following model	Median and 95% probability interval after adjustment for uncertainties	Probability for MOET < 100	Corresponding percent certainty that the MOET is equal to or greater than 100, and associated probability term <sup>(a)</sup>
Belgian adults	102 [72–162]	471 [163–1182]	< 1%	> 99% certainty(almost certain)
Czech Rep. adults	120 [87–176]	552 [191–1369]	< 1%	> 99% certainty(almost certain)

Population	MOET at the 99.9th percentile of exposure			
	Median and 95% confidence interval following model	Median and 95% probability interval after adjustment for uncertainties	Probability for MOET < 100	Corresponding percent certainty that the MOET is equal to or greater than 100, and associated probability term <sup>(a)</sup>
German adults	95 [73–120]	429 [152–1013]	< 1%	> 99% certainty(almost certain)
Italian adults	96 [75–149]	443 [156–1091]	< 1%	> 99% certainty(almost certain)
Bulgarian children	49 [36–63]	218 [77–518]	1–10%	90–99% certainty(very likely to extremely likely)
French children	59 [46–74]	271 [97–633]	< 5%	> 95% certainty(extremely likely to almost certain)
Dutch children	52 [45–62]	239 [86–550]	1–10%	90–99% certainty(very likely to extremely likely)
Danish toddlers	60 [50–69]	270 [97–627]	< 5%	> 95% certainty(extremely likely to almost certain)
Dutch toddlers	40 [33–50]	183 [66–424]	5–20%	80–95% certainty(likely to very likely)
United Kingdom toddlers	61[47–76]	274 [98–643]	< 5%	> 95% certainty(extremely likely to almost certain)

(a): The probability terms used in this table are recommended in the EFSA guidance on communication of uncertainty (EFSA, 2019c).

Regulation (EC) 1107/2009 concerning the placing of plant protection products on the market requires in annex II, chapter 3.6.1, that when a health-based guidance value is established a 'safety margin of at least 100 shall be ensured taking into account the type and severity of effects and the vulnerability of specific groups of the population'. The factor of 100 comprises a factor of 10 for interspecies differences and a factor of 10 for human interindividual differences. The MOET of 100 required as threshold for regulatory consideration is coherent with this principle.

For certain classes of pesticides specific information on toxicokinetics or toxicodynamics may be available, and when this is the case, the International Programme on Chemical Safety (IPCS) of the World Health Organization (WHO) provides that chemical-specific adjustment factors (CSAFs) can be derived to replace the defaults (IPCS, 2005). In line with this recommendation, among others the Joint Meeting on Pesticides Residues of the WHO has on several occasions used CSAFs to derive specific safety factors lower than the default of 100 to establish a health-based guidance value for N-methyl carbamate insecticides for e.g. for carbofuran (JMPPR, 2008) regarding AChE inhibition.

In the present risk assessment, the conservatism of the default MOET of 100 for specific (classes of) pesticides was not considered.

## 4.2. Functional alterations of the motor division of the nervous system

Based on the above findings and analyses, the cumulative risks for functional alterations of the motor division can be summarised as follows:

- 1) Very similar results in probabilistic modelling of cumulative exposure were obtained by EFSA and RIVM and showed six populations with median estimate of the MOET below 100 at the 99.9th percentile of the exposure (Table 2A, second column Table 15). At 99th percentile of the exposure, the MOET was above 100 in all cases. Toddlers and children had similar levels of exposure, which were higher than the exposure levels observed for adults.
- 2) Uncertainties in the assessment of toxicology and exposure were quantified by a formal process of expert judgement and combined with the MCRA model results by calculation. For all population groups, this increased the median estimate of the MOET at the 99.9th percentile of exposure by about a factor of about 5 (Table 11, third column of Table 15), reflecting the effect of conservative assumptions in the assessment, as called for by the legislation (see Section 1.2).



- 3) The 95% probability intervals for the adjusted results are much wider, because only a small proportion of the uncertainties is quantified in the MCRA and EFSA models. Calculated probabilities for the MOET at the 99.9th percentile of exposure being below the threshold for regulatory consideration were much less than 1% for the four adult populations and 0.2–2% for the children and toddlers (right-hand column of Table 11).
- 4) The impact of dependencies between the toxicology and exposure uncertainties and differences between populations was not assessed formally for this CAG. However, this impact is not expected to differ substantially from the impact of these factors on the MOET at the 99.9th percentile of exposure for the CAG-NAN. Applying the same reasoning less formally to CAG-NAM led to the results shown in the fourth column of Table 15. For all four adult populations (BE, CZ, DE and IT) and for Dutch children, the probability of the MOET at the 99.9th percentile of exposure being below the threshold for regulatory consideration was assessed to remain below 1%. For other populations of children (FR, BG) and for the three toddlers' populations (UK, DK and NL) toddlers, the probability was assessed to remain below 5%.
- 5) As for CAG-NAN, the results for CAG-NAM are expressed in terms of percent certainty in the right-hand column of Table 15.

**Table 15:** CAG-NAM: Outcome of the CRA of functional alterations of the motor division of the nervous system resulting from dietary exposure to pesticides for each population in 2014–2016

Population	MOET at the 99.9th percentile of exposure			
	Median and 95% confidence interval following MCRA model	Median and 95% probability interval after adjustment for uncertainties	Probability for MOET < 100	Corresponding percent certainty that the MOET is equal to or greater than 100, and associated probability term <sup>(a)</sup>
Belgian adults	176 [115–228]	867 [281–2635]	< 1%	> 99% certainty(almost certain)
Czech Rep. adults	172 [131–236]	872 [286–2638]	< 1%	> 99% certainty(almost certain)
German adults	171 [127–211]	851 [282–2539]	< 1%	> 99% certainty(almost certain)
Italian adults	141 [109–185]	706 [234–2110]	< 1%	> 99% certainty(almost certain)
Bulgarian children	63 [53–81]	323 [108–962]	< 5%	> 95% certainty(extremely likely to almost certain)
French children	84 [65–102]	422 [141–1249]	< 5%	> 95% certainty(extremely likely to almost certain)
Dutch children	89 [75–111]	452 [152–1333]	< 1%	> 99% certainty(almost certain)
Danish toddlers	80 [63–100]	402 [134–1189]	< 5%	> 95% certainty(extremely likely to almost certain)
Dutch toddlers	68 [56–85]	344 [115–1016]	< 5%	> 95% certainty(extremely likely to almost certain)
United Kingdom toddlers	73 [61–89]	371 [124–1095]	< 5%	> 95% certainty(extremely likely to almost certain)

(a): The probability terms used in this table are recommended in the EFSA guidance on communication of uncertainty (EFSA, 2019c).

### 4.3. Risks for other European populations

During the Standing Committee on Plants, Animals, Food and Feed of 18–19 September 2018 (European Commission, 2018), MSs recommended considering, in CRA, all population subgroups of consumers included in the EFSA PRIMo model (EFSA, 2018b). For reasons of resources, it was however not possible to extend the calculations for the 10 selected populations to all consumer subgroups of the PRIMo model. However, from the information given in note 1 of Appendix B.2, Dutch

toddlers, constituting one of the populations selected for the calculations, have the highest consumption of food of plant origin of the PRIMo model. This suggests that the populations selected for the calculations are representative of European populations with highest vulnerability in terms of dietary exposure potential, and cover teenagers from 9 to 18 year of age and adults above 65 years old, although not represented by any of the assessed populations.

In contrast, infants from 16 weeks to 1 year of age have a higher consumption rate per kg body weight than any of the toddlers and other children populations used for the calculations. However, in its scientific opinion on pesticides in foods for infants and young children (EFSA PPR Panel, 2018), the PPR panel has shown through five case studies that their acute and chronic exposure to pesticide residues in post-marketing scenario was similar to the exposure of toddlers (12–36 months).

## 5. Conclusions

As a result of the uncertainty analysis, the MOETs at the 99.9th percentile of exposure and their confidence intervals were adjusted to take account of the identified uncertainties. For both CAGs, the adjusted MOETs were around four to five times higher compared to those calculated in tier II by the probabilistic tools. This is consistent with the intention of MSs, when selecting the parameters and assumptions to be used, to ensure that the tier II calculations are sufficiently conservative.

Considering all uncertainties identified by experts, for brain and/or erythrocyte AChE inhibition, it was concluded that, with varying degrees of certainty, cumulative exposure does not reach the threshold for regulatory consideration for all the population groups considered. This certainty exceeds 99% for all four adult populations, 95% for two children populations and one toddler population, 90% for one children population and one toddler population and 80% for the remaining toddler population. For functional alterations of the nervous system, the same conclusion was drawn with a certainty exceeding 99% for all adult populations and one children population and 95% for two populations of children and all toddler populations. These populations can be considered as representative of the European populations with the highest vulnerability in terms of exposure potential.

## 6. Recommendations

Based on the experience gathered throughout this new type of risk assessment, and in order to reduce the impact of uncertainties in future similar CRAs, it is recommended to:

With respect to the *toxicological assessment*:

- Include in probabilistic calculations the sources of uncertainty which can be modelled (e.g. CAG membership).
- Use Benchmark Dose (BMD) modelling to characterise the active substances included in the CAG for the specific effect.
- Consider other recommendations listed in the scientific report on the establishment of CAGs of pesticides for their effects on the nervous system (EFSA, 2019a), in particular regarding developmental neurotoxicity and the regular update of the CAGs. Neurodegenerative diseases should also be considered in the context of CRA.

With respect to the *exposure assessment*:

- Identify commodities not included in the calculations performed in this report which may significantly contribute to the intake of residues and consider incorporating them in future CRAs.
- Consolidate the list of processing factors available for CRAs.
- Collect of information from competent organisations on national authorisations, use statistics of plant protection products and pesticide residues in drinking water, on risk-based criteria.
- 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).

In addition, it is recommended to perform a chronic CRA for CAG-NAN considering that organophosphorus insecticides are the main risk drivers of acute brain and/or erythrocyte AChE inhibition, draw up a new CAG for developmental neurotoxicity (DNT) and further perform CRA to assess the combined impact of organophosphates, pyrethroids and other insecticides with DNT potential on infant, toddler and children populations.

Furthermore, it is recommended to evaluate the scientific strategy and technical processes used to perform the different steps (hazard characterisation/identification, exposure assessment, risk characterisation and uncertainty analysis) of the reported assessment and identify options for optimisation and/or alternative simpler ways to perform future assessments. This includes consideration of the criteria to identify the effects of relevance for CRA and to group substances into CAGs. This may also encompass the evaluation of the magnitude of the impact of assumptions elaborated to compensate missing data or information (e.g. impact of assumptions for left-censored occurrence data, pesticides in drinking water...). It is recognised that some CAGs may require more or less detailed analysis than the others.

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## Abbreviations

AChE	Acetylcholinesterase
ADI	Acceptable daily intake
AOP	Adverse Outcome Pathway
APS	Approximate Probability Scale
ARfD	Acute Reference Dose
BMD	Benchmark Dose
BMDL	Lower confidence limit of the benchmark dose
bw	Body weight
CAG	Cumulative Assessment Group
CAG-NAM	Cumulative Assessment Group for the acute assessment of functional alterations of the motor division
CAG-NAN	Cumulative Assessment Group for the acute assessment of brain and/or erythrocyte AChE inhibition



CRA	Cumulative Risk Assessment
CSAF	chemical-specific adjustment factor
EKE	Expert Knowledge Elicitation
EUCP	European Coordinated Programme
IC	Index Compound
IPC	International Programme on Chemical Safety
KE	Key event
LOQ	Limit of Quantification
MCRA	Monte Carlo Risk Assessment (software)
MIE	Molecular Initiating Event
MOE	Margin of Exposure
MOET	Combined Margin of Exposure
MoA	Mode of Action
MRLs	Maximum Residue Levels
MS	Member State
NOAEL	No Observed Adverse Effect Level
PPR	EFSA Panel on Plant Protection Products and their Residues
RfP	(toxicological) Reference Point
RIO	Rational Impartial Observer
RIVM	(Dutch) National Institute for Public Health and the Environment
RPC	Raw Primary Commodity
SC PAFF	Standing Committee on Plants, Animals, Food and Feed
SSD	EFSA Standard Sample Description
WHO	World Health Organisation

## Appendix A – Assessment of individual sources of uncertainty affecting the CRA for active substances causing brain and/or erythrocyte AChE inhibition (CAG-NAN) and functional alterations of the motor division of the nervous system (CAG-NAM)

The ranges for the values of multiplicative factors that would adjust the median estimate of the MOET for CAG-NAN and CAG-NAM at the 99.9th percentile of exposure at Tier II were estimated for each source of uncertainty identified in Section 3.1, assuming that it was fully resolved and addressed in the modelling.

These estimations were first conducted for the German population (EKE Q1A), based on information specific to the cumulative exposure of this population (see EFSA, 2019b; van Klaveren et al., 2019). The scale and methods used for this estimation are described in Section 2.3.4. For example: ‘– – –/•’ means at least a 90% chance the true factor is between  $\times 1/10$  and  $+ 20\%$ ; ‘++/++’ means  $\geq 90\%$  chance between  $2\times$  and  $5\times$ , etc. These estimations are reported in the fourth column of Table A.1 and in third column of Table A.2. The estimated ranges were in most cases the same for CAG-NAN and CAG-NAM. When this was not the case, this was explicitly indicated.

It was secondly assessed whether the same multiplicative factor would apply to the other populations for which a CRA is performed (EKE Q1B). The reply to this question (Yes/No) is given in the fifth column of Table A.1 and the fourth column of Table A.2. It was ‘yes’ for all sources of uncertainty except one (excluded consumption data).

In the last column of Table A.1 and Table A.2, reference is given to notes in Section B.2 of Appendix B which summarise information used to address EKE Q1A and Q1B.

**Table A.1:** CAG-NAN and CAG-NAM: Assessment of individual sources of uncertainty affecting the input data with respect to EKE Q1A and EKE Q1B

Assessment input	Type of uncertainty	Description of the uncertainty	Range of multiplicative factor of MOET at 99.9th percentile of tier II <sup>(a)</sup>	Multiplicative factor identical for all populations <sup>(b)</sup>	Informative notes
<b>Consumption data</b>	Excluded data	Animal commodities and plant commodities not in the list of the 30 selected commodities and their processed derivatives were excluded	–/•	No	Note 1 Note 2 Note 3
	Ambiguity	The consumption data do not always discriminate between different commodities of a same group (e.g. tomatoes and cherry tomatoes are considered as tomatoes)	•/+	Yes	Note 4
	Accuracy	The accuracy of the reported amount of food consumed in surveys may be affected by methodological limitations or psychological factors	•	Yes	Note 5 Note 6
	Sampling variability	Small population size (number of consumers in the 10 populations) may affect the reliability of risk estimates at 99.9th percentiles	See confidence intervals of MOET estimates at 99.9th percentile of exposure distribution (Tables 1A and 2A)		Note 7
	Sampling bias	Representativeness of the consumption data	•	Yes	Note 8
	Use of fixed values	One invariable recipe and conversion factor are used to convert the amount of food consumed into the respective amount of RPC	–/•	Yes	Note 9

Assessment input	Type of uncertainty	Description of the uncertainty	Range of multiplicative factor of MOET at 99.9th percentile of tier II <sup>(a)</sup>	Multiplicative factor identical for all populations <sup>(b)</sup>	Informative notes
<b>Occurrence data</b>	Missing data	Active substance/commodity combinations, for which occurrence data are missing and extrapolation from another commodity is not possible, were excluded	•	Yes	Note 10
	Excluded data	The contribution of metabolites and degradation products has not been considered	–/•	Yes	Note 11
	Ambiguity	The occurrence data do not always discriminate between different commodities of a same group (e.g. tomatoes and cherry tomatoes are considered as tomatoes)	•	Yes	Note 4
	Accuracy	Laboratory analytical uncertainty	–/+	Yes	Note 12
	Sampling variability	A small number of occurrence data may affect the reliability of risk estimates at 99.9th percentile. This number varies from one pesticide/commodity combination to the other.	See confidence intervals of MOET estimates at 99.9th percentile of exposure distribution (Tables 1A and 2A)		Note 7
	Sampling bias	Representativeness of the monitoring data	•/++	Yes	Note 13
	Extrapolation uncertainty	Extrapolation of occurrence data between crops	•	Yes	Note 14
	Extrapolation uncertainty	Extrapolation of occurrence data between countries	•	Yes	Note 15
	Imputed data	Imputation of unmeasured residues in food samples	•	Yes	Note 16
	Assumption	Assumption of the active substance present on the commodity in case of unspecific residue definition for monitoring	•	Yes	Note 17
	Assumption	Assumption of the authorisation status of all pesticide/commodity combinations	•	Yes	Note 18
	Assumption	Assumption of the use frequency for authorised pesticide/commodity combinations	•	Yes	Note 19
	<b>Processing factors</b>	Assumption	Assumption on the residue level (1/2 LOQ) when an active substance is used, and its residues are below the LOQ	•	Yes
Assumption		Occurrence of residues in drinking water	•	Yes	Note 20
Assumption		Pesticide residues are transferred without any loss to processed commodities when processing factors are not available	•/+	Yes	Note 21
Ambiguity		Application of processing factors, derived from a limited number of standardised studies, to the EFSA food classification and description system (FoodEx)	•	Yes	Note 22

Assessment input	Type of uncertainty	Description of the uncertainty	Range of multiplicative factor of MOET at 99.9th percentile of tier II <sup>(a)</sup>	Multiplicative factor identical for all populations <sup>(b)</sup>	Informative notes
	Accuracy	Laboratory analytical uncertainty	•	Yes	
	Accuracy	Calculation of processing factors is affected by residue levels below the LOQ	•	Yes	Note 23
	Accuracy/use of fixed values	Only one value of processing factor is used in the calculations, which is the mean or median value of a limited number of independent trials	•	Yes	Note 24
	Excluded data	Some processing factors are not considered (e.g. peeling and washing of commodities with edible peel)	•/+	Yes	Note 25
<b>Variability factor</b>	Use of fixed values	The variability factor used in the calculations is 3.6 for all commodities about 25 g	•	Yes	Note 26
<b>NOAELs</b>	Adequacy of the CAG	Uncertainty on whether the CAG contains all the active substances causing the effect	•	Yes	Note 27
	Adequacy of the CAG	Uncertainty on whether the CAG contains only the active substances causing the effect	• (CAG-NAN) •/+ (CAG-NAM)	Yes	Note 28
	Accuracy	Uncertainties affecting the characterisation of active substances included in the CAG (quality of data and NOAEL setting process)	+ /++	Yes	Note 29

(a): The range shown is the same for CAG-NAN and CAG-NAM unless otherwise indicated.

(b): The experts considered that only the first source of uncertainty was expected, on its own, to have an impact varying between populations, as indicated in this column, but noted that more differences might be expected if multiple uncertainties were considered together.

**Table A.2:** CAG-NAN and CAG-NAM: Assessment of individual sources of uncertainty affecting the assessment methodology with respect to EKE Q1A and EKE Q1B

Element of the assessment methodology	Description of the uncertainty	Range of multiplicative factor of MOET at 99.9th percentile of tier II <sup>(a)</sup>	multiplicative factor identical for all populations	Informative notes
<b>Dose-addition</b>	Uncertainty about the actual mode of combined toxicity	• (CAG-NAN) -/+ (CAG-NAM)	Yes	Note 30
<b>Dose-response relationship</b>	Uncertainty about the slope and the shape of the dose-response, and consequently about the effect size of individual active substances at the actual exposure levels	• (CAG-NAN) -/+ (CAG-NAM)	Yes	Note 31

Element of the assessment methodology	Description of the uncertainty	Range of multiplicative factor of MOET at 99.9th percentile of tier II <sup>(a)</sup>	multiplicative factor identical for all populations	Informative notes
<b>Combination of occurrence and consumption data</b>	Uncertainty regarding the combination of occurrence and consumption data	•/+	Yes	Note 32
<b>Adequacy of the acute exposure calculation model</b>	Uncertainty about the fitness of the acute exposure calculation model to human toxicokinetic and toxicodynamic processes related to the effect	-/ <b>•</b> (CAG-NAN) -/+ (CAG-NAM)	Yes	Note 33

(a): The range shown is the same for CAG-NAN and CAG-NAM unless otherwise indicated.



## Appendix B – Information used in the uncertainty analysis

### B.1. Risk drivers

The assessment of the impact of several sources of uncertainty depends on the specific active substance/commodity combinations which contribute the most to the cumulative risk. Therefore, information of interest on the active substances identified as risk drivers was collected and summarised in Tables B.1 and B.2:

**Table B.1:** Risk drivers for CAG-NAN

Active substance	CAG membership probability	Processing factors used	Water solubility pH 7	Log Kow	Residue definitions
Chlorpyrifos	Almost certain (> 99%)	Oranges and mandarins: juicing and peeling	1.05 mg/L (EC review report, 2005)	4.7 (EC review report, 2005)	Monitoring: chlorpyrifos Risk assessment: sum of chlorpyrifos and its desethyl metabolite, expressed as chlorpyrifos (EFSA MRL review, 2017)
Dichlorvos	Almost certain (> 99%)	none	18 g/L (EFSA conclusions 2006)	1.9 (EFSA conclusions 2006)	Monitoring: dichlorvos Risk assessment: not available (EFSA conclusions 2006)
Formetanate	Almost certain (> 99%)	none	822 g/L (EFSA conclusions 2006)	-0.0014 (EFSA conclusions 2006)	Monitoring: Formetanate: Sum of formetanate and its salts expressed as formetanate Risk assessment: Formetanate: Sum of formetanate and its salts expressed as formetanate (EFSA conclusions 2006)
Omethoate	Almost certain (> 99%)	none	4.69 mol/L (EPA DSSTox <sup>(a)</sup> )	-0.9 (EFSA conclusions dimethoate, 2018)	Monitoring: omethoate Risk assessment: omethoate (EFSA conclusions 2018)
Triazophos	Almost certain (> 99%)	none	9.92e-05 mol/L (EPA DSSTox <sup>(b)</sup> )	3.34 (EPA DSSTox)	Monitoring: triazophos Risk assessment: not available

(a): <https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID4037580#details>

(b): <https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID9037612>

**Table B.2:** Risk drivers for CAG-NAM

Active substance	CAG membership probability	Processing factors used	Water solubility pH 7	Log Kow	Residue definition for RA
Acrinathrin	Almost certain (> 99%)	None	0.0022 mg/L (EFSA conclusions 2013)	6.3 (EFSA conclusions 2013)	Monitoring: acrinathrin Risk assessment: sum of Acrinathrin and its 15 isomers (EFSA conclusions 2013)
Beta-cypermethrin	Almost certain (> 99%)	Olives: oil production	0.01 mg/L (Toxnet <sup>(a)</sup> )	5.8 (EFSA conclusions 2014)	Monitoring: Cypermethrin (cypermethrin including other mixtures of constituent isomers (sum of isomers)) Risk assessment: beta-cypermethrin (EFSA conclusions, 2014)
Chlormequat	Almost certain (> 99%)	None	> 886 g/L (EFSA conclusions 2009)	-3.47 (EFSA conclusions 2009)	Monitoring: Chlormequat (sum of chlormequat and its salts) Risk assessment: Chlormequat (sum of chlormequat and its salts) (EFSA MRL review, 2014)

Active substance	CAG membership probability	Processing factors used	Water solubility pH 7	Log Kow	Residue definition for RA
Deltamethrin	Almost certain (> 99%)	Potatoes: cooking in water, stewing, frying	0.0002 mg/L (EC review report 2002)	4.6 (EC review report 2002)	Monitoring: Deltamethrin (cis-deltamethrin) Risk assessment: sum of deltamethrin and its trans-isomer and alpha R-isomer
Omethoate	Almost certain (> 99%)	None	4.69 mol/L (EPA DSSTox <sup>(a)</sup> )	-0.9 (EFSA conclusions dimethoate, 2018)	Monitoring: omethoate Risk assessment: omethoate (EFSA conclusions 2018)
Thiram	Likely to very likely (66–95%)	None	18 mg/L (EFSA conclusions 2017)	1.84 (EFSA conclusions 2017)	Monitoring: CS <sub>2</sub> Risk assessment: CS <sub>2</sub> × 1.58 (correction for molecular weight)
Triazophos	Almost certain (> 99%)	none	9.92e-05 mol/L (EPA DSSTox <sup>(b)</sup> )	3.34 (EPA DSSTox)	Monitoring: triazophos Risk assessment: not available

(a): <https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@rn+@rel+67375-30-8>

(b): <https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID9037612>

## B.2. Notes supporting the assessment of individual uncertainties

### Note 1 (Contribution of the selected 30 commodities to the overall diet of plant origin)

The contribution of the selected 30 commodities to the overall long-term diet of plant origin has been calculated for the 30 population groups of the EFSA PRIMo (Revision 3.1) Model (EFSA, 2018b) in Table B.3. In populations of infant/children/toddlers, the selected 30 commodities contribute to 62–96% of the overall diet of plant origin with a median of 80%. In adult populations, this contribution varies from 49 to 94 %, with a median of 80.5%. In Germany, for the general population and for the population of women of child-bearing age, this contribution is 61% and 63%, respectively.

Similar calculations were conducted based on the RPC model (EFSA, 2019d) with the survey data of the 10 population groups used in this report and are also reported in Table B.3 as shaded rows. To improve comparability with the calculations conducted for the diets of the EFSA PRIMo diets, sugar plants were excluded. However, considering the extensive processing that is applied to sugar plants, this does not alter the value of this information for the uncertainty analysis. The calculations showed that the contribution of the 30 commodities used for the cumulative exposure assessments to the overall diet of plant origin ranges from 72 (BG children) to 86% (IT adults). The contribution was 78% in the case of the German adult population.

The calculations for the population groups of the EFSA PRIMo model used the entries for mean consumption of individual products, as they were provided by MSs from national food surveys. These data were provided before the RPC model became available. For this reason, there are differences for the calculated contribution of the selected commodities between the population groups used for the cumulative exposure assessments and those reported in PRIMo model, even if derived from the same survey.

**Table B.3:** Contribution (in percent) of the selected 30 commodities to the overall diet of plant origin in population groups of the EFSA PRIMo Model

Long-term diet <sup>(a)</sup>	Subgroup of population/ age group	Mean body weight (kg)	Total average consumption of the selected 30 commodities (g/kg bw per d)	Total average consumption of plant commodities (g/kg bw per d)	Contribution of selected 30 commodities to overall diet of plant origin (%)
BE adults	18–64				77
BG children	3–5				72
CZ adults	18–64				77

Long-term diet <sup>(a)</sup>	Subgroup of population/ age group	Mean body weight (kg)	Total average consumption of the selected 30 commodities (g/kg bw per d)	Total average consumption of plant commodities (g/kg bw per d)	Contribution of selected 30 commodities to overall diet of plant origin (%)
DE child	Children between 2 and 5 years	16.2	33.42	38.26	87
DE adults	18–64				78
DE general	General population	76.4	11.63	18.87	61
DE women 14–50 years	Women of child-bearing age	67.5	12.49	19.96	63
DK adult	15–74 years	75.1	8.19	8.71	94
DK toddlers	1–3				83
DK child	4–6 years	21.8	22.25	23.08	96
ES adult	Adults > 17 years	68.5	10.00	12.19	82
ES child	7–12 years	34.5	15.19	17.77	85
FI adult	Adults	77.1	6.19	12.59	49
FI child 3 years	Children up to 3 years	15.2	14.44	16.73	86
FI child 6 years	Children up to 6 years	22.4	11.05	13.08	84
FR infant	7–18 months	9.1	8.62	11.06	78
FR toddler 2–3 years	25–36 months	13.6	15.47	20.87	74
FR child 3 to < 15 years	Children from 3 to less than 15 years	18.9	17.36	24.88	70
FR children	3–9				82
FR adult	Adults > 15 years	66.4	9.29	12.48	74
IE adult	Adults 18–64 years	75.2	14.05	25.60	55
IE child	5–12 years	20.0	3.22	3.61	89
IT adults	18–65				86
IT adult	18–64 years	66.5	9.86	12.12	81
IT toddler	1–17 years	41.6	13.44	16.42	82
LT adult	19–64 years	70.0	9.57	10.20	94
NL child	2–6 years	18.4	23.09	37.27	62
NL children	3–6				80
NL general	General population, 1–97 years	65.8	10.72	17.31	62
NL toddlers	2				81
NL toddler	8–20 months	10.2	40.50	60.61	67
PL general	General population, 1–96 years	62.8	8.31	9.71	86
PT general	General population	60.0 <sup>(a)</sup>	18.23	20.84	87
RO general	General population	60.0 <sup>(a)</sup>	18.08	23.13	78

Long-term diet <sup>(a)</sup>	Subgroup of population/ age group	Mean body weight (kg)	Total average consumption of the selected 30 commodities (g/kg bw per d)	Total average consumption of plant commodities (g/kg bw per d)	Contribution of selected 30 commodities to overall diet of plant origin (%)
SE general	General population, 1–74 years	60.0 <sup>(a)</sup>	16.65	19.65	85
UK infant	6 months–1 year	8.7	14.36	18.58	77
UK toddlers	1–2				83
UK toddler	18 months–4 years	14.6	15.76	21.04	75
UK adult	19–64 years	76.0	7.41	8.97	82
UK vegetarian	No information	66.7	8.69	10.80	80

(a): Shaded rows refer to the 10 population groups selected for modelling cumulative exposure

*Note 2 (Contribution of animal commodities to the pesticide residues intake)*

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. Although no direct comparison of chronic dietary intake of pesticide residues from plant and animal commodities is available, the results of the short-term risk assessments conducted by EFSA for pesticide/crop combinations covered by the 2014, 2015 and 2016 EUCP clearly show much higher acute exposures resulting from the consumption of plant commodities (EFSA, 2016a, 2017a, 2018a).

Over this 3-year cycle, during which liver of ruminants, swine and poultry, poultry meat, butter, chicken eggs, swine meat and cow's milk were part of the EUCP, only chlordane (in poultry meat, swine meat and cow's milk), heptachlor (in poultry meat and swine meat), dieldrin (in butter and cow's milk) and deltamethrin (in cow's milk) were found at level exceeding 1% of the ARfD. Heptachlor and chlordane were present at levels corresponding to 10–25 % of the ARfD, but these assessments were conducted with the ADI used as a surrogate of the ARfD.

**CAG-NAN:** None of the active substance mentioned above are included in the CAG for brain and/or erythrocyte AChE inhibition.

**CAG-NAM:** From the active substances mentioned above, heptachlor, dieldrin and deltamethrin are included in the CAG for functional alterations of the motor division. The review of MRLs for deltamethrin has also demonstrated that residues in feed are likely to migrate to the commodities of animal origin (EFSA, 2015b). Furthermore, CAG-NAM includes fipronil. For this compound, previous assessments of EFSA have demonstrated that residues in food of animal origin are potentially important contributors to the overall exposure (EFSA, 2012). Nevertheless, a detailed examination of the occurrence data used for the cumulative exposure assessment indicated that, in practice, animal commodities were minor contributors to the intake of deltamethrin and fipronil in the reference period.

*Note 3 (Contribution of the selected 30 commodities to the overall intake of pesticide residues):*

Based on the occurrence data collected under the 2016 EUCP on pesticide residues, long-term exposures to residues of individual pesticides were calculated deterministically with the PRIMo model using either the full diet or only the food products (31 food products) covered by the 3-year cycle of the EUCP (2014, 2015 and 2016 monitoring years). These calculations used samples taken by 'surveillance' sampling strategies only and were performed for all the substances included in the 2016 EUCP programme and for which an ADI was available (162 active substances). They were done with two alternative assumptions for samples at the LOQ (upper and lower bound approaches). In the upper bound approach, a level equal to the LOQ was assumed for samples reported below the LOQ, if at least one sample of the respective substance/commodity combination had quantifiable residues. In contrast, when all samples of a substance/commodity combination were reported to be below the LOQ, the contribution of this combination to the total dietary intake was considered as being nil. In the

lower- bound approach, the assumption was that residues in samples reported to be below the LOQ were in all cases true zeros.

The calculations were conducted with EFSA PRIMo model for all populations included in the model and the results for the population with the highest intake can be found in Table B.4.

**Table B.4:** Calculated contributions of the EUCP 31 commodities to total long-term exposure

Active substance	Total Long-term exposure (% of ADI)		Long-term exposure EUCP 31 commodities <sup>(a)</sup> (% of ADI)		Contribution of EUCP 31 commodities to total long-term exposure (%)	
	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound
2-phenylphenol	0.30	0.22	0.29	0.21	97	98
Abamectin (RD)	3.6	0.016	3.4	0.012	95	75
Acephate	0.22	0.011	0.21	0.007	95	64
Acetamiprid (RD)	1.2	0.31	1.0	0.24	87	76
Acrinathrin	2.6	0.17	2.6	0.17	98	100
Azinphos-methyl	0.15	0.000	0.15	0.000	100	100
Azoxystrobin	0.23	0.057	0.21	0.052	90	91
Bifenthrin	1.8	0.07	1.7	0.069	95	99
Biphenyl	0.03	0.015	0.02	0.000	69	1
Bitertanol	1.7	0.05	1.7	0.05	100	100
Boscalid (RD)	1.7	0.98	1.5	0.83	87	84
Bromopropylate	0.52	0.001	0.51	0.001	98	100
Bupirimate	0.40	0.017	0.39	0.017	97	100
Buprofezin	2.8	0.2	2.7	0.19	95	95
Captan (RD)	0.85	0.69	0.80	0.66	94	95
Carbaryl	2.7	0.003	2.6	0.002	98	72
Carbendazim (RD)	1.6	0.22	1.4	0.16	89	75
Carbofuran (RD)	27	1.1	26	0.017	95	2
Chlorantraniliprole	0.02	0.003	0.02	0.003	93	93
Chlordane (RD)	34	0.066	34	0.055	99	84
Chlorfenapyr	0.68	0.029	0.61	0.010	91	34
Chlormequat	2.4	2.0	1.9	1.5	78	75
Chlorothalonil (RD)	2.4	0.19	2.3	0.12	94	65
Chlorpropham (RD)	3.7	3.3	3.6	3.3	99	100
Chlorpyrifos	46	12	42	11	91	90
Chlorpyrifos-methyl	3.6	0.77	3.5	0.70	95	91
Clofentezine (RD)	0.98	0.009	0.95	0.009	97	98
Clothianidin	0.27	0.002	0.26	0.002	97	83
Cyfluthrin	9.4	0.049	9.1	0.037	97	76
Cymoxanil	0.38	0.002	0.38	0.002	99	100
Cypermethrin	1.4	0.18	1.3	0.15	94	81
Cyproconazole	0.59	0.004	0.56	0.003	94	75
Cyprodinil (RD)	1.7	0.69	1.5	0.68	91	99
DDT (RD)	9.5	0.073	9.3	0.036	99	49
Deltamethrin	7.1	1.0	6.8	0.46	96	45
Diazinon	22	0.90	21	0.14	94	15
Dichlorvos	145	2.8	145	2.8	100	100
Dicloran	1.5	0.61	0.26	0.004	17	1
Dicofol (RD)	2.9	0.006	2.9	0.006	99	100
Dieldrin (RD)	518	1.6	509	0.55	98	35



Active substance	Total Long-term exposure (% of ADI)		Long-term exposure EUCP 31 commodities <sup>(a)</sup> (% of ADI)		Contribution of EUCP 31 commodities to total long-term exposure (%)	
	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound
Diethofencarb	0.01	0.000	0.01	0.000	100	100
Difenoconazole	3.3	0.36	2.9	0.18	88	49
Diflubenzuron (RD)	0.18	0.006	0.17	0.005	94	89
Dimethoate (RD) – dimethoate assumption	33	2.0	30	1.6	93	82
Dimethoate (RD) – omethoate assumption	101	6.1	94	4.9	93	82
Dimethomorph	0.66	0.16	0.61	0.15	93	98
Diniconazole	0.15	0.000	0.15	0.000	100	100
Diphenylamine	0.29	0.038	0.28	0.038	99	99
Dithianon	4.7	2.6	4.6	2.6	97	97
Dithiocarbamates (RD) – mancozeb assumption	11	2.7	10	2.2	93	81
Dithiocarbamates (RD) – maneb assumption	10	2.6	9.7	2.1	93	81
Dithiocarbamates (RD) – metiram assumption	73	18	67	14	93	81
Dithiocarbamates (RD) – propineb assumption	76	19	71	15	93	81
Dithiocarbamates (RD) – thiram assumption	30	7.5	28	6.0	93	81
Dithiocarbamates (RD) – ziram assumption	101	25	94	20	93	81
Dodine	0.25	0.10	0.23	0.099	93	98
Endosulfan (RD)	0.90	0.007	0.80	0.001	89	11
Epoxiconazole	1.3	0.022	1.3	0.021	99	99
Ethephon	3.0	0.58	2.9	0.39	95	68
Ethion	0.81	0.010	0.72	0.010	88	98
Ethirimol	0.46	0.006	0.45	0.006	97	97
Etofenprox	0.96	0.17	0.87	0.15	91	88
Famoxadone	1.5	0.051	1.3	0.050	91	98
Fenamiphos (RD)	6.6	0.073	5.3	0.012	80	16
Fenarimol	0.48	0.000	0.47	0.000	98	88
Fenazaquin	4.0	0.015	3.9	0.013	97	87
Fenbuconazole	3.8	0.078	3.6	0.031	94	40
Fenbutatin oxide	0.36	0.046	0.30	0.035	84	76
Fenhexamid	0.25	0.21	0.24	0.20	97	97
Fenitrothion	3.4	0.006	3.4	0.006	100	98
Fenoxycarb	0.33	0.004	0.31	0.004	94	100
Fenpropathrin	0.71	0.007	0.70	0.002	99	23
Fenpropidin (RD)	0.48	0.004	0.48	0.004	100	100
Fenpropimorph (RD)	3.0	0.10	3.0	0.10	99	97
Fenpyroximate	2.2	0.036	2.1	0.030	95	85
Fenthion (RD)	0.06	0.000	0	0	0	0
Fenvalerate (RD)	1.4	0.013	1.3	0.011	93	82
Fipronil (RD)	45	0.23	43	0.11	96	50

Active substance	Total Long-term exposure (% of ADI)		Long-term exposure EUCP 31 commodities <sup>(a)</sup> (% of ADI)		Contribution of EUCP 31 commodities to total long-term exposure (%)	
	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound
Fludioxonil (RD)	0.35	0.30	0.18	0.098	50	33
Flufenoxuron	0.40	0.001	0.40	0.001	100	100
Fluopyram (RD)	2.1	0.65	1.8	0.51	88	79
Fluquinconazole	11	0.018	11	0.018	100	100
Flusilazole (RD)	1.6	0.012	1.0	0.012	65	98
Flutriafol	2.5	0.016	2.3	0.011	94	67
Folpet (RD)	0.95	0.69	0.94	0.69	98	100
Formetanate	1.4	0.044	1.4	0.044	100	100
Fosthiazate	3.8	0.043	3.6	0.043	97	100
Glyphosate	0.33	0.14	0.32	0.035	100	25
Heptachlor (RD)	8.5	0.021	0	0	0	0
Hexaconazole	1.8	0.043	1.7	0.043	94	100
Hexythiazox	0.85	0.021	0.80	0.020	93	93
Imazalil	17	16	16	15	94	94
Imidacloprid	0.65	0.057	0.58	0.047	89	82
Indoxacarb	4.2	0.26	3.9	0.23	92	90
Iprodione (RD)	3.5	1.5	3.2	1.3	89	87
Iprovalicarb	0.54	0.18	0.51	0.18	93	100
Kresoxim-methyl (RD)	0.05	0.001	0.05	0.001	98	80
Lambda-cyhalothrin (RD)	11	0.72	9.9	0.61	91	84
Lindane	4.4	0.003	4.4	0.003	100	100
Linuron	1.7	0.26	1.6	0.19	91	74
Lufenuron	1.4	0.005	1.3	0.004	99	70
Malathion (RD)	0.80	0.012	0.78	0.011	97	95
Mandipropamid	0.08	0.015	0.08	0.012	92	80
Mepanipyrim	0.32	0.041	0.32	0.041	99	100
Mepiquat	0.17	0.050	0.16	0.047	98	95
Metalaxyl	0.22	0.031	0.19	0.031	86	97
Methamidophos	4.9	0.089	4.7	0.042	96	47
Methidathion	19	0.066	18	0.062	98	94
Methiocarb (RD)	0.48	0.029	0.41	0.007	85	24
Methomyl (RD)	1.3	0.262	0.88	0.014	70	5
Methoxychlor	0.02	0.000	0	0	0	0
Methoxyfenozide	0.23	0.025	0.22	0.0248	94	98
Monocrotophos	1.7	0.033	1.7	0.033	99	100
Myclobutanil (RD)	1.4	0.13	1.2	0.12	92	94
Oxadixyl	0.07	0.000	0.06	0.000	87	44
Oxamyl	4.3	0.40	4.3	0.006	100	1
Oxydemeton-methyl (RD)	0.09	0.000	0	0	0	0
Paclobutrazol	0.59	0.005	0.58	0.005	98	100
Parathion	1.7	0.002	1.7	0.001	100	70
Penconazole	0.63	0.021	0.60	0.021	95	100
Pencycuron	0.04	0.004	0.04	0.002	98	42
Pendimethalin	0.23	0.002	0.22	0.002	95	100
Permethrin	0.49	0.01	0.46	0.010	93	95

Active substance	Total Long-term exposure (% of ADI)		Long-term exposure EUCP 31 commodities <sup>(a)</sup> (% of ADI)		Contribution of EUCP 31 commodities to total long-term exposure (%)	
	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound
Phosmet (RD)	2.9	0.24	2.7	0.24	95	97
Pirimicarb (RD)	0.64	0.10	0.59	0.095	92	93
Pirimiphos-methyl	17	13	15	11	87	91
Procymidone (RD)	3.4	0.014	3.0	0.008	88	56
Profenofos	0.25	0.038	0.23	0.004	91	10
Propamocarb (RD)	0.19	0.13	0.18	0.13	97	98
Propargite	0.84	0.016	0.77	0.013	92	79
Propiconazole	1.2	0.59	1.1	0.54	93	91
Propyzamide (RD)	0.04	0.002	0.03	0.002	67	100
Pymetrozine (RD)	0.25	0.015	0.19	0.015	77	100
Pyraclostrobin	1.0	0.31	0.93	0.27	89	88
Pyridaben	2.3	0.045	2.2	0.026	95	58
Pyrimethanil (RD)	1.1	0.92	1.0	0.89	96	97
Pyriproxyfen	0.23	0.013	0.22	0.011	94	87
Quinoxifen	0.08	0.008	0.07	0.002	93	24
Spinosad	0.93	0.11	0.84	0.11	91	97
Spirodiclofen	1.4	0.14	1.3	0.14	94	98
Spiromesifen	0.64	0.047	0.62	0.044	97	95
Spiroxamine (RD)	0.68	0.043	0.65	0.043	95	100
tau-Fluvalinate	5.1	0.039	4.7	0.034	93	87
Tebuconazole (RD)	1.4	0.23	1.2	0.14	88	63
Tebufenozide	1.2	0.074	1.1	0.074	93	100
Tebufenpyrad	2.7	0.065	2.6	0.057	94	87
Teflubenzuron	2.0	0.006	2.0	0.006	99	100
Tefluthrin	0.69	0.018	0.61	0.008	89	46
Terbuthylazine	2.5	0.007	2.5	0.006	100	96
Tetraconazole	6.7	0.14	6.5	0.13	96	96
Tetradifon	0.33	0.000	0.33	0.000	98	77
Thiabendazole (RD)	1.9	1.8	1.6	1.3	81	73
Thiacloprid	2.6	0.40	2.3	0.31	90	77
Thiamethoxam (RD)	1.1	0.032	1.0	0.021	94	64
Thiophanate-methyl (RD)	0.46	0.024	0.42	0.017	91	71
Tolclofos-methyl	0.13	0.002	0.12	0.002	93	100
Tolyfluanid (RD)	0.01	0.000	0.01	0.000	79	69
Triadimenol (RD)	0.66	0.073	0.57	0.007	87	9
Triazophos	2.3	0.34	2.0	0.34	89	100
Trifloxystrobin (RD)	0.28	0.045	0.25	0.040	91	88
Triflumuron	1.1	0.032	1.1	0.022	96	69
Vinclozolin	0.13	0.014	0.11	0.000	90	1

(a): Apples, aubergines (egg plants), bananas, bean (with pods), bovine liver, broccoli, carrots, chicken eggs, cucumbers, head cabbages, leeks, lettuce, mandarins, olives for oil production, oranges, peaches, pears, peas (without pods), peppers, potatoes, poultry meat, rice, rye, spinach, strawberries, swine meat, milk, table grapes, tomatoes, wheat, wine grapes.

This table shows that, in the lower bound approach, the contribution of commodities covered by the 3-year cycle EUCP exceeds 80% of the total intake of about 65% of the active substances and is below 20% of the total intake of 9% of active substances. The median value for the contribution of commodities covered by the 3-year cycle EUCP is 88.3%. In the cases where the contribution of commodities of the EUCP is low, the overall exposure to the respective active substance is also very low (around or below 1% of their ADI).

Regarding CAG-NAN, the contribution of the RPCs under the EUCP to the total exposure ranges from 81 to 100% for all five active substances identified as risk drivers. Therefore, for the risk drivers, no major additional contribution is expected from the excluded RPCs. On the other hand, active substances for which minor commodities (not covered by the EUCP) contribute to at least 50% of the total long-term intakes include eight substances included in the CAG on AChE inhibition (oxamyl, carbofuran, methomyl, profenofos, diazinon, fenamiphos, methiocarb and methamidophos). In the most critical cases (contribution of minor commodities to more than 80% of the total long-term intake), the most important part of the dietary exposure results from residues present in the food group of herbs (e.g. thyme, basil, water cress). In view of the high toxicity of the eight active substances mentioned above, especially carbofuran, it was considered, based on the actual findings, whether coincidence of very high residue levels in these commodities with very high consumption could result in acute intakes of concern. The probability of these cases was concluded to be very low, and not to impact significantly the MOET at 99.9th percentile of exposure.

Regarding CAG-NAM, the contribution to the total exposure of the RPCs under the EUCP ranges from 75 to 100% for six out of the seven active substances identified as risk drivers. In case of deltamethrin, a significant contribution (about 55%) from excluded RPCs is observed, mainly due to maize.

In the upper bound approach, the contribution of foods covered the 3-year cycle EUCP programme exceeds 80% of the total intake of 92% of the active substances and is below 20% of the total intake for 3% of active substances.

The list of the 31 food products covered by the 3-year cycle of the EUCP used for the above calculations is not the same as the list of commodities used in the cumulative exposure assessments, but the similarity is sufficient to ensure a reasonable insight into the degree of underestimation of the cumulative risk resulting from the excluded commodities. Indeed:

- The cumulative exposure assessments reported in EFSA (2019b) included the contribution of four additional food products of plant origin: courgettes, melons, cauliflower and oats. The inclusion of these four commodities in the calculations presented in Table B.4 would tend to increase the percentages given in the last two columns.
- In contrast, they did not include animal commodities while the EUCP programme included five animal commodities (bovine liver, poultry meat, eggs, milk and swine meat). The exclusion of these five commodities from the calculations presented in Table B.4 would tend to decrease the percentages given in the last two columns. However, this decrease would be in practice limited because, despite the high consumption of animal commodities by EU consumers, the occurrence rate and levels of pesticide residues in animal commodities are much lower than in plant commodities. Out of the 173 pesticide residues covered by the EUCP, the number of pesticides detected at or above the LOQ in at least one sample of each of the animal matrices were: eggs, 12 pesticides; milk, none; poultry meat, 6 pesticides; bovine liver, 8 pesticides; and swine meat, 7 pesticides. Generally, the contribution of these five animal commodities to the total chronic exposure is very marginal. Residues found in animal commodities are essentially chlorinated, obsolete pesticides (DDT, dieldrin, endosulfan, lindane, chlordane, heptachlor hexachlorocyclohexane (alpha and beta) and hexachlorobenzene) and pyrethroids used as veterinary drugs (i.e. antiparasitic agents).

*Note 4 (Ambiguity of consumption and occurrence data)*

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 Standard Sample Description (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 2014, 2015 and 2016, a mechanism to differentiate commodities listed in part B of Annex I from the leading

commodity 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 based on the same level of aggregation of RPCs as for occurrence data. The practical consequence of this is that probabilistic modelling will combine indiscriminately occurrence and consumption data for the different commodities of this group, although the residue profiles and consumption level may differ between these commodities.

The proportion of occurrence data that are allocated to one of the 30 RPCs in the scope of this CRA, but which are in fact different commodities, is expected to be low (less than 5%, based on rough estimation), but precise information about the exact cases and proportions is not available.

In chronic exposure assessment, as both the occurrence and consumption data are averaged, this source of uncertainty is not expected to have a significant effect. In acute exposure assessments, this may lead to overestimated intakes of pesticide residues in the upper part of the distribution.

*Note 5 (Quality check of consumption data)*

Food consumption data provided to EFSA are subject to a validation process upon reception (EFSA, 2011). First, the food classification is compared to the food descriptions 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 6 (Impact of psychological factors in consumption surveys)*

There is not enough information substantiating the impact of psychological factors in collection of food consumption data (e.g. tendency to under-report unhealthy food and to over-report healthy food etc.) to draw reliable conclusions.

*Note 7 (Population size and sampling variability – Consumption and occurrence data)*

With respect to consumption data, the number of subjects in the 10 populations used to perform CRA ranges from 322 (NL, toddlers, 2 years old) to 10419 (Germany, adults). 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 ( $\alpha$ ) 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.

With respect to occurrence data, the number of data (measurements) for each pesticide/commodity combination in the scope of the conducted CRAs varies widely, from zero to several thousands.

Therefore, cases where occurrence data for authorised substance/commodity combinations were poor were identified:

- Pesticide/commodity combinations for which no data is available and for which no extrapolation is possible are addressed in *Note 10*.
- Pesticide/commodity combinations with less than 10 occurrence data in the original data set and for which extrapolation of other occurrence data was not possible included glufosinate/wine grapes and penflufen/peas without pods. These two combinations concern CAG-NAM only and represent less than 0.2 % of the total number of authorised combinations concerned by the exposure assessments conducted for this CAG.
- Pesticide/commodity combinations with less than 10 occurrence data in the original data set and for which extrapolations were possible are addressed in *note 14*.

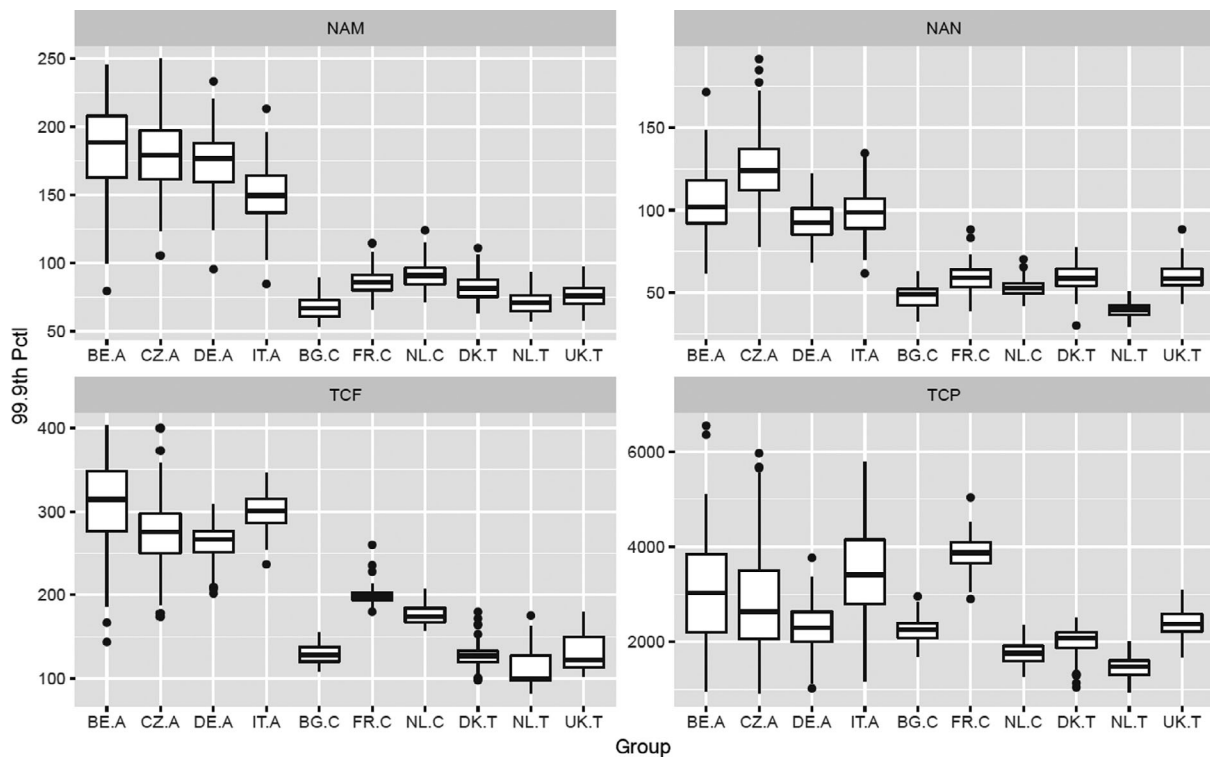
The overall sampling variability associated with consumption and occurrence data was quantified by outer loop execution and the resulting confidence intervals can be found in Sections 2.2.2.1 and 2.2.2.2. However, it is acknowledged that bootstrapping performs less well for small data sets (EFSA Scientific Committee, 2018b, annex B.11), especially when the focus is on the tail of the variability distribution as is the case here (99.9th percentile). Therefore, to address the additional uncertainty associated with the use of the bootstrap method, given the sample sizes involved in the exposure



assessment, model outputs for different populations were compared to look for any indication of influence of sample size on the estimates obtained. It was noted that:

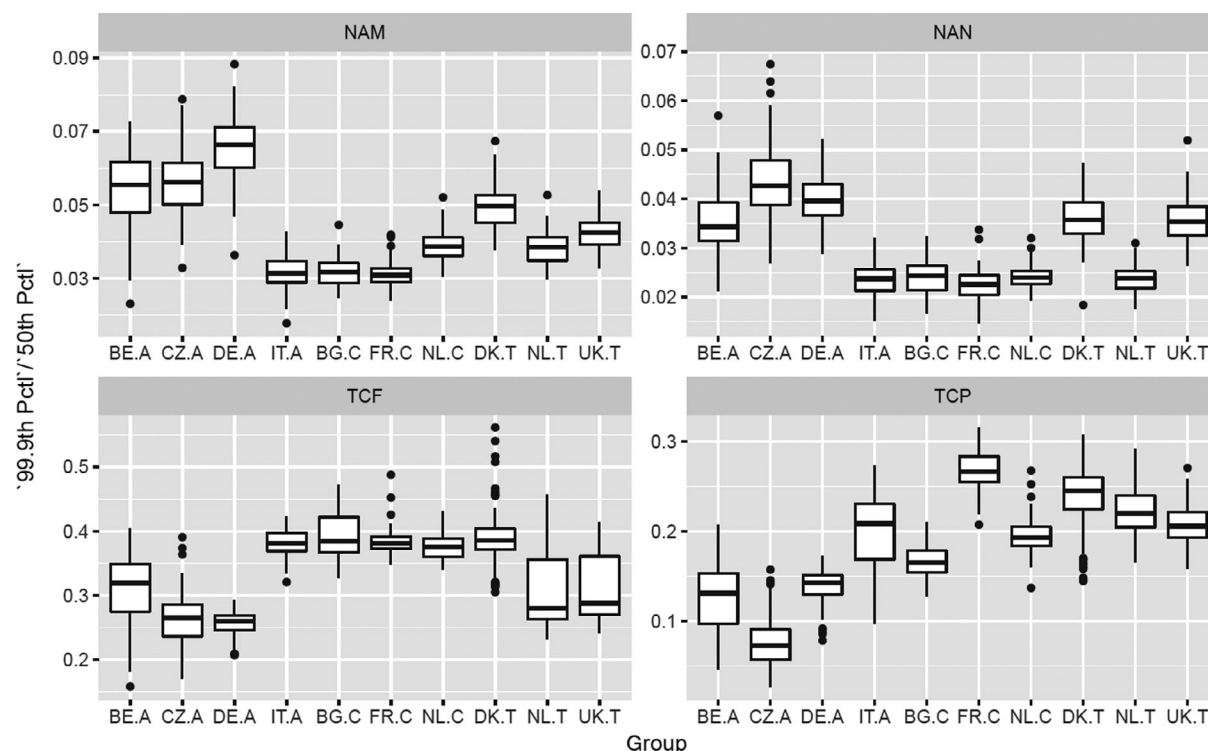
- Boxplots of 99.9th percentiles from MCRA bootstrap samples for the different consumer groups show no sign of instability for the groups having smaller numbers of participants in consumption surveys (Figure B.1).
- Boxplots of the ratio of the 99.9th percentile to the 50th percentile from MCRA bootstrap samples for the different consumer groups also show no sign of instability for the groups having smaller numbers of participants in consumption surveys (Figure B.2).

Overall, this supports the results from the probabilistic models showing estimates of different percentiles which indicate that estimating the 99.9th percentile is not particularly problematic but that estimating the 99.99th percentile is often problematic, giving very similar outcomes as for the 99.9th percentile. The interesting question is why this should be, given the expectation that bootstrapping would perform less well for the smaller consumption surveys. It may indicate that occurrence data are a much bigger driver of uncertainty than consumption data. However, it may also be driven by the fact that for a sample of just 700 values, the median value of the percentile corresponding to the sample maximum is the 99.9th percentile. Even with only 300 values, the median percentile corresponding to the maximum of the sample is the 99.7th percentile.



**Figure B.1:** Boxplots of 99.9th percentiles from MCRA bootstrap samples for the different consumer groups. NAM, NAN, TCF and TCP refer to CAG-NAM, CAG-NAN, CAG-TCF and CAG-TCP,<sup>20</sup> respectively

<sup>20</sup> CAG-TCF and CAG-TCP are CAGs related to chronic effects on the thyroid and used for a CRA reported in a separate scientific report.



**Figure B.2:** Boxplots of the ratio of the 99.9th percentile to the 50th percentile from MCRA bootstrap samples for the different consumer groups. NAM, NAN, TCF and TCP refer to CAG-NAM, CAG-NAN, CAG-TCF and CAG-TCP, respectively

*Note 8 (Representativeness of consumption data)*

Biases can arise from a survey sample that does not represent the population group at national level. The EFSA guidance on the use of the comprehensive European food consumption database gives information about the sampling strategy in dietary surveys (EFSA, 2011) for six of the 10 populations used in the present report (Table B.5).

**Table B.5:** Sampling information for six dietary surveys included in the EFSA Comprehensive European food consumption database

Country and Name of the dietary survey (Acronym)	Sampling method	Stratification variable (Yes/No)			% record according to the day of the week		% of record according to the season			
		gender	age	region	weekday	weekend	spring	summer	autumn	winter
BE, Diet National 2004	Random from national population register	yes	yes	yes	76	24	26	25	27	23
BG, NUTRICHILD	Random from register of general practitioner's practices	yes	yes	Yes	54	46	60	40	0	0
CZ, SISP04	Random from the address register	yes	yes	Yes	74	26	34	23	12	31

Country and Name of the dietary survey (Acronym)	Sampling method	Stratification variable (Yes/No)			% record according to the day of the week		% of record according to the season			
		gender	age	region	weekday	weekend	spring	summer	autumn	winter
FR, INCA2	Random from the general population census	yes	yes	yes	71	29	20	17	24	39
DE, NATIONAL NUTRITION SURVEY II	Random from national population register	yes	yes	yes	75	25	2	27	40	13
IT, INRAN SCAI 2005-06	Random from the telephone book	no	no	yes	78	22	26	24	25	25

Another factor affecting the representativeness of consumption data is the temporal gap between the period of the surveys and the reference period of the assessment (2014–2016). Depending on the survey, the consumption data used in this CRA were collected from 2001 to 2007. Possible changes in food consumption practices over a period of 10 years needed 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.<sup>21</sup>

Over this period of 5 years, the consumption of cereal products and vegetables was rather stable, while a slight increase of the fruit consumption, including nuts and olives were noted. Decrease in the consumption of potatoes, milk products and meat products was also noted. These observations are supported by the observation of a positive trend in daily fruit and vegetable consumption between 2002 and 2010 by adolescents in 33 countries (Vereecken et al., 2015).

#### Note 9 (RPC model)

In order to perform cumulative exposure assessments, the new EFSA RPC model (EFSA, 2019d) was used to convert the consumption data for composite foods and RPC derivatives into the equivalent quantities of RPCs.

The main sources of uncertainty of the RPC model result from the following:

- 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, 2015c). 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.
- The assignment of foods and food components using probabilities 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 we are using only major commodities, the

<sup>21</sup> <https://www.waetnederland.nl/resultaten/voedingsmiddelen/verandering>

exclusion or rare food components results in possible overestimation of the consumption/exposure related to the 30 commodities leading to lower MOET than they should be.

- The probability table and the disaggregation table do not incorporate 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 data.
- As there is currently no harmonised list of reverse yield factors available on either an EU or worldwide level, 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 will 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.

Populations with the highest consumption of RPC derivatives and composite foods are the most sensitive to this source of uncertainty. The identification of these populations was not conducted for reasons of resources.

#### *Note 10 (Missing occurrence data)*

Based on the original occurrence data set (without bootstrapping), the following authorised pesticide/commodity combinations did not have any occurrence data:

- Ethephon: olives for oil production (CAG-NAN and CAG-NAM).
- Glufosinate: olives for oil production (CAG-NAM).
- Penflufen: olives for oil production and rice (CAG-NAM).

For these combinations, it was not possible to extrapolate occurrence data from any other commodities. Therefore, their contribution to the cumulative risk has not been accounted for. This represents less than 0.5% of the total number of authorised combinations concerned by the cumulative exposure assessments, both in case of CAG-NAN and CAG-NAM.

#### *Note 11 (Contribution of metabolites)*

The residue definition for monitoring is not always suitable for risk assessment. It is estimated that in 30–40% of cases, the residue definition for risk assessment includes more compounds than the residue definition for monitoring. When this is the case and when enough data are available, a conversion factor is determined to translate residues expressed following the residue definition for monitoring into its counterpart for risk assessment. In the present exercise, the occurrence data were used without any correction for reason of resources, and because the existing residue definition for RA established with respect to the critical effect (e.g. leading to the ADI) are not necessarily valid for the specific effect related to the CAG.

CAG-NAN: Assuming that the residue definition for risk assessment established with respect to the critical effect would also be valid for brain and/or erythrocyte AChE inhibition, the residue definition for risk assessment of the identified risk drivers is the same as the residue definition for monitoring in two cases (formetanate and omethoate). In one case (chlorpyrifos), the residue definition for risk assessment includes additional components. In the last two cases (triazophos and dichlorvos), information on the residue definition for risk assessment is not available (See Table B.1).

CAG-NAM: Assuming that the residue definition for risk assessment established with respect to the critical effect would also be valid for the functional effects on the motor division, the residue definition for risk assessment of the identified risk drivers is the same as the residue definition for monitoring in four cases. In two cases (acrinathrin, deltamethrin), the residue definition for risk assessment includes additional components. In the last case (triazophos), information on the residue definition for risk assessment is not available (See Table B.2).

#### *Note 12 (laboratory analytical uncertainty)*

The guidance on the use of the EFSA SSD (EFSA, 2014b) provides official laboratories in MSs 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 have to always analyse and quantify the residue according to the harmonised EU residue definition which is available from the pesticide legislation in Annexes II and III

of Regulation (EC) No 396/2005, even for those residues for which an unspecific residue definition applies. In reporting the results, and for the sake of comparability of data, the analytical uncertainty shall not be taken into account, but can be reported as a separated information under a dedicated field of the reporting model.

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, 2017a). 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 13 (sampling strategy and representativeness of occurrence data)*

Various sampling strategies are used by MSs (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, 2014b). To perform the CRAs reported in the present document, EFSA and RIVM used samples collected under the official monitoring programmes of MSs for years 2014, 2105 and 2016 and coded following sampling strategies ST10A or ST20A. The sampling strategies corresponding to these codes are defined as follows:

- 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. Information about the sampling strategy at MS level can be found in the EFSA technical reports compiling the yearly national summary reports of MSs (EFSA, 2016b, 2017b, 2018c).

Although a representative sampling of occurrence data includes lots of commodities pertaining to various distribution channels (e.g. products for local consumption, bioproducts...) and a representative survey of consumption data includes consumers adhering to the respective distribution channels, occurrence and consumption data are randomly associated by the model, losing therefore existing relationships. This was considered and it was concluded that this has a very minor impact at overall population level, especially at the percentile of interest of the cumulative exposure distribution.

*Note 14 (extrapolation of occurrence data between crops)*

Crop to crop extrapolation of occurrence data was conducted between specific pairs of commodities as foreseen in guidance document SANCO 7525/VI/95 (European Commission, 2017b), for cases where the last application of the pesticide takes place after forming of the edible part of the crop when the number of occurrence data for the 'minor' commodity was less than 10. The conditions for extrapolation were supposed to be met when the MRLs were the same for the two crops and when the use of the pesticide was authorised on both crops.

Based on the original occurrence data set, no occurrence data were extrapolated from one commodity to another to conduct the cumulative exposure assessments for CAG-NAN. For CAG-NAM occurrence data were extrapolated for penflufen in aubergines (from tomatoes) and in cauliflower (from broccoli). This represents less than 0.2 % of the total number of authorised combinations concerned by the exposure assessments conducted for CAG-NAM.

*Note 15 (Pooling of occurrence data from all EU MSs)*

Occurrence data from all countries were pooled into one single data set that was used to calculate the cumulative risk for the 10 populations. This was done to increase the statistical robustness of the outcomes. This leads, however, to losing the country specificity of the residue concentration in commodities.

It should be noted that samples analysed and reported in a national monitoring programme are not only taken from lots intended for the internal market (local produce or imported commodities), 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. This would require reporting specific information and/or applying specific data extraction.

*Note 16 (Imputation of missing measurements)*

In many samples, the occurrence levels of certain active substances are missing, 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 active/substance combinations. Only empirical data were imputed. All details of the implementing procedure are given in appendix D of EFSA (2019b).

Table A.1.10 of the EFSA report on cumulative exposure assessments give the total number of samples available for each commodity and the number of these samples which were analysed for each pesticide. This provides the reader with an insight into the proportion of missing values.

**CAG-NAN:** In a first cumulative exposure assessment performed with unfinalised CAGs (van Klaveren, 2017), a sensitivity analysis conducted in tier I showed that imputing all missing values by real zeros resulted in increases of the MOET by 12–40%. In a second sensitivity analysis, imputing missing values at random resulted in increases of the MOET not exceeding 17%.

**CAG-NAM:** Similar sensitivity analyses (van Klaveren, 2017) showed that imputing all missing values by real zeros resulted in increases of the MOET by 37–90%, and that imputing missing values at random resulted in increases of the MOET not exceeding 27%.

*Note 17 (Unspecific residue definitions for monitoring)*

In tier II, in the absence of information related to the use frequency of pesticides, occurrence data for unspecific residue definition for monitoring were randomly allocated 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 Appendix A of EFSA (2019b).

The residue definitions for monitoring concerning the active substances included in CAG-NAN and CAG-NAM are given annexes A.1.03 and A.2.03, respectively, of EFSA (2019b).

**CAG-NAN:** The unspecific residue definitions which include at least one active substance included in CAG-NAN are the following:

- Carbofuran (sum of carbofuran (including any carbofuran generated from carbosulfan, benfuracarb or furathiocarb) and 3-OH carbofuran expressed as carbofuran)
- Dimethoate (sum of dimethoate and omethoate expressed as dimethoate)
- Methomyl and Thiodicarb (sum of methomyl and thiodicarb expressed as methomyl)

This source of uncertainty is relevant for one risk driver:

- omethoate (apples, wine grapes): There is no authorised use assumed for dimethoate or omethoate in apples and wine grapes. Therefore, in case of samples with residues exceeding the LOQ, the assumption has been that either dimethoate or omethoate was applied, with equal probability (0.5/0.5). When dimethoate was assumed to have been applied, the sample was considered as containing dimethoate and omethoate in a 50/50 ratio, because dimethoate is metabolised into omethoate. When omethoate was assumed to have been applied, the sample was considered as containing omethoate only. The impact of this is expected to be moderate as this combination is not a strong risk driver.

In a first cumulative exposure assessment performed with unfinalised CAGs (van Klaveren, 2017), sensitivity analyses conducted in Tier 1 showed no significant change to the MOET (maximum increase was 7%) between worst-case (all occurrence data allocated to the most potent authorised substance) and best-case (all occurrence data allocated to the less potent authorised substance) assumptions for the residue definition.

**CAG-NAM:** The unspecific residue definitions which include at least one active substance included in CAG-NAM are the following:

- Carbofuran (sum of carbofuran (including any carbofuran generated from carbosulfan, benfuracarb or furathiocarb) and 3-OH carbofuran expressed as carbofuran).
- Cyfluthrin (cyfluthrin including other mixtures of constituent isomers (sum of isomers)).

- Cypermethrin (cypermethrin including other mixtures of constituent isomers (sum of isomers)).
- Dimethoate (sum of dimethoate and omethoate expressed as dimethoate).
- Dithiocarbamates (dithiocarbamates expressed as CS<sub>2</sub>, including maneb, mancozeb, metiram, propineb, thiram and ziram).
- Fenvalerate (any ratio of constituent isomers (RR, SS, RS & SR) including esfenvalerate or Fenvalerate (sum of fenvalerate (any ratio of constituent isomers including esfenvalerate) and CPIA (chlorophenyl isovaleric acid), expressed as fenvalerate).
- Methomyl and Thiodicarb (sum of methomyl and thiodicarb expressed as methomyl).
- Triadimefon and triadimenol (sum of triadimefon and triadimenol).

This source of uncertainty is relevant for three risk driver:

- Omethoate (wine grapes, olives for oil production): There is no authorised use assumed for dimethoate or omethoate in wine grapes. Therefore, when positive residues were observed, suggesting a misuse, the assumption has been that either dimethoate or omethoate was applied, with equal probability (0.5/0.5). When dimethoate was assumed to have been applied, the sample was considered as containing dimethoate and omethoate in a 50/50 ratio, because dimethoate is metabolised into omethoate. When omethoate was assumed to have been applied, the sample was considered as containing omethoate only. In contrast, in olives for oil production, there is an authorised use for dimethoate. In all samples of olives, it was therefore considered that only dimethoate was used and the two substances were present in 50/50 ratio.
- Beta-cypermethrin (wheat). Four substances falling under this residue definition (cypermethrin, alpha-cypermethrin, beta-cypermethrin and zeta-cypermethrin) have authorised uses in wheat. Therefore, the occurrence data were randomly allocated to these substances, with a proportion of 25% per substance.
- Thiram (wine grapes and lettuce): In wine grapes, the following active substances are authorised: mancozeb, maneb, metiram, propineb, thiram, ziram. Therefore, the occurrence data were randomly allocated to these substances, with a proportion of 16.7% per substance. In lettuce, the following active substances are authorised: mancozeb, metiram, thiram. Therefore, the occurrence data were randomly allocated to these substances, with a proportion of 33.3% per substance.

The two most important risk drivers are not affected by this source of uncertainty.

In the first cumulative exposure assessment performed with unfinalised CAGs (van Klaveren, 2017), the sensitivity analysis conducted in Tier 1 showed increases of the MOET ranging from 35 to 90% between worst-case (all occurrence data allocated to the most potent authorised substance) and best-case (all occurrence data allocated to the less potent authorised substance) assumptions for the residue definition.

#### *Note 18 (Authorisation status of pesticide/commodity combinations)*

In the absence of country-specific information on authorised used of pesticides, it was assumed that an authorisation exists in all EU countries for an active substance/commodity combination when a use has been reported to EFSA in the context of article 12 and subsequent article 10 reasoned opinions. For active substances not reviewed yet under article 12, an authorised use was assumed in commodities for which the MRL in place on 31 December 2016 was above the LOQ (See Sections 2.3.1 and 2.3.2 of EFSA (2019b)). This source of uncertainty is only affecting the treatment of occurrence data below the LOQ, i.e. the decision to consider or not a residue present at a level equal to 1/2 LOQ.

The consequence might be an overestimation of the risk when an authorisation for an active substance/commodity combination exists in certain MSs, but not in all MSs.

The consequence might also be an underestimation of the risk when the assumption of the authorisation status is based on the MRL in place because authorised uses are not necessarily resulting in MRLs above the LOQ. The relevance of this source of uncertainty is however depending on the toxicological potency of the active substance: if a child with a body weight of 20 kg consumes within one day 200 g of a commodity containing 0.01 mg/kg (common LOQ level) of a substance with a NOAEL of 0.1 mg/kg body weight (bw) per d, the MOE associated with the intake of this substance would still be 1000.

**CAG-NAN:** Six substances have an NOAELs for brain and/or AChE inhibition below 0.1 mg/kg bw per d: triazophos, azinphos-ethyl, carbofuran, aldicarb, pyrazophos, ethion (sorted from smallest to largest NOAEL). However, none of them is approved in the EU.

**CAG-NAM:** The CAG for functional alterations of the motor division of the nervous system does not contain any substance with NOAELs below 0.1 mg/kg bw per d. Three substances have, however, an NOAEL of 0.1 mg/kg bw per d: aldicarb, oxamyl and triazophos. However, none of them is approved in the EU.

*Note 19 (Use frequency of pesticides)*

Statistics on the use frequency of pesticides in crops are not available to EFSA.

Therefore, the proportion of the samples of a commodity which might have been treated, and for which residues might be present below the LOQ, needs to rely entirely on assumptions. The European Commission and MSs have defined the assumptions to be made in tiers I and II of probabilistic modelling (European Commission, 2018). All details of the implementing procedure are given in appendix C of EFSA (2019b).

This source of uncertainty has been subject to sensitivity analyses in the EFSA report on cumulative dietary exposure assessment of pesticides that have acute effects on the nervous system using SAS<sup>®</sup> software (EFSA, 2019b), which are briefly summarised in Section 2.2.2.3.

*Note 20 (Drinking water)*

EFSA does not have access to monitoring data on pesticides in drinking water. Therefore, assumptions were used, which are based on Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption. This regulation sets an MRL of 0.1 µg/L to each individual pesticide, and of 0.5 µg/L to the sum of all individual pesticides detected and quantified. In tier I, it was assumed that the five most potent pesticides of the CAG were at a level of 0.1 µg/L. This corresponds to the worst exposure possible complying with the legal provisions. In tier II, it was assumed that the five most potent pesticides of the CAG were at 50% of the allowed level (0.05 µg/L).

In a first cumulative exposure assessment performed with unfinalised CAGs (van Klaveren, 2017), sensitivity analyses were conducted in Tier I and did not show any significant difference between worst- (residues of the five most potent substances of the CAG present at 0.1 µg/L) and best-case (no residue present in drinking water) assumptions for drinking water.

*Note 21 (Missing information about the effect of processing)*

When consumption data are reported for the raw agricultural commodity, information on the type of processing that was applied prior to consumption is not always available and therefore remains unknown to EFSA. This is particularly true for household processes such as peeling and washing. Furthermore, even when that information is available, processing factors are not available for all active substances and all possible types of industrial or household processing. Hence, in the absence of processing factors or information on the processing type, it was assumed in the model that all residues in the raw commodity are transferred to the processed commodity and will reach the end consumer.

This source of uncertainty was subject to sensitivity analyses in EFSA (2019b), which are briefly summarised in Section 2.2.2.3. In average, assuming that residues will not be present in any processed food when a processing factor is not available increased the MOET at 99.9th percentile of the exposure by factors of ranging from 1.6 to 2.5 and from 1.9 to 3.5 for CAG-NAN and CAG-NAM, respectively. In practice the actual transfer to processed commodities will result from many factors and properties of the active substance, including their capacity of being absorbed and translocated in plants, hydrolysis stability, solubility in water, partition coefficient. . .

Information regarding the availability of processing factors for risk drivers, as well as about their properties, is available in Section B.1.

Although not related to the effect of processing, it is known that residue levels decline between the market distribution and the time of consumption. The impact of this decline is an overestimation of the risk, which was considered and estimated to be minor compared to the effect of missing information on the effect of processing and to the effect of washing and peeling (note 24). 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. 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 much less efficient than industrial or household processing with hydrolysis conditions involving heating or simple physical treatments such as fractionation of commodities, peeling or washing. Collecting factual

information on this source of uncertainty would be cumbersome, due to the complexity of this phenomenon, its substance specificity and the multiple influencing factors.

*Note 22 (Use of processing factors under the EFSA food classification and description system)*

The new database of processing techniques and processing factors compatible with the EFSA food classification and description system FoodEx 2 (Scholz, 2018) defines how the information from regulatory processing studies can be used within the EFSA food classification and description system, and the inherent limitations. The accompanying report describes the underlying methodological approach and rationales.<sup>22</sup>

*Note 23 (Accuracy of processing factors)*

Processing factors are calculated as the ratio between the residue concentrations in the processed commodity and in the RPC. A new database has been produced (Scholz, 2018). When residues in the processed commodity are below the LOQ, the calculation assumes as worst case that the actual residue concentration in the processed commodity is equal to the LOQ and in this case the calculated processing factor represents a maximum value. When residues in the raw commodity are below the LOQ, the calculation assumes as best-case scenario that the actual residue concentration in the raw commodity is equal to the LOQ and in this case the calculated processing factor represents a minimum values. In such case, the processing factor was not considered reliable in the processing factor database and therefore not considered in the calculations.

The new database<sup>23</sup> of processing factors (Scholz, 2018) identifies these cases by using '<' and '>' signs.

This source of uncertainty has a limited impact because the overall amount of processing factors used in the exposure calculations, especially regarding risk drivers is low.

*Note 24 (Use of a fixed value of processing factors)*

Only one value of processing factor 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, 2018; Information on the number of independent trials performed to determine processing factors and individual results can be found in Scholz, 2018.

*Note 25 (Effect of washing and peeling of commodities)*

The effects of peeling and washing on pesticide residue levels for fruits and vegetables with edible peel and which are consumed raw is not normally considered in deterministic risk assessments because the default worst-case assumption used is that these commodities may also be consumed unwashed including the peel. Consequently, the available processing factors for peeling and washing of commodities with edible peel are not included in the standard regulatory data set of processing factors (Scholz, 2018). In the absence of these processing factors, it was assumed in all cases that all residues in the raw commodity are transferred to the commodity as eaten, even if it is washed or peeled. This assumption leads to an overestimation of the levels of pesticide residue in the exposure assessment. For fruits and vegetables which are mainly consumed cooked, the effect of washing is covered by the available processing factors for cooking techniques.

For CAG-NAN, an important fraction of the risk drivers relate to apples, table grapes and sweet peppers which might in theory be sensitive to this source of uncertainty. For CAG-NAM, the impact of this source of uncertainty is expected to be less important given the nature of the risk drivers.

Information on the effects of washing of fruits and vegetables on pesticide active substance residue levels from published literature was combined and quantified 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 generalised conclusion can 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 recently 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

<sup>22</sup> <http://www.efsa.europa.eu/en/supporting/pub/en-1509>

<sup>23</sup> <https://efsa.onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2018.EN-1510>

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 mode of action in terms of whether an active substance is systemic or non-systemic (contact) was one of several factors used to explain the differences in processing factors for various household processing conditions, including washing and peeling, for various pesticide/commodity combinations.

The effect of peeling and washing on residue levels is not normally reported in EFSA Conclusions or EFSA Article 12 MRL Reviews. However, this information is sometimes available as supplementary information in the EU evaluation DRARs and in JMPR evaluations. For the active substance/commodity combinations identified as risk drivers for CAG-NAN and CAG-NAM, these sources were consulted to retrieve reported processing factors for peeling and washing for commodities with edible peel which are consumed raw. The findings are summarised in Tables B.6 and B.7, which also includes information available in published literature. The processing factors for peeling and washing are not considered for active substances where the mode of action is reported to be systemic.

**Table B.6:** Processing factors for peeling and washing commodities with edible peel consumed raw for active substance/commodity combinations identified as risk drivers for CAG-NAN

Active substance	Risk driver commodities with edible peel consumed raw	Processing factors washing	Processing factors peeling
Chlorpyrifos	apples	<u>DRAR Spain, 2017</u> Processing studies on apples: no data available for washing  <u>JMPR Evaluation 2000</u> Processing studies on apples: no data available for washing  <u>Published literature review</u> Apples, washing: 17–21 % residue dissipation (Chung, 2018)	<u>DRAR Spain, 2017</u> Processing studies on apples: no data available for peeling  <u>JMPR Evaluation 2000</u> Apple, distribution in peel and flesh: indicative information from metabolism study. Spray application, 14 day post-harvest interval (PHI), radiolabel found at 0.8 mg e.q./kg in peel and 0.005 mg e.q./kg in flesh. Indicative transfer factor: 0.006 (apple, flesh)
	peaches	<u>DRAR Spain, 2017</u> Processing studies on peaches: no data available for washing  <u>JMPR Evaluation 2000</u> No data available  <u>Published literature review</u> Peach, soaking: 16–17% residue dissipation), nectarines, washing soak 3 min then spray for 15 s: 26–32% residue dissipation) (Chung, 2018)	Not relevant
	table grapes	<u>DRAR Spain, 2017</u> Processing studies on table grapes: no data available for washing  <u>JMPR Evaluation 2000</u> No data available	Not relevant



Active substance	Risk driver commodities with edible peel consumed raw	Processing factors washing	Processing factors peeling
Formetanate	table grapes	Not considered where the mode of action is reported to be systemic	Not considered where the mode of action is reported to be systemic
Triazophos	sweet peppers/ bell peppers	<u>EU Evaluation</u> No data available. Not assessed at EU level, not Approved under Reg. (EC) 1107/2009. <u>JMPR Evaluation 2007, 2010</u> No data available	Not relevant

**Table B.7:** Processing factors for peeling and washing commodities with edible peel consumed raw for active substance/commodity combinations identified as risk drivers for CAG-NAM

Active substance	Risk driver commodities with edible peel consumed raw	Processing Factors washing	Processing factors peeling
Thiram	lettuce	<u>DRAR France, 2015</u> No data available <u>JMPR Evaluation 1996</u> No data available	Not relevant
Triazophos	sweet peppers/bell peppers	<u>EU Evaluation</u> No data available. Not assessed at EU level, not Approved under Reg. (EC) 1107/2009 <u>JMPR Evaluation 2007, 2010</u> No data available	Not relevant

Based on this search, specific information relevant to the pesticide/commodity combinations identified as risk drivers were found only for chlorpyrifos in peach (soaking, 16–17% residue dissipation), nectarines (washing soak 3 min then spray for 15 s, 26–32% residue dissipation) and apples (washing, 17–21% residue dissipation) (Chung, 2018).

Information on the occurrence of peeling and washing prior to consumption of commodities with edible peel which are consumed raw is not available to EFSA.

*Note 26 (Uncertainty associated to the unit-to-unit variability of residues)*

A fixed value (and not a distribution) has been used for the variability factor. In tier II, this value is 3.6, the average estimate of observed variability factors in market samples concluded by the PPR panel (EFSA PPR Panel, 2005). The EFSA 2005 opinion does not give credible intervals or confidence intervals for the average of 3.6. The median was reported as 3.4 with a 95% credible interval of 3.1–3.7. This credible interval reflects the uncertainty in estimating the variability factors in the data sets available to the Panel and the sampling variability in estimating the distribution of the 'true' variability factors between data sets. It does not take into account the additional contribution of six other sources of uncertainty.

Note that, despite the fixed value of the variability factor, varying residue levels are simulated for each commodity unit, by multiplying the sample mean residue by a stochastic factor sampled from a beta distribution the width of which is governed by the variability factor of 3.6. This distribution is bounded following the assumption that the simulated unit concentration cannot be higher than the concentration in the composite sample multiplied by the number of unit in the composite sample.

CAG-NAN: In a first cumulative exposure assessment performed with unfinalised CAGs (van Klaveren, 2017), a sensitivity analysis was conducted in tier 1 and showed that ignoring unit to unit variability increases the MOET by 5–45% for the CAG on AChE inhibition.

CAG-NAM: Similar sensitivity analyses were conducted and showed that ignoring unit to unit variability increases the MOET by 5–25% for the CAG on functional alterations of the motor division of the nervous system.

*Note 27 (Active substances missing from the CAGs)*

If the CAG does not contain active substances contributing to the risk, the outcome of the risk assessment might be underestimated.

Four hundred and twenty-two active substances were under the scope of the initial data collection (EFSA, 2019a). These substances were all substances approved until 31 May 2013 and additional non-approved substances present in the EU consumer's diet as evidenced in the 2011 annual report on the Rapid Alert System for Food and Feed (European Commission, 2011) and/or the 2010 annual report on pesticide residues in food (EFSA, 2013). However, from one year to the other, different non-approved may be found by EU control laboratories. It is therefore likely that substances affecting the nervous system, but not in CAG-NAN or CAG-NAM, were present in food.

From 2014 to 2016, several non-approved organophosphorus, N-methyl carbamate, pyrethroid and neonicotinid insecticides, not included in the list of 422 substances, were indeed present at quantifiable levels in samples of some commodities. This is shown in Table B.8.

**Table B.8:** Non-approved pesticides from chemical classes N-methylcarbamate, organophosphate, organothiophosphate, pyrethroid and neonicotinoid present in food, based on the 2014, 2015 and 2016 European Union report on pesticide residues in food

Active substance	Chemical class	Toxicological information (EU Pesticides database)			Year of detection	Number of analytical determinations	Quantification rate (% results > LOQ)	Levels detected on commodities (mg/kg) <sup>(a)</sup>
		ADI	ARfD	Source				
Allethrin	Pyrethroid	–	–	–	2014	11,939	0.01	Cocoa beans (0.017)
					2016	9,994	0.02	Cocoa beans (0.012), Pears (0.019)
Aspon	Organothiophosphate	–	–	–	2015	5,975	0.03	Lettuces (0.006)
Bendiocarb	N-methylcarbamate	0.004	–	JMPR 1984	2014	21,749	0.03	Fungi, mosses and lichens (0.07), Teas (0.011, 0.012, 0.017, 0.056, 0.09)
					2015	23,012	< 0.01	Cultivated fungi (0.015)
Bioallethrin	Pyrethroid	–	–	–	2016	2,928	0.03	Oranges (0.011)
Bromophos	Organothiophosphate	0.04	–	JMPR 1977	2014	40,665	< 0.01	Herbs and edible flowers (0.012)
Bromophos-ethyl	Organothiophosphate	0.003	–	JMPR 1975	2014	52,627	< 0.01	Courgettes (0.011)
					2016	50,501	< 0.01	Head cabbages (0.010)
Chlorthiophos	Organothiophosphate	0.0002	–	AUS 1978	2014	13,808	0.01	Peaches (0.015)
Coumaphos	Organothiophosphate	–	–	–	2014	25,218	0.03	Honey (0.014, 0.015, 0.019, 0.02, 0.021, 0.025, 0.041, <b>5.8</b> )
					2015	28,393	0.01	Honey (0.011, 0.015)
					2016	35,164	0.01	Honey and other apicultural products (0.011, 0.021), Lemons (0.014)
Cyphenothrin	Pyrethroid	–	–	–	2016	3,874	0.03	Cassava roots (0.028)
Dichlofenthion	Organothiophosphate	–	–	–	2014	20,994	0.04	Basil and edible flowers (0.014, 0.015), Chervil (0.017), Chinese cabbages/pe-tsai (0.013), Kales (0.018, 0.019), Parsley (0.018), Roman rocket/rucola (0.01), Spinaches (0.027)
Dicrotophos	Organophosphate	–	–	–	2014	47,958	< 0.01	Bananas (0.01), Teas (0.038)
					2015	49,719	< 0.01	Herbs and edible flowers, not specified (0.002)
Fenchlorphos	Organothiophosphate	–	–	–	2016	21,565	< 0.01	Rosemary (0.007)

Active substance	Chemical class	Toxicological information (EU Pesticides database)			Year of detection	Number of analytical determinations	Quantification rate (% results > LOQ)	Levels detected on commodities (mg/kg) <sup>(a)</sup>
		ADI	ARfD	Source				
Fenobucarb	N-methylcarbamate	–	–	–	2014	14,094	0.09	Beans (with pods) (0.011), Celery leaves (0.02, 0.047, <b>0.3</b> , <b>0.34</b> , <b>1.4</b> ), Oranges (0.018), Rice (0.001, 0.003), Teas (0.012, 0.016)
					2015	14,529	0.01	Teas (0.019, 0.057)
					2016	16,617	0.07	Mulberries (0.012), Sweet peppers (0.036), Tomatoes (0.012, 0.024, 0.027, 0.029, 0.035, 0.041, 0.044, 0.052, 0.068)
Fensulfothion	Organothiophosphate	–	–	–	2015	25,474	0.01	Wine grapes (0.047)
Flucythrinate	Pyrethroid	0.02	–	JMPR 1985	2016	26,019	0.01	Peas (with pods) (0.012), Table grapes (0.005)
					2015	33,682	0.01	Herbs and edible flowers, not specified (0.01), Spring onions (0.01)
Iprobenfos	Organophosphate (phosphorothioate)	–	–	–	2014	10,539	0.02	Celery leaves (0.037), Teas (0.013)
					2015	12,654	0.01	Cumin seed (0.044)
Isocarbophos	Organothiophosphate (phosphoramidothioate)	–	–	–	2014	42,863	0.01	Teas (0.025, 0.03, 0.05, 0.055), Wild fungi (0.039)
					2015	52,166	0.01	Grapefruits (0.051, 0.053), Small fruit and berries, not specified (0.015), Teas (0.023, 0.063), Wild fungi (0.001)
					2016	54,450	0.01	Grapefruits (0.021, <b>0.280</b> ), Tomatoes (0.011, 0.017, 0.019, 0.062)
Isofenphos-methyl	Organothiophosphate (phosphoramidothioate)	–	–	–	2014	55,391	0.01	Pumpkin seeds (0.007, 0.076), Teas (0.359)
					2015	58,730	< 0.01	Pumpkin seeds (0.042)
					2016	58,320	< 0.01	Oilseeds (0.016)
Isoprocarb	N-methylcarbamate	–	–	–	2014	40,335	< 0.01	Pumpkin seeds (0.015), Teas (0.009)
					2015	45,824	< 0.01	Teas (0.01, 0.065)
					2016	49,642	0.01	Grapefruits ( <b>0.120</b> ), Teas (0.009, 0.039)

Active substance	Chemical class	Toxicological information (EU Pesticides database)			Year of detection	Number of analytical determinations	Quantification rate (% results > LOQ)	Levels detected on commodities (mg/kg) <sup>(a)</sup>
		ADI	ARfD	Source				
Mecarbam	Organothiophosphate	0.002	–	JMPR 1986	2014	49,834	< 0.01	Bananas (0.028), Pears (0.018)
					2015	52,082	0.01	Broccoli (0.032), Grapefruits (0.031), Head cabbages (0.015), Pears (0.04), Tarragon (0.02)
					2016	50,855	< 0.01	Tarragon (0.013)
Methacrifos	Organothiophosphate	0.006	–	JMPR 1990	2015	42,233	< 0.01	Plums (0.015)
					2016	41,333	0.01	Sea weeds (0.005, 0.017), Sweet peppers (0.017)
Metolcarb	N-methylcarbamate	–	–	–	2014	11,606	0.01	Teas ( <b>0.15</b> )
Mevinphos	Organophosphate	–	–	–	2014	53,827	< 0.01	Celery leaves (0.01)
Nitenpyram	Neonicotinoid	–	–	–	2016	49,489	< 0.01	Prickly pears (0.007), Table grapes (0.036)
Phenothrin	Pyrethroid	0.07	–	JMPR 1988	2014	9,165	0.03	Beans (with pods) (0.047, 0.068), Oranges (0.014)
					2015	10,837	0.01	Wheat (0.014)
Phorate	Organothiophosphate	0.0007	0.003	JMPR 2005	2014	40,941	0.03	Coriander seed (0.041), Cumin seed (0.039, 0.05), Pumpkin seeds (0.078), Turmeric/curcuma (0.007, 0.008, 0.013, 0.073, 0.094, <b>0.13</b> ), Wild fungi ( <b>1.4</b> )
					2015	42,257	0.01	Bay leave (0.076), Cumin seed (0.04, <b>0.12</b> ), Escaroles ( <b>0.4</b> ), Pumpkin seeds (0.052), Spices, not specified (0.034)
					2016	36,387	0.01	Cumin seed (0.037), Ginger (0.005), Pears (0.015), Turmeric/curcuma ( <b>0.120, 0.470</b> )
Phosphamidon	Organophosphate	0.0005	–	JMPR 1986	2015	46,231	< 0.01	Peaches (0.017)
					2016	45,198	< 0.01	Lemons (0.012)
Promecarb	N-methylcarbamate	–	–	–	2014	32,443	< 0.01	Cucumbers (0.01)
					2016	36,292	0.01	Lettuces (0.020), Oranges (0.005), Potatoes (0.010)



Active substance	Chemical class	Toxicological information (EU Pesticides database)			Year of detection	Number of analytical determinations	Quantification rate (% results > LOQ)	Levels detected on commodities (mg/kg) <sup>(a)</sup>
		ADI	ARfD	Source				
Propoxur	N-methylcarbamate	0.02	–	JMPR 1989	2014	52,550	0.04	Aubergines/eggplants (0.02), Common millet/proso millet (0.063), Cultivated fungi (0.04), Kales (0.013), Peanuts/groundnuts (0.018), Teas (0.01, 0.034, 0.063), Turmeric/curcuma (0.056), Wild fungi (0.01, 0.026, 0.032, <b>0.13, 0.15, 0.16, 0.19, 0.194, 0.69</b> )
					2015	56,540	0.02	Beans (dry) (0.01, 0.011, 0.06, 0.08, 0.09, <b>0.12</b> ), Cauliflowers (0.09), Celery leaves (0.014), Herbal infusions, not specified (0.022, 0.023), Pulses (dry), not specified (0.014), Rice (0.014, 0.019)
					2016	56,224	0.02	Beans (dry) (0.002, 0.020, 0.021, 0.040, 0.050, 0.070, 0.071, <b>0.160</b> ), Okra (0.010), Rye (0.012), Wild fungi (0.028, 0.058, <b>0.210</b> )
Prothiofos	Organothiophosphate	–	–	–	2014	58,484	0.01	Mangoes ( <b>0.16</b> ), Oranges (0.029), Plums (0.005)
					2015	58,376	0.01	Aubergines (0.01), Herbs and edible flowers, not specified (0.05), Pears (0.001), Plums (0.001), Sweet peppers (0.086)
					2016	58,658	0.01	Bay leave ( <b>0.150</b> ), Celery leaves (0.026, <b>12.200</b> ), Papayas (0.015)
Quinalphos	Organothiophosphate	–	–	–	2014	55,683	0.02	Grapefruits (0.012, 0.044), Head cabbages (0.018), Other fresh herbs and edible flowers ( <b>0.198</b> ), Rice (0.013), Table grapes (0.003, 0.012, 0.02, 0.056, <b>0.173</b> ), Teas (0.025, 0.047, <b>0.11</b> )
					2015	57,928	0.02	Beans (with pods) (0.031), Cardamom ( <b>1.1</b> ), Ginger ( <b>0.51</b> ), Grape leaves and similar species (0.013), Grapefruits (0.007, 0.009), Lemons (0.038), Peas (without pods) (0.008), Teas (0.01, 0.011, 0.035, <b>0.144</b> )

Active substance	Chemical class	Toxicological information (EU Pesticides database)			Year of detection	Number of analytical determinations	Quantification rate (% results > LOQ)	Levels detected on commodities (mg/kg) <sup>(a)</sup>
		ADI	ARfD	Source				
					2016	58,545	0.02	Basil and edible flowers (0.014), Celeries (0.011), Coriander seed (0.055), Ginger (0.085), Gooseberries (0.075), Grapefruits (0.006), Lychees (0.021, 0.040), Sweet peppers (0.012), Teas (0.015)
					2015	16,726	0.01	Lettuces (0.039), Rice (0.02)
					2016	18,414	0.01	Millet (0.015)
Sulfotep	Organothiophosphate	–	–	–	2014	38,879	< 0.01	Beans (with pods) (0.011)
					2015	41,359	< 0.01	Basil and edible flowers (0.0128, 0.013)
					2016	40,737	< 0.01	Herbs and edible flowers (0.015)
Terbufos	Organothiophosphate	–	–	–	2014	33,636	< 0.01	Wild fungi (0.06)

(a): Bold: levels exceeding 0.1 mg/kg.

As can be seen in the table, cases of positive occurrence concern essentially minor commodities and the frequency of positive occurrence is low in all cases. The measured levels are also generally low but exceed 1 mg/kg in some cases (coumaphos/honey, fenobucarb/celery leaves, phorate/wild fungi, prothiofos/celery leaves, quinalphos/cardamom). Overall, the contribution of these events to the risk is expected to be low, but toxicological reference values are missing for many of the substances concerned.

There is also some probability that active substances causing neurotoxicity might have not been identified during the data collection procedure (possibility that available repeated-dose toxicity studies do not capture/examine potential effects on motor division, possibility that information of relevance in original toxicological studies is omitted or misreported in summary documents used as source of information) or during the assessment of collected data.

Based on a check of the initial list of 422 active substances considered for the establishment of CAGs, it was indeed found that two active substances belonging to the chemical class of pyrethroids (etofenprox and resmethrin) were not included in CAG-NAM. Quantifiable of resmethrin were present in food samples at a rate of 0.01–0.02 % in 2014–2016. The quantification rate of etofenprox is much higher (around 1%), but its toxicity is very low. EFSA reported in 2009 acute neurotoxicity studies with no adverse effect or sign of neurotoxicity including functional and neuro-histopathological observations up to 2000 mg/kg bw.

*Note 28 (Active substances wrongly assigned to CAGs)*

If an active substance, not causing the effect, is included in the respective CAG, the cumulative exposure and risk will be overestimated.

For the CAG-NAN, the Scientific report on CAGs for the effects of pesticides on the nervous system concluded that the possibility of including substances not contributing to the risk was non-existent (EFSA, 2019a).

For the CAG-NAM, the same report includes the outcome of an EKE session concluding that the median estimate for the total number of active substances actually causing the effect, either acutely or chronically, was 104 out of a total of 119 active substances. It is, however, certain that six out of the seven risk drivers identified for the CAG-NAM are actually causing functional alterations of the motor division of the nervous system, because they have chemical structures and MoAs of direct relevance for functional alterations of the motor division. Only thiram has a presumed mode of neurotoxic action and is likely to very likely (66–95% probability) to cause the effect.

*Note 29 (Uncertainties regarding the NOAEL-setting)*

There are uncertainties affecting the characterisation of active substances included in the CAG. NOAELs can be either under- or overestimated.

The robustness of the establishment of the NOAELs in the successive steps of the data collection and assessment may be affected by several factors: initial dossier quality/completeness, variation in the interpretation or analysis of raw data by laboratories performing guideline studies and/or regulatory reviewers, transfer of information from the original toxicological studies to the source documents (DARs, JMPR evaluations), transfer of information from the source documents to the excel spreadsheets and principles and expert judgement used in the NOAEL-setting. These different phases of the process are described in the EFSA scientific report dealing with the establishment of CAGs for the nervous system.

With respect to CAG-NAN, the database is in general of moderate quality for the establishment of NOAELs for the brain and/or erythrocyte AChE inhibition. This is because many substances in the CAG are old substances, withdrawn since decades. In one case, an LOAEL was used to derive an NOAEL using an UF of 10 (thiodicarb). Additional points of specific attention include the fact that in about two-thirds of cases, the NOAEL was established on a study where the administration was via gavage or capsule, and that in about one-third of cases, the acute NOAEL for AChE inhibition was derived from repeated-dose studies (90-day, 1-year or 2-year studies). This is of importance for organophosphorus pesticides, because the average life span of circulating erythrocytes is about 120 days. This means that erythrocyte AChE targeted by these pesticides the first day of treatment will remain inhibited over the whole study period and chronic NOAELs might be significantly lower than NOAELs resulting from exposure to single doses.

With respect to CAG-NAM, the database is in general of moderate quality for the establishment of NOAELs for this effect. As for CAG-NAN, this is because many substances amongst AChE inhibitors in the CAG are old substances, withdrawn since decades. In three cases, an LOAEL was used to derive

an NOAEL using an UF of 10 (flufenacet, heptachlor, pymetrozine, but none of these substances emerged from the cumulative exposure assessment as a risk driver).

Effects on the motor division are comprised by a number of indicators that are of subjective nature (i.e., clinical observations), which may have not been characterised accurately either during the conduct of the regulatory study or the NOAEL setting process. For about 20% of substances included in the CAG, neurotoxicity studies were missing. This was the case of chlormequat, one of the risk drivers. In the absence of neurotoxicity studies, the NOAEL was established in most cases on the basis of indicators of functional alteration of the motor division observed in other repeated-dose toxicological studies. In a few cases, the NOAEL for AChE inhibition was used as surrogate value (triazophos).

Additional points of specific attention include the fact that a high proportion of the NOAELs were established based on an acute neurotoxicity study where the usual mode of administration is gavage, and that in a number of cases, the acute NOAELs were derived from repeated-dose studies (90-day, 1-year or 2-year studies). Specific information for risk drivers is collected in Section B.1.

Another significant weakness of scientific nature is the fact that the current practice consists in using NOAELs for the toxicological characterisation of pesticides. The NOAEL-setting is influenced by several factors including group size, between-animals variability (strains, sex), experimental errors and, importantly, dose spacing in toxicological studies. As this relies on one single point (i.e. a single experimental dose), when the doses are widely spaced in relation to the slope of the dose–response curve, important differences can be observed in the NOAEL across experiments with varying dose levels. In particular, for AChE inhibition, the critical adverse effect size has been defined by risk managers to be 20%. If the dose spacing in a study is large (e.g. 15- or 30-fold), the likelihood of the observed NOAEL being substantially lower than the actual dose that would cause a 20% AChE inhibition is considerable. Thus, the NOAEL in a study with large dose spacing is likely to be lower than the NOAEL in a similar study with small dose spacing. Accordingly, the modelled estimate of the MOET at 99.9th percentile of the exposure distribution is likely to be smaller if the NOAEL is derived from a study with large dose spacing.

Furthermore, as the NOAEL is a dose level where no statistically significant differences in response are observed compared with control group, it cannot be considered as a 'no adverse effect dose'. In the update of the guidance of the Scientific Committee on the use of the benchmark dose approach in risk assessment (EFSA Scientific Committee, 2017), it was found that the size of the estimated effect at NOAEL is, on average over a number of studies, close to 10% (quantal responses) or 5% (continuous responses). For this reason, the EFSA scientific Committee proposed, for animal studies, that a default BMR value of 5% (change in mean response) be used for continuous data and 10% (extra risk<sup>24</sup>) for quantal data when toxicological reference values are established by BMD modelling. This was considered to define the meaning of 'perfect information' in the EKE Q2 with respect to uncertainties relating to the hazard characterisation of substances included in CAG-NAM.

*Note 30 (Adequacy of the dose addition model)*

The rationale behind the use of dose addition 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).

Adequacy of the dose addition model as the default assumption was, amongst other aspect of CRA, recently investigated in the EuroMix collaborative EU research project. Although neurotoxicity was not addressed specifically, the results of a range of bioassays for steatosis, craniofacial malformations and endocrine-related effects were in agreement with the dose addition model. This applies to test mixtures containing substances eliciting the common adverse effect through both, similar and dissimilar modes of action. Confidence intervals of the dose–response curves for the mixtures overlapped with those of the single substances when all were scaled to the IC using relative potency factors. Confirmatory evidence was drawn from the comparison of relative potency factors calculated based on tests with the substance alone or in combination with the IC (Final (3rd) periodic Technical Report Part B, EuroMix Collaborative Project H2020-SFS-2014-2). As part of the EuroMix project, an Expert Panel Meeting was organised involving eight EU and four 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 characterization of chemicals of an established group or of those with

<sup>24</sup> Absolute change in frequency of response (additional risk in %) divided by the non-affected fraction in the control population (100 minus the background response in %).

sufficient similarity to that group also when there are differences in the molecular initiating events (MIEs) or some of the key events (KEs) in the respective AOPs of those substances (FAO/WHO, 2019).

Supra-additive (potentiation) effects on the nervous system have been reported for acetyl cholinesterase inhibiting insecticides and pyrethroid insecticides, but this is not expected to occur at dietary exposure levels (Hernández et al., 2013; and Hernández et al., 2017).

Moreover, based on drill-down information, the cumulative exposure of individuals exceeding the 99th percentile of the distribution is in the majority of cases dominated by one substances contributing in its own to at least 80% of that exposure. For CAG-NAN, analysis of the individual records above the 99th percentile of the exposure distribution revealed that, for toddlers and children, 75% of the extracted individual days were driven by single substance–commodity combinations, each contributing for more than 80% of the total exposure within that day. For CAG-NAM, the percentage of the extracted individual days driven by single substance–commodity combinations was 78%.

The CAG-NAN includes exclusively N-methyl carbamates and organophosphorus pesticides, two chemical classes of AChE inhibitors, but following different mechanisms at biochemical level (reversible or irreversible AChE inactivators). The risk drivers are mostly organophosphorus pesticides.

More than two-thirds of the substances included in CAG-NAM have known MoAs. Eleven MoAs have been directly associated with these effects. N-methyl carbamates, organophosphorus pesticides and pyrethroids are quantitatively the most represented chemical classes. Risk drivers are organophosphorus pesticides, pyrethroids, chlormequat and to a lesser extent thiram.

*Note 31 (Dose/response at the actual exposure levels)*

At low doses of exposure, around or below the NOAEL, there is uncertainty regarding the shape and the slope and the shape of the dose–response curve, particularly in poor quality studies from which the NOAEL is derived. The use of a limited number of animals, the inconsistent dose-spacing and the sensitivity of the test system contributes to increase the uncertainty at such low-dose levels. The lack of knowledge on the dose–response curve at doses around and below the NOAEL makes it uncertain to assess magnitude of the effect per unit change in dose, which can be larger or smaller than expected under the common assumption of proportionality.

On the other hand, the risk assessment model, using an MOET of 100 as the protection target, implies the assumption that the sensitive human is 100 times more susceptible to the effect than the tested animals. This implies that, for the sensitive human, the dose–response curve is shifted to the left by two orders of magnitude and that the tested doses would be similar to dietary exposure levels causing concern.

*Note 32 (Combination of consumption and occurrence data)*

One single substance concentration sampled from the occurrence data is used for all consumption events related to a same processing type taking place during the 24-hour period. This is considered the most realistic scenario, although consumption of commodity either raw or processed from a same lot is possible.

*Note 33 (Adequacy of the acute exposure calculation model)*

Short-term food consumption levels are calculated by summing up quantities of food commodities consumed over a period of 24 h. This is not reflecting the time course of AChE inhibition by organophosphorus and N-methyl carbamate insecticides.

OPs with a P=O moiety bind covalently to the serine residue in the active site of AChE, thus impeding the hydrolysis of the neurotransmitter acetylcholine. The phosphorylated enzyme then undergo the so-called 'ageing' process, which consist of the spontaneous loss of one of the two O,O-dialkyl groups of the phosphate moiety. When the phosphorylated AChE has aged, the enzyme is considered to be irreversibly inhibited, and only synthesis of new enzyme can restore the catalytic activity. Conversely, in case of N-methyl carbamates, AChE inhibition is transient and rapidly reversible, since there is rapid reactivation of the carbamylated enzyme, which does not undergo the ageing reaction. (Costa et al., 2008). Pyrethroids disrupt nerve function by altering the rapid kinetic transitions between conducting (open) and non-conducting (closed or inactivated) states of voltage-gated sodium channels that underlie the generation of nerve action potentials. This takes only milliseconds and the effect does not accumulate over time. It is known that pyrethroids are readily metabolised by cleavage of the ester bond, by which mechanism they are inactivated. Therefore, when exposure to pyrethroids occurs during several meals in a single day, the effects of the first exposure may have dissipated by the time the second exposure occurs.



For these reasons, the time frame of 24 h will tend to create an overestimation of the contribution of N-methyl carbamates and pyrethroids, and an underestimation of the contribution of organophosphorus compounds. As risk drivers are essentially organophosphorus compounds, this source of uncertainty tends to underestimate the actual risks in the case of CAG-NAN.