TECHNICAL REPORT

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Outcome of the public consultation on the draft scientific report on the cumulative dietary risk characterisation of pesticides that have acute effects on the nervous system

European Food Safety Authority (EFSA)

Abstract

The European Food Safety Authority (EFSA) carried out a public consultation to receive input from interested parties on its draft scientific report on the cumulative dietary risk characterisation of pesticides that have acute effects on the nervous system. The document describes the process and the outcome of a risk assessment and an uncertainty analysis regarding the cumulative effects of pesticide residues on acetylcholinesterase and the motor division of the nervous system. The web-based public consultation took place from 17 September to 15 November 2019. EFSA received comments from 17 parties including academia, national agencies, non-governmental organisations and private bodies. This report lists the individual comments received and explains in detail how they were taken into account during the finalisation process of the scientific report. EFSA wishes to thank all the commenters for their valuable contributions.

Key words: acetylcholinesterase inhibition, cumulative risk assessment, motor division, nervous system, pesticides, public consultation

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1. Introduction

Regulation (EC) No. 396/2005[1] on Maximum Residue Levels (MRLs) of pesticides in or on food and feed provides 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[2] concerning the placing of plant protection products on the market also provides 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 the Authority to assess such effects are available.

In this legal context, the Panel on Plant Protection Products and their Residues (PPR Panel) developed the necessary methodologies to carry out a cumulative risk assessment (CRA) of pesticide residues and EFSA started in 2014 a pilot phase to implement them for the assessment of the cumulative effects of pesticide residues on the nervous system and the thyroid.

1.1. Background and Terms of Reference

As part of this pilot phase, EFSA has prepared a scientific report on the cumulative risk characterisation of pesticides that have acute effects on the nervous system.

In line with EFSA's policy on openness and transparency, EFSA engages in public consultations on key issues to receive comments on its work from the scientific community and its stakeholders. Therefore, the Pesticide Residues Unit has been requested to proceed with a public written consultation on a draft of this report.

2. The public consultation

On 17 September 2019 EFSA launched the online public consultation to collect inputs from interested parties on the draft scientific report on the cumulative risk characterisation of pesticides that have acute effects on the nervous system. This draft was dealing with a retrospective risk assessment of cumulative dietary exposure to pesticide regarding acetylcholinesterase (AChE) inhibition and functional alterations of the motor division.

The instructions on how to submit the comments were available at the following link:

http://www.efsa.europa.eu/en/consultations/call/public-consultation-draft-efsa-scientific-reports

The consultation closed on 15 November 2019.

3. Screening and evaluation of comments received

In total, 95 comments were collected from one person and 16 organisations. A list of the parties submitting comments is provided in Table 1.

Table 1: Parties submitting comments on the draft scientific report

Public consultation respondent	Country
Centre National de Recherche Scientifique/Museum National d'Histoire Naturelle (CNRS)	FR
CHEM Trust	DE
Dutch Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL
European Crop Protection Association (ECPA)	BE
Experimental Toxicology Services Nederland BV (ETS)	NL
Fresh Produce Centre	NL
German Federal Institute for Risk Assessment (BfR)	DE
Health and Safety Executive	UK

[1] Regulation (EC) No. 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EECText with EEA relevance. OJ L 70, 16 March 2005, pp. 1–16.

[2] Regulation (EC) No. 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24 November 2009, pp. 1–50.

Istituto Superiore di Sanità – Department of Food Safety, Nutrition and Veterinary Public Health	IT
National Farmers' Union of England and Wales (NFU)	UK
Netherlands Food and Consumer Product Safety Authority (NVWA)	NL
Norwegian Scientific Committee for Food and Environment (VKM)	NO
Pest Management Regulatory Agency (PMRA, Health Canada)	CA
Pesticide Action Network Europe	BE
Private citizen[3]	BE
United States Environmental Protection Agency (US EPA) Office of Pesticide Programs	US
Wageningen University & Research	NL

All the comments received and the respective responses from EFSA were tabulated in Appendix A referring to their author(s) and the relevant section of the draft scientific report. References to sections, lines and annexes in the comments and answers to the comments refer to the draft scientific report as published at the time of the consultation.

4. Recurring comments

Upon analysis, some recurring comments were identified, and the detailed answers provided in Appendix A are summarised below:

a) Problem formulation

In section 1.1 of the draft scientific report, the precise questions addressed by the reported assessments were defined. However, from comments received, it appeared that the scope of the assessments was not adequately explained. To address this, section 1.1 was extended to make explicit what is not covered in the assessments, e.g. chronic effects, exposure by non-dietary route, chemicals other than pesticides, developmental neurotoxicity, neurodegenerative diseases. This should make the scope and limitations of the scientific report more transparent and give insight into the methodological developments that are still needed in the area of CRA of the effects of pesticides on the nervous system.

b) Cumulative assessment groups

Some comments on the EFSA grouping strategy submitted in the context of an earlier EFSA public consultation on the draft report on the establishment of cumulative assessment of pesticides for their effects on the nervous system were reiterated in the present public consultation.

The EFSA approach differs from the approach developed by the US EPA and the Canadian PMRA. The US EPA and Canadian PMRA are basing the grouping of substances on the similarity of mechanism of action. This is based in the USA on specific provisions of the Food Quality Protection Act (1996).

In contrast, the EFSA methodology is tailored to the EU pesticide legislation which calls for the possibility for risk managers to use the precautionary principle when there is scientific uncertainty and implies to address the combined effect of substances capable of causing a same effect by different mechanisms (independent or dissimilar action). Grouping substances on the basis of the similarity of mode/mechanism of action (MoA) only would not allow considering adequately risks of alteration of apical endpoints resulting from multiple mechanisms or pathways and would not reduce the possibility of underestimating adverse effects to a minimum.

The approaches used on the one hand by PMRA and US EPA, and on the other hand by EFSA, do not reflect actual scientific divergences, but rather fit to different jurisdictions and address different assessment questions. These considerations are repeated in the responses to the respective comments.

c) Clarity of the assessment

It is acknowledged that the reported assessments are complex and use methodologies that are not familiar yet [CRA itself, probabilistic modelling, uncertainty analysis and expert knowledge elicitation (EKE)]. Many comments reflected the wish of respondents to understand in detail the scientific process. These triggered changes and additions to the body text, tables, graphs and notes in appendix B of the scientific report (EFSA, 2020), increasing clarity and understandability.

[3] In accordance with the instructions on the submission of comments, those submitted by individuals in a personal capacity are presented anonymously.

d) Sources of uncertainty

Some respondents rightfully suggested sources of uncertainties that had not been identified (e.g. effect of bulking and blending of lots of commodities subject to industrial processing, variation in the interpretation or analysis of raw data by risk assessors). These additional sources of uncertainties were considered and discussed by the same experts who participated in the original assessments and changes and additions were made to the text, tables and graphs and to the notes in appendix B when appropriate. After careful consideration, the experts agreed that these changes did not alter their consensus judgements on the overall conclusions of the assessment, shown in Tables 13 and 14 of the scientific report (EFSA, 2020). Detailed responses to individual comments are provided in Appendix A.

e) Perception of biased assessment

As uncertainty analysis resulted in upwards adjustments to the total margin of exposure (MOET) calculated by modelling, three respondents suggested that the assessment of uncertainties was biased to produce more favourable results. It is true that the uncertainty analysis increased the median estimates of the MOET for all populations. However, it is not surprising that the adjustment is upwards, given that model assumptions specified by the Member States were intentionally conservative.

The adjustment of the MOET is not a biased process but a balanced judgement based on reasoned assessment by seven experts of the combined effect of all the identified uncertainties. Explicit steps to ensure the quality of the expert judgements and avoid bias are described in EFSA's procedures for the selection of experts, for eliciting the judgements, and complemented through conducting a public consultation on the draft report (for more detail, see the response to comment 73 in Appendix A).

f) Wording of conclusions

Seven respondents commented on the overall conclusion in the draft report, which was 'cumulative exposure to pesticides that have acute effects on the nervous system does not exceed the threshold for regulatory consideration'. One respondent agreed with this conclusion but commented that interpretation of the results and their risk management implications needs to be as transparent as possible. Five respondents suggested that the wording of the conclusion was too strong. One questioned whether (at least) 80% certainty that the MOET is not below the threshold for regulatory consideration (the result for Dutch toddlers) is sufficient and whether assessors and decision-makers have a shared opinion about the required level of certainty. In response to these comments, the overall conclusion in the final report has been revised to:

> '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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Abbreviations

AChE	acetylcholinesterase
ADI	acceptable daily intake
ALALA	as low as reasonably achievable
AOP	adverse outcome pathway
ARfD	acute reference dose
BMD	benchmark dose
BMDL	lower confidence limit of the benchmark dose
BMR	benchmark response
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
CCA	comparative cholinesterase assay
CNS	central nervous system
CRA	cumulative risk assessment
DAR	draft assessment report
DNT	developmental neurotoxicity
EKE	expert knowledge elicitation
GAP	good agricultural practice
GLP	good laboratory practice
IATA	integrated approach for testing and assessment
IC	index compound
JMPR	Joint Meeting on Pesticide Residues
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOQ	limit of quantification
MoA	mode/mechanism of action
MCRA	Monte Carlo risk assessment (software)
MOE	margin of exposure
MOET	combined (total) margin of exposure
MRL	maximum residue level
NMC	*N*-methyl carbamate (insecticide)
NOAEL	no observed adverse effect level
OP	organophosphorus (insecticide)
PF	processing factor
PMRA	Pest Management Regulatory Agency

PPR	EFSA Panel on Plant Protection Products and their Residues
RAR	Renewal Assessment Report
RPC	raw primary commodity
RIVM	Dutch National Institute for Public Health and the Environment
SAS®	Statistical Analysis System (software)
SC PAFF	Standing Committee on Plants, Animals, Food and Feed

Appendix A – Comments received during the public consultation on the draft scientific report on the cumulative dietary risk characterisation of pesticides that have acute effects on the nervous system and EFSA response

N.	Affiliation	Chapter	Comment	EFSA response
1	ETS Experimental Toxicology Services Nederland BV	1 Introduction	I have worked on neonicotinoid insecticides over the last 10 years and published a number of papers on their risk assessment and ecological properties. In essence, these compounds are so hazardous because their toxicity to arthropods is reinforced by exposure time. If ecological risk assessments continue to be based on acute toxicity tests there is a distinct possibility that the risks are seriously ec. In the case of neonicotinoids this is one of the main factors involved in massive insect decline.	This comment concerns environmental risk assessment and, therefore, is not applicable to the report under consideration.
2	CNRS/ Museum National d'Histoire Naturelle	1 Introduction	The basic premise is that pesticides are sorted into cumulative assessment groups (CAGs) on the basis of their toxicological characteristics. However, the sources used are the documents provided for approval of active substances, principally the draft assessment reports (DARs) and renewal assessment reports (RARs). However, by definition these reports do not contain the most sensitive tests for the target organs. The mere fact that Europe has commissioned four different research projects to improve testing on developmental neurotoxicity (ENDPOINTS) and on thyroid (three others) including notably ATHENA to address thyroid interactions on brain development, underlines the incomplete nature of the current draft and renewal assessments reports.	See response to comment 25 of this report and response to comment 4 of the technical report of the public consultation on the cumulative dietary risk characterisation of pesticides that have chronic effects on the thyroid for the acknowledged limitation of the assessment under consideration with respect to developmental neurotoxicity.
3	Norwegian Scientific Committee for Food and Environment (VKM)	1.1 Background and Terms of Reference	Line 218: Suggest mentioning the three additional effects on the nervous system in order for the reader to get an overview/better picture of the endpoints covered. The CRA is a mixture of adverse outcomes (alteration of motor function) and MoAs (AChE inhibition). What is the adverse outcome associated with AChE inhibition?	Two CRAs were conducted in the report under consideration, precisely fitting to the assessment questions given in section 1.1 (cumulative risk of AChE inhibition and of functional alteration of the motor division of the nervous system). With respect to AChE inhibition in particular, the assessment was conducted with respect to AChE inhibition solely, irrespectively of the possible apical adverse outcomes. This is in line with current practice of risk assessment for pesticides in the EU, where inhibition of red blood cell or brain AChE is frequently used to define the point of departure for reference value derivation.

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				Section 1.1 of the final report was updated to include a reference to the additional effects on the nervous system that are relevant in acute risk assessment (functional alterations of the sensory and autonomic divisions).
4	ETS Experimental Toxicology Services Nederland BV	1.1 Background and Terms of Reference	The dose–response characteristics of pesticides are determined by the nature of receptor binding. Only in cases of reversible receptor binding are effects determined by the exposure level only and can a threshold be determined. Slowly reversible or irreversible receptor binding leads to cumulative effects that also depend on exposure time. A threshold level cannot be defined.	The EFSA scientific report addressed cumulative exposure to pesticides that have acute effects on the nervous system (in this case, acute AChE inhibition). Decreased AChE activity can be achieved following single or sequential exposure to reversible or irreversible AChE inhibitors [e.g. *N*-methylcarbamates (NMC) and organophosphorus (OP) insecticides, respectively]. While AChE inhibition by NMC has a recovery half-life of a few hours due to spontaneous decarbamylation of the enzyme, restoration of OP-inhibited AChE largely depends on *de novo* synthesis of AChE as the phosphorylated enzyme is usually very slowly regenerated, or not at all, and remains inhibited. As stated in note 33 of the Scientific Report: 'short term food consumption levels are calculated by summing up quantities of food commodities consumed over a period of 24 hours. This is not reflecting the time-course of AChE inhibition by organophosphorus and N-methyl carbamate insecticides'. A 20% threshold of blood/brain AChE inhibition following exposure to anticholinesterase insecticides (OPs and NMCs) has been widely accepted for regulatory purposes to determine whether the decreased AChE activity is toxicologically significant. The WHO-FAO Joint Meeting of Experts on Pesticide Residues (JMPR) has given recommendations on interpretation of cholinesterase inhibition. In line with the WHO (1998, 2015), Solecki (2005), the Netherlands National Institute for Public Health and the Environment (RIVM) regards a statistically significant inhibition of AChE ≥ 20% in the central or peripheral nervous system and in erythrocytes as toxicologically relevant or 'adverse' (Luttik and Raaij, 2001). The inhibition of 20% may be considered with respect to the concurrent control group or with respect to the 'pre-exposure' values in the treated groups.

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5	Pest Management Regulatory Agency, Health Canada	1.1 Background and Terms of Reference	EFSA's CRAs included consideration of dietary exposure only. In Canada, CRAs take into consideration dietary exposures as well as all sources of non-occupational exposure. As such, residential exposures in addition to food and drinking water are considered in a cumulative assessment. The exclusion of other sources of exposure (residential) may underestimate actual exposure levels.	We recognise that the present EFSA assessments do not address the aggregated risks resulting from dietary and non-dietary routes of exposure, which are higher than dietary risks alone. They were conducted in the context of the Article 32 of Regulation (EC) No. 396/2005 on maximum residue levels of pesticides in food and feed. So, they address risks for the health of consumers resulting from pesticide residues only. This is precisely reflected in the assessment questions in section 1.1 of the scientific report. For clarity, this section was updated to make explicit that non-dietary exposure is not considered. With respect to non-dietary exposure, Regulation (EC) No. 1107 provides that: 'a plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use, shall have no immediate or delayed harmful effect on human health, including that of vulnerable groups, or animal health, directly or through drinking water (taking into account substances resulting from water treatment), food, feed or air, or consequences in the workplace or through other indirect effects, taking into account known cumulative and synergistic effects…'. EFSA is aware of the regulatory expectations regarding non-dietary routes of exposure and submitted to the Advisory Forum[4] a proposal for a high-level roadmap on Combined Exposure to Multiple Chemicals, including methodological development and integration of non-dietary routes of exposure into software tools used for the assessment of multiple chemicals.
6	The National Farmers' Union of England and Wales	1.1 Background and Terms of Reference	The NFU welcomes the work by EFSA to prepare a scientific report on the CRA of pesticides residues regarding two acute effects on the nervous system. It is right for a proper scientific approach to be taken to better understand actual risks around the cumulative impacts of dietary exposure to pesticide residues.	Thank you.

[4] http://www.efsa.europa.eu/sites/default/files/event/191127-minutes.pdf

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7	US EPA Office of Pesticide Programs	1.1 Background and Terms of Reference	Residential exposure was not taken into account for this CRA. The impact of such exposures, in addition to diet, should be considered for cumulative purposes, if there are pesticides in the Cumulative Assessment Groups (CAGs) that have residential uses in Europe. Otherwise, it would be informative to state up front that there are no residential uses for any of the chemicals assessed.	See response to comment 5.
8	ETS Experimental Toxicology Services Nederland BV	1.2 Input from Risk Managers and threshold for regulatory consideration	The dose–response characteristics are key to the assessment of cumulative effects. If the total dose required for an effect is much lower upon prolonged exposure compared to acute exposure this is pretty solid evidence of cumulative effects reinforced by exposure time. Consequently, there is no threshold.	The total dose of an OP required to produce a 20% AChE inhibition differs according to the individual OPs, the daily dose of exposure, and the duration of exposure. Consequently, there is no single threshold dose but a threshold effect instead (i.e. 20% AChE inhibition) and a dose causing this threshold effect depending on exposure characteristics. Besides, as *de novo* synthesis of AChE occurs very slowly in the brain, with a half-time (t½) of *c.* 12 days (Moss et al., 2017), irreversible inhibition of AChE can accumulate dose after dose, until reaching the threshold effect (20% AChE inhibition). Conversely, no observed adverse effect levels (NOAELs) have been identified for both acute and long-term exposure to different anticholinesterase insecticides (EFSA, 2019a). Although NOAELs are clearly lower in repeated dose toxicity studies with OPs than in acute studies for comparable experimental conditions, the total dose required for an effect not necessarily has to be much lower upon prolonged exposure than following acute exposure. In contrast with acute OP exposures, small but continuous OP exposures can gradually decrease AChE activity to very low levels and with little symptomatology. This suggests that, in the context of chronic exposure, cholinesterase activity does not correlate quite well with clinical manifestations.
9	German Federal Institute for Risk Assessment (BfR)	1.2 Input from Risk Managers and threshold for regulatory consideration	Lines 238–252, p. 7. Older adults represent a highly relevant vulnerable population group as there is evidence showing associations between pesticide exposure and increased risk of neurodegenerative diseases. It is mentioned in the report that 'infants from 16 weeks to 1 year of age, teenagers from 9 to 18 year of age and adults above 65 years old are not represented by any of the	There is some evidence that for certain neurodegenerative diseases, the current testing is not sufficiently sensitive and appropriate. In particular, neurodegenerative effects have been shown at doses of pesticides lower than those triggering effects on motor division (EFSA PPR Panel, 2017). Also, there is epidemiological evidence linking pesticide exposure with Parkinson's disease and

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			assessed populations'. However, it is currently concluded that 'the populations selected for the calculations are well representative of the vulnerable European populations' by referring to the Dutch toddlers as a group with especially high exposure potential. This conclusion cannot be applied for older adults because there are different concerns regarding the central nervous system (CNS) of toddlers and of older adults (developing brain vs neurodegeneration, respectively).	amyotrophic lateral sclerosis (Ntzani et al., 2013). Recent meta-analyses have shown that occupational exposure to pesticides increased the risk of developing different neurodegenerative disorders, such as Parkinson's disease (risk ratio: 1.66), Alzheimer's disease (risk ratio: 1.50), and amyotrophic lateral sclerosis (risk ratio: 1.35) (Gunnarsson and Bodin, 2019). An increased prevalence of these three neurodegenerative diseases has been observed in individuals occupationally exposed to pesticides (Voorhees et al., 2017). For specific pesticides, long-term/low-dose exposure to pesticides such as paraquat, dieldrin, organochlorine and OPs has been associated with neurodegenerative diseases, although the mechanisms underlying the influence of pesticides remain to be elucidated (Yan et al., 2016). However, inconsistencies across epidemiological studies have been reported (Naughton and Terry, 2018). Conversely, AChE inhibition is a key strategy to treat dementia disorders that involve a critical loss of acetylcholine in the CNS. AChE inhibitors indeed have neuroprotective effects that can delay or modify the clinical course of the disease (Moss et al., 2017). Assuming, that pesticides might be a risk factor for developing certain neurodegenerative diseases, the evidence points to that sustained exposure is needed, i.e. exposure during earlier life stages such as intrauterine and perinatal periods (Faa et al., 2014). Neurodegeneration may result from long-term low-dose exposure to pesticides (or other chemicals) over a lifetime in combination with genetic background, the so-called gene X environment interaction (Bradley et al., 2018). Although susceptibility may vary, it is more pronounced during developmental stages such that neurodegeneration can start at early life stages and remains silent for years until manifested in adult life and the elderly population (Aschner and Costa, 2015). Altogether, there is uncertainty to what extent the current testing approach for hazard assessment of pesticides presently captures these effects in elderly populations. As appropriate testing to address this type of effects has not

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				been developed, CRA cannot be performed at this moment and, therefore, it is not specifically recommended. In section 1.1 of the final report, the fact that neurodegenerative diseases were not considered due to the weakness of the current testing methodology has been highlighted.
			Furthermore, this section compares exposure scenarios between infants (3–12 months) and toddlers (12–36 months), but nothing is mentioned about exposure of older adults. This aspect should be further elaborated.	Revised considerations about the risk of European populations and age groups not covered by the calculations have been moved to section 4.3. Adults above 65 years old have been addressed.
			It is assumed that the CNS sensitivity is reflected by the NOAEL. On the exposure side, infants need to be assessed more critically than all adults, because food intake (exposure) per kg of body weight is considerably higher. The model approach does not consider NOAEL differences based on age.	Food intake per kg body weight is indeed the highest in the earliest stages of life. To cover vulnerable ages due to high consumption, the assessments included populations of toddlers from the age of 1 year. In terms of exposure to pesticide residues, this approach offers an appropriate protection because, as explained in section 1.2 of the report under consideration, the exposure of younger infants (3–12 months) is similar to the exposure of toddlers (12–36 months). The issue of NOAEL differences based on age is not well understood. If it is related to developmental neurotoxicity, see response to comment 25.
			It is mentioned in the report that 'infants from 16 weeks to 1 year of age, teenagers from 9 to 18 year of age and adults above 65 years old are not represented by any of the assessed populations'. Concerning the German database this seems strange. The National Nutrition Survey II covers age groups from 14 to 80 years – however the maximum was outlined as 65 years (also in Table B.3). Was there a decision to use a subset of the German population and why? The explanations are not sufficient to follow what was really used for the modelling.	In accordance with EFSA's harmonised terminology for scientific research, the different age classes are defined as follows: • Infants: < 12 months old • Toddlers: ≥12 months to < 36 months old • Other children: ≥36 months to < 10 years old • Adolescents: ≥10 years to < 18 years old • Adults: ≥18 years to < 65 years old • Elderly: ≥65 years to < 75 years old • Very elderly: ≥75 years old When this pilot assessment was initiated, one of the risks identified was the potential lack of computational capacity to perform Monte Carlo simulations for all countries and age classes. It was therefore decided to limit the assessment to 10 population groups (i.e. combinations of country and age class). The selection took into consideration the age coverage, the size of the dietary

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				surveys and the geographical distribution. For the same reasons, the selection of subjects within a dietary survey was limited to the three most representative age classes (i.e. toddlers, children and adults). Therefore adolescents, elderly and very elderly who participated to the German National Nutrition Survey II, were excluded from this pilot exercise. In the future, EFSA will explore possibilities to integrate all relevant population classes in the assessment.
10	Pest Management Regulatory Agency, Health Canada	1.2 Input from Risk Managers and threshold for regulatory consideration	Limiting the CRA to food of plant origin only, i.e. excluding food of animal origin may be considered a shortfall in this work rather than an uncertainty.	It was decided to restrict the scope of the assessment to 30 plant commodities for reasons of human resources and computing capacity. Increasing the number of commodities would have required the collection of additional data (e.g. monitoring data, authorisation data, processing data), some of which being collected manually. To call this a shortfall implies that it is an omission that will result in biased results. In fact, the impact of limiting the assessment to the selected commodities was considered in detail, referring to relevant data (see notes 1–3 in appendix B2 of the report) and explicitly taken into account in the uncertainty analysis (see lines 866 and 1001 in the draft report). Therefore, it is more correct to describe it as a technical limitation, of which the impact on the assessment was taken carefully into account in the uncertainty analysis.
			It would be helpful to provide the scientific rationale for choosing an MOET of 100 at 99.9th percentile as target of safety.	This was agreed by the EU Member States during the Standing Committee on Plants, Animals, Food and Feed (European Commission, 2018). EFSA understands this choice as meeting an objective of high level of consumer protection, which is a purely political/risk management consideration and outside the remit of EFSA. The Member states' document states that estimates at the percentile of interest 'should be considered with the associated uncertainties (e.g. the statistical reliability of results at high percentiles) and with an evaluation of their potential to cause an overall overestimation or underestimation of the real risks'. Assessment of these uncertainties is a scientific consideration, within the remit of EFSA, and was therefore addressed as part of the uncertainty analysis. Results reported in note 7 of appendix B.2 of the draft report

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				indicated that estimates at the 99.9th percentile were not problematic, and accordingly this was given little weight by the experts when making the judgements in section 3 of the draft report. It is sometimes suggested that the choice of target percentile should be influenced by the reliability with which it can be estimated, given the available data. For example, the Member States' document also states: 'It could be that the upper percentiles of the exposure distributions will be determined by extreme values … and missing information... This might need to be considered when selecting an appropriate threshold for regulatory consideration'. Note that this would require a similar analysis to that in note 7 of the scientific report, to inform the choice of target percentile. However, the approach taken in the draft reports is more transparent, since it clearly distinguishes the scientific considerations from the risk management ones. It is also more flexible, since it allows differences between assessments in the reliability of the model estimates (e.g. due to differing sample sizes and/or tail distributions) to be taken into account without having to alter the target percentile.
			The default application of the same target margin of exposure (MOE) for all members within a CAG may be considered a source of additional uncertainty. When conducting CRAs, the PMRA establishes target MOEs for each chemical in a CAG on an individual basis, which can result in different target MOEs for chemicals within the group. The appropriate uncertainty factors, as well as Canada's Pest Control Product Act factor (applied to provide additional protection for infants and children), would be applied for each member of the CAG, taking into consideration the acceptability of the available data, any necessary extrapolations for study duration or the use of a lowest observed adverse effect level (LOAEL), and the potential of each chemical to be of greater sensitivity in the young.	An overall MOET of 100 is indeed applied as a regulatory threshold for the assessment of risks related to AChE inhibition and functional alteration of the motor division. Besides this, when there were shortcomings in the quality of data for some compounds, specific/additional factors were used to set NOAELs. This was the case of compounds for which no NOAEL could be derived from studies and for which a factor of 10 was applied to the LOAEL to derive a NOAEL. In the CAG on functional alterations of the motor division, for emamectin benzoate, an additional factor of 5 was applied to the NOAEL of an acute neurotoxicity study in rats, due to small dose spacing and steep dose–response curve, and possible acute effects in dog at the NOAEL in rats. Other uncertainties affecting the toxicity data were

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				considered by expert judgement in the uncertainty analysis (see note 29 of the scientific report). Additional safety factors were not applied for the risk assessment in infant or children populations as the legislation in the EU does not prescribe specific factors as the Canada's Pest Control Product Act does.
11	Pesticide Action Network Europe	1.2 Input from Risk Managers and threshold for regulatory consideration	Lines 238–239: We regret to see that risk managers agreed on an MOET of 100. The threshold 100 is the typical uncertainty factor used to calculate the acceptable daily intake (ADI) from NOAEL, 10 for animal-to-human and 10 for human-to-human variations. Nevertheless, studies have shown that this could be an underestimation, particularly for extrapolations of data from humans to humans. This factor does not take into account the vulnerable groups of our population, such as children, the elderly and patients under medical treatment. A higher error may occur when data are extrapolated from adult animal studies (where animals do not reach ageing) to infants, children or elderly. A higher factor would be expected for a dietary risk assessment where all population groups might be exposed to pesticides via food. Ideally a different factor should be applied for each study used to calculate each MOE or a truly conservative approach would be to apply altogether a higher threshold for MOET (KEMI, 2003). Lines 246–252: Although a big part of the population is covered, infants and elderly, whose chemical metabolism is slower (leading to potentially longer retention of chemicals) are not covered in the analysis. This should be addressed at least in the uncertainty analysis.	In most human neurodegenerative diseases the neural network is gradually damaged after adulthood, resulting in a loss of neurons. The large reserve capacity of the nervous system may partially account for the late onset of neurodegenerative disorders, which remain latent until clinically manifested with ageing. This does not necessarily mean that the elderly are more vulnerable to pesticides in general (or OP in particular). However, the toxicokinetic behaviour of pesticides can be altered during ageing. Indeed, toxicokinetics of chemicals undergoes changes in elderly people; for instance, the cardiac output declines with age, so reducing blood flow to the liver and kidneys. Reduced blood flow and decreases in liver and kidney size (that also occurs with age) contribute to slow detoxification and removal of pesticides from the body. In addition, older adults are more likely to suffer from diseases of the liver and kidneys that collectively contribute to a reduced excretion of pesticides from the body (Risher et al., 2010). As a result of the longer life time of pesticides in the body, adverse health effects can be produced more easily. Additionally, the compensatory mechanisms of the body are gradually disturbed with age. It is recognised that the issue raised by this comment deserves further consideration. However, due to its generic nature, it goes beyond the scope of the report under consideration and cannot be addressed here.
			Lines 259–262: PAN Europe regrets to see that the probabilistic approach has been adopted (see previous comments https://www.pan-europe.info/sites/pan-europe.info/files/201809_Briefing%20mixture%20toxicity.pdf) which incorporates several assumptions. Even by using	Based on the paper referred to, we understand that the commenter is arguing for a deterministic calculation. In 2009, the PPR panel tested the possible methodologies to assess the cumulative exposure to pesticides from the triazole class and compared deterministic and probabilistic methodologies (EFSA PPR Panel, 2009). In this opinion, the Panel proposed a deterministic approach applicable to

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			conservative assumptions (as explained in the text), when these are 'corrected' the results are questionable.	specific events of MRL exceedances requiring immediate enforcement actions by competent regulatory authorities. However, it was not possible to develop a deterministic methodology capable of reflecting the overall level of actual acute cumulative risk using the entire amount of monitoring data. Only a probabilistic methodology could be developed to perform a retrospective risk evaluation addressing the assessment questions quoted in section 1.1 of the report under consideration. Using the 99.9th percentile of the probabilistic exposure distribution as threshold for regulatory consideration can be considered as offering a high level of consumer protection.
12	ETS Experimental Toxicology Services Nederland BV	2 Methodology, data and uncertainty analysis	The dose–response characteristics can be assessed in a common test organism such as *Daphnia* or *Drosophila*. The time to effect must be determined for at least 5 dose levels, and Total doses required for an effect must be calculated.	This comment concerns environmental risk assessment and, therefore, is not applicable to the report under consideration.
13	Wageningen University & Research	2.1 Methodology	p. 8, L294: 'EFSA used the direct calculation method and RIVM used the method based on index compounds (ICs)' Whereas both options are in principle equivalent for the estimation of MOET, two remarks are relevant to include in this section for the guidance of future users:	
			1. Note that the indirect method calculates the cumulative exposure as such (∑Ei × RPFi) as an intermediate result. Further analysis of the cumulative exposure is often very useful, e.g. to identify risk drivers. This in in fact used in the present report section 2.2.2.1 and as evidence informing the experts on EKE question 2 (see section 2.3.5). Whereas the identity of the IC is not relevant for the percentage contributions of risk drivers, it is natural to see these percentages as applying to cumulative exposure (as in the indirect method) rather than as applying to the inverse MOET (as would be the interpretation in the direct method).	1. This is a rather rhetorical comment. Contributions of different substances (i) to cumulative exposure are obtained in the direct method as 1/MOEi and in the direct method as Ei × RPFi (where RPFi is the relative potency factor of substance i and Ei its exposure), and outcome of both methods is therefore equivalent. Further details are provided in the report on exposure assessment (EFSA, 2019b).
			2. A technical difference is that upper percentiles of an exposure distribution correspond with lower percentiles of a MOE(T) distribution. Percentile functions in statistical software are often	2. The commenter is correct to say that such differences can arise. There is also an issue that changing the scale (from MOET to 1/MOET for example) would change the answer for all methods because some interpolation is

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			not exactly symmetric with respect to the lower and upper tail, and therefore differences can arise with extreme percentiles.	performed when there is no directly corresponding order statistic. Hyndman and Fan (1996) review the functions provided by different software packages for calculating quantiles, and make a specific recommendation to address this issue. A further method has been proposed by Harrell and Davis (1982; Biometrika, 69, 635–640) and was found to perform better than the others in an earlier EFSA opinion (EFSA PPR Panel, 2005). These issues with quantile estimation can also be reduced by increasing the number of Monte Carlo samples. However, these issues had little impact in the present assessment, because the exposure calculations were repeated using the direct and indirect methods (i.e. on both the MOET and 1/MOET scales) and gave closely similar results. The threshold for regulatory consideration is defined for the 99.9th percentile of the exposure distribution. Therefore, the percentiles were derived for the 1/MOET distribution and percentile functions applied to both methods were the same. Further details are provided in the report on exposure assessment (EFSA, 2019b).
14	Norwegian Scientific Committee for Food and Environment (VKM)	2.1 Methodology	Line 268: Our main concern on this report is the choice of the NOAEL. In most cases, the NOAEL is based on chronic studies and not on acute studies. In this case, acute exposure is probably more relevant as is mentioned in the discussion. We suggest including a list per CAG and for each pesticide on what critical effect the NOAEL was based upon. We assume that most NOAELs were not based on CNS related adverse outcomes and we believe it would have been better to use NOAELs based on either motor activity or AChE inhibition. The slope of the dose–response curve is also important in judging the NOAELs and this should be mentioned. It would be helpful to indicate for how many active substances motor activity and AChE inhibition data were available.	An exhaustive description of the method used to characterise the active substances included in the CAGs for AChE inhibition and functional alteration of the motor division is given in the respective report (EFSA, 2019a). The descriptors/indicators of these two specific effects (endpoints) were also specific and tailored to the precise definition of these effects.
			In general, the exposure and uncertainty analyses are well described in the report, but the hazard identification and hazard characterisation could be expanded. It is worth noting that in the uncertainty part of the document a number of uncertainties related to hazard are identified.	Please refer to EFSA (2019a) for the hazard identification and characterisation.

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15	ETS Experimental Toxicology Services Nederland BV	2.1 Methodology	Median time to death is the recommended parameter. If the total dose decreases with the duration of exposure, cumulative toxicity reinforced by time has been identified.	This comment concerns environmental risk assessment and, therefore, is not applicable to the report under consideration.
16	ECPA – European Crop Protection Association	2.1 Methodology	The chosen methodology is intentionally conservative in identifying the members of the CAGs and running the exposure assessments (Tier 1 and Tier 2). In a further step an extensive uncertainty assessment is needed to take into account missing information, thereby increasing MOETs. Considering the difficulty in communicating the methodologically complex uncertainty assessment (using EKE approach), wouldn't it be more appropriate to start the assessment with more realistic and thereby less precautionary assumptions (e.g. starting with less and more probable CAG group members, taking additional available data such as processing and peeling factors that have not yet entered the EFSA database, or that may be found in the BfR's database and put less efforts in the uncertainty analysis of the risk drivers?	We acknowledge that there are multiple options to conduct a CRA. To perform these pilot assessments, the adopted approach included the recommendations of the Standing Committee on Plants, Animals, Food and Feed and the main guiding principles were to: • Reduce to a minimum the risk of underestimation of the adverse effects on the consumer. • Make use of data having been reviewed/assessed for quality in the context of a regulatory process (e.g. approval procedure of active substances, assessment of existing MRLs, applications for MRLs, monitoring data generated within the European Union control programme). • Make best uses of the available human, budgetary and technical resources. The commenter implies that the uncertainty analysis could have been simpler and that EKE might not have been necessary if the assessment had started with fewer CAG members. If this was done, the potential contribution of the excluded substances would have to be considered as part of the uncertainty analysis, to avoid underestimating the risk. This would be difficult and rely entirely on expert judgement. When lower probability CAG members are included in the assessment, their contributions can be examined quantitatively by drill-down of the model output, so the extent of potential overestimation is much more easily and reliably assessed. It is acknowledged that available data may not have been used, either because they have not been reviewed yet at EU level [e.g. some processing factors (PFs)] or because they would have required more resources (e.g. food commodities not included in the assessments). However, the consequences of these limitations have been considered in detail in appendix B2 and taken into account in the uncertainty analysis in section 3 of the report.

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			With the complexity of the approach, how is this compounded uncertainty to be explained and communicated in relation to the MOETs 'passing or failing' (based on current interpretation/understanding of risk assessment language)?	The commenter implies that the result of the assessment should be expressed in terms of MOETs 'passing' or 'failing'. This would be possible if risk managers had specified what level of certainty (i.e. probability) was required that the MOET at 99.9th percentile of the exposure distribution is above 100. Instead, they stated that: 'a threshold for regulatory consideration at the 99.9th percentile could be an acceptable target value, provided that the tier 2 assumptions are sufficiently conservative'. To address this, the degree of conservatism in the assessment was quantified. However, deciding whether the quantified degree of conservatism is 'sufficient' is a risk management consideration (weighing the desire for high certainty of safety against the costs of achieving that certainty either by obtaining more data or regulating to reduce the estimated risk). However, it is acknowledged that both stages (scientific assessment of the uncertainty and risk management considerations) are complex and require careful communication. The revised report includes changes aimed at improving understanding of the scientific assessment.
17	Health and Safety Executive	2.1 Methodology	Line 274: The terminology at line 274 is not consistent, the term MOEn is referred to but the term MOEi is then defined. For clarity it would be helpful to have the calculation for both MOET and 1/MOET presented (i.e. as shown in EFSA, 2008).	Agreed. This was corrected in the final report. It is now explained that the MOET is obtained by taking the reciprocal of 1/MOET.
18	CNRS/ Museum National d'Histoire Naturelle.	2.1 Methodology	A significant point in this assessment is whether banned, now legacy, pesticides should have been included in the CRA. As far as I can see this problem is not addressed. One example is DDE (the main metabolite of DDT) that is still present in European populations (Fini et al., 2017) and is known to affect brain development through modification of thyroid hormone levels and other mechanisms. Other legacy pesticides could have been cited (HCB etc.).	DDT was in the list of the substances evaluated when CAGs for the effects of pesticides on the nervous system were established. JMPR evaluations of 2000 (WHO, 2001) were the source of information for this substance. No indicator of AChE inhibition and functional alterations of the motor, sensory and autonomic division were reported. Please note that, as stated in EFSA (2019a), developmental neurotoxicity was not addressed when the CAGs were established. See response to comment 25.

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			A second point is that only acute toxic effects are considered for cumulative assessment, even though it is known that continued exposure and individual differences (e.g. in paraoxonase-1 or cytochrome P450 variations) can affect outcome adversely and significantly.	The section 1.1 of the final report was updated to make explicit that chronic cumulative effects of pesticide residues are not included in the assessments. In addition, section 6 (Recommendations) includes a recommendation to perform a chronic CRA for the AChE inhibition.
19	Pest Management Regulatory Agency, Health Canada	2.1 Methodology	The PMRA makes the same general assumption regarding dose addition when conducting CRAs.	This is noted.
20	ETS Experimental Toxicology Services Nederland BV	2.2 Data	Such data must be established for at least five dose levels.	This comment is not clear. Regulation No. 1107/2009 on the placing of plant protection products on the market defines precise data requirement for the toxicological investigation of active substances.
21	ETS Experimental Toxicology Services Nederland BV	2.2.1 Cumulative assessment groups (CAGs)	If cumulative toxicity has been identified, the as low as reasonably achievable (ALARA) principle must be adopted.	The ALARA principle is a risk management tool, and therefore not under the EFSA's competence.
22	German Federal Institute for Risk Assessment (BfR)	2.2.1 Cumulative assessment groups (CAGs)	Lines 308–313, pp. 8–9 (comment also refers to: lines 1250–1260, p. 35).	
			The acute CRA for 'functional alterations of the motor division' with 100 included active substances and 11 relevant MoAs intrinsically presents significantly higher amount of uncertainty and unknowns compared to AChE inhibition, and it is not exactly clear in this report as to how it is possible to group these substances with various MoAs for the CRA. This could be further summarised.	The motor function of the nervous system is a very specific and specialised function of the organism, and for this reason, its alteration is considered as a phenomenological effect of relevance for CRA. Indicators of alteration of the motor activity, coordination, muscle strength and equilibrium were defined to support evidence that a substance is causing this effect (EFSA 2019). When it triggers at least one of these indicators, an active substance is included in the CAG. The MoA may be variable or even unknown. The rationale behind the application of dose addition when the cumulative risks are calculated can be found in the opinion of the PPR Panel (EFSA PPR Panel, 2013) and in Nielsen et al. (2012).

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			Without knowing the types of pesticides that the populations from the different countries are exposed to, it seems premature to conclude that cumulative exposure to pesticides that functionally alter the motor division of the nervous system do not exceed the threshold for regulatory consideration.	See response to comment 37.
			The overall uncertainty analysis of CAG-NAM ("Cumulative Assessment Groups - Nervous system/Acute/Motor division effects") is limited, and given the complexity of this CAG, it is unfortunate that a detailed discussion of the individual assessments for CAG-NAM did not take place.	Most of the uncertainty analysis was carried out at the same level of detail for both CAG-NAN and CAG-NAM. The exception is the final step of the assessment for CAG-NAM, described in section 3.4.2. This was still completed for CAG-NAM, but by a shorter process in which the experts proceeded directly to discussing their consensus judgement without first making separate individual judgements. Indeed it would have been preferable to have included the extra step as for CAG-NAN, but that was not possible within the agreed timetable. If this had been anticipated, it is possible that the greater complexity of the CAG-NAM would have deserved priority. However, this has to be weighed against the fact that the estimated MOETs for CAG-NAN were closer to the threshold for regulatory consideration and therefore of higher priority. Furthermore, the specific sources of complexity that are mentioned in the text referred to by the commenter (lines 308–313 of the draft report) are toxicological issues that were considered in detail for both CAGs in the earlier steps of the uncertainty analysis and are less likely than exposure uncertainties to differ between countries (which is what is considered in the final step). Therefore, although it would have been preferable to carry out the final step of the uncertainty analysis for CAG-NAM in the same way, it is likely that the abbreviated procedure had negligible impact on the conclusions.
23	ECPA – European Crop Protection Association	2.2.1 Cumulative assessment groups (CAGs)	The identified risk drivers for the acute nervous system neurochemical group were chlorpyrifos, formetanate, omethoate, triazophos and dichlorvos in different active substance–crop combinations. The major risk drivers of the acute motor division CAG were assigned to subgroup 4 (chlorpyrifos, triazophos) according to the EFSA scientific report on the nervous system groups (2018), indicating a lower likelihood, that these compounds truly belong to this group. These uncertainties could	Actually, it was concluded almost certain that all substances from subgroups 1 to 4 were causing the effect, because these subgroups contained only substances with relevant chemical structures and MoAs (EFSA, 2019a).

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			also have [been] taken into account in the uncertainty assessment for grouping?	
24	Pest Management Regulatory Agency, Health Canada	2.2.1 Cumulative assessment groups (CAGs)	For CRAs, the PMRA identifies the human health risk associated with co-exposures to two or more pesticides that cause a common toxic effect by the same, or essentially the same, sequence of major biochemical events. The PMRA takes a step-wise approach for identifying pesticides that belong to a common mechanism group. Identification of a preliminary grouping of pesticides, based upon structural similarity, similarity of MoA (in target pests or in mammals), or similarity of toxic effect, considered within a weight-of-evidence context, is undertaken early in the process of cumulative assessment. During the next phase of the review process, the mechanisms by which the pesticides of the preliminary group cause the common toxic effect are determined. Accordingly, the PMRA will conduct separate CRAs for the *N*-methyl carbamate insecticides and the organophosphorus pesticides since they exert their cholinesterase inhibition through different mechanisms.	This is noted. The EFSA approach is different and tailored to the EU pesticide legislation, which calls for the possibility for risk managers to use the precautionary principle when there is scientific uncertainty. In this context, it was necessary to address the combined effect of substances capable to cause a same effect by different mechanisms (independent or dissimilar action). In this respect, the PPR panel advised to group substances acting by dissimilar MoAs into common CAGs and to assume (EFSA PPR panel, 2013) dose addition to conduct CRA. This approach offers the practical advantage of being readily applicable by comparing exposure doses of concentration, easily available from food monitoring activities, to reference values (EFSA Scientific Committee, 2019). Not doing so and grouping substances on the basis of the similarity of mode/mechanism of action only does not allow considering adequately risks of alteration of apical endpoints resulting from converging mechanisms or adverse outcome pathways (AOPs) and may therefore underestimate them. Nevertheless, as reliable substance-specific mechanistic information was available for OPs and NMCs with respect to AChE inhibition, a mechanism-based CAG could be established for this effect, enabling CRAs based on a similar MoA. Should similar reliable substance-specific information be available at biochemical level for substances from other chemical classes, additional mechanism/mode of action-based CAGs would also be established. The approaches used on the one hand by PMRA and US EPA, and on the other hand by EFSA, do not reflect actual scientific divergences but rather reflect the principles applied when dealing with scientific uncertainty as described above. They fit to different jurisdictions and address different assessment questions.

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25	Pesticide Action Network Europe	2.2.1 Cumulative assessment groups (CAGs)	Unfortunately, the selection of the studies inevitably leads to misleading NOAELs (higher than real NOAELs). The data used for CAGs derive from DARs/RARs but some key studies, that use lower doses and therefore would result in effects with lower NOAEL have been omitted (e.g. neurodevelopmental toxicity). Developmental neurotoxicity (DNT) is a hazard that has been addressed only recently in pesticides risk assessment. The data requirements before 2013 were focusing mainly on adult toxicity and therefore did not include specific tests to address neurotoxicity during vulnerable periods of life time. DTN is even missing from dossiers approved after 2013. These studies, even if scarce, should had been included where available, and these data gaps should have a significant weight in the uncertainty analysis, since NOAELs tend to be much lower in DNT studies. For example, in the case of DNT studies for chlorpyrifos, effects on brain morphology were observed at dose levels of 0.3 and 0.1 mg/kg/day (Mie et al., 2018). Several other effects on the nervous system were excluded, even if reported, at lower NOAELs (e.g. neurophysiological effects). Further, behavioural tests assessing the effects of pesticides on the cognitive function should had been used were available. A consideration of these effects should be taken into account especially when taking place at lower NOAEL. A wider range of neurotoxic effects were selected in the 2012 report that seem to be missing here (Nielsen, 2012).	We understand that this comment concerns the fact that developmental neurotoxicity is not covered in the report under consideration. This important limitation, due to the current lack of sufficient data in pesticide dossiers, was acknowledged when CAGs were established (EFSA, 2019a). In order to establish a CAG covering this effect, EFSA recommended the development of tailored testing and assessment methodology (EFSA, 2019a). This is however not a source of uncertainty affecting the CRAs as precisely defined in section 1.1 of the final report.
			Furthermore, the dossiers of some of the pesticides had data gaps, even for the selected studies. According to EFSA analysis on establishing CAGs for the nervous system, for many old substances even the neurotoxicity study for acute effects was not available. The report states: 'This absence of a neurotoxicity study may result in overestimated NOAELs for some ASs (and thus underestimating the actual risk) as information on some indicators is missing in this case.'	This source of uncertainty was considered in the uncertainty analysis and supported by note 29 of appendix B.
			Furthermore, peer-reviewed scientific literature should had been revised to evaluate whether lower NOAELs have been reported, and identify further studies reporting neurotoxicity (also proposed by Nielsen et al., 2012). Peer-reviewed literature could help to establish additional CAGs when data were not sufficient. Since the dossiers have data gaps the academic literature should	The sources of information used for the establishment and characterisation of the CAGs are indeed regulatory documents produced by national or international authorities. Peer-reviewed scientific literature was consulted for gathering information on MoA.

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			had been consulted. It is incredible that peer-reviewed literature was dismissed even when incorporated in the RARs/DARs. Not using the most recent studies to address nervous system toxicity makes the current assessment to be out of date.	Furthermore, Regulation (EC) No. 1107/2009 requires the submission of all relevant data from the scientific peer-reviewed open literature on the active substances, metabolites and breakdown or reaction products and plant protection products. The respective guidance (EFSA, 2011a) needs to be considered. It is assumed that any impact of this information on the evaluation of the effects on the nervous system has been captured during the elaboration and characterisation of CAGs as the EFSA conclusions on the peer review of active substances finalised until the end of 2018 were considered to retrieve any element of expert judgement on these effects. In addition, the knowledge of the experts on findings in the scientific literature was taken into account in the uncertainty analysis where relevant.
26	US EPA Office of Pesticide Programs	2.2.1 Cumulative assessment groups (CAGs)	'Functional alteration of the motor division of the nervous system' is not a single apical outcome but rather comprises multiple effects (e.g. locomotor activity, muscle strength, coordination and equilibrium), so it is unclear why these effects were all grouped together.	In the context of our assessment, 'functional alteration of the motor division' is considered as one single and unambiguous effect, which may take various forms (reduction or increase of the motor activity, alteration of the muscle strength and of the coordination) and be reflected by various indicators (hypoactivity, tremor, reduced grip strength, ataxia…). Appendix C of EFSA (2019) shows that these various forms of alteration of the motor division are observed following exposure to most of the chemical classes and their respective MoAs. Therefore, the indicators of these various alterations are all considered as reflecting one single functional effect.
27	US EPA Office of Pesticide Programs	2.2.1 Cumulative assessment groups (CAGs)	The hazard assessment should be reconsidered and based on specific MoAs.	See response to comment 24.
			The CAG for AChE inhibition includes carbamates and organophosphates. While both of these chemical groups inhibit AChE, they do so by binding at distinct parts of the enzyme resulting in differences in the nature of the enzyme binding (reversible vs irreversible) and the temporal response. Thus, these two groups of chemicals have separate MoAs and should be analysed separately. See EPA's rationale and peer-review recommendations in the following documents:	There is evidence that although OPs and NMCs have different 'mechanism of toxicity' (wording according to the US EPA, 1999) when combined, dose addition is applicable. This has been reviewed in Hernández et al. (2013) which states the following: 'The combined effect of pesticides that have similar chemical structures and/or modes of toxic action can be predicted by an additive toxicity approach that assumes that the cumulative

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			https://www.federalregister.gov/documents/2004/02/04/04–2157/carbamate-cumulative-assessment-group-availability https://archive.epa.gov/scipoly/sap/meetings/web/pdf/finalrpt-2.pdf The CAG for functional alterations of the motor division is described as comprising 100 substances that act by either one of 11 MoAs or have unknown MoAs. Separating these chemicals into 11 CAGs based on their MoAs would allow for a more robust analysis.	toxicity of the mixture can be estimated from the sum of the individual toxic potencies of each individual compound (Lydy et al., 2004; Hernández et al., 2011a). This is the case of organophosphates (OP) pesticides, (di)thiocarbamates or chloroacetanilides. In concurrent multiple OP exposure, a summation of the inhibitory effects of individual compounds on acetylcholinesterase (AChE) activity is usually observed. This also applies to OPs and *N*-methylcarbamates (NMC), two different classes of insecticides that share a common mode of toxic action: inhibition of AChE. According to acute oral toxicity (LD_{50}), the combined effects of two insecticides have been reported to be additive for OPs plus OPs and for OPs plus NMC in most cases (Sun et al., 2000)'.
			The addition of large uncertainties in the assessment was likely a necessity due to the large amount of chemicals in the CAG with no shared MoA. Use of CAGs that only incorporate chemicals that share a common MoA would decrease uncertainty in the CRA.	The commenter suggests that including a large number of substances with uncertain CAG membership was responsible for a large part of the uncertainty in the assessment and hence for the large impact of the uncertainty analysis on the conclusions. In fact, uncertainty about CAG membership was judged to have had little impact on the assessment for AChE inhibition and functional alterations of the motor division. This is clearly implied by note 28 of appendix B of the scientific report. Furthermore, uncertainty about dose additivity (arising from known or potential differences in MoA) was also judged to have had little impact on the assessment because drill-down information showed that, in individual records above the 99.9th percentile of the exposure distribution, single substance/commodity combinations were responsible for at least 80% of the cumulative exposure in about 75% of the cases.
28	US EPA Office of Pesticide Programs	2.2.1 Cumulative assessment groups (CAGs)	Inhibition of AChE leads to neurotoxic effects. Thus, it is unclear why chemicals such as the organophosphates are added to two separate CAGs that have the same apical outcomes.	See responses to comment 26. The 2 CAGs are associated to two different assessment questions, which are quoted in section 1.1.

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			It would have been useful to ask the expert group to weigh in on the CAG definitions (e.g. combining multiple effects and MoAs under 'functional alteration of the motor division of the nervous system').	See response to comment 26.
29	US EPA Office of Pesticide Programs	2.2.1 Cumulative assessment groups (CAGs)	The document titled 'Establishment of cumulative assessment groups of pesticides for their effects on the nervous system' states that reproductive and teratogenicity studies were not considered for the establishment of CAGs. These studies provide relevant information with regards to age-related sensitivity and should be included in the analysis.	The US EPA-OPP developed a CRA for the OPs that includes specific evaluation of life-stage susceptibility using the comparative cholinesterase assay (CCA), a study specifically designed to assess various early life stages (fetal, pregnant females, postnatal), across duration (single dose, repeated dose; US EPA, 2002), which was further reported as an integrated approach for testing and assessment (IATA) case study in 2017 (OECD, 2017) In the IATA case study, for all the OPs except chlorpyrifos, a benchmark dose (BMD) analysis was performed on the brain cholinesterase data in juvenile and adult animals extracted from comparative cholinesterase studies; Table 3 gives a summary of the data for 10 OPs, summarising the BMDL10 for males and females adult and juveniles. Overall, the BMDLs were comparable. This has also been the conclusion when CCA studies have been evaluated for the EU-evaluations and these types of studies have been considered for hazard characterisation of substances included in the CAG when they were part of the regulatory dossier for the EU-evaluations. For chlorpyrifos, a meta-analysis found comparable sensitivity between adults and juveniles (Reiss et al., 2012). Also, the recent evaluation of chlorpyrifos in the EU found that pups in terms of red blood cell AChE inhibition, was less sensitive than the adults (EFSA, 2019c). Regarding risk drivers, dichlorvos was included in the IATA study. For this compound, the BMDLs were very similar between adults and pups. Overall, the above shows that the effect levels are comparable between adults and juvenile with regard to inhibition of AChE. As for studies on teratogenicity and reproduction, these were not considered since they are not specifically addressing neurotoxicity.

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30	US EPA Office of Pesticide Programs	2.2.1 Cumulative assessment groups (CAGs)	For specific effects known to be initiating events in an adverse outcome pathway, such as the inhibition of AChE, the use of BMDs/BMDLs would be more suitable than using NOAELs/LOAELs, especially for studies where a NOAEL had to be extrapolated from the LOAEL.	Agreed. Our approach was aligned with the current practice of using NOAELs to characterise the toxicological properties of active substances under the approval process of Regulation (EC) No. 1107/2009. In section 6, we recommend using BMDs/BMDLs.
31	Wageningen University & Research	2.2.2 Cumulative exposure assessments	p. 9, Lines 316–328 'They included…in the model'. This text applies not only to the SAS runs, mentioned in lines 315–316, but also to the MCRA runs mentioned in lines 329–332. Therefore this text block would be better placed after line 332, and the reference to 'EFSA (2019b)' in line 325 should be extended to 'EFSA (2019b) and van Klaveren [et al.] (2019)'.	Agreed. The final report was corrected.
			p. 9, Lines 331–332: 'and commented in section 3.3 of EFSA (2019b)' Add: 'and in section 5.3 of van Klaveren et al. (2019)'.	Agreed. The final report was corrected.
			pp. 10–11, tables 1 and 2: Why are there three columns with SAS results and only one column with MCRA results? Is there a preference for the SAS results? If so, explain why. If not, add two more columns in each table to restore the symmetry.	The most important results are the SAS® and MCRA results for the 99.9th percentile of the exposure distribution, which are both reported in the last two columns of the table. Results at 50th and 90th percentiles from the SAS® model only, for reason of space, are given for information. There is no preference for one or another model. A footnote was included in the final report.
			p. 11, Lines 375: 'EFSA (2019b)' Add: 'or van Klaveren [et al.] (2019)'.	Agreed. The final report was corrected.
32	German Federal Institute for Risk Assessment (BfR)	2.2.2 Cumulative exposure assessments	Lines 314 ff., p. 9. Please add the number of individuals in the tables to each of the consumption data used. The number of 100k iterations vs n gives an impression of the coverage by the modelling.	This is agreed. The number of individuals included in the modelling of the cumulative exposure is reported in tables 1 and 2 of the final report.
			Chapter 2.2.2.1, Cumulative exposure assessment for CAG-NAN, lines 337–339, pp. 9–10 (Comment also refers to: lines 1200–1219, p. 34). Not much is discussed about the representativeness of the monitoring data across the EU. It is mentioned on page 34 that 'the difference in occurrence of pesticide residues in food commodities between populations and countries are expected to have a lower impact, due to the common market', but the monitoring data are mainly based on central Europe. 'Differences in food consumption' are only discussed in context of eating food with edible peels among populations of different ages (e.g. Dutch	Differences in the food consumption were taken into account both in the modelling and the uncertainty analysis. From the exposure assessments conducted over the 10 selected population groups, it results that differences in exposure, resulting from food consumption, are much wider between age classes than between countries. For further information in the final report echoing the comment, please refer to section 1.2, notes 1 and 15 of appendix B.

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			toddlers eating more unpeeled apples than adults) but not across countries. It would be informative to know here if this CRA could be applied for other EU countries with different food staples and consumption habits.	
			Chapter 2.2.2.1, Cumulative exposure assessment for CAG-NAN, lines 349–354, p. 10. Please add the percentile the risk driver is based on.	This information was already given in lines 344–346 of the draft report for public consultation: 'Risk drivers were defined as pesticide/commodity combinations contributing on average, in at least one out of the ten populations, at least 5% of the exposures exceeding the 99th percentile estimate.' In this section, the information on the actual contribution of the identified risk drivers has been reorganised in the final report and is now given on population basis.
			Chapter 2.2.2.3, Sensitivity analyses, lines 382–384, p. 11. The statement 'Assuming that no residue would be transferred to any processed food when a PF is missing, the MOETs increased by a factor of 1.3 to 2.6'. is a very unusual regulatory assumption. Normally, the general approach would be that ALL residues are transferred into processed foods and factors are used for refinement. Thus, please make clear that the factors stated represent the MAXIMUM theoretical impact processing may have.	This is not presented as a regulatory assumption, but the sentence is placed clearly in the context of a sensitivity analysis. The outcome of sensitivity analyses did not serve as a basis to express the result of the exposure/risk assessments, but solely to inform the uncertainty analysis process. Therefore, no change is justified.
33	ECPA – European Crop Protection Association	2.2.2 Cumulative exposure assessments	Line 389/Line 390: We agree that increased use of existing peeling, processing and cooking factors could improve future assessments. We note that existing EFSA peer review and Article 12 publications for each active ingredient may contain some of this missing information, depending on the active.	The PFs for the active substances and commodities under assessments were extracted from a recent database (Scholz, 2018). This data collection covered all processing studies assessed by EFSA in Conclusions and Scientific Reports (in the context of Regulation (EC) No. 1107/2009) and in Reasoned Opinions (in accordance with Article 12 of Regulation (EC) No. 396/2005) issued until 30 June 2016. Therefore, more information is available in other EFSA outputs, and it is recommended in section 6 to consolidate the database on PFs. It must however be noted that, for reason of conservatism, PFs reflecting the effect of washing and the effect of peeling of commodities with edible peel are not used in the assessment.
34	Pest Management		In its 2007 N-Methyl Carbamate CRA, the US EPA conducted a sensitivity analysis with regard to the imputation of left-censored	Based on the EFSA scientific report on the cumulative dietary risk characterisation of pesticides that have acute

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	Regulatory Agency, Health Canada	2.2.2 Cumulative exposure assessments	monitoring data and reached the same conclusions: replacing non-detects with either 1/2 limit of detection (LOD) or true zero has only a minimal effect on estimated high-end exposures. Generally, the LODs for monitoring data are very low and the vast majority of exposures at the upper percentiles are derived from detectable residues in a single commodity rather than from multiple commodities having 1/2 LOD residue values. Therefore, the US EPA found it reasonable to use the 'zero' assumption for non-detects to avoid inflating estimated risks with compounded conservative assumptions which would reduce the interpretability and ultimately the utility of the assessments. The US EPA stated: 'For purposes of estimating residues in samples reported as less than the LOD, a proportion of the samples equal to the estimated percent crop treated (PCT) is assigned a residue level of 1/2 LOD and the remaining samples, which are assumed to come from untreated crops, are assigned a residue value of zero. This procedure becomes problematic for a cumulative assessment. It is not enough to simply estimate the PCT for each of the pesticides in the cumulative assessment; it is also important to consider the potential for co-occurrence of residues of multiple chemicals on the same crop. As such, some of the conservative assumptions appropriately used in the single chemical risk assessments are not appropriate or reasonable for use in a CRA'.	effects on the nervous system (EFSA, 2020), the impact of the mode of imputation of left-censored monitoring data is indeed limited, as concluded by the US EPA in the NMCs assessment. EFSA is currently investigating possibilities to make the overall process leaner and less resource demanding, based on the acquired experience. These investigations may also include 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…).
			Assuming that no residue would be transferred to any processed food when a PF is unavailable is an unrealistic assumption. Depending on the chemical, while some food processing practices may result in residue reduction, others may result in residue concentration. Thus, it does not seem reasonable to assume that the lack of a PF would imply 'zero residues' for the processed commodity.	See response to comment 32.
35	Pesticide Action Network Europe	2.2.2 Cumulative exposure assessments	See comments under paragraph 1.2. Lines 315–316 and 329–330. Both models are based on Monte Carlo simulation. It would be more interesting to compare two completely different models and	Indeed, both SAS® and MCRA software are based on Monte Carlo simulation, and moreover rely on the same conceptual model. One of the reasons motivating this choice was to demonstrate the reliability of the results through cross-validation.

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			evaluate the differences in the results.	Using another conceptual model would potentially lead to different results which would in turn require a specific uncertainty analysis before allowing meaningful comparisons. This has not been envisaged because this would have been very demanding in terms of resources and because the conceptual model behind the SAS® and MCRA calculations allow an optimal use of the currently available data. See response to comment 11 on the possibility of using a deterministic approach.
			2.2.2.4 There is no justification to exclude EFSA monitoring data that exceed MRLs. MRLs change all the time (with authorisation or following a review or request), and until the market adjusts to the new MRLs food items may contain residues above the new MRLs for some period resulting in human population being exposed to higher levels than the permitted ones. Since this is the reality there is no justification to exclude monitoring data that are above MRLs. These are official monitoring data from food that is consumed from the general public.	We did not exclude data exceeding the MRLs from the main assessment which is the basis of the overall conclusions. We did a sensitivity analysis in which the samples with residues exceeding the MRL were excluded, to provide information that might be useful to risk managers.
36	US EPA Office of Pesticide Programs	2.2.2 Cumulative exposure assessments	The document should clarify whether dietary percentiles of exposure are based on per capita or consumer-only calculations. With the inclusion of drinking water and wheat in the dietary assessment, the percent of consumers will be close to 100% if the dietary assessment is for consumers only. However, explicitly stating which type of assessment would be helpful.	These retrospective assessments were made on whole population basis. This information was included in section 2.2.2 of the final report.
37	US EPA Office of Pesticide Programs	2.2.2 Cumulative exposure assessments	Additional discussion of the risk drivers would be helpful to determine if pesticide–commodity combinations associated with higher exposures are markedly different between adult and children subpopulations.	Detailed information on risk drivers is available in EFSA (2019b) (annex C.2, figure C.2.03) and in the RIVM Scientific report on the cumulative dietary exposure assessment of pesticides that have acute effects on the nervous system using MCRA software (annex B.2.02) (van Klaveren, 2019). Nevertheless, the information on risk drivers has been reorganised in the final report and is now given on population basis. Note that this information was used by the experts during the EKE Q3 to inform their judgements about differences between countries in the final step of the uncertainty analysis.

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38	US EPA Office of Pesticide Programs	2.2.2 Cumulative exposure assessments	Conceptually, the initial probabilistic (i.e. Monte Carlo) exposure model run is very similar to DEEM (e.g. dietary consumption values × monitoring residues). Additionally, a first stage uncertainty analysis is performed using 2-D Monte Carlo, which performs 99 additional probabilistic runs, which resample the consumption and residue data. Thus, providing not only MOEs at various percentiles of the exposure distribution (e.g. the 99.9th percentile of exposure), but an interval around each percentile of exposure (e.g. the MOE at the 99.9th percentile of exposure ranges from 71 to 131). This stage primarily addresses the sampling uncertainty.	This is noted. It is recognised in the report that the calculations the commenter refers to address primarily sampling variability: other uncertainties were therefore addressed in the subsequent stages of our analysis. Section 2.2.2 was further clarified.
39	Wageningen University & Research	2.3 Uncertainty analysis	p. 15, Lines 542–543: 'EFSA (2019b)'. Add: 'and (section 5.3 of) van Klaveren [et al.] (2019)'.	References were checked and corrected in the final report.
40	Health and Safety Executive	2.3.1 Identification of sources of uncertainty affecting the assessment	Line 464: The incorrect section reference is given.	References were checked and corrected in the final report.
41	Pesticide Action Network Europe	2.3.1 Identification of sources of uncertainty affecting the assessment	PAN Europe would like to include the following points that are missing from the uncertainty assessment: • The sources of data seem outdated to carry out an assessment 'in the light of current scientific and technical knowledge' on the acute and chronic toxicity of the nervous system. This is particularly the case for pesticide dossiers submitted prior to Commission Regulation (EU) No. 283/2013, which lack specific data to assess neurotoxicity, particularly in vulnerable population groups. Even some old dossiers appear to have data gaps. This will lead to higher NOAELs and overestimation of MOETs.	This source of uncertainty was identified and addressed in the uncertainty analysis, based on information collected under note 29 of the appendix B.
			• Peer-reviewed scientific literature was not used at all, even when included in the pesticide dossiers. Lower NOAELs have been reported in the scientific literature and these should be taken into account. According to Reg (EC) 1107/2009 Article 8(5), an assessment is not complete without including studies from the scientific peer-reviewed open literature.	See response to comment 25.
			• It is of concern the numerous articles in the open scientific literature that report the impact of pesticides, particularly	See response to comment 25.

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			insecticides in the brain development, were not addressed in the assessment. For example: Bellanger et al. (2015) have shown that exposure to endocrine disruptors in Europe contribute substantially to neurobehavioral deficits and disease, and organophosphate pesticides is one of the main drivers. A systematic review of 27 studies (Muñoz-Quezada et al., 2013) has shown that prenatal and early childhood exposures to organophosphate (OP) pesticides among children lead to neurodevelopmental effects such as cognitive deficits (memory loss), behavioural deficits and motor deficits. Another review also demonstrates the neurotoxic impact of insecticide exposure during the period of cerebral development (Cassereau et al., 2017).	See the EFSA scientific reports on the establishment of CAGs for the effects of pesticides on the thyroid (EFSA, 2019d) with respect to the state of play on thyroid-mediated developmental neurotoxicity.
			• Human data were not included in the assessment, even when available. These may involve lower exposures and result in lower NOAELs.	It is not clear which human data are meant in this comment.
			• Studies from dossiers were not validated against raw data. Recent reports show that in many cases the reporting of the protocol studies is poor and adverse effects are often not reported (Mie et al., 2018) for DNT; Clausing (2019), chronically underrated; Portier et al. (2016).	The peer-review process offers tools to mitigate significantly the risk of occurrence of reporting or appraisal inaccuracies: • Obligation of conducting studies under the Good Laboratory Practice (GLP) conditions • Delivery of original study reports to all Member States and EFSA • Peer review of the DARs • Public consultation on DARs • Evaluations not based on single observation, but on a spectrum of consistent observations in several studies. Nevertheless, it is acknowledged that variation in the interpretation or analysis of raw data by laboratories performing guideline studies and/or regulatory reviewers is possible. However, the experts for this assessment consider that the contribution of this to the uncertainty related to the setting of NOAELs for effects on the nervous system is minor. Note 29 was updated in appendix B of the final report.
			• A MOET of 100 doesn't allow to take into account human-to-human differences (vulnerable groups of the population such as babies, toddlers, children and elderly, as well as people with diseases). When studies are extrapolated from adult animals the	We acknowledge that the actual human-to-human (and animal-to-human) variability in toxicological sensitivity may vary according to the type of toxicological effects. This source of uncertainty was considered by the Working

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			uncertainty factor could be much higher than 100 (KEMI, 2003, Human health risk assessment: Proposals for the use of assessment (uncertainty) factors 2003). Considering all the uncertainties due to the use of old studies a MOET higher than 100 would be more appropriate.	Group, but not included in the uncertainty analysis itself because the targeted MOET of 100 was a pre-requisite set by risk managers. In section 4.1 (risk characterisation of AChE inhibition), reference was made to evaluations of the Joint Meeting on Pesticide residues on the applicability of the MOET of 100 for NMCs. Please note that developmental neurotoxicity is not covered by the report under consideration as explained in response to comment 25.
			• Metabolism in infants and elderly may be lower, leading to higher retention of chemicals in the system and therefore higher likelihood of toxic effects.	See response to comment 11.
			• Line 422: AS were selected it is possible that other substances not incorporated in the assessment but detected in monitoring data could have effects on the nervous system.	This is correct and considered as a source of uncertainty with limited effect (section 3.3.1). See also note 27 in appendix B.
			• Baseline exposure is assumed to be zero although all human population groups already have chemicals in their system due to previous exposures, these include pesticides and other chemicals (Human biomonitoring: facts and figures. Copenhagen: WHO Regional Office for Europe, 2015; HBM4EU: Scoping paper on the development of an indicator on chemical exposure in the European population Deliverable Report D 5.3 WP5 – Translation of results into policy, 2017). The likelihood that these chemicals may contribute and lead to toxicity cannot be disregarded.	Indeed, only the contribution of pesticides, and from dietary route, is considered in the assessment conducted in the report under consideration. Section 1.1 of the final report was updated with the explicit statement that only pesticide residues are considered in the reported assessments.
			• People are also exposed to pesticides through other routes, particularly if they are residents of agricultural areas. Furthermore about 10% of pesticides are used in the pest management of public areas (parks, gardens, cemeteries and golf courses) and people use them in their private gardens. This non-dietary exposure to pesticides is evident from studies showing that even people that eat organic food are exposed to pesticides. Therefore, the level of exposure is likely to be higher than the one estimated.	See response to comment 5.
			• Around 7% of the imported food (non-EU) samples from the official monitoring programmes exceed the MRLs. This means that a fraction of the food sold in EU market, particularly raw fruit and vegetables, may have pesticide residues that exceed the EU MRLs.	Imported food commodities are covered by the European coordinated and/or national programmes of pesticide residue monitoring. Their contribution to the intake is therefore covered in the assessments that were conducted.

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42	Ctgb, Board for the Authorisation of Plant Protection Products and Biocides	2.3.2 Model and process for characterising overall uncertainty	Lines 480–482. The uncertainties were assessed with reference to only one of the ten modelled populations (German adults). German adults were chosen because the size of the consumption survey used in the modeling for this population is larger than for other populations, and therefore the estimates of the model are less influenced by uncertainty. For the other populations, this simplification introduces additional uncertainties in the assessment. We believe it is important that conclusions to be made are as reliable as possible for the most critical/vulnerable population. Therefore, in order to minimize the uncertainty range for the most critical/vulnerable population, we would rather prefer to focus on the most critical/vulnerable population as a starting point when analyzing uncertainties in risk assessments.	Although the uncertainties were assessed in detail for German adults (for the reasons stated in the comment) and then applied also to other populations, differences in the uncertainties between populations were taken into account in a subsequent step of the uncertainty analysis (EKE Question 3, section 3.4 of the draft report). In this process, the additional uncertainties referred to by the commenter are taken into account. Nevertheless, we agree that in principle it would be preferable to focus the more detailed analysis of uncertainty on the most critical population and will consider doing this in future assessments.
43	ECPA – European Crop Protection Association	2.3.2 Model and process for characterising overall uncertainty	The assessment is supported by an assessment of authorised uses (table 3) and the EKE refinements of uncertainties. The EKE system is documented to be resource intensive and is not very transparent. Nonetheless, the uncertainties especially for exposure may be similar across CAGs – it would be useful for the document to project which parts of the existing EKE methods and uncertainty curves are transferable for other CAG assessments. The EKE method was also used for the weight-of-evidence assessment of toxicology, however it is suggested to use a clearer defined weight-of-evidence approach earlier (during the time when CAGs are established). This has been commented during the public commenting period of the scientific report on the establishment of CAGs of pesticides for their effects on the nervous system and thyroid. Also, please provide more information on the way the distribution on the uncertainty factors has been conducted (gamma vs beta functions…).	The protocol, process, supportive information and outcome of each module of EKE supporting the uncertainty analysis have been described in detail. Only individual assessments are kept as internal documentation and not included in the report, because they do not contain additional factual information and are superseded by the outcome of the consensus discussion. The transferability to CRAs related to other CAGs is limited: Sources of uncertainties as such are mostly transferable, but their impact is not transferable when they depend on the risk drivers. We assume that the commenter is requesting more information on how the distributions were fitted to the quantiles provided by experts in the elicitation process. The elicitation of distributions is mentioned only briefly in the section the comment refers to (lines 495–497), which refer to section 2.2.2.5 for details. Unfortunately this reference was incorrect and should have referred to section 2.3.5 in the draft report, where it is stated that the experts' judgements 'were entered into the SHELF Shiny app for eliciting a single distribution and the best-fitting distribution

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				provided by the app was displayed for review by the experts' (lines 673–675). A link to the app on the internet was provided in a footnote, but no further details of the software. The software fits a selection of parametric distributions (normal, lognormal, Student's *t*, log Student's *t*, gamma, beta) using least squares on the cumulative distribution function and indicates which of them gives the best fit. This information has been added to the footnote in the revised report.
44	Pesticide Action Network Europe	2.3.2 Model and process for characterising overall uncertainty	Children are more sensitive to exposure, therefore, to be more protective (Regulation (EC) No. 1107/2009 calls for a high level of protection), children or toddlers should also be selected for the uncertainty assessment, even though the numbers were lower. Extrapolating from adults to children creates additional uncertainty. By selecting an adult population all the sources of uncertainty due to potential effects in infants, toddlers and children or the vulnerable groups of society are downplayed. Most of the studies collected are done in adult animals. Also, toddlers and small children will be exposed to fruit by grabbing the fruit and then putting then putting their fingers in their mouth or grabbing their food. The choice to carry out the uncertainty assessment in adults is already biased as several questions will be answered only focusing on adults (e.g. peeling of the fruit or data gaps in toxicity studies).	See response to comment 42.
45	Wageningen University & Research	2.3.3 Choice of probabilistic model output for use in the uncertainty analysis	p. 15, Line 544: 'the MCRA software conducted a smaller number (100) of outer loop iterations'. This contradicts footnote 4 on p. 9, which states, at least for SAS, that the inner loop was repeated 100 times in the 'outer-loop execution'. Please correct.	It is agreed that this statement is inaccurate. The sentence is removed from the report.
46	Norwegian Scientific Committee for Food and Environment (VKM)	2.3.4 Evaluation of individual uncertainties (EKE Question 1)	p 16, Line 555 onwards: The EKE identified 34 sources of uncertainty affecting the input data. EKE: Seven experts participated in 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.	

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			The consensus process was conducted partly during a physical meeting and completed remotely. Our main concerns are as follows: • How did the experts identify the uncertainties, and how was the consensus developed? • Is the identification of uncertainties based on scientific data? We are of the view that expert identification of uncertainties should be based on scientific evidence or the lack thereof.	In section 2.3.1, a systematic approach was used to identify all sources of uncertainties, as recommended by the guidance on uncertainty analysis in scientific assessments (EFSA Scientific Committee, 2018a). This was indeed based on considering the scientific evidence and the gaps and limitations in the evidence. The type of consensus judgement aimed at by the elicitation method used in this assessment is defined in section 2.3.5. Each consensus judgement was developed by a process in which experts discussed their individual judgements and worked towards agreement on a shared judgement, which they considered to be consistent with the definition of a consensus. More details on these processes have been given in sections 2.3.1 and 2.3.5.
			For example, the seven experts state that the differences between populations are essentially induced by differences in food consumption. Based on this statement the experts assumed that the effect of peeling and/or washing 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 about 30 and 10% of total exposure above the 99th percentile, respectively. This would tend to shift the overall distribution of the multiplicative factor of the MOET towards higher values. It was assumed that the estimated 99.9th percentile of the MOET at 99.9th percentile of exposure would increase by at least 10% in toddlers and children populations. • Is the judgment that peeling of apples would tend to shift the overall distribution of the multiplicative factor of the MOET towards higher values based on scientific data or is it a hypothesis?	The effectiveness of peeling and washing on the decrease of residues (and so resulting in higher MOETs) is based on factual information, as described in note 25 of appendix B. The reference to the peeling and washing of commodities as factors with higher effects on the intake of residues in children than in adult populations is based on the experts' expectation that some commodities with edible peel (e.g. of apples and grapes) are washed or peeled more frequently before consumption by toddlers and children than before consumption by adults. This is not an assumption or hypothesis (in the sense of being an assertion or theory which is treated as if it was true), but a reasoned judgement that people are more likely to wash or peel apples and grapes when feeding them to children than when eating them themselves. Furthermore, experts recognised that this expectation is uncertain, due to being based on reasoned judgement rather than data and took account of that when assessing its impact on the exposure assessment.
			The seven experts state that the difference in occurrence of pesticide residues in food commodities between populations and	This was a judgement based on reasoning, but not based on factual information or data allowing comparison

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			countries are expected to have a lower impact, due to the common market. • Is this an evidenced-based expectation or is it an assumption? The EU monitoring in 2014, 2015 and 2016 may help to draw relatively firm conclusions regarding differences in exposures between countries. However, our main concern regarding the uncertainty analyses is that the report lacks information about sources (scientific data) and methods used by EKE to identify sources of uncertainty.	between different countries. It is not simply assumed to be correct; instead, the uncertainty of the reasoning was taken into account. See revised note 15 of appendix B. More details on this process have been given in section 2.3.1. The notes in appendix B of the scientific report contain extensive details of the data and information used by the experts to identify and assess each source of uncertainty.
47	Wageningen University & Research	2.3.5 Evaluation of combined uncertainties relating to exposure and toxicology (EKE Question 2)	p. 18, Line 663: The experts agreed to define 'perfect information' in toxicology as 'the lowest BMDL'. This is clearly wrong, because BMDL is a lower uncertainty limit for BMD. Therefore 'perfect information' (where no uncertainties exist) is by definition BMD rather than BMDL.	Although it is natural to interpret 'perfect information' as implying that the BMD rather than the BMDL is required, the logical of the approach taken in this assessment makes the BMDL more appropriate. Text has been added to both CRA reports to explain this. The BMDL – or, more commonly, the NOAEL – is used in the risk assessment together with the appropriate uncertainty factor (or MOE threshold), for which the general default is 100. Together, these provisions are considered to achieve an appropriate level of conservatism for regulatory decision-making. The EC and Member States set the indicative target for the combined MOE based on NOAELs to 100 'in line with the safety margin currently used for establishing the toxicological reference values' (European Commission, 2018), implying that an equivalent degree of conservatism should be applied in the CRA. If the BMD was used in place of the BMDL the conservatism of the CRA would decrease, since the BMDL should be below the true BMD for most chemicals. Therefore, to maintain the level of conservatism, the expert judgements required in the CRA considered a 'perfect' BMDL rather than the BMD. Specifically, the judgements were made considering what the lowest BMDL from well-conducted studies on the relevant endpoints would be. In this way, the judgements take account of any uncertainties affecting the available toxicity data without changing the level of conservatism.

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48	Norwegian Scientific Committee for Food and Environment (VKM)	2.3.5 Evaluation of combined uncertainties relating to exposure and toxicology (EKE Question 2)	Line 655: Miss a discussion regarding the application of dose addition to the selected endpoints (AChE inhibition and motor activity) since MoA is important.	See note 30 of appendix B.
49	ECPA – European Crop Protection Association	2.3.5 Evaluation of combined uncertainties relating to exposure and toxicology (EKE Question 2)	The uncertainty assessment done for the establishment of the thyroid and nervous system CAGs (2018 and 2019 reports) was overall more transparent (using factors for specific effect descriptors), than the EKE assessment conducted on the toxicology of the risk drivers in these reports. A pragmatic solution to reducing the technical challenges of additional uncertainty assessment, which could also have a positive impact on the computation demands of probabilistic risk assessment, could be to exclude active ingredients from CAGs that are recognised to have lower probabilities of true CAG membership (e.g. subgroups 5–7 from the CAG).	This is noted. EFSA is considering possible additional methodological development for CRA. An option is to incorporate the CAG membership into probabilistic modelling, as recommended in EFSA (2019). This would be preferred to the total exclusion of substances with low CAG membership probability. If this was done, the potential contribution of the excluded substances would have to be considered as part of the uncertainty analysis, to avoid underestimating the risk. This would be difficult and rely entirely on expert judgement. When lower probability CAG members are included in the assessment, their contributions can be examined quantitatively by drill-down of the model output, so the extent of potential overestimation is much more easily and reliably assessed.
50	Pest Management Regulatory Agency, Health Canada	2.3.5 Evaluation of combined uncertainties relating to exposure and toxicology (EKE Question 2)	EFSA's expert panel agreed that the definition of 'perfect information' regarding toxicology parameters was 'the lowest BMDL20 (for CAG-NAN) or BMDL10 (for CAG-NAM) from a perfect set of toxicity studies and perfect knowledge of CAG membership, the toxicity–exposure relationship and how substances combine'. With regards to benchmark dose–response (BMR) or critical effect levels, the PMRA routinely establishes the BMR at 10% for brain AChE inhibition, and at 20% for erythrocyte AChE inhibition. The PMRA recommends that clarification be provided regarding the basis for a critical effect level of 10% for the endpoints related to functional alterations of the motor division of the nervous system, especially given that many of the specific indicators that were included in this category are often associated with relatively high variability (e.g. increases or decreases in motor activity).	It was needed to have a fixed BMD level to conduct the uncertainty analysis on an unambiguous basis. Such critical effect level should normally be defined by risk managers, because it relates to protection goals. In practice, this was not available and therefore the decision was made by the Working Group. This was clarified by a footnote in the final report.

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51	Wageningen University & Research	2.3.6 1-D Monte Carlo simulations to combine uncertainties related to exposure and toxicology	p. 19, Lines 694–707: Why have very many (10^5) values been sampled for the two experts' exposure- and toxicity factor distributions and just 100 for the model's uncertainty distribution? In the exposure assessments (EFSA, 2019b; van Klaveren [et al.], 2019), it was agreed that 100 would be enough to characterise the uncertainties with 90% or 95% confidence intervals (If not, it would be easy to repeat the calculations with a higher number). In comparison, the expert's distributions are less precise by their way of construction and in view of the very small number of experts. What is then a valid reason to use a 1000-fold higher sample size for these distributions? In addition, why are the two expert distributions combined by Monte Carlo, whereas an 'all possible combinations' strategy is used for combining the model distribution with the expert distribution? (leading to a total of 10^7 values!) A more symmetric strategy would be to sample 100 values from each distribution. These could be combined by Monte Carlo, leading to a final set of 100 values, which is typically enough for the usual 90% or 95% confidence intervals. Even if this is thought to be not sufficient, then combining the three sets in all possible combinations would provide a total set of 10^6 values in a more symmetric and therefore more reasonable procedure.	In fact, no unfairness or bias is introduced by taking a large number of samples from the exposure and tox expert distributions. The choice of a smaller number of samples for the uncertainty distributions of the exposure models was influenced by the cost of taking more computational resource/time but implies more Monte Carlo sampling error than would occur with larger samples. A larger number was possible when combining the model output with the expert distributions because the calculation ran very quickly and avoided introducing further Monte Carlo sampling error into the output. Effectively, there is no Monte Carlo error for the expert distributions and the only Monte Carlo error in the output is what derives directly from the Monte Carlo error for the model results. The way the distributions were combined ensured even treatment of each of the 100 model values. In hindsight, it is questionable whether sampling 100 values is typically enough for 90% or 95% confidence intervals. Consider, for example, a situation where the estimate has a standard normal distribution so that the 95% confidence interval should be [−1.96, 1.96]. Taking 100 samples, using the R software's default rules for percentiles and repeating 100,000 times, the lower endpoint varies from about −3 to −1 (quartiles are −2.03, −1.87, −1.71). Using the method recommended by Hyndman and Fan (1996) (see response to comment 13), the quartiles are −2.14, −1.96, −1.80. So, there's quite a large relative MC error with only 100 samples (as well as the bias involved in the default R method and many others), perhaps a 10% typical relative error on the width of the interval. This may or may not matter in any particular case but should not be ignored as a general rule.
52	German Federal Institute for Risk Assessment (BfR)	3 Results of uncertainty analyses	Lines 784 ff., p. 20 ff. A general comment to the uncertainty analysis: The procedure in general does not add confidence in the results. In principle, expert judgement was the key methodology to quantify the impact of uncertainties to the result. The outcome	The purpose of an uncertainty analysis is not to add confidence in the results, but to determine the confidence that can be given to those results. The final outcome of the risk characterisation is not arbitrary, but the result of a structured and documented process, taking into account all available evidence and the

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			that all CAGs are probably above a MOET of 100 when overall factors are multiplied sounds arbitrary. It should be noted that some monitoring samples result in a MOE below 100 per se. 'Scaling' up and down of the upper percentiles considering uncertainties affecting the total distribution (missing foods, missing PFs, differences in the consumption etc.) is not necessarily correct and the sensitivity to the P99.9 (as questioned) and to the rest of the exposure is probably different.	impact of missing information, and expressed in objective terms. The commenter does not explain why they regard 'scaling up and down' of the upper percentiles as 'not necessarily correct'. It is clear that uncertainties affecting assessment of the MOET will result in some probability of the MOET changing either up or down, and therefore it is appropriate that the uncertainty analysis aims to quantify this. However, assessment of the impact of the uncertainties necessarily involves expert judgement (especially where the uncertainties relate to missing information). Expert judgement is subjective and so it would be right to say it is 'not necessarily correct'. However, this applies to every risk assessment, because uncertainty and expert judgement are always involved. Using a structured, evidence-based approach, as was performed here, increases the reliability of expert judgement and makes it more likely that the conclusions are correct. The commenter is correct to say that the impact of the uncertainties is probably different at other percentiles. This is why the uncertainty analysis focused specifically on the percentile selected by risk managers as the focus for decision-making, and the report conclusions refer specifically to this.
53	Ctgb, Board for the Authorisation of Plant Protection Products and Biocides	3.1 Sources of uncertainty	Lines 791–793. Table 4: Sources of uncertainties 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). A source of uncertainty that influences the assessment is the limited availability of PFs. This source of uncertainty was identified and explicitly described and assessed in the uncertainty analysis. However, we believe that another source of uncertainty related to processing on an industrial scale has been overlooked: the degree of dilution due to bulking and blending. The effect of bulking and blending is completely independent of	We confirm that one individual occurrence value was randomly selected to calculate the intake resulting from the consumption of industrially processed commodities, even if subject to bulking or blending. This differs from current practice in pre-marketing acute exposure assessment. However, in the context of the retrospective assessments under consideration: • Available consumption data do not specify whether the commodity was processed industrially, or at home with commodities coming from the same lot; • Using a median of the observed monitoring values (the notion of STMR does not apply here) would probably in nearly all cases result in a zero level for pesticides in such commodities. Such an assumption is not considered

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			the use of PFs. In PRIMo 3.1, bulking and blending is considered a relevant factor for determining the risks of residues in e.g. cereals and juices; not only in the sense that a variability factor of 1 is used, but above all in the sense that the supervised trials median residue (STMR) is used instead of the highest residue (HR). For CAG-NAN in particular, apple juice is a typical risk driver, while residue levels obtained from individual monitoring data of apple are not representative of residue levels after bulking and blending on an industrial scale. The lack of data on the degree of dilution due to bulking and blending leads to an additional overestimation of the exposure.	realistic because in practice bulking and blending is only expected to occur over a limited number of lots. Furthermore, depending on how industrial production lines are designed in practice (e.g. continuous production lines from start to end), the effect of blending may be very limited. • Therefore, we admit that this might be a source of uncertainty, which should be documented and considered in the future. However, in the absence, at present, of factual information allowing the evaluation of its impact, it was not justified to review the outcome of our assessments.
54	Norwegian Scientific Committee for Food and Environment (VKM)	3.1 Sources of uncertainty	Line 800, table 5, row 3: What is meant by 'uncertainty regarding the combination of occurrence and consumption data'?	See note 33 of appendix B.
55	ECPA – European Crop Protection Association	3.1 Sources of uncertainty	Missing information on washing, peeling and processing is likely to be beneficial to finding realistic exposure estimates. Table 4: It is unclear why EFSA didn't have access to more PFs for foods related to risk drivers; there are many available PFs are in published EFSA publications. Are there specific additional criteria for use in a cumulative assessment? For example, NAM table A.2.03 contains 119 measured substances for the CAG but PFs in A.2.08 were only listed for 27 of the actives and only a total of 156 PF were available. Deltamethrin is a stated risk driver for NAM and EFSA (2015a) is included in the reference list, but none of the indicative PF were considered. As recognised within the draft EFSA/RIVM reports, only a few of the 47 total risk drivers identified by EFSA across the four CAGs have PFs listed. Use of known indicative PFs and extrapolations within crop groups or similar matrices would be more realistic than a default of 1.	The PFs for the active substances and commodities under assessments were extracted from a recent database (Scholz, 2018). This data collection covered all processing studies assessed by EFSA in Conclusions and Scientific Reports (in the context of Regulation (EC) No. 1107/2009) and in Reasoned Opinions (in accordance with Article 12 of Regulation (EC) No. 396/2005) issued until 30 June 2016. Therefore, more information is available in other EFSA outputs, and it is recommended in section 6 to consolidate the database on PFs. For deltamethrin, processing studies reported in the EFSA (2015a) were reviewed by Scholz (2018), and those assessed as acceptable or indicative according to uniform quality criteria were used for the assessment under consideration. Extrapolations between raw primary commodities (RPCs) with similar properties were also conducted.
			Also, can procedures to use monitoring values of processed food be developed, especially as a cross check on the conversion and use of consumption data as RPC?	It is indeed envisaged in the future to make use of monitoring data of processed commodities when available to perform the exposure assessment. These data would

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				however not be used to check the RPC model (EFSA, 2019e).
			Future procedures for the reduction of uncertainty due to measurement of a common moiety or unspecific residue definition could employ additional details on frequency of use.	Agreed. In section 6, we recommend the collection of use statistics of plant protection products, on a risk-based basis.
56	Pest Management Regulatory Agency, Health Canada	3.1 Sources of uncertainty	Exclusion of consumption data of animal commodities and plant commodities not in the list of the 30 selected plant commodities and their processed derivatives is a deliberate choice made by EFSA, probably due the lack of monitoring data on those commodities. This appears to be a shortfall of the CRA rather than an uncertainty.	See response to comment 10. Anyway, this results in a source of uncertainty which was considered using the information collected in notes 1, 2 and 3 of appendix B.
			Missing occurrence (monitoring) data for certain active/commodity combinations and their exclusion from the CRA would be considered a shortfall of the CRA rather than an uncertainty.	This results anyway in a source of uncertainty which was considered using the information collected in note 10 of the appendix B.
			Exclusion of the contribution of all metabolites and degradation products from the CRA is a deliberate choice made by EFSA and, therefore, would not be considered an uncertainty.	This choice was made for reasons of resources and anyway results in a source of uncertainty which was considered using the information collected in note 11 of appendix B.
			The assumption that pesticide residues are transferred without any loss to processed commodities when PFs are not available (i.e. assuming a PF of 1) is a good approximation in contrast with the 'zero residue' assumption used in the sensitivity analysis (see section 2.2.2).	As an assumption, this was anyway resulting in a source of uncertainty which was considered using the information collected in note 21 of the appendix B.
57	US EPA Office of Pesticide Programs	3.1 Sources of uncertainty	No specific evidence was presented showing that there is dose additivity among chemicals with different MoAs, thus it is unclear why chemicals with different MoAs were put together into the same CAG.	In 2013, the PPR Panel adopted an opinion on the appropriate way to deal with dissimilar MoAs in the context of CRA (EFSA PPR Panel, 2013). The use of dose addition was later advised by the EFSA Scientific Committee (2019). Additional information is given in note 30 of appendix B).
59	US EPA Office of Pesticide Programs	3.3 Combined impact of uncertainties (EKE Question 2)	Based on expert judgement, the uncertainties associated with selecting the hazard/toxicological and exposure input parameters (e.g. selection of NOAEL and monitoring programs' limited sampling of commodities) quantified in the latter stages of uncertainty analysis is much smaller than the uncertainty associated with model resampling of the consumption and residue data quantified in the first stage of the uncertainty analysis.	Assuming that the word 'smaller' in your comments is a mistake and that 'larger' was intended, we agree with your comment. The relative magnitude of these uncertainties is shown by a comparison between the blue box plot ('model uncertainties' reflecting the effect of occurrence and consumption data sampling uncertainty) and the green box plot ('expert' reflecting the effect of all other uncertainties), and is noted in the accompanying text (lines 971–972).

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59	Wageningen University & Research	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 (brain and/or erythrocyte AChE inhibition)	The key to figure 5 as printed next to the figure (identifying 'model', 'experts' and 'both') is misleading. The graph shows that the 'experts' assessment is almost the same as the 'both' assessment. Without a close reading of the text under the graph, readers could easily draw the wrong conclusion that the 'model' assessment is not needed at all. In fact, the 'experts' assessment needs everything of the 'model' assessment (note that the 'experts' assessment uses the median of the 99.9th percentile from the model, so all model uncertainty runs have to be performed). The true message of the figure is that experts can provide a bias correction for the model and specify additional uncertainty quantification, and that this added uncertainty is much larger than the uncertainty quantified in the model. A more useful and less misleading graph would only show two assessments: 'model' and 'both', and rename the latter to 'model + expert adjustment' The current 'experts' assessment should technically be described as 'model + experts' adjustment, but without the uncertainties quantified in the model, however using the median of the model uncertainty runs', This type of assessment is not practical nor very informative and would better be omitted. If there is a wish to have a third assessment plotted, then it would be better to plot 'model + expert bias correction', i.e. the model results displaced to the corrected median but still with the smaller 'model' uncertainty	It is agreed that 'experts' is a misleading description because the boxplot it refers to combines the sources of uncertainties elicited by the expert with the median from the model, and that including this boxplot in the figure could lead to misinterpretation. In the final report, the 'experts' boxplot is omitted and the 'both' boxplots are relabelled as 'model + experts'.

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60	Norwegian Scientific Committee for Food and Environment (VKM)	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 (brain and/or erythrocyte AChE inhibition)	Line 871: Overall, the uncertainty part of the report is very well written, but these tables are not easy to understand for people not familiar with this approach. Some description of the results and the consensus distribution in figure 3 would be helpful. This applies also for the other tables and figures presented in subsequent sections.	Thank you for this suggestion, which is accepted. The revised report contains added explanations with the first example of each type of figure and table in section 3, either directly or in a footnote. The legends of subsequent tables and figures refer back to the first instance for explanation.
			Line 892: Why is toxicity overestimated for the group with gavage administration?	The argument given in these lines concerns *N*-methyl carbamates only. In case of gavage (or bolus), a massive absorption of the substance is expected shortly after the administration resulting in a high Cmax (maximal concentration) in blood. The AChE inhibition will be maximised during the peak concentration, but brief as it is quickly reversible. In contrast, when the substance is incorporated to the diet (as it is mostly the case when the substance is present as residue), the absorption is expected to be spread over time and not leading to similar levels of AChE inhibition. This argument does not hold for organophosphorus insecticides, as they produce an irreversible AChE inhibition, and therefore the level of this inhibition is not depending on the absorption rate.
			Line 960: In figure 5, it will be helpful to describe what 'both' and 'model' stand for.	The meaning of 'both' and 'model' in figure 5 is already explained in the draft report in the footnote to the figure and further explained in the following text. Nevertheless, figure 5 was further clarified. See response to comment 59.
61	Pest Management Regulatory Agency, Health Canada	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 (brain and/or erythrocyte AChE inhibition)	b) Combined impact of uncertainties related to toxicology The tendency of the NOAEL to underestimate the BMDL20 (which EFSA uses as the critical effect level for AChE inhibition) due to the wide dose interval between the NOAEL and LOAEL in the critical studies was listed as a potential source of increasing the modelled estimate of the MOET. The basis of this statement is unclear, especially within the given context regarding the 'wide dose interval between the NOAEL and LOAEL'. It is recommended that clarification be provided.	The smaller the dose spacing between the subsequent doses in a toxicity study is, the closer the observed NOAEL is likely to be to actual/theoretical dose that would cause an effect at the extent of the predetermined critical effect size. For AChE inhibition the critical adverse effect size is set up by risk managers at 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. So, 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

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				MOET is likely to be smaller if the NOAEL is derived from a study with large dose spacing. If the uncertainty around the NOAEL, which is larger in studies with large dose spacing, would be resolved it was judged by the experts that this would increase the modelled estimate of the MOET. Performing a BMD analysis will give a better estimate of the dose inducing the effect at the level of the critical effect size. Indeed, we recommend the use of BMD modelling in section 6. Note 29 of the appendix B has been updated.
			In EFSA's document on establishing cumulative assessment groups for pesticides for their effects on the nervous system (June 2019), it was stated that if only a LOAEL was available for a certain indicator, a default NOAEL was determined from this LOAEL by applying an additional uncertainty factor, and that this was not defined on a case-by-case basis, but was instead set at 10 in all cases. When applying uncertainty factors to extrapolate from a LOAEL to a NOAEL, the PMRA would use a factor of 1- to 10-fold. The magnitude of the selected factor is based on several considerations, including the level of the response at the LOAEL, the nature of the effect, and the steepness of the dose–response curve.* These considerations are unique to each chemical. Therefore, the PMRA suggests that the application of a standard default uncertainty factor of 10-fold for all chemicals be considered as an additional potential source of uncertainty, under the category of 'NOAEL setting'. *The application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides. SPN2008–01. Health Canada, 29 July 2008.	The application of an uncertainty factor to derive a default NOAEL from a LOAEL has actually been considered as contributing to the source of uncertainty related to the setting of NOAELs – see note 29). Nevertheless, we agree with the PMRA approach and will consider using it in forthcoming CRAs.
			It is not obvious how monitoring data that occasionally showed quantifiable residues of non-approved pesticides that are not included in the assessed CAG-NAN would be a source of uncertainty and lead to an overestimation of the MOET since those data would not be included in the exposure and risk calculations anyway.	Following the assessment question, pesticides not approved, but nevertheless present in the commodities and contributing to the effect of concern need to be considered and included in the CAG. As long as they are missing from the CAG, this is causing a source of uncertainty. This was assessed by expert judgement using the information in note 27 of appendix B.
62	Wageningen University & Research	3.3.2 Impact of uncertainties on the MOET	Figure 8: same comments as for figure 5 in section 3.3.1.	See response to comment 59.

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		estimates at 99.9th percentile of exposure in the German adult population for CAG-NAM (functional alterations of the motor division)		
63	German Federal Institute for Risk Assessment (BfR)	3.3.2 Impact of uncertainties on the MOET estimates at 99.9th percentile of exposure in the German adult population for CAG-NAM (functional alterations of the motor division)	Line 1111, p. 32 (comment also refers to: line 1251, p. 35, line 1355, p. 38, line 2304, p. 75). In general, the phrase 'as for…CAG-NAN…' (when comparing it with CAG-NAM) should be revised to 'Similar to CAG-NAN …' for easier comprehension.	This is agreed. This was corrected in the final report.
64	ECPA – European Crop Protection Association	3.3.2 Impact of uncertainties on the MOET estimates at 99.9th percentile of exposure in the German adult population for CAG-NAM (functional alterations of the motor division)	Line 1057 ff.: The individual compounds (triazophos and chlormequat), which were identified to be the risk drivers in the acute CRA were actually considered to be in subgroup 4 or 5 of the acute motor division CAG, indicating a lower probability, that these two compounds truly belong to this CAG. This would have a strong (+) rather than a limited impact on the MOET.	Triazophos was listed in subgroup 4, and it was concluded almost certain that all substances from subgroups 1 to 4 were causing the effect, because these subgroups contained only substances with relevant chemical structures and MoAs (EFSA, 2019a). Chlormequat was listed in subgroup 5. Substances in this subgroup had still a high probability to cause the effect, especially chlormequat as this substance has a neurotoxic MoA.

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65	Pest Management Regulatory Agency, Health Canada	3.3.2 Impact of uncertainties on the MOET estimates at 99.9th percentile of exposure in the German adult population for CAG-NAM (functional alterations of the motor division)	EFSA notes that there is a possibility that some of the substances that were considered for inclusion in this cumulative assessment group might have been wrongly excluded due to failure of the available studies to detect effects on the motor division. The PMRA acknowledges that this is a very real possibility given the fact that most of the available toxicity studies would not have been examining potential effects on motor division. As well, without a very thorough analysis of the raw data, it is possible that these effects might not have been consistently reported in the regulatory reviews. It is not obvious how monitoring data that occasionally showed quantifiable residues of non-approved pesticides that are not included in the assessed CAG-NAM would be a source of uncertainty and lead to an overestimation of the MOET since those data would not be included in the exposure and risk calculations anyway.	Agreed. See note 27 of appendix B. See response to comment 61.
66	CNRS/ Museum National d'Histoire Naturelle.	4.1 Brain and/or erythrocyte AChE inhibition	I find it most disquieting that the highest exposure levels were found for toddlers (see for instance line 1279) a particularly vulnerable group.	This is noted. It is clearly reflected in the conclusions that toddlers have indeed the lowest MOETs at 99.9th percentile of the exposure distribution.
67	Private citizen	5 Conclusions	I have analysed (https://www.ncbi.nlm.nih.gov/sites/myncbi/anthony.tweedale.1/collections/56120454/public/) the almost 1,600 chlorpyrifos (only) toxicity findings I found in PubMed, (up until a couple of years ago). Nine findings of toxicity were below its alleged LOAEL of 0.3 mg/kg d^{-1}; and 16 below the alleged NOAEL of 0.1 mg/kg d^{-1} (two; very close/at the alleged ADI) (six more whose abstracts only say 'low-dose' narratively). At least two further industry studies in the RAR find toxicity below the claimed NOAEL (p. 107 and p. 117 of chapter B6 of the RAR), but these were never discussed!	For chlorpyrifos, for the assessments under consideration (acute CRA), we used a NOAEL of 0.5 mg/kg bw, based on the effects of single dose in a CCA (EFSA, 2019a). This NOAEL served as basis of the acute reference dose (ARfD) set up by EFSA in 2014 (EFSA, 2014a). In the RAR referred to by the commenter: On p. 107, a 6-week study in dogs is reported where erythrocyte AChE inhibition was evident at all dose levels (0.5, 1.0 or 2.0 mg/kg bw/day), but after 1 week of treatment. On p. 117, a 13-week study in dogs is reported. In that study, erythrocyte AChE activity for dogs receiving 0.22 mg/kg/d was reduced from week 6. No inhibition of erythrocyte AChE was observed at the lower dose (0.01 mg/kg bw/d). The RAR concluded, based on findings in the 2-year dog study, that the NOAEL for (long-term) erythrocyte AChE inhibition in dog was 0.1 mg/kg bw/d. These were not used in the present CRA because they refer to longer exposures than is relevant for an acute

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				assessment. Please note that in a forthcoming CRA for chronic erythrocyte AChE, we will use a NOAEL of 0.1 mg/kg bw/d, as established in EFSA (2019c).
			Hundreds of chlorpyrifos studies find synergistic toxicity with other agents, be they pesticides or stress, etc.; and some 41 of these so find it at fairly low chlorpyrifos dose. About half of these low-dose chlorpyrifos published findings concern neurotoxicity. To the extent other insecticides are as heavily used for as long, they will also elicit similar findings, available on PubMed, etc., awaiting only a curious mind. Not evaluating such findings makes your conclusion 100% unreliable. True, the accuracy ('reliability') of competing test methods must be assessed, but no one will even raise the issue…as academia's low-dose findings continue to accelerate, simply because biochemistry must function with low signal strengths! [If you like, contact me & I will email you my spreadsheet of the 1,600 found; noting lead author, year, endpoint, and if low dose or synergy finding.]	See response to comment 25.
68	Ctgb, Board for the Authorisation of Plant Protection Products and Biocides	5 Conclusions	Lines 1371–1373. 'Overall, taking account of the available data and the uncertainties involved, it is concluded that cumulative exposure to pesticides that have acute effects on the nervous system does not exceed the threshold for regulatory consideration established by risk managers.' For CAG-NAN, this conclusion could be drawn for Dutch toddlers with 80% certainty. The question is whether an 80% guarantee is sufficient and whether assessors and decision-makers have a shared opinion about the required level of certainty. Unless something about this is included in the report, the final conclusion of EFSA is therefore, in our opinion, a little premature. It seems that the scientific analysis and advice to Standing Committee on Plants, Animals, Food and Feed (SC PAFF) are mixed up there. It would be better if the scientific analysis is concluded with an overall conclusion that says '…is (highly) unlikely to exceed the threshold for regulatory consideration established by risk managers'. This can be followed up with a recommendation stating that regulatory measures are not	Following the multiple comments received, the overarching conclusion proposed in the draft scientific report has been reworded as follows: '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%

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			considered needed. Please note that we agree with a recommendation stating that regulatory measures are not needed. In addition to the conclusion that it is unlikely that the threshold for regulatory consideration has been exceeded, another argument can be given for consideration to risk managers: the analysis shows that the highest acute exposures at the 99.9 percentile are not so much the result of cumulative exposure to multiple substances. The majority of the high exposures are determined by a single substance in a specific raw commodity and by MRL exceedances. Because MRLs have been lowered for some of these substance–commodity combinations, exposure to these combinations is now expected to have decreased.	for two populations of children and all toddler populations.'
69	Norwegian Scientific Committee for Food and Environment (VKM)	5 Conclusions	Line 1373: Consider clarifying that the conclusions made here are solely based on the populations studied. For example by adding a statement such as 'for the populations studied'.	The conclusions are indeed based on the outcome of the assessments performed for the 10 selected populations. However, for the reasons given in section 4.3, these populations offer a fair coverage of the full EU population.
70	ECPA – European Crop Protection Association	5 Conclusions	ECPA agrees that after taking account of the data used and the uncertainties involved, that the cumulative exposure to pesticides that have acute effects on the nervous system does not exceed a threshold of concern for public health identified by risk managers.	See response to comment 68.
71	CHEM Trust	5 Conclusions	In particular we question the final conclusion 'taking account of the available data and the uncertainties involved, it is concluded that cumulative exposure to pesticides that have acute effects on the nervous system does not exceed the threshold for regulatory consideration established by risk managers' or in other words – the cumulative exposure to pesticides that have acute effects on the nervous system is considered as safe. We are aware that this conclusion is based on the available data and uncertainty analyses as described by the term of references. We note that the risk characterisation is based on very sophisticated exposure modelling and assessment, however, the same advanced level is not at all the case when it comes to the hazard assessment. As also stated by the authors there are several limitations in the available knowledge and data that affect	See response to comment 68. A sophisticated hazard assessment was undertaken in the scientific report on the establishment of CAGs of pesticides for their effects on the nervous system (EFSA, 2019a). This comprised the calculation of a probability distribution of the proportion of substances in the CAG actually causing functional alterations of the motor division and the identification of sources of uncertainties affecting the

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			the assessment. These uncertainties should be properly reflected by the hazard characterisation.	toxicological characterisation, including the limitations in data and knowledge referred to by the commenter. Based on this, the uncertainties related to toxicology were extensively assessed in the report under consideration. Section 6 (Recommendations) of the final report has been revised to give equal prominence to recommendations pertaining to both toxicology and exposure.
			CHEM Trust would like to point out that many assumptions have been included and several decisions have been taken which may add to the level of uncertainty and bias the uncertainty assessment in a more favourable direction. In particular, we are concerned about the estimated MOETs for toddlers and children which are below 100 for several populations and which then are adjusted to a level which consequently will not lead to regulatory considerations.	Assumptions were made in the calculations, as is necessary in any model. However, the impact of the associated uncertainties was taken into account in the subsequent uncertainty analysis. Some uncertainties would tend to reduce the MOET (if resolved) and others to increase it. The adjustment of the MOETs is not a biased decision but a balanced judgement based on reasoned assessment by seven experts of the combined effect of all the uncertainties. The adjustment of the MOET after consideration of all uncertainties could be perceived as a process bias mitigating the concerning outcome delivered by the exposure calculation model. This is not the case, but rather an expected effect of the uncertainty analysis, reflecting the degree to which the regulatory assumptions were overall purposely conservative (see section 1.2 of the report). Sections 4.1 and 4.2 (Risk characterisation for AChE inhibition and functional alterations of the motor division, respectively) and section 5 (Conclusions) of the final report have been slightly revised to avoid a potential misperception.
			We find the overall conclusion of the cumulative dietary risk characterisation biased and overly firm also in the light that estimates for MOETs for toddlers are uncertain and may be below 100. It could easily be misinterpreted in the way that cumulative exposure to pesticides is considered safe and with no risks of causing effects on the nervous system which is not based on scientific evidence. We therefore recommend changing the final conclusion and providing cautionary language which highlights the limitations of the database as well as the fact that the assessment does not include neurodevelopmental toxicity. This lack of knowledge	See response to comment 68.

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			should be highlighted and properly reflected by the conclusion and it should be considered whether a judgement about whether a threshold for regulatory consideration is exceeded is reasonable based on the current database and uncertainties.	
72	The National Farmers' Union of England and Wales	5 Conclusions	The NFU finds it re-assuring to read the overall conclusion that cumulative exposure to pesticides that have acute effects on the nervous system does not exceed the threshold for regulatory consideration established by risk managers.	See response to comment 68.
73	Pesticide Action Network Europe	5 Conclusions	Addressing cumulative and synergistic effects of pesticide products and their residues it is a legal requirement that has not been implemented for 14 years now. Therefore, an assessment on the safety of these products taking into account mixture effects is urgent.	
			Although we welcome EFSA's intention to develop CRA, we are very disappointed with the current procedure, particularly with the numerous assumptions, the uncertainty analysis and the questionable conclusion. The overall uncertainty analysis appears completely biased to favour a result that wouldn't require any regulatory action to address mixture effects.	The commenter expresses disappointment with the 'numerous assumptions' and procedure for uncertainty analysis. All risk assessments include assumptions: this is unavoidable. Therefore, it is normal scientific practice to document assumptions and explain the rationale for them, as has been done in this assessment – partly in the present report, and partly in the preceding reports on CAG membership (EFSA, 2019a) and the exposure models (EFSA, 2019b). The present assessment adds a critical extra step, by assessing the impact of the assumptions on the uncertainty of the conclusions. The procedure used for the uncertainty analysis follows guidance published by EFSA in 2018 (EFSA Scientific Committee, 2018a), accompanied by a detailed scientific opinion (EFSA Scientific Committee, 2018b) which documents the scientific basis for the approach and provides extensive detail and references on the methods involved. These were developed in a process that included a public consultation and a trial period of one year when the draft guidance was applied to case studies from all areas of EFSA's work. EFSA's approach was also discussed at an international conference hosted by BfR in 2019 and in a report by the Commission's Chief Science Advisors, which commented favourably on EFSA's guidance and concluded that it was suitable for use beyond the field of food safety area (European Commission, 2019).

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				The commenter is also disappointed by the conclusion. They describe this as 'questionable' and say it 'appears completely biased to favour a result that would not require any regulatory action'. Substantial efforts have been made to avoid bias in this assessment. These start with the normal procedures of EFSA for selecting suitable experts to participate in Working Groups and for requiring comprehensive declarations of interests which are updated at every meeting and published to enable external scrutiny. Each step of the assessment procedure is documented in detail in draft reports, which are subjected to external scrutiny by public consultation and revised to take account of comments received. The uncertainty analysis involved a formal EKE process, following guidance prepared for EFSA by international experts in elicitation methodology (EFSA, 2014b). The EKE guidance explicitly recognises the potential for bias in expert judgement and recommends methods for addressing it. These include appropriate selection of experts and various aspects of the elicitation protocol itself. In the Sheffield protocol, used in this assessment, judgements are elicited separately from each expert and then compared and discussed in detail by the group before working towards a consensus judgement. This process is led by an experienced facilitator, who focuses the discussion on differences between experts and asks them to explain the evidence and reasoning their judgements are based on. This process is designed both to take account of differing scientific perspectives and to uncover, challenge and correct any biases, whether intentional or not. Further details of the procedure are designed to mitigate subconscious psychological biases that affect all human judgements (EFSA, 2014b), e.g. eliciting a plausible range before the median, to avoid the tendency to underestimate uncertainty when the central estimate is elicited first. In summary, the approach taken in this assessment contains numerous aspects designed to counter bias. The present public consultation was undertaken to provide a further opportunity to check for bias by publishing a detailed account of the assessment for external scrutiny,

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				including the evidence, reasoning and judgements leading to the overall conclusions. In reviewing the comments received, EFSA has paid particular attention to identifying comments that provide additional evidence and/or challenge the judgements and reasoning contained in the draft report and to considering whether, in the light of the comments, there is a need to revise the assessment and/or the conclusions. EFSA's responses to individual comments by this commenter and others are presented at the relevant points in this report, and changes have been made to the assessment report where needed. EFSA's view on the main recurring comments, including this one, is presented in section 4 of this report on the public consultation. See also response to comment 71.
			The experts' judgement alters remarkably an already conservative exposure assessment (tier II is less conservative than tier I) with missing toxicity-related data and certain neurotoxicity endpoints (neurochemical effects other than AChE inhibition, behavioural or cognitive effects). The assessment has great limitations from the start because it excludes some of the most sensitive studies available not only from open scientific literature but even protocol studies such as the neurodevelopmental toxicity.	See response to comment 25 on the use of open scientific literature and on developmental neurotoxicity.
			Even with these limitations a risk (MOET < 100) was identified in eight populations for CAG-NAN and six populations for CAG-NAM, including all children and toddlers' populations in both CAGs. It is incredible that expert judgement results in five or six times higher MOETs! This uncertainty analysis seems to be a strategic approach to conclude on purpose that there is no human risk due to pesticide exposure.	See above. See also response to comment 71.
			Dietary risk assessment has to be adapted to the worst-case scenario, where the most vulnerable groups of the population will be exposed to the highest number of pesticides possible through the food that act on the nervous system. The CRA and uncertainty analysis should be repeated, using a precautionary approach, focusing on the vulnerable groups of the population, addressing the missing data and taking into consideration that pesticides are not the only pesticides we're exposed to and	The assessment included groups representing different parts of the population including the most vulnerable age groups. The assessment also included all pesticides identified by EFSA as potentially causing AChE inhibition or motor effects. The possibility that some additional pesticides might also belong in these CAGs was considered in the uncertainty analysis. Missing data were addressed in the uncertainty analysis. Exposure through non-dietary

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			neither food is the only route of exposure (refer to additional sources of uncertainty in section 2.3.2).	routes and to chemicals other than pesticides was outside the scope of the present assessment; see comment 5 on future EFSA activity on these topics. Invocation of the precautionary principle is a risk management option, and deciding when to invoke it is the responsibility of risk managers. One of the considerations for invocation of the precautionary principle is the degree of scientific uncertainty affecting the assessment of the risk (European Commission, 2000). The role of risk assessors is therefore to provide information on the degree of scientific uncertainty, to support risk managers in their role. The present report fulfils that function by including a detailed uncertainty and providing clear information on the degree of uncertainty associated with the conclusions on cumulative risk. See also response to comment 42.
			Moreover, one wonders why EFSA decided to examine acute neurotoxic effects of pesticides via food consumption even though it collected data addressing both chronic and acute neurotoxic effects. It seems that chronic neurotoxic effects would be more relevant if exposure takes place through food.	The purpose of the pilot phase of implementation of CRA was to test the methodologies in the two main types of dietary risks: acute and chronic risks. Considering the available resources, the chronic effects on the thyroid and the acute effects on the nervous system were selected for the pilot tests, because these effects are prominent effects of pesticides in regulatory studies. In the next implementation phases of CRA, it is the intention of EFSA to address the chronic cumulative risks of AChE inhibition, as recommended in section 6 of the scientific report.
74	Istituto Superiore di Sanità – Dept of Food safety, Nutrition & Veterinary Public Health	6 Recommendations	Lines 1377–1379: The risk characterisation of CAG's for acute effects on the nervous system is primarily based on residue monitoring data. As outlined elsewhere in the document (e.g. lines 1914–1916) the residue definition for monitoring does not always coincide with the residue definition for risk assessment (see also EFSA PPR Panel, 2016): more compounds (plant metabolites, abiotic/biotic degradation products) should be considered for a significant fraction of active substances. This aspect is repeatedly pointed out in the opinion, starting from the Summary, line 100) and it should be reflected in the Recommendations, for example:	A recommendation was added to section 6 for the assessment of the contribution of metabolites to cumulative effects.

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			'Regularly update the CAGs established in the present report, and in particular (i) include more residues (metabolites and degradation products) relevant to CAGs that are currently not considered in residue monitoring programmes; (ii) include non-approved active substances.' Recommendations on developmental neurotoxicity (lines 1380–1381 and 1398–1400): these recommendations are fully endorsed and they should be duly considered also by regulators and policy makers.	Recommendations related to developmental neurotoxicity and regular update of the CAGs are already present in the respective report (EFSA, 2019a).
75	ECPA – European Crop Protection Association	6 Recommendations	In general, ECPA supports the aim to use all the available data for CRAs (e.g. available compound-specific PFs or PFs from databases, mechanistic toxicological data). Line 1382: For the CAG membership it is suggested to exclude the low probability substances, starting from subgroup 4 down to subgroup 7 (in case of the acute motor division group). However, a probabilistic modelling of the different likelihoods to belong to CAG membership might be an alternative option. EPCA agrees with the EFSA draft report regarding the need for exposure refinement, and especially: • Consolidation of PFs for use in CRA. • Collection of information on use frequency of plant protection products. Have sources of information been identified (e.g. market share data, sales records)?	This is noted. EFSA is currently investigating leaner approaches to perform CRA of pesticide residues in the forthcoming years. This could involve simple and quick approaches applicable for low-risk situations and refined approaches using all relevant available data in other situations. See also the response to comment 49 on the suggestion of excluding low probability substances.
76	Health and Safety Executive	6 Recommendations	General: Information/a database on EU wide registered uses is also required. The use of the limit of quantification (LOQ) and Article 12 Reasoned Opinions to determine if there are registered uses will not always be appropriate. Under the interim procedures for the MRL reviews Member States may not necessarily have provided good agricultural practice (GAP) information and data when residues were below the LOQ. Similarly, after an MRL review Member States will not notify uses that have been authorised that give residues below the LOQ.	Agreed. Recommendations in section 6 were extended to the collection of information on national registrations.

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			General: Additional work should be undertaken to support the application of the default proportion of 0.5 (50%) when associations for residues are not exclusive.	This can indeed be envisaged on a case-per-case basis in the assessment of uncertainties. Metabolism data could be considered, especially those for risk drivers.
77	CHEM Trust	6 Recommendations	CHEM Trust is very concerned about the effects on nervous system in vulnerable populations as summarised in our CHEM Trust report 'No Brainer: The impacts of chemicals on children's brain development: a cause for concern and a need for action' (https://chemtrust.org/brain/) where we summarised the state of the science regarding the concerns about the human health exposure to substances which can impact on brain development. Therefore, we agree with the following recommendation made in the report, namely: • Develop a testing and assessment methodology covering developmental neurotoxicity of pesticides, and, if appropriate, to establish CAGs and perform CRAs in this area; and • Draw up a new CAG for DNT and further perform CRA to assess the one combined impact of organophosphates, pyrethroids and other insecticides with DNT potential on infant, toddler and children populations.	This is noted. See section 6 (Recommendations) of the final report and response to comment 25.
78	Istituto Superiore di Sanità – Dept of Food safety, Nutrition & Veterinary Public Health	Appendix B – Information used in the uncertainty analysis	Appendix B2, Note 11 (Contribution of metabolites). Lines 1914–1916: The residue definition for monitoring does not always coincide with the residue definition for risk assessment: this aspect is thoroughly discussed in the 'Guidance on the establishment of the residue definition for dietary risk assessment' (EFSA PPR Panel, 2016): therefore, this EFSA document should be included in the references.	See response to comment 74.
79	ECPA – European Crop Protection Association	Appendix B – Information used in the uncertainty analysis	Line 1850 (table B5): The sampling information for six of the 10 populations used in the Pilot Project is described in note 8. It would be useful if criteria for assessing the suitability of a survey for probabilistically modelling acute and chronic exposure assessment could be added. A comparison of the design of the surveys against criteria used by the EU Menu Guidance in order to understand the representativeness of the surveys.	General information about the sampling strategy in dietary surveys is given in the EFSA guidance on the use of the comprehensive European food consumption data (EFSA, 2011b). Notes 7 and 8 of appendix B deal with the sampling uncertainty and the representativeness of consumption data, respectively. It is not possible to propose absolute criteria for assessing the suitability of a survey for probabilistic modelling. The suitability and representativeness should be evaluated by

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				uncertainty analysis on a case-by-case basis, considering in particular the assessment question, the percentile of the exposure distribution of interest and the commodities considered in the assessment. Please also note that drill-down information might be useful to assess the plausibility of consumption data at the percentile of interest.
80	Fresh Produce Centre	Appendix B – Information used in the uncertainty analysis	Line 2075, p. 65, note 18: Actual use of pesticides. As no information on the actual application in the Member States or third countries of the pesticide on the commodities is available, as is the percentage of use, the 1/2 LOQ for the 'zero' potentially could be an overestimation. Effort should be taken to refine the modelling for by collecting data on the actual use. As many RPCs are from third countries effort should be limited to the Member States only.	Agreed. In section 6, we recommend the collection of information from competent organisations on national authorisations and use statistics of plant protection products, on risk-based criteria.
			Line 2105, p. 65, note 20: Drinking Water. The five most potent active substances of the CAG were assumed to be present at 0.05 ppb in the drinking water. Are these active substances expected to be present in drinking water in the EU? Are they detected in the monitoring of (surface) water or drinking water by the Member States within the EU? Are the data collected by the Member States on the bases of 'Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy' taken into account? According to this Directive the water status should be monitored by Member States on a systematic and comparable basis throughout the Community. This is obliged for each river water basins district used for the abstraction of drinking water. The Directive also requires the monitoring of surface water status, groundwater status and protected areas within all Member Status. Monitoring procedures, sampling and analyses procedures are harmonised. If the five most potent active substances of the CAG are never in the water bodies detected but within the analytic scope of the Member States, the assumption 0.05 ppb might be very much worse case. Are the priority substances in the field of water policy as published in Directive 2013/39 taken into account when assessing the most potent substances in CAG?	See response to comment 81. In section 6, we recommend the collection of information from competent organisations on pesticide residues in drinking water, on risk-based criteria.

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			The drinking water companies within the EU are obliged to perform testing on presence of chemical residues of pesticides and medicine residues to guarantee the quality of drinking water. Are both the chemical properties (water solubility, accumulation, persistency in water) and GAPs of the five most potent active substances taken into account? For example, if the application is post-harvest on fruit or full field on an arable crop the risk of contaminating water source is totally different. Is it realistic that (drinking) water is contaminated with these five most potent active substances of the CAG or are other active substances of the CAG present? The data on water monitoring of the Members States are available and a valuable and trustworthy source to refine the assumption of drinking water in the qualitative risk assessment. In combination with GAPs and chemical properties of the assessed compounds the calculation might be refined.	
			Line 2135, p. 66, note 23: Accuracy of PFs. The limited availability of PF for pesticide residues in food the effect of processing is not adequately addressed in the current calculations. The collection of reliable PF and publishing these regularly is important and should have priority. Is information on PF part of the application of active substances or MRLs within the EU by the applicant? A procedure to structurally include the PF used in the application is recommended to keep the PF database up-to-date. PFs were extrapolated between RPC with similar properties (oranges and mandarins, apples and pears) and applies in the calculations. It would be very helpful to include these extrapolations in the EFSA data as published in 2018. This would contribute to the harmonised application of the PF also in application of PRIMo3 for the ARfD calculation when assessing the risk of an MRL exceedance. For example, for the substance thiabendazole reliable PFs (PFs) were only derived for the peeling of bananas and citrus fruits. For other commodities with inedible peel also impacts the real exposure by these commodities. Other PFs derived in the framework of the MRL review are considered tentative and are taken into account of assessment of the proposed MRL (e.g.	The European database on PFs is the most recent and the most comprehensive compilation of PFs currently available at EU level (Scholtz, 2018). It covers all processing studies assessed by EFSA in their Conclusions and Reasoned Opinions issued until 30 June 2016, which were re-evaluated according to uniform quality criteria. The PFs used to perform the cumulative exposure assessments were extracted from that database, when they were reported as 'reliable' or 'indicative'. Additional information about the use of these PFs can be found in the EFSA Scientific report on the cumulative dietary exposure assessment of pesticides that have acute effects on the nervous system using SAS® software (EFSA, 2019b). Of course, only PFs related to the 30 commodities selected for the assessments were considered. In section 6, we recommend consolidating the list of PFs available for CRAs.

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			thiabendazole on avocado; the tentative PF for peeling factor was 0.15) but not in PF database of EFSA (Scholz, 2018). In the period assessed (2014–2016) for example there was also an MRL for thiabendazole mango with a PF for peeling of the commodity but also not included in the PF database of the EFSA. By 'rejecting' the tentative PFs, which were used for MRL setting, results in higher exposure for all cases were PF < 1. We strongly support the regular update and expansion of PF databases with both the extrapolations and the tentative PF used for MRL setting and reviews of the EFSA.	
81	Pest Management Regulatory Agency, Health Canada	Appendix B – Information used in the uncertainty analysis	Note 20: Drinking water. It is unclear what data were used to estimate drinking water concentrations for cumulative assessments. It appears that arbitrary values of zero, 0.05, or 0.1 µg/L were imputed, which is a significant uncertainty. The Terms of Reference from EFSA directed RIVM to 'apply specific limits for drinking water as a special component of food'. Do the above values represent the limits? What is the basis for these limits?	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 sum of all individual pesticides detected and quantified. In tier 1, 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 2, it was assumed that the five most potent pesticides of the CAG were at 50% of the allowed level (0.05 µg/L). Note 20 was revised to better incorporate this information.
			Note 28: Active substances wrongly assigned to CAGs. EFSA noted that if an active substance, not causing the specific effect, is included in the respective cumulative assessment group the cumulative exposure and risk will be overestimated. The PMRA agrees, and therefore considers examination of the original studies to determine with accuracy whether these specific effects on the nervous system are actually induced by exposure to each active substance to be important.	We agree that the consultation of original studies would contribute to reducing the impact of this source of uncertainty. This is however extremely demanding in terms of resources. In the future, the elaboration of a structured format for data submission could greatly facilitate the access to this essential first-hand information, if the need arose. However, there will always be inconclusive cases for which the weight of evidence will need to be considered to evaluate the probability that a substance is actually causing the effect of interest.
			Note 29: Uncertainties regarding the NOAEL setting. EFSA noted that a significant weakness of this CRA involves the use of NOAELs for the toxicological characterisation of pesticides since the NOAEL setting is influenced by group size, between	We agree and recommend the use of BMD modelling in section 6.

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			animal variability, experimental errors and dose spacing. The process of NOAEL setting uses only single points without considering the shape of dose–response curve which means that a NOAEL might not match precisely the dose corresponding to a well-specified change in toxicological response. Since using NOAELs/LOAELs is dependent on the doses tested in each study, the PMRA would suggest using benchmark dose modelling for the conduct of the CRA where possible. As routine practice, the PMRA performs BMD analyses for brain and/or erythrocyte cholinesterase inhibition data in order to establish toxicological endpoints for risk assessment purposes. EFSA acknowledged that 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 during the NOAEL setting process. The PMRA agrees that this is a significant source of uncertainty in EFSA's CRA, which points to the importance of examining the original studies to determine whether the proper indicators of nervous system toxicity were examined and included.	As above we agree with the importance of examining original studies.
82	US EPA Office of Pesticide Programs	Appendix B – Information used in the uncertainty analysis	The exposure assessment doesn't consider all potential contributors to dietary exposure since only focuses on the consumption of 30 specific commodities. The cited report 'Cumulative exposure assessment to pesticides that affect the nervous system using SAS® software' states: 'Water and foods specifically intended for infants and young children were integrated in the exposure assessment based on their importance in (certain) diets.' It would be beneficial to explicitly state the criteria (e.g. at 50% of children consume the commodity) for including certain commodities. The document should clarify how residue values (i.e. occurrence data) are assigned to 'baby foods' as this description is not commodity specific (e.g. banana baby food).	The selected plant commodities used to perform the CRAs were selected based on their importance in the diet, as reported in an assessment of the pesticide monitoring conducted by EFSA in 2015 (EFSA, 2015b). This reference was included in the final report. Food for infants and young children (as defined by Regulation (EU) No. 609/2013 on food intended for infants and young children) were also included because they form an important part of the diet until 3 years of age, irrespective of the percentage of toddlers/other children consuming these commodities within the considered population. Under Article 31 of Regulation (EC) No. 396/2005, occurrence data for foods for infants and young children are collected for the final product instead of the RPCs. These data are classified into four different categories (infant formulas, follow-on formulas, cereal-based and others). These occurrence data were directly matched to

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				the relevant consumption data. Further details are provided in the report on exposure assessment (EFSA, 2019b).
83	US EPA Office of Pesticide Programs	Appendix B – Information used in the uncertainty analysis	As noted in the draft report, PCT information (referred to as 'market share data') is preferable for determining which commodity samples should have concentrations that are true zeroes. The draft EFSA CRA attempts to use detection frequencies as a surrogate for PCT in a very complex manner (as described in appendix C of the cited report 'Cumulative exposure assessment to pesticides that affect the nervous system using SAS® software'). Even with the PCT information that is available for the US market, EPA finds incorporating such information for multichemical assessments difficult and favors assuming any values below the LOD are true zeroes. EPA agrees that exposure in the upper percentiles of the exposure distribution tend to be driven by higher, detectable residues. Therefore, we assert that imputation methods unnecessarily complicate CRAs with minimal impact on exposures of concern. For example, there are only seven pesticide–commodity combinations from the CAG-NAN that have more than 10% quantifiable measurements: mandarins/chlorpyriphos (35%), oranges/chlorpyriphos (33%), table grapes/ethephon (23%), pears/chlorpyriphos (14%), bananas/chlorpyriphos (13%), olives for oil production/dimethoate (12%), peaches/chlorpyriphos (10%).	See response to comment 34. We agree that the use of factual information on PCT would be a better option than the assumption used in Tier II of the exposure calculations. In section 6 we recommend collection of use frequency data on risk-based criteria. In the context of the investigation of optimised approaches to CRA, we may also consider evaluating the magnitude of the impact of some of the current assumptions and revise them if appropriate.
84	US EPA Office of Pesticide Programs	Appendix B – Information used in the uncertainty analysis	The drinking water exposure is very simplistic with all water consumption occurrence assumed to be 0.0005 mg/kg for the five most toxic pesticides from the CAG.	Agreed. However, as stated in note 20, the effect of this (worst-case) assumption is minimal. A recommendation was nevertheless added to section 6 for the collection of information on pesticide residues in drinking water.
85	US EPA Office of Pesticide Programs	Appendix B – Information used in the uncertainty analysis	Includes what EPA would consider to be a misuse (e.g. the inclusion of omethoate in wine grapes and apples although there is no authorised use of dimethoate or omethoate on grapes or apples).	Note 17 was clarified.
86	US EPA Office of Pesticide Programs	Appendix B – Information used in the uncertainty analysis	For medium (25 to 250 g) and large (250 g or more) commodities that are not subject to blending or bulking processes, the residues from composite samples are decomposited into single samples, which results in lower residue values.	In these cases, we indeed allocate residue values to single commodity units, which can in fact be either higher or lower (and not only lower) than the residue in the composite sample.

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87	Norwegian Scientific Committee for Food and Environment (VKM)	General comments	We appreciate the initiative to estimate the cumulative risk characterisation of pesticides and the risk of acute effects on the nervous system. We understand that this has been both a demanding and complicated process. We think the process is well described and well formulated. However, we have some suggestions for consideration.	
			Line 22: Consider clarifying that the conclusions made here are solely based on the populations studied. For example by adding a statement such as 'for the populations studied'.	See response to comment 69.
			Line 56: Suggest including what the clinically observable adverse outcome associated with brain and or erythrocyte AChE inhibition are.	See response to comment 3.
			Line 65: What is the evidence that these models predict the real-life exposure to pesticides? Including discussions on this issue would be appreciated.	This would require duplicate diet studies and consistency check with the exposure model used in the reported assessment. This is however not available for the time being.
			Line 66: Is there a reason why sensitive risk groups such as the elderly (with potential CNS related diseases as Parkinson's and dementia) and pregnant women were not considered?	Adult populations used for the reported assessments included pregnant women and individuals up to the age of 64–65 years.
88	Netherlands Food and Consumer Product Safety Authority (NVWA)	General comments	We are pleased that EFSA, in collaboration with RIVM, undertook work on combined exposure to multiple pesticides. The setup of the reports is clear, however the information is sometimes presented in a rather technical way and therefore difficult to read for a non-expert. In addition, the document could emphasise more on the criteria used for establishment of the CAGs.	Additional explanatory information to assist understanding by non-experts has been added in the final report. With respect to the establishment of CAGs, only key information is given in the report under consideration. Complete information can however be found in EFSA, 2019a.
			In our opinion the credibility of the results could be improved by addressing the uncertainties first before making any calculations, especially since many uncertainties are related to the dataset. This requires setting criteria for use. The available data must first be screened for the specific purpose before being used.	The assessment used regulatory datasets on occurrence, consumption and toxicology, which have already been subjected to rigorous screening for their quality. Additional screening was performed to select the data relevant for this assessment. The comment suggests that uncertainties be addressed before calculations by setting further criteria for the data to be used. Presumably the intention would be to exclude data that was subject to more than some acceptable level of uncertainty. However, the result of this would be to create more data gaps, which would need to be replaced by assumptions or default values or result in substances being excluded from the assessment due to lack of data. So, while the specific uncertainty associated

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				with the excluded data might be removed, it would be replaced by other uncertainties associated with missing data, assumptions and excluded substances. The present assessment therefore applied criteria that were considered reasonable and practical, and took account of the resulting uncertainties.
			For example, for data on pesticides that are no longer authorised, it should be decided beforehand whether or not to include these data in the database; for CAG-NAN all risk drivers are product/compound combinations for which there are no authorisations in the Netherlands.	The criteria triggering to consider a pesticide no longer authorised for eventual inclusion in a CAG is its occurrence as residue in human's diet. If there is factual exposure, this should be modelled in the exposure assessment. Otherwise the risk is underestimated.
			Furthermore, data obtained from non-representative samples (selective and suspect samples) should be excluded.	An important fraction of the occurrence data selected to perform the assessment were reported by Member States as falling under the category 'selective sampling'. These data were used, instead of being excluded, to increase the population size of occurrence data but might affect the result by a certain bias. This source of uncertainty was considered under note 13 of appendix B.
			A solid dataset should be the basis of the assessment, which allows a transparent conclusion without the requirement for expert interpretations afterwards. In the present document EFSA has apparently used all available data and when the calculated results were judged to most likely represent overestimates, uncertainties were listed and expert elicitation applied to conclude on no risk. This is difficult to explain to non-experts.	Generally, and in this assessment, EFSA does not use all available data uncritically, but instead screens available data for their reliability and relevance for each assessment. Details of this are given in the reports and in responses to other comments. The commenter seems to imply that uncertainty analysis and expert elicitation were introduced in response to the calculated results, but in fact they were planned from the start of the process. The methods used are not biased 'to conclude on no risk'. Uncertainties tending to underestimate and overestimate risk were considered together in a balanced process. See also the response to comment 71.
			The model used is fine, but apparently the quality of the data (and conversion/PFs) was low. Furthermore, we question whether you can use composition data from all over Europe for national food consumption data.	For several quantities, we indeed used fixed values instead of a distribution of values. This is for instance valid for PFs and conversion factors of the RPC model. This was recognised as sources of uncertainties, which were considered (see notes 9 and 24).
			Furthermore, we noticed that the cumulative assessment focused on two endpoints, only, and was very labour-intensive. We do give credit for this huge amount of work, but we foresee that it	EFSA is currently investigating possibilities to make the overall process leaner and less resource demanding, based on the acquired experience. This may include the

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			may take many years to develop the methodology for other endpoints. We therefore make a plea for a dual approach: (a) to continue this type of cumulative assessment work for other endpoints, and (b) to establish a tiered approach for either those endpoints or pesticides which have not been assessed before. For example, as most cumulative risks are based on addition, the sum of the concentration: ADIs could be taken as first tier assessment for cumulative risks. If that would exceed a certain threshold, further work would be needed. If that would not exceed the threshold, it could be concluded that there is no risk.	development of a tiered process, where substances, organs or effects associated to low-risk levels would be identified by appropriate screening methods.
89	German Federal Institute for Risk Assessment (BfR)	General comments	The efforts taken by EFSA and the working group to establish CRA are highly appreciated. The extensive compilation and discussion of potential sources of uncertainty is of particular interest and might be a valuable approach and model for future activities even though some details of the methodology might need further clarification (see comment above).	Thank you.
			However, for a reader who has not been familiar with the development of this EFSA document from the very beginning, following its logic on its own is difficult. All the previous work performed (e.g. selection of the cumulative assessment groups (CAGs), monitoring data collected for the exposure assessment) relevant for this publication are briefly mentioned and cited in the report without further elaboration. As a result, it is doubted if the document could be indeed used as a stand-alone document. Moreover, it is not that easy to understand how the conclusions have been reached. While this report should not focus on expanding on what has already been published and the readers, if interested, could be expected do some background reading, mentioning some background and outcomes of the previous work in this report would certainly expedite the reading and the comprehension of this work undertaken here. It might be the easiest solution to expand the existing Summary section by such information.	We acknowledge the complexity of the scientific process to produce CRAs. As the three main constitutive steps [(1) hazard identification and characterisation (establishment of CAGs); (2) cumulative exposure assessments; and (3) cumulative risk characterisation and uncertainty analysis] are quite distinct and complex, they are reported in individual reports for reason of convenience. A thorough understanding of the entire process requires the reader to consult the three types of report. Nevertheless, to facilitate the usability of the cumulative risk characterisation report, the most prominent outcome of the two underlying reports have been summarised in section 2.2. In addition, in the final version, the Summary section was extended to give more details on the content of the scientific report on the establishment of the CAGs.
			The CAG approach chosen requires further explanation. Have CAGs been refined based on mechanistic considerations or have they been compiled based on (histo)pathological observations only?	The approach has been extensively described in the respective report (EFSA, 2019a). The approach largely relied on biological, functional and mechanistic observations, for reasons detailed further in the respective report.

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			The concluding statement of the abstract '…cumulative exposure to pesticides that have acute effects on the nervous system does not exceed the threshold for regulatory consideration established by risk managers' seems too general, as this assessment only focuses on two specific acute CNS effects (AChE inhibition and altered motor function). There are also other acute effects on the nervous system (e.g. altered sensory or autonomic functions) from pesticide exposure not addressed here. Thus, this statement should be more specific and reflect on these two effects.	See response to comment 68. In addition, in section 1.1 of the final report, it is explained that the effect on the sensory and autonomic divisions are covered by the assessment of the risk of functional alterations of the motor division.
90	ECPA – European Crop Protection Association	General comments	ECPA commends EFSA/RIVM for the significant amount of work and improved procedures (relative to previous work in 2013). We also acknowledge both papers include explanations of the EKE procedures in attempt to be as transparent as possible. Nonetheless improvements to replace EKE and instead use more of the existing data to address several of the underlying uncertainties would continue to improve the methodology. Specifically, information on use frequency data, additional processing, peeling and cooking factors and extrapolations of PFs within crop groups or matrix types could be useful to improve procedures. ECPA appreciates EFSAs/RIVMs sensitivity analysis of left-censored data and we support future efforts to collect better data on use frequency (i.e. market share) in order to better assign zero or half LOQ values as pragmatic approaches to deal with results that are below LOQs. Although an attempt was made to describe the EKE process and the underlying questions in detail, it would be useful to understand how translatable this detailed process is to another CAG?	Thank you. EFSA is currently investigating leaner approaches to perform CRA of pesticide residues in the forthcoming years. This could involve simple and quick approaches applicable to low-risk situation to refined approaches using all relevant available data in other situations. In addition, some recommendations are made in section 6 for collecting data of different types which would contribute to solve some sources of uncertainties. See above. The protocol, process, supportive information and outcome of each module of EKE supporting the uncertainty analysis were described in detail. Individual assessments are kept as internal documentation and not included in the report, because they do not contain additional factual information and are superseded by the outcome of the consensus discussion. The transferability to CRAs related to other CAGs is limited: Sources of uncertainties as such are mostly transferable,

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				but their impact is not transferable when they depend on the risk drivers.
			Comment for the Summary section Risk drivers are listed on lines 86 and 87 and 91 and 92. Do the stated drivers make sense relative to actual use pattern information for EU? Public statements identifying a particular active ingredient can have additional political and/or commercial consequences beyond a risk assessment. On this basis it is considered important to take into account all most up-to-date registration status for the driver active substances (e.g. MRL, PFs, additional mechanistic data).	The information related to risk drivers is objective and is a core part of the outcome of the risk assessment. Risk drivers are of course valid for the reference period and were identified in the context of the available data and using the assumptions defined by risk managers. EFSA is not necessarily aware of the current registration status at Member State level and of the latest scientific data available to Member States and therefore cannot communicate on these aspects.
			With these points in mind, it is proposed to comment on the approximate nature of Risk Driver identification to support risk communication.	See above. In section 2.2.2.1, the definition of risk drivers has been slightly changed to 'pesticide/commodity combinations, which, under the precise modelling conditions and assumptions of the Tier II scenario, contribute on average, in at least one out of the ten populations, at least 5% of the exposures exceeding the 99th percentile estimate'.
91	CHEM Trust	General comments	CHEM Trust acknowledges the extensive work EFSA has carried out to address the cumulative effects of exposure to various pesticides on certain endpoints. In our view this is a very important area which deserves more urgent attention from risk assessors and policymakers (https://chemtrust.org/tag/mixtures/). We welcome the approach to use common assessment groups and the concept of dose addition. We appreciate the approach used for allocation of substances to the common assessment groups which is based on their common specific effects as this is the approach that most realistically reflect the actual cumulative risk.	Thank you.
			We have, however, some general comments as regards the whole approach for assessing and concluding on the cumulative risks for acute effects on the nervous system. In particular we question the final conclusion 'taking account of the available data and the uncertainties involved, it is concluded that cumulative exposure to pesticides that have acute effects on the nervous	See response to comment 71.

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			system does not exceed the threshold for regulatory consideration established by risk managers' or in other words – the cumulative exposure to pesticides that have acute effects on the nervous system is considered as safe. We are aware that this conclusion is based on the available data and uncertainty analyses as described by the term of references. We note that the risk characterisation is based on very sophisticated exposure modelling and assessment, however, the same advanced level is not at all the case when it comes to the hazard assessment. As also stated by the authors there are several limitations in the available knowledge and data that affect the assessment. These uncertainties should be properly reflected by the hazard characterisation. CHEM Trust would like to point out that many assumptions have been included and several decisions have been taken which may add to the level of uncertainty and bias the uncertainty assessment in a more favourable direction. In particular, we are concerned about the estimated MOET's for toddlers and children which are below 100 for several populations and which then are adjusted to a level which consequently will not lead to regulatory considerations. We find the overall conclusion of the cumulative dietary risk characterisation biased and overly firm also in the light that estimates for MOET's for toddlers are uncertain and may be below 100. It could easily be misinterpreted in the way that cumulative exposure to pesticides is considered safe and with no risks of causing effects on the nervous system which is not based on scientific evidence. We therefore recommend changing the final conclusion and providing cautionary language which highlights the limitations of the database as well as the fact that the assessment does not include neurodevelopmental toxicity. This lack of knowledge should be highlighted and properly reflected by the conclusion and it should be considered whether a judgement about whether a threshold for regulatory consideration is exceeded is reasonable based on the current database and uncertainties.	
			CHEM Trust is very concerned about the effects on nervous system in vulnerable populations as summarised in our CHEM Trust report 'No Brainer: The impacts of chemicals on children's	This is noted. See section 6 (Recommendations) of the final report and response to comment 25.

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			brain development: a cause for concern and a need for action' (https://chemtrust.org/brain/) where we summarised the state of the science regarding the concerns about the human health exposure to substances which can impact on brain development. Therefore, we agree with the following recommendation made in the report, namely: • Develop a testing and assessment methodology covering developmental neurotoxicity of pesticides, and, if appropriate, to establish CAGs and perform CRAs in this area; and • Draw up a new CAG for DNT and further perform CRA to assess the one combined impact of organophosphates, pyrethroids and other insecticides with DNT potential on infant, toddler and children populations.	
92	Fresh Produce Centre	General comments	The CRA and exposure calculations are very much welcomed as it important to assure the safety of fresh produce put on the market. Use of different pesticides is part of conducting of GAP with integrated pest management. It is important not to induce resistance of the pests and also to have different application routes e.g. seed coating, spraying. With the development of precision agriculture, the application of pesticides can also be refined for example by very local applications. Potentially resulting in multiple residues with in total better results for people, animals and the environment. Unfortunately, the public opinion is totally the opposite and these studies hopefully contributes to the trust in the very rigorous procedures of allowing active substances on the EU market and the trust in the safety of the food on the EU market both produced in the EU and imported from third countries. Furthermore, it showed that the MRLs are set on safe levels. So it is important to continue the work on setting CAGs also for the other pesticides and do the cumulative exposure assessments regularly and to refine the modelling were possible.	This is noted.
93	The National Farmers' Union of England and Wales	General comments	The NFU welcomes that this work is using a rigorous science approach based on the principle of dose addition. We would also like to acknowledge and support how it has been made clear in the report that there are high levels of conservatism in the assumptions, resulting in low risk of underestimation of effects.	Thank you

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			Often, many readers will only get as far as the summary of a report like this. While the conclusions of the report are clear, and while note 18 (line 2075) makes clear the authorisation status of pesticide/commodity combinations, we believe it should be made clearer in the Summary that many of the highlighted issues with exposure were driven by the occurrence of pesticides that are no longer authorised for use in the EU, including triazophos, omethoate, dichlorvos, carbofuran, beta-cypermethrin and thiram. In addition, authorisation of chlorpyrifos is set to end soon in the EU.	EFSA is not aware of the precise registration status of plant protection products on national basis. Therefore, it is difficult to include the proposed considerations in the scientific report. To conduct the assessments, the authorisation status relied on the assumptions described in note 18, which, in particular, considered the applicable MRLs on 31 December 2016. It is acknowledged that the authorisations of plant protection products and respective MRLs are constantly evolving, and that some assumptions, valid for the reference period of the assessment, might no longer be valid at the date of delivery of the report.
94	Pest Management Regulatory Agency, Health Canada	General comments	General comments: For CRAs, the PMRA identifies the human health risk associated with co-exposures to two or more pesticides that cause a common toxic effect by the same, or essentially the same, sequence of major biochemical events. The PMRA uses the WHO/IPCS framework for CRA that involves a tiered approach to the assessment of exposure and hazard, with each tier being more refined than the previous tier. The last step in the CRA is risk characterisation. While the approaches taken by EFSA and the PMRA to conduct a CRA are similar, there are notable differences. One major difference relates to how EFSA groups active substances that produce a similar specific effect, while the PMRA narrows this grouping down further to only include the active substances that produce a specific effect by the same MoA. Comments relating to the background document, 'Establishment of cumulative assessment groups of pesticides for their effects on the nervous system' (EFSA, 2019): 2.1 Data EFSA notes that human data were collected when available but were never used for the establishment of cumulative assessment groups. The PMRA does not use toxicity studies conducted with humans in health risk assessments, and as such, would similarly not include any human toxicity studies in CRAs.	See response to comment 24. This is noted.

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			3.1 Identification of the specific effects: All nervous system specific effects for the CRA were considered to result from systemic exposure, to be adverse, relevant for humans, specific in nature, and could be observed as primary effects. Several observations for clinical signs of toxicity were found often occurring secondary to general systemic toxicity after exposure to high doses, and were therefore not deemed appropriate to characterise any of the active substances in the CAG. The PMRA agrees. Toxic effects that have many possible unrelated causes, are not considered adverse, or could be defined as non-specific in origin are not appropriate as a basis for grouping for CRA.	This is noted.
			3.3.1 General provisions: In order to establish NOAELs for active substances with a known MoA regarding functional alterations of the motor, sensory and autonomic divisions, preference was given to neurotoxicity studies, unless the dog or mouse appeared to be more sensitive than rats. In the absence of acute neurotoxicity studies, available 28-day or 90-day neurotoxicity studies were used to set NOAELs for acute risk assessments and other options were considered if these studies were unavailable. The PMRA agrees with this approach. Typically, functional alterations of the motor, sensory and autonomic divisions are only thoroughly investigated in neurotoxicity studies, and therefore using standard acute or repeat-dose toxicity studies for risk assessment might only serve to add more uncertainty.	This is noted.
			4.1 General considerations: Original studies used to establish the CAGs were only occasionally consulted. Instead, regulatory documents, where information from the original studies is reported in a condensed form, were used as the primary source of information. Information of relevance for the establishment of CAGs might not have been captured properly in these regulatory documents. The PMRA agrees that this could lead to considerable uncertainty, as well as the possibility that active substances that potentially induce toxic effects on the nervous system could have been wrongly excluded from the CRAs.	See response to comment 81. This source of uncertainty is discussed in note 29.
			EFSA indicated that for several active substances the quality of the database does not conform to the current standards and	See response to comment 10.

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			causes an additional source of uncertainty. The PMRA notes that this can present substantial limitations for the CRA that may result in underestimating risk. The PMRA applies additional uncertainty factors to the risk assessment if key data are missing or inadequate in the context of both individual and CRAs.	
			Further, when the PMRA initiates a more complex CRA, a data call-in step is undertaken to request any new data that might be relevant to the assessment. It would be of interest to include information on whether EFSA undertook a similar exercise prior to conducting this CRA to locate new data that might have become available since the time of the original reviews of the individual chemicals.	No, such data call-in step was not conducted before the initiation of this CRA. The (toxicological) information was collected as described in the report on the establishment of CAGs (EFSA, 2019a). A public consultation on a draft version of the report was conducted in summer 2018.
			6. Recommendations EFSA indicated that if the outcome of CRAs conducted with these CAGs, as currently characterised by NOAELs, exceeds the regulatory thresholds of acceptance, an alternative CRA should be considered with BMDLs used as reference points. The PMRA notes that regardless of whether or not this CRA exceeds the regulatory threshold of acceptance, it would be beneficial to update the assessment with benchmark dose modelling where possible to refine the toxicological endpoints and decrease the uncertainty that is inherent with taking a NOAEL/LOAEL approach.	See response to comment 30.
			EFSA notes that the CAGs established in this report should be regularly updated in light of the toxicological information provided to EFSA in the context of its regulatory activities. The PMRA agrees that going forward, EFSA's CRA should be updated to include any new toxicity studies and any methods of refinement that helps to reduce or alleviate any uncertainty.	This is noted.
95	US EPA Office of Pesticide Programs	General comments	Commendable effort to quantify and document expert judgement as part of the uncertainty assessment using a very structured and systematic expert evaluation and elicitation process. However, there are some issues to note:	Thank you.
			• Expert evaluation of uncertainty assumes experts are not only disciplinary experts (e.g. exposure and toxicology experts), but also experts in probabilistic and uncertainty assessments and cumulative assessments.	Indeed, this was the case. All experts involved in the exercise had thorough knowledge of the CRA methodologies and of uncertainty analysis. Experts in exposure were furthermore very familiar with probabilistic methodology and all were trained in the practice of the EKE

N.	Affiliation	Chapter	Comment	EFSA response
				technique and in how to make the probability judgements involved. This information was included in section 2.3.2 of the final report.
			• Experts were asked to evaluate the impact on distribution of MOEs directly based on uncertainty of individual parameters, specifically the median MOE from a distribution of MOEs at the 99.9th percentile.	Yes, because this was the threshold for regulatory consideration defined by risk managers.
			• One would need to be experienced and familiar with probabilistic (i.e. Monte Carlo) modelling and uncertainty analysis in addition to being disciplinary experts.	See above.
			• Although less practical and more time consuming, a more optimal approach to leverage the expertise of the panel members would be to ask them to quantify distributions around the input parameters with which they are most familiar. For example, a toxicologist could provide a range of NOAELs that has 'at least a 90% probability of containing the true' NOAEL if value from a study is 0.5 mg/kg (e.g. 0.2 to 1.2 mg/kg).	Such approach could indeed be considered in the future for certain input parameters but would not remove the need for the assessment of overall uncertainty. This is because, it is not possible to quantify all uncertainties using distributions for input parameters, not least because some relate to model structure (e.g. dose addition). Therefore, it would still be necessary to conclude the uncertainty analysis with an assessment of the combined effect of those uncertainties not quantified within the calculations. EFSA's guidance on uncertainty provides a flexible approach, in which the assessor quantifies uncertainties individually where this adds value to the assessment and considers the rest collectively in the assessment of overall uncertainty. With respect the toxicological characterisation, it would indeed be preferable to use BMD modelling.
			• Since expert judgement is inherently subjective, there should be documentation of the selection process and specific areas of expertise for the expert panel to increase transparency and allow for replication of results, if needed.	Seven authors of the present report participated to the EKE, in their respective areas of expertise. They are listed in section 2.3.2. They were all members of the Working Group and were selected according to the respective EFSA policies.