Cumulative exposure and risk assessment for the German population with respect to pesticide residues in foods

(Kumulative Expositions- und Risikobewertung für die deutsche Bevölkerung gegenüber Pestizidrückständen in Lebensmitteln)

von

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Abstract

For the first time, population based approaches estimating the dietary exposure for German consumers to pesticide residues were applied to assess health risks from single compounds as well as for their cumulative effects. Using probabilistic Monte-Carlo based modelling tools, the complete data on daily consumption patterns for children and adults could be correlated with food monitoring results from the years 2009-2014 for over 700 pesticidal active substances. Based on the results, the food market-basket used in monitoring programmes was revisited and refined towards future estimations of the consumer exposure.

In the first part, both chronic and acute dietary consumer risks arising from single substances were characterised. For 693 compounds, the estimated dietary exposure was unlikely to present a chronic or acute public health concern for the German population. Potential consumer risks were identified for chlorpyrifos and the combination of dimethoate and omethoate. Since maximum residue levels in plant and animal commodities have been lowered significantly in the meantime for these compounds on European level, it is very likely that potential consumer risks have also been removed. Due to missing crucial information on the toxicological properties of dimethylvinphos, halfenprox and tricyclazole, no conclusions on the dietary risk for consumers could be drawn.

In the second part, the acute and chronic cumulative dietary risk for German consumers to pesticide residues was assessed based on cumulative assessment groups (CAGs) as defined by the European Food Safety Authority (EFSA) in 2013. It was shown, that the exposures for the CAGs on chronic neurochemical effects (erythrocyte acetylcholinesterase inhibition) and chronic hyperthyroidism were below or near a margin of exposure (MoE) of 100 to the no-effect level at the 99.9^{th} percentile, which should be above this limit to exclude a public health concern. A similar result was reported in the most recent studies by EFSA, also assessing the cumulative dietary risks for European consumers with comparable probabilistic methodologies and food consumption data. In addition, EFSA analysed involved uncertainties and estimated that the certainty to not reach the threshold for regulatory consideration was between 80% to >99% for the nervous system and between 85% and >99% for thyroid effects. In all studies, single compounds were identified as the driving contributor to the total exposure for neurochemical effects on individual level instead of a complex mixture of components, suggesting a low probability for true dose addition. For the German population, this result was also confirmed for the chronic CAGs.

The third part utilised the previous findings on the cumulative dietary exposure assessment to propose a refined food market-basket for monitoring programmes specifically focussed on estimating consumer risks. In contrast to previous approaches, in which food commodities were selected primarily based on their contribution to the total daily diet, the newly proposed market-basket was identified by estimating the sensitivity of each food to the chronic and acute total daily exposure. Depending on the desired degree of conservatism, a set of 16 or 41 raw food commodities were identified covering the total dietary exposure by at least 85%.

In summary, the methodologies applied to assess the dietary risk for the German population provided realistic results when compared with approaches from other European countries or EFSA. While dietary risks arising from single pesticidal compounds have mostly been revised in the meantime, the cumulative risk assessments may still result in exposure levels not allowing exclusion of public health concerns. With the proposed improvements on the design of food monitoring programmes, involved uncertainties can be lowered in the future to allow more robust estimations of consumer risks.

Zusammenfassung

Im Rahmen dieser Arbeit wurde erstmalig die Verbraucherexposition der deutschen Bevölkerung gegenüber Pflanzenschutzmittelrückständen in der Nahrung sowohl für Einzelverbindungen als auch für kumulative Bewertungsgruppen geschätzt. Für diese Aufgabe wurden Monte-Carlo basierte Wahrscheinlichkeitsmodelle verwendet, welche es erlauben, alle zur Verfügung stehenden Daten zum Verzehrverhalten von Kinder und Erwachsene mit Befunden für über 700 Stoffe aus dem Lebensmittelmonitoring der Jahre 2009 bis 2014 zu korrelieren. Basierend auf den Ergebnissen wurde der bestehende Warenkorb für das Lebensmittelmonitoring hinsichtlich zukünftiger Schätzungen des Verbraucherrisikos verfeinert.

Im ersten Teil der Arbeit wurde sowohl das chronische als auch das akute Verbraucherrisiko gegenüber Einzelstoffen charakterisiert. Für 693 Verbindungen konnte durch die Schätzung der täglichen Aufnahme über alle Lebensmittel ein gesundheitliches Risiko praktisch ausgeschlossen werden. Mögliche gesundheitliche Risiken wurden für die Wirkstoffe Chlorpyrifos und die Kombination aus Dimethoat und Omethoat identifiziert. Da seit Abschluss der Arbeit all diese Stoffe auf europäischer Ebene neu geregelt und Rückstandshöchstgehalte in Lebensmitteln signifikant gesenkt wurden, ist davon auszugehen, dass nun ebenfalls keine Gesundheitsrisiken mehr bestehen. Aufgrund fehlender Informationen zur Toxikologie konnte weiterführend keine abschließende Bewertung des Verbraucherrisikos für die Wirkstoffe Dimethylvinphos, Halfenprox und Tricyclazole erfolgen.

Im zweiten Teil der Arbeit wurde auf Grundlage derselben Datenlage wie im ersten Teil das kumulative chronische und akute Risiko deutscher Verbraucher ermittelt. Hierfür wurde auf kumulativen Bewertungsgruppen (CAGs) zurückgegriffen, wie sie die Europäische Behörde für Lebensmittelsicherheit (EFSA) 2013 formuliert hat. Es konnte gezeigt werden, dass die 99.9ten Perzentile der Gesamtexpositionen für die CAGs zu chronischen neurochemischen Effekten (erythrozytische Acetylcholinesterasehemmung) und chronischem Hyperthyroidismus in der Nähe oder Unterhalb eines Faktors von 100 zum toxikologischen Endpunkt lagen. Dieser Faktor sollte nicht unterschritten werden, um mögliche Verbraucherrisiken mit ausreichender Sicherheit ausschließen zu können. In der Zwischenzeit wurde von EFSA ebenfalls eine vergleichbare Modellierung der kumulativen Exposition veröffentlicht, welche zu ähnlichen Ergebnissen kommt und eine ergänzende Charakterisierung der Unsicherheiten beinhaltet. Hierbei wurde durch EFSA geschlussfolgert, dass eine Überschreitung des regulatorischen Schwellenwerts zu 80% bis >99% für Effekte auf das Nervensystem sowie zu 85% bis >99% für Schilddrüseneffekte ausgeschlossen werden kann. In beiden Studien konnte weiterhin festgestellt werden, dass die akute kumulative Gesamtexposition auf individueller Ebene überwiegend durch Einzelstoffe hervorgerufen wird und nicht durch komplexe Kombinationen mehrere Substanzen. Für die deutsche Bevölkerung wurde diese Beobachtung auch für die chronische Gesamtexposition auf individueller Ebene bestätigt.

Der dritte Teil nimmt die vorangehenden Ergebnisse zur Grundlage, um den bestehenden Warenkorb für das Lebensmittelmonitoring hinsichtlich zukünftiger Schätzungen der Verbraucherexposition zu verfeinern. Im Gegensatz zu bisherigen Konzepten, in welchen Lebensmittel auf Basis ihres prozentualen Anteils am täglichen Verzehr ausgewählt wurden, ist für den überarbeiten Warenkorb die jeweilige Sensitivität auf die chronische und akute tägliche Gesamtexposition entscheidend. Je nach erwünschter Konservativität wurden 16 bzw. 41 Roherzeugnisse identifiziert, welche mindestens 85% der täglichen Gesamtaufnahmemenge an Pflanzenschutzmittelrückständen ausmachen.

Zusammenfassend erlaubten die angewendeten Methoden eine realistische Schätzung des Verbraucherrisikos der deutschen Bevölkerung gegenüber Pflanzenschutzmittelrückständen und erzielen vergleichbare Ergebnisse zu Studien aus anderen europäischen Mitgliedsstaaten oder durch EFSA. Auch wenn mögliche Gesundheitsrisiken durch Einzelstoffe inzwischen praktisch ausgeschlossen sind, kann dieses nicht für alle kumulativen Bewertungsgruppen mit ausreichender Sicherheit bestätigt werden. Auf Basis des verfeinerten Warenkorbs für das Lebensmittelmonitoring können in Zukunft robustere Schätzungen der Verbraucherrisiken erfolgen.

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1 Introduction

For the agricultural production of foods, plant protection products (PPP) are globally used on crops to ensure sufficient and reliable harvest yields. The pesticidal active substances (pesticides) included in these products are capable of controlling a broad range of pests. Their field of use is large, ranging from the frequently used fungicides, herbicides and insecticides to more specific agents like acaricides, growth regulators or nematicides. Currently, over 1400 individual pesticide entries are included in the pesticide database of the European commission [1] and thereof over 450 are approved according to Regulation (EU) 1107/2009 [2].

The use of PPPs is strictly regulated and requires an authorisation procedure in most regulatory frameworks in the world. In the EU, one part of these procedures is the assessment of residues remaining in foods or feeds and the related dietary risk of consumers. The principles, how such assessments shall be conducted, are harmonised on international level under the Organisation for Economic Co-operation and Development (OECD). Applicants have to provide studies conducted according to these OECD Guidelines[1] investigating key aspects relevant for the assessment. In terms of residues, data on the metabolic fate of pesticides in plants, animals and rotational crops, the behaviour during industrial processing, the concentrations remaining on treated foods and feeds after application and the carry-over into foods of animal origin are required. Mandatory data requirements are normally set legislatively, e.g. via Regulation (EU) 283/2013 [3] for active substances used in PPPs. In addition, OECD also provides guidance documents on the scientific interpretation and assessment of respective studies.

Currently, general regulatory procedures to assess pesticides are based on each active substance *per se*. In the EU, this is related to a mandatory approval of active substances according to Regulation (EU) 1107/2009, before PPPs including these pesticides can be authorised. For this approval, pesticide are evaluated according to their physical/chemical properties, their toxicological properties, their environmental fate, the availability of appropriate analytical methodologies and the risk to operators, by-standers, consumers and the environment. Also, maximum residue levels are derived all foods put on the European market have to comply with. However, all of these aspects are currently considered active substance wise.

In reality, consumers are exposure not only to residues of one active substance, but to a broad mixture of multiple components. Starting on the field, different pesticides are applied at the same site to control various pests during nearly all seasons of a year. After harvest and before sowing, herbicides may be used to control weeds and to prepare the seedbed for the crop. During crop cultivation, a mix of pesticides can be applied against fungal diseases or insects and even after harvest, storage treatments may become necessary to protect the commodity. In Germany, the Julius Kühn-Institute monitors the average annual number of pesticide treatments per crop [4], showing a range of 1.9 treatments/year for maize up to 26.9 treatments/year for pome fruit in 2018. One treatment represents the application of one PPP, which may already contain more than one pesticide to increase its efficacy and to avoid the formation of resistances. Due to this common agricultural practice, the occurrence of residues from more than one pesticide in foods represents no exception but the usual case. In the most recent German food monitoring programme from 2018 [5], about half of the investigated commodities contained residues of more than one pesticide per sample. The highest numbers were found samples of aubergines, kale and parsley leaves,

1 https://www.oecd.org/env/ehs/pesticides-biocides/pesticides-testing-assessment.htm

each containing residues of 12 different pesticides. Also on European level, the 2016 European Union report on pesticide residues in food by EFSA [6] found that a total of 30.1% of all samples contained residues of more than one pesticide. Besides the high number of treatments in agriculture, also marketing procedures in trade may lead to multiple residues. Agricultural co-operations often collect commodities from several farmers and sort them according to market criteria like their size. Since monitoring programmes involve analysis of composite samples consisting of multiple individual units, mixing of commodities before marketing may represent an additional source for the presence of different pesticides.

For consumers, another aspects is of high relevance. In the daily diet, the range of foods eaten is enormous and many foods are composed of multiple ingredients. During the day, consumers may be exposure to pesticides via many sources of agricultural commodities, each of them potentially containing residues of more than one active substance.

The necessity to address the cumulative dietary risk of consumers versus pesticide residues was recognised early. Already in 2005, the European Regulation (EC) 396/2005 [7] included the demand to take into account "...known cumulative and synergistic effects, when the methods to assess such effects are available" when setting maximum residue levels (MRLs) for pesticides. However, until today, no harmonised methodologies have been implemented to consider these aspects.

Such complex cumulative scenarios are beyond the approach currently used for the assessment of single pesticides in regulatory context. To address such situations, consideration of the toxicological interaction between different components is required first. Mixture toxicity is still an ongoing field of research. In parallel, suitable methodologies for estimating the cumulative exposure of consumers need to be developed. For example, the EU Commission funded the EuroMix Project [8], setting the framework for multinational research projects addressing many aspects of mixture toxicity and cumulative exposure estimation.

In principle, all puzzle pieces to address the cumulative dietary risk have been developed. However, putting them together into a comprehensive assessment is difficult and has not yet been conducted for Germany or for most other European countries. In the current work, a strategy was developed to utilise the available data on pesticide residues found in the representative German food monitoring programme and to combine them with consumption data for the German population. Since individuals are exposed via multiple food sources, the established regulatory models based on deterministic methodologies are not suitable for such a task. Instead, a Monte-Carlo based probabilistic approach was chosen, allowing simultaneous consideration of the complete daily consumption on individual level in combination with all analytical results from the food monitoring.

Part 1: Single substance assessment

The first part of the work focussed on a population based assessment of the dietary risk for single pesticidal compounds. Although the final aim is to address the cumulative dietary risk, this part becomes crucial for the interpretation of results. When compounds already pose a potential dietary risk *per se*, also cumulative considerations including these compounds will show potential risks and relevant additive effects might be overshadowed. The assessment of compound specific exposures was conducted using the same residue and consumption data and by applying the same probabilistic methodology as for the cumulative assessments later. However, only the residue data for one compound was used instead of the residue data for all components sharing cumulative effects. A conservative two-tier screening approach was implemented to quickly identify compounds with a low potential for chronic or acute dietary risks. In total, over 800 individual pesticides were screened. For the remaining substances, a refined assessment was conducted considering compound specific aspects like processing information or data on the variability of residues between individual units.

Part 2: Cumulative assessment

In the second step, the approach described for individual compounds was expanded by considering complete cumulative assessment groups (CAGs), as defined by EFSA in 2013 [9]. Initially, the combined exposures were estimated and assessed for the related dietary risks. In addition, compounds and food commodities with a high sensitivity towards the cumulative risk of the CAG were identified. Under consideration of the findings for the dietary risk of individual compounds under step 1, conclusions were drawn whether the CAG is dominated by single substances or if multiple components add equally to the exposure. The latter is of high importance, since potential dietary risks could remain unnoticed when pesticide exposures themselves are slightly below HBGVs but in combination may lead to harmful effects.

Part 3: Development of an exposure based food market basket to suitable to estimate the cumulative dietary exposure

Finally, the knowledge from the population based dietary risk assessments for single and multiple compounds was used to develop a refined programme for the generation of food monitoring data. Especially for cumulative dietary risk assessments, the efforts to estimate the exposure is enormous and usually requires information on a broad range of food commodities. However; many of these foods are of low sensitivity for the upper range of exposures and their inclusion into the assessment does not significantly affect the overall outcome. Consequently, a market-basket was designed providing high coverage of the estimated daily exposure both for single compounds and for CAGs. In parallel, food commodities without relevance for the exposure assessment were identified. By law, food monitoring programmes by EU Memberstates shall be primarily designed to allow exposure estimations [7]. Currently, the design of national food monitoring concepts [10], [11] and of the European Coordinated Control Programme rely on the proportion of food commodities in the daily diet, not on considerations of potential residue concentrations present in these foods. The newly developed concept represents the first systematic approach to consider consumption data, occurrence data and the resulting exposure to identify food commodities truly relevant for an exposure based market-basket.

2 Materials and methods

For all three parts of the current work, the following materials and methods were applied. Further details on their individual usage can be obtained from the respective publications.

2.1 Consumption data

Consumption data for the German population was selected from three food consumption surveys covering different age groups. The dietary exposure estimates in different parts of the current work were not based on completely identical approaches. In principle, the following consumption surveys were considered, but not all data were used in each of the three steps. However, for all surveys, only consumption data describing the food intake per day on individual level were taken into account to allow their implementation into the probabilistic exposure models used.

For infants and young children aged 6 months up to 4 years, the VELS-study ("**V**erzehrsstudie zur **E**rmittlung der **L**ebensmittelaufnahme von **S**äuglingen und Kleinkindern für die Abschätzung eines akuten Toxizitätsrisikos durch Rückstände von Pflanzenschutzmitteln" [12]) was used. The study measured the daily consumption of 816 individuals (divided into five subgroups) for three consecutive days via weighed/estimated food records. The measurements were repeated after 3–6 months (4–8 weeks for children < 1 year), resulting in total record of 2×3 days per individual. The VELS-study was specifically designed to allow estimations of the dietary exposure for pesticide residues. The target population of infants and young children was selected due to their general high sensitivity for dietary exposures. Since their consumption to bodyweight ratio is higher than for adolescents and adults, the resulting exposure per kg bodyweight is increased compared to other sub-populations [13, Ch. 3.2.1].

The food consumption by older children and adolescents from 6-11 years was reported within the EsKiMo study by the Robert Koch-Institute and the University of Paderborn in 2006 [14]–[16]. Although the survey collected consumption data for individuals aged 6–17 years, only the data for 6–11 years old children were used. The daily consumption was recorded with different tools, either by using a consecutive 3-day food protocol on 1234 individuals (sub-group of 6–11 years) or by a 4-week food frequency questionnaire (sub-group of 12–17 years). The food frequency questionnaire was not suitable to estimate the daily consumption on a daily basis.

The third resource for consumption data for the German population was provided by the German Nutrition Survey II (NVS II) conducted by the Max Rubner-Institute between November 2005 and December 2006 [17], [18]. Again, different sampling techniques to measure the daily consumption were used in the NVS II. For the current work, daily consumption data on individual level were obtained from EPIC-SOFT [19] assisted recall interviews. In these interviews (2 × 24 h interviews for 13926 individuals with one to 6 weeks interval), the consumption pattern was recorded for the German population aged 14-80 years.

In addition to the three German food consumption surveys cited above, data from other European countries was made available by EFSA. In the EFSA RPC-model ("raw primary commodity model") [20] food consumption surveys on 51 sub-populations from 23 European Memberstates were collected and expressed in terms of the "raw agricultural commodity" (RAC). The RPC-model provides statistical parameters for each RAC on the daily consumption for the total population (eaters and non-eaters) and for consumers only, both in absolute amounts of g/day and in relative amounts of g/kg bodyweight and day.

2.2 Food conversion into raw agricultural commodity equivalents (RAC)

For all consumption data used, an approach was selected to express each food eaten in terms of its RAC equivalents. The RAC represents the unprocessed item directly obtained from agricultural crops (e.g. wheat grain) or livestock animals (e.g. chicken meat or cow milk). The classification of RACs in context to pesticide residues is given in Appendix I of Regulation (EC) 396/2005 [7]. This regulation provides the basis for setting maximum residue levels (MRLs) for pesticide residues in foods on the European market. Corresponding to these RAC definitions, the German and other European food monitoring programmes for pesticide residues are designed to allow compliance checks with legal limits as well as generating data suitable for dietary exposure assessments.

The use of RAC equivalents instead of ready-to-eat foods, as typically recorded in consumption surveys, has advantages for pesticide exposure assessments. The RAC equivalent forms a common basis to consider the total amount of one raw food consumed within one day. For example, within 24 hours, multiple foods with identical ingredients might be consumed (e.g. café latte for breakfast, yogurt for lunch and cheese for dinner). All these example foods are based on cow milk, but each of them was subject to a different kind of food processing. With knowledge on the composition of complex foods via recipes and information about the transformation of each ingredient from RAC to the ready-to-eat food, the total amount of RAC-equivalents consumed within one day can be estimated for each individual.

However, it should be noted that this approach tends to overestimate the exposure. Since all sources of one RAC are added into a single RAC equivalent, variation of residue concentrations between different foods consumed within one day are omitted. The correlation of the resulting total daily consumption as RAC equivalents with residues also measured for the RAC leads to an overestimate, since many foods had been subject to food processing potentially decreasing the concentrations. But on the other hand, the RAC approach has the advantage that the contribution from all foods to the daily consumption can be taken into account easily. For pesticide residues, very limited quantitative information on their transfer into processed foods is know. Mostly, regulatory studies are available conducted according to harmonised OECD guidelines [21] to support the authorisation of plant protection products. These studies provide compound specific data on some primary processed products like flour, oil or juice, but cannot cover the complexity of aggregated foods on the market. When studies on the compound specific transfer are available, so called “processing factors” are used, describing the ratio of residues between the raw and processed commodity [22]. For example, a database for processing factors originating from regulatory studies was published by EFSA [23]. This situation makes the inclusion of the full variety of foods in the diet into exposure assessments very complicated, since processing factors are only available for the minority of commodities. Alternatively, the approach of expressing all foods in terms of their RAC equivalents and adding all sources on a daily basis ensures coverage of the maximum amount consumed, but with the drawback of potentially overestimating the true exposure.

To calculate RAC equivalents, food conversion factors are required addressing both the composition of complex foods and the influence of food processing itself. The VELS-study design already included conversion of the daily consumption into RAC equivalents. For the NVS II- and EsKiMo-study, the BfR in cooperation with the University of Paderborn funded two research projects [24], [25] to generate appropriate data. In the end, representative recipes for all foods reported within both surveys were identified, providing quantitative data on the RAC amounts of each ingredient. In parallel, for all relevant processing steps from the RACs as defined in Annex I of Regulation (EU) 396/2005 [7] to the consumed commodities, food conversion factors addressing both industrial or home-made preparation techniques were derived. By combination of the recipe data with the food conversion factors, it became possible to express the complete daily consumption collected in the NVS II- EsKiMo-study in terms of RAC equivalents for each individual on a 24h basis. However, to allow the implementation of processing factors from regulatory studies, differentiation of basic processed products (e.g. raw, juice, dry product, oil or other processed products) was maintained.

2.3 Food monitoring data

For the probabilistic modelling of the dietary exposure against single compounds and cumulative assessment groups, German food monitoring data from the years 2009-2014 were used [26]–[31]. Within these six years, a programme specifically designed to address exposure aspects was followed and completed [10], [11]. The underlying food market-basket contained 120 commodities, which were identified to add a significant contribution to the average daily consumption reported in the VELS-study for children up to 4 years. In total, more than 80% of the average daily consumption was covered by the food market-basket. The majority of foods were raw agricultural commodities, accompanied by simple processed foods like fruit juices, plant oils or butter. During the monitoring programme, 115 of the 120 proposed food commodities were sampled as intended. Sample sizes and sampling frequencies of each commodity differed. For foods mostly eaten raw like fruits or vegetables, annual differences in the pest occurrence on the field may lead to a higher variability of residues. These foods were scheduled to be sampled once every three years (two cycles within six years), to capture the expected change in residue patterns and to generate a sample size sufficiently large to address the variability. Additionally, the national monitoring programme has to align with the EU Coordinated Control Program, which uses a three year sampling cycle for approximately 30 raw food commodities. For food commodities with a lower expected variability of residues due to large scale marketing, bulking or blending (e.g. cereal grains, oilseed or juices), one sampling within six years was implemented. The number of samples per commodity and year were based on the relevance of the commodity for the acute dietary exposure according to the IESTI-methodology. Single food items normally consumed raw are considered based on the highest observed residues, demanding a sample size sufficiently large for a robust estimate of the upper range of residues on the market. In contrast, for bulked and blended commodities, the median or mean residue becomes relevant to address mixing effects and consequently a smaller sample is sufficient. In the end, sample sizes of 188 or 94 items per commodity, respectively, were implemented to address the two different scenarios.

2.4 Toxicological data

Health based guidance values

For pesticidal active substances, the European regulatory framework [2] includes an assessment of toxicological properties of the parent compound and of relevant metabolites. For this purpose, applicant´s studies following specific data requirements [3] and conducted according to harmonised OECD test guidelines are reviewed before approval/authorisation. Taking into account multiple toxicological endpoints, health based guidance values (HBGVs) are derived suitable for dietary or worker/by-stander risk assessments.

For the dietary risk assessments performed within this work, HBGVs in form of the acceptable daily intake (“ADI”) and the acute reference dose (“ARfD”) were used to evaluate the estimated exposure. The ADI is defined as “...the amount of a chemical in food or drinking-water, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk to the consumer:” [32, Ch. Glossary]. It is used in comparison with the long-term (or chronic) dietary exposure, which describes the average exposure of one agent over a lifetime. Since it is very difficult to measure the exposure of individuals over their complete lifetime, the average exposure for sensitive sub-populations (e.g. children) is normally used. It is expressed on a daily basis as an upper-limit for the lifetime exposure.

However, since the range and amount of consumed foods varies over days and between individuals, the health risk arising from a single, high dose of one agent need to be considered additionally. When pesticidal active substances show the potential to cause harmful effects even after single doses, an ARfD is derived. It was defined as “...the amount of a substance in food or drinking-water, expressed on a body weight basis, that can be ingested in a period of 24 h or less without appreciable health risk to the consumer.” [32, Ch. Glossary]. For compounds with negligible acute toxicity, an ARfD may also become unnecessary.

The European Commission hosts a database [1] on all ADI and ARfD values derived during the assessment of pesticidal active substances for their approval according to Regulation (EU) 1107/2009. For the current work, it was the primary source of information to obtain HBGVs. When pesticides have not been notified or evaluated within EU, data were considered either from the WHO database of the JMPR [33] or the Australian Department of Health Office of Chemical Safety [34], [35].

Threshold of toxicological concern

For several pesticides, no information on their HBGVs are available. Most of them are old compounds, which are no longer used as pesticides. Often, they show environmental persistence and can still be detected in foods (especially in fatty compartments) although banned since decades under the Stockholm Convention on Persistent Organic Pollutants [36]. Another reason may be that specific pesticides are only used in few countries and have not been assessed in one of the large global regulatory frameworks. However, foods produced in these countries, might have been exported to the EU and residues were found in the monitoring programs.

To compensate missing toxicological information, the concept of the threshold of toxicological concern (TTC) [37], [38] was used. The TTC concept is based on structural similarity of chemicals. Different exposure threshold levels have been defined after review of a high number of chemicals with know oral toxicological properties to define an exposure level, which does not lead to harmful effects with high probability. The lowest threshold is for genotoxicity, followed by three categories based on the classification scheme by Cramer (Cramer Class I-III) [39].

The use of the TTC concept for the assessment of unknown substances found in foods was already suggested by Koster et al [40]. His approach deals with findings in single samples in food control situations. For the current work, the TTC was used for the first time much broader to systematically assess the dietary risk of single compounds without established HBGVs based on a full probabilistic exposure modelling for the German population.

Cumulative assessment groups

The key part of the current work is related to the dietary risk arising from the simultaneous exposure of residues from multiple different pesticidal active substances present in various food items (cumulative risk). The toxicological hazard assessment within regulatory frameworks focusses on individual pesticidal compounds. Although the demand to consider the effect from multiple residues was included into the legislation (e.g. in Reg. (EU) 396/2005) early, the implementation was postponed until proper methodologies for such a task have been developed. The first approaches cumulative dietary risk assessments were made by the US EPA [41]–[45] in the 2000´s. The principle of the approach was linked to chemical similarity of the pesticides belonging to the same group of agents (e.g. organo-phosphates, pyrethroids or triazoles). From the range of members within each group, a lead compound was identified supported with a well known toxicological database. The similar mode of action for toxicity formed the common basis to group pesticides and the potency of all compounds in relation to this mode of action characterised their contribution to the overall effect. Their potency was expressed as a “relative potency factor” (RPF), describing the strength of the effect in relation to the lead compound (attributed with a relative factor of 1). The exposure from all members of the chemical group were added and – in terms of relative toxicity compared to the lead compound – assessed for their cumulative dietary risk. However, this approach has the drawback, that very detailed data on the mode of action for each compound is required, which is rarely the case. Also, similar toxicological effects observed, like liver toxicity, may be induced by compounds with different chemical structures and deviating modes of action.

Alternatively, EFSA proposed another approach to group chemicals into “cumulative assessment groups” (CAGs) [9], which was recently refined [46], [47]. This concept introduced a shift from chemical structures towards organ based toxicological effects for the grouping, considering dose addition both for similar and dissimilar modes of action [48]. This means that all kind of pesticides, which show potential to induce a common toxicological effect, may add their potency. In contrast to the former approach taken the US EPA, a CAG may contain a range of compounds belonging to different chemical classes, as long as they induce the same toxicological effect. Until today, pesticide compounds were categorised by EFSA into CAGs related to their potential to harm the nervous or the thyroid system. For the nervous system, several specific effects were identified and grouped into individual CAGs, namely autonomic division, motor division, sensory division, neurochemical and neuropathological effects. For the thyroid group, effects on parafollicular C-cells or the calcitonin system and effects on follicular cells and/or the thyroid hormone (T3/T4) system were covered by individual CAGs.

For all compounds in a CAG, “no observed adverse effect levels” (NOAELs) were derived describing their potency for the respective effect. NOAELs may differ between CAGs for the same compounds, since their potency to induce a specific effect varies and depends on the properties of the substance. Also, in absence of a respective toxicological effect, their inclusion into CAGs becomes unnecessary. For calculating the contribution of individual compounds to the cumulative exposure, prior normalisation related to an index compound is required. While the approach selected by the US EPA involved detailed consideration of the mode of action and quantification of the potency for each substance, the information on EFSA CAGs is not sufficiently detailed to follow the same approach. Instead, the normalisation merely represents a mathematical operation without qualitative consideration of the underlying toxicological properties. Based on the following equation, the ratios of all NOAELs related to the selected index compound were calculated.

Equation 1: Calculation of potency factors for CAGs

$$Potency\ Factor = \frac{NOAEL_{Compound\ 1-n}}{NOAEL_{Index\ compound}}$$

These factors are used to adjust the exposure for each substance into potency equivalents of the index compound to provide a common basis for adding them. The resulting cumulated exposure is compared to the HBGVs for the index compound to draw conclusions on the cumulative dietary risk for the whole CAG. In principle, each of the CAG members is suitable as index compound, because the total amount of relative substance equivalents remains the same for each individual and day.

2.5 Probabilistic model

For all three parts of the current work, the MCRA (“Monte-Carlo Risk Assessment”) software developed by the Dutch RIVM (“Rijksinstituut voor Volksgezondheid en Milieu”) was used [49]–[51]. MCRA was specifically designed to allow population based exposure assessments for single compounds and for CAGs following the approach suggested by EFSA´s Guidance on the Use of Probabilistic Methodology [52].

In principle, Monte-Carlo based probabilistic methodology is characterised by randomly selecting data points out of the total database and combine these into a distribution of single model results. In the current case, random individuals are selected from consumption surveys. Foods eaten by these individuals within one day are combined with random residue concentrations found in the food monitoring. The total daily exposure will be calculated for each individual by adding the exposure contributions from all sources. The whole process is repeated a high number of times (iterations). MCRA typically operates with 100.000 to 1.000.000 iterations per exposure assessment. The generated distribution of total daily exposures defines the probability and magnitude of the exposure and consequently of the risk, when compared to HBGVs. Especially the upper percentiles of the generated exposure distribution describe vulnerable sub-populations and individuals with preference to foods containing high residue concentrations.

EFSA´s Guidance on the Use of Probabilistic Methodology suggests the use of multiple scenarios to characterise the range of results. In a conservative scenario, parameters shall be selected according to the potentially worst outcome (“pessimistic scenario). In parallel, a second simulation with a positive selection of parameters is foreseen (“optimistic scenario”), providing a realistic or even slightly underestimating result. Based on the total information from these scenarios, an overall conclusion on the risk can be draw.

For probabilistic dietary risk assessments, the limit of quantification (LOQ) for each analyte in food monitoring programmes poses a high source of uncertainty. In most samples, the number of pesticides found is very limited and approximately half of all samples did not contain quantifiable residues at all. However, it remains unknown whether all of these compounds are truly absent or if some pesticides were still present at minor levels below the quantification limit. In reality, the assumption to consider all values below the LOQ as “zero” is probably correct for most cases, but tends to underestimate the true situation slightly. Thus, in the pessimistic scenario LOQ values were directly considered as the concentration present in foods (LOQ×1), while a “zero” concentration was assumed in the optimistic scenario (LOQ×0). In addition, cumulative assessments were calculated with an intermediate scenario using half of the LOQ (0.5×LOQ) to describe the sensitivity of the LOQ to the result. When the total exposure was close to a linear relation from LOQ×1 over LOQ×0.5 to LOQ×0, very few quantifiable analytical results were found and the true exposure is close to the optimistic scenario. If compounds were found more frequently above the LOQ, results for the LOQ×0.5 and LOQ×0 scenarios become very similar since the exposure at upper percentiles is driven by the positive findings in both cases.

Adjustment of consumption data for the long-term exposure

For the probabilistic modelling, data was considered describing the consumption on a daily basis using survey tools like weighting protocols or 24h recall interviews. However, for the long-term or chronic exposure estimation, both the frequency and the portion sizes are important to characterise the “usual” consumption over a long period of time. In a scientific research project initiated by EFSA, available methodologies were investigated to align consumption data collected over a limited number of days to the “usual” exposure over a long time [53].

To address this effect, two of the approaches described were used for chronic exposure assessment in the probabilistic exposure modelling. Preferably, transformation of the data using the LogisticNormal-Normal (LNN) model [54] was applied. This model was also identified as first choice in the EFSA research project. In some cases, the consumption data did not allow fitting of the LNN approach. Alternatively, the observed individual mean (OIM) approach was used, which is more robust in terms of computation. Both approaches are included in the MCRA Software and were used accordingly.

Use of variability factors for the short-term exposure

For the estimation of the acute exposure, the deterministic IESTI methodology introduced the use of variability factors. These factors describe the variation of residue concentrations between individual units of a food commodity and were defined as the ratio of the 97.5th percentile of residues in individual units compared to the overall mean [55]. It was recognised, that analytical results measured in a composite sample consisting of multiple individual units represent a good estimate for the average residue concentration for the whole lot but may significantly underestimate potential residues in single food items. While for small sized commodities like berry fruits or grains, where the differences between single units are levelled out, this effect cannot be ignored for medium and large sized commodities.

For example, food monitoring sampling procedures [56] request collection of a composite sample of at least 12 pieces or 1 kg for medium sized fruits or vegetables like apples or tomatoes. Residues are measured from the representative composite homogenate of the whole sample. In reality, not all of these fruits contain the same residue concentration – in the worst-case only one of the items contains the complete residue at a concentration 12-times higher than measured.

The distribution of variability factors was investigated in several reviews [57], [58], which showed that average factors approximate a value of 3 while upper factors may reach a value of 7 or higher. Since all occurrence data used in this work was generated in food monitoring programmes by analysis of composite samples, the variability of residues also needs to be considered for the acute probabilist exposure estimates.

Considerations on cumulative co-exposure by using maximum cumulative ratios (MCR)

For the cumulative risk assessment, analysis of potential correlations between substances and their relative contribution to the total exposure was conducted. For such a purpose, the approach of maximum cumulative ratios (MCR) as described by Price et al [59] was used. In the MCRA software, the MCR is calculated based on the ratio between the total cumulative exposure for the CAG in relation to the specific exposure to a single compound (i):

Equation 2: Maximum Cumulative Ratio as used in MCRA

$$Maximum\,cumulative\,ratio\left(MCR\right)=\frac{Total\,cumulative\,exposure}{Exposure_{Compound\,(i)}}$$

This means, a compound with a MCR close to 1 represents a main driver to the total exposure whereas higher values indicate potential co-exposure with other compounds. For example, a MCR of 2 shows 50% contribution to the total exposure whereas a MCR of 4 would only represent 25% contribution of the respective compound to the total exposure.

For each individual, MCRs are calculated for every compound present in the total daily exposure randomly generated. These MCRs are graphically displayed in a log-normal bivariate plot provided by the MCRA software [60]. The x-axis describes the complete range of total cumulative exposures while the y-axis displays the MCRs calculated for each compound. Differently coloured 95 percent confidence regions describe the range, where compounds contribute to the total cumulative exposure based on their calculated MCRs. The MRCA in-build methodology to calculate these confidence regions requires at least 3 observations, which may lead to very simplified plots for some CAGs. Since individuals may either be exposed to only one dominating substance (flat line at a MCR of 1) or the detection frequencies were generally low and the minimum number of observations was not reached, only few compounds might be displayed in plots.

In general, MCR plots are a helpful tool to identify potential co-exposure for compounds within a CAG. Compounds at the upper percentile of the total exposure (right plot side) and with high MCRs (upper plot part) indicate a strong co-exposure with other compounds around the P99.9, which may demand further investigation. On the other hand, low MCRs (lower plot part) or occurrence of compounds in the middle or left plot part of the total exposure suggest that the risk is mainly driven by single substances and/or co-exposure does not result at high concentrations relevant for regulatory decisions.

3 Part 1: Probabilistic dietary risk assessment of pesticide residues in foods for the German population based on food monitoring data from 2009 to 2014

Reference

C. Sieke, B. Michalski, and T. Kuhl, ‘Probabilistic dietary risk assessment of pesticide residues in foods for the German population based on food monitoring data from 2009 to 2014’, J. Expo. Sci. Environ. Epidemiol., vol. 28, p. 46, online 2017, doi: 10.1038/jes.2017.7 [61]

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Authors contribution

Christian Sieke: Conceptualisation, analysis, software, visualisation, writing – original draft

Britta Michalski: Conceptualisation, supervision

Thomas Kuhl: Conceptualisation

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ORIGINAL ARTICLE

Probabilistic dietary risk assessment of pesticide residues in foods for the German population based on food monitoring data from 2009 to 2014

Christian Sieke, Britta Michalski and Thomas Kuhl

Dietary risks for the German population owing to pesticide residues in foods were assessed based on food monitoring data, consumption surveys for children and adults and compound specific toxicological reference values or general thresholds of toxicological concern. A tiered probabilistic modelling was conducted to screen 700 pesticides for significant long- and short-term dietary exposures. Especially for the short-term dietary exposure, the probabilistic methodology used allows simultaneous consideration of the complete daily consumption, whereas most regulatory bodies still rely on single commodity approaches. After screening, refined exposure assessments were conducted for 19 compounds under consideration of conversion factors for toxicologically relevant metabolites, processing information, experimentally derived variability factors and the edible portion for each food item. In total, for 693 compounds the dietary exposure was unlikely to present a chronic or acute public health concern for the German population. In contrast, the refined assessments indicate that the short-term dietary exposure for chlorpyrifos and the cumulative short-term dietary exposure for dimethoate and omethoate may present a public health concern. For copper, owing to exposure assessment limitations, as well as for dimethylvinphos, halfenprox and tricyclazole, which exceeded the thresholds of toxicological concern, the dietary risk assessment remained inconclusive.

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Keywords: dietary exposure; emperical/statistical models; exposure modelling; pesticides

INTRODUCTION

For pesticides, national and international monitoring programmes are in place to measure their occurrence in foods. These programmes are primarily focused on finding exceedances of established maximum residue levels (MRLs) but also on providing representative data to assess health risks for consumers.

With the German food monitoring, a concept was started in 2009 based on a representative food market basket covering at least 80% of the average daily consumption for German children over a 6-year period.[1,2] With the data generated, probabilistic modelling of the long- and short-term dietary exposure was conducted to assess chronic and acute risks for the German population and to identify possible areas of concern. Especially the probabilistic short-term dietary exposure estimation considering the complete daily consumption goes beyond the deterministic single commodity based International Estimated Short-Term Intake (IESTI) methodology (ref. 3: p.15, ref. 4: p.29, ref. 5: p.127) used on European level for MRL setting and the authorisation of plant protection products.[6]

This work represents the first pesticide dietary risk assessment for German consumers using population based models and German residue monitoring data. With the new focus of German residue monitoring in 2009, shifting from identifying MRL exceedances toward better suitability for consumer dietary risk assessments, more comprehensive conclusions on possible health concerns become possible.

MATERIALS AND METHODS

Probabilistic Methodology

The probabilistic modelling was performed with the Monte-Carlo Risk Assessment software (MCRA) Version 8.1, which was developed by the Dutch National Institute for Public Health and the Environment (RIVM).[7] MCRA was designed primarily for the field of pesticide residues and addresses the "Guidance on the use of probabilistic modelling for pesticides" issued by the European Food Safety Authority (EFSA).[8]

According to this guidance (p.8), a "pessimistic" and an "optimistic" run shall be calculated to estimate the upper (1st tier) and lower (2nd tier) bound of the exposure, respectively. For 1st tier runs residues below the limit of quantification (LOQ) were substituted by the LOQ value, whereas 2nd tier runs consider all residues below the LOQ value to be present at "zero". Each run was generally based on 1,000,000 iterations, which means that one random individual was selected and each consumed food reported was correlated with an also randomly selected residue concentration (empiric sampling) per iteration. The sum of residues via all foods represents the total exposure for the selected individual.

The 1st and 2nd tier runs were used for a screening to identify substances with significant long- and short-term exposure levels. In general, the 99.9th percentile (P99.9) of the exposure distribution was used as basis for further considerations.[9] In addition, the 90th, 95th, 99th and 99.99th percentile were reported to show the sharpness of the exposure distribution, to allow comparison between 1st and 2nd tier runs to consider the sensitivity of LOQs and detection frequencies and to identify possible exceedances of toxicololgical reference values at the very upper end of the exposure distribution.

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Cumulative exposure and risk assessment for the German population with respect to pesticide residues in foods

Table 1. Parameters considered for the refined probabilistic modelling.

Compound	*Conversion factors (CF)*	*Processing factors*	*Experimentally derived variability factors for acute exposure assessment*
Chlorobromuron	–	–	–
Chlorpropham	All commodities: 1 (ref. 35: Table 3–2)	Potatoes, unpeeled and boiling: 0.57 (ref. 35: p.18)	Potatoes: 3 (ref. 35: p.24)
Chlorpyrifos	No CF required[36] (p.8).	Mandarin, pulp: 0.08 (extrapolated to all citrus fruit)[24] (p.63)	–
Copper	–	–	–
Cyhalothrin (excl. lambda-cyhalothrin)	Except for lambda-cyhalothrin, residues of all cyhalothrin-isomers were reported as total cyhalothrin. To address the unknown composition of total cyhalothrin, it is assumed that only the most critical isomer is present (gamma-cyhalothrin), for which an ADI of 1.2 μg/kg bw and an ARfD of 2.5 μg/kg bw was proposed).	Processing factors for lambda-cyhalothrin extrapolated to all cyhalothrin-isomers: Citrus, pulp: 0.25 (ref. 37: p.49) Banana, pulp: 0.66 (ref. 37: p.50) Melon/watermelon, pulp: 0.5 (ref. 37: p.50) Wheat, flour: 0.75 (ref. 37: p.50)	–
Deltamethrin	Plant commodities: 1.25 (ref. 38: p.12)	Potato, unpeeled and boiled: 0.26 (ref. 38: p.81) Dry pulses, cooked: 0.1 (ref. 38 p.81) Barley, beer: 0.02 (ref. 38: p.81) (applied to barley as primarily consumed food) Wheat, flour: 0.31 (ref. 38: p.81)	–
Diazinon	Not necessary[39] (p.46)	–	–
Dimethoate and Omethoate	Chronic risk: equivalence factor of 3 for omethoate to dimethoate Acute risk: equivalence factor of 6 for omethoate to dimethoate[34] (p.18)	–	–
Dimethylvinphos	–	–	–
Dithiocarbamates	Not applicable, dithiocarbamates were determined as a common moiety (CS_2). No information on the actual present active substance(s) is available.	Not applicable, dithiocarbamates were determined as a common moiety (CS_2). No information on the actual present active substance(s) is available.	–
Ethephon	Cereal grains: 2 (ref. 40: p.46)	Pineapple, pulp: 0.29 (ref. 41: p.146) Wheat, patent flour: 0.3 (ref. 40: p.49)	–
Halfenprox	–	–	–
Hexachlorobenzene	Hexachlorobenzene is a persistent organic pollutant according to the Stockholm Convention.[33] The major part of the exposure occurs through butter due to the high fat-solubility of hexachlorobenzene. In this special case the general approach of using the RAC for an overall exposure assessment is overly conservative. For the refined assessment consumption data for butter were used "as-eaten".		
Imazalil	Plant commodities: not necessary Animal commodities: no data[42] (p.31)	Citrus, pulp: 0.07 Potato, boiled with peel: 0.14 (ref. 42: p.34)	A variability factor of 1.5 was reported for Imazalil in apples following post-harvest treatment[43] (p.4).
Maleic hydrazide	Not necessary[44] (p.11)	Single processing information on potatoes is reported. However, the database is very limited and no significant reduction of the residue was observed[44] (p.15). No PF is taken into account.	–
Mirex	Mirex is a persistent organic pollutant according to the Stockholm Convention.[33] No further refinement conducted.		
Pirimiphos-ethyl	–	–	–
Prochloraz	Cereal grains: 2.5 (ref. 45: p.35) Ruminant products (bovine meat, bovine liver, goat meat and milks): 2 (ref. 45: p.35)	Lemon (pulp/whole fruit ratios): 0.04, 0.05, 0.05, 0.06 → median PF: 0.05 (ref. 46: p.167) Mandarine (pulp/whole fruit ratios): 0.01, 0.02, 0.02, 0.03, 0.04, 0.04, 0.05, 0.05, 0.1, 0.13, 0.13 → median PF: 0.04 (ref. 46: p.167)	–

Table 1. (Continued)

Compound	Conversion factors (CF)	Processing factors	Experimentally derived variability factors for acute exposure assessment
		Oranges (pulp/whole fruit ratios): 0.04, 0.08, 0.09, 0.09, 0.11, 0.14, 0.17 → median PF: 0.09 (ref.46: p.167) (also extrapolated to grapefruit) Barley, beer: 0.08 (ref. 45: p.40) (applied to barley as primary consumed food form) Wheat, flour type 550: 0.6 (ref. 45: p.40) (applied to wheat as primary consumed food form)	
Tricyclazole	Pending: 1.3 for cereals (ref. 31: p.32)	–	–

-: no data available.

When the highly conservative 1st tier run indicated a dietary exposure higher than 10% of the Acceptable Daily Intake value (ADI) or of the Acute Reference Dose (ARfD) at the P99.9, a 2nd tier run was calculated. The 10% criterion was selected to compensate for the lack of information on potentially relevant metabolites not covered by the residue definition for enforcement purposes. In current guidance documents more than 10% contribution of a metabolite to the total residue is considered as a major factor for its inclusion into a residue definition (ref. 5: Table 3. Ref.1,10: Table 1).

The 2nd tier run provides a more realistic estimate of the exposure. Although residues may have occasionally been present in foods at concentrations below the LOQ, which would cause an underestimation of the exposure when substituted by zero, the use of consumption data expressed as raw agricultural commodity (RAC) still provides an overall conservative exposure assessment since inedible parts are still included in the assumed portion sizes. Again, the 10% ADI/ARfD-threshold was used as screening criterion. In case of compounds with a very high rate of detected residues (e.g., chlorpyrifos or chlorpropham), the outcome of the 2nd tier run might be almost identical or even slightly higher than the 1st tier run. Upper percentiles of the exposure distribution are dominated by measured concentrations instead of LOQ values, making the impact of substituting the LOQ with "zero" insignificant. Especially for the short-term exposure, the variability between runs may be large and both the 1st and 2nd tier runs still represent a single point estimate of percentiles and depend on the random selection of data. Modelling uncertainty to describe this variability was only taken into account for in the refined assessments; however the range of expected variability is also covered by the 10% ADI/ARfD-threshold in the 1st and 2nd tier runs. For substances which exceeded the 10% ADI/ARfD-threshold in 2nd tier runs, additional information on conversion factors (CFs), food processing factors, experimentally derived variability factors and the percentage of the edible portion was used for a refined assessment (Table 1). The modelling uncertainty of the probabilistic runs was quantified by 100 additional resampling cycles of 10000 iterations each, estimating the 2.5th and 97.5th interval as lower and upper modelling range, respectively. For the interpretation, a large range around the results reflects high variability in the data.

The probabilistic modelling of long-term dietary exposures required adjustment of the consumption data collected for single days to address differing consumption frequencies in the long-term to avoid significant underestimation of the intake. The adjustment was primarily done parametically by using the MCRA built-in LogisticNormal-Normal (LNN) model suggested for a realistic "right-tail assessment"[11] (p.20). This procedure requires a reasonable number of consumers for an acceptable correlation of data, which is not always reached especially for infrequent eaten foods. When correlations were not significant, the observed individual mean was used instead. Although all food surveys used were designed to generate representative consumption data for all seasons, the long-term consumption of some rarely eaten foods may be underestimated. However, owing to very low frequency of consumption, the average contribution to the overall long-term exposure is considered small.

In the probabilistic modelling of short-term exposures unit-to-unit variability was taken into account by applying a beta-distribution model based on default variability factors of 5 or 7 used in the European Union for commodities with unit-weights ≥ 25 g (ref. 6: Table:Acute_overview_children). These default factors are the highest currently used in regulatory systems. Within Codex Alimentarius, a general variability factor of 3 is used since 2003 (ref. 12: p.11). Experimentally derived variability factors, when available, were only used in refined assessments. For commodities with < 25 g unit weight or for mixed/blended commodities (e.g., juices or cereal grains) a variability factor of 1 was considered.

Consumption Data

For the German population three different consumption surveys were used for the probabilistic assessment covering different sub-populations. In the VELS-study[13] from 2003 the daily consumption of children aged 6 months up to 4 years ($n = 816$) was surveyed using a 3-day weighed/estimated food record repeated after 3–6 months (4–8 weeks for children aged < 1 year). Older children aged 6–17 years were part of the EsKiMo-study[14,15] conducted by the Robert Koch-Institute and the University of Paderborn in 2006.[16] In EsKiMo, the daily consumption for the sub-group of 6–11 years was recorded using a 3-day food protocol on 1234 individuals. For older children, a 4-week food frequency questionnaire was used in the EsKiMo-study, unsuitable for short-term exposure assessments on a daily basis. The third survey available was the German Nutrition Survey II (NVS II), conducted by the Max Rubner-Institute between November 2005 and December 2006.[17,18] The NVS II study part used for the probabilistic modelling measured the consumption behaviour of Germans aged 14–80 years by using two EPIC-SOFT[19] assisted recall interviews per individual (2 × 24 h interviews for 13,926 individuals plus 1156 individuals with 1 × 24 h interview). The methodology selected in this work is based on the consumption of food items on a daily basis for each individual, making the additional information from food frequency interviews unsuitable for the modelling. In absence of consumption surveys covering all ages, daily based consumption data (food records or 24 h recalls) from all surveys were combined. Longitudinal differences between surveys were not assessed; however since each probabilistic iteration of the model estimates the total daily exposure on an individual level, the P99.9-criterion is considered sufficiently conservative to also identify vulnerable sub-populations without further stratification.

For the probabilistic modelling all consumption data (VELS, EsKiMo and NVS II) were converted into underlying RACs as defined in Annex I of Regulation (EU) No. 396/2005 and aggregated into 115 foods (Supplementary information, "SI"). This kind of conversion was already part of the VELS-study. For EsKiMo and NVS II, subsequent conversion of all foods was conducted using recipe data from the German Nutrient Data Base,[20] amended by public literature on food processing and direct communication by manufacturers. These factors address the contribution of each RAC to the composition of complex foods (e.g., tomato in Pizza Napoli) as well as the yields for each processing step involved (e.g., juicing, baking, cooking, peeling). Consumption equivalents of the same particular RAC originating from different foods consumed within 1 day were aggregated into an overall RAC consumption equivalent like "wheat grain" or "tomato". Exceptions were made for fruit juices, which were also referred back to their RAC but kept separate to avoid an overestimation due to their high daily consumption. This results into separate categories for e.g., "apple excluding juice" and "apple juice". For refined assessments the percentage of edible portion was considered for a RAC, if applicable, as reported for the NVS II-model by the BfR.[21]

Residue Data

The German Food Monitoring provides representative data for pesticide residues in foods on the market.[22–27] In 2009 a national concept[1,2] laid out for a period of six years was implemented focusing on the dietary exposure for the German population. It was complemented by commodities scheduled in the EU Coordinated Control Program. Considering the degree of expected variability of residues in market samples, at least 188 samples have to be collected for commodities with high variability (e.g., most fresh fruit and vegetables) while mixed/blended commodities have to be monitored with at least 94 samples each. In addition, the importance of food commodities in the diet was considered to decide whether sampling has to be conducted once every three years (like apples or oranges) or once within six years (e.g., fresh herbs, Brussels sprouts). Measured residue concentrations or reported LOQ values were per se used for the modelling (empiric), however for pesticides with complex enforcement residue definitions including multiple analytes a total sum expressed as parent compound equivalents was calculated.

Toxicological Information

ADI and ARfD values were primarily drawn from the European Pesticide database of the European Commission,[28] summarising agreed toxicological information for pesticides covered under the framework of Regulation (EC) No. 1107/2009.[29] When no toxicological information from this database was available, ADI and ARfD values derived by other regulatory/scientific bodies (e.g., WHO) were taken into account. When no decision was made that an ARfD is unnecessary, but a specific ARfD has not been established yet for a particular compound, the ADI value was used as a conservative surrogate in the short-term dietary risk assessment. For compounds with no agreed ADI or ARfD values, the dietary exposure was expressed on a μg/kg bodyweight basis. Thresholds of toxicological concern (TTC),[30] which represent empirically derived exposure levels under which toxicological effects are assumed to be of no concern, were considered for these substances. When an ARfD was not considered necessary due to low acute toxicity, no short-term dietary exposure was calculated.

The use of CF, addressing the difference between residue definitions for enforcement and risk assessment purposes, was not taken into account in screening tiers but accommodated for indirectly by applying the 10% criterion. For refined assessments, compound specific CFs were taken into account, if available.

RESULTS AND DISCUSSION

In the German food monitoring from 2009 to 2014, a total of 392 analytes were not found above the LOQ in any of the samples investigated (SI). No exposure assessment was conducted for these compounds and they are unlikely to present a public health concern for the German population.

Chronic Dietary Risk Assessment

For the chronic risk assessment, the 1st and 2nd screening tier indicated no exceedance of the 10% ADI value criterion (P99.9) for 183 and 113 compounds, respectively. In addition, 16 compounds without established toxicological reference values gave exposure levels below the lowest TTC of 0.0025 μg/kg bw/d for genotoxicity (P99.9) in the 2nd tier screening. Based on the results of both screening tiers, a chronic public health concern for the German population (SI) was not identified for residues of these substances.

A refined long-term dietary exposure assessment was conducted for 12 compounds (Table 2). For chlorpyrifos, diazinon, dimethoate and omethoate, dimethylvinphos, dithiocarbamates, hexachlorobenzene, imazalil, maleic hydrazide, pirimiphos-ethyl and prochloraz no exceedances of their respective ADI values or of the TTC for genotoxicity of 0.0025 μg/kg bw were identified at any selected percentile of the exposure distribution. These compounds are unlikely to present a chronic public health concern for the German population.

Chlorpropham gave a long-term dietary exposure of 40% of the ADI value (P99.9), which is also unlikely to present a chronic public health concern for the German population. However, the upper range of the modelling uncertainty for the extreme end of the exposure distribution (P99.99) exceeded the ADI with 170% utilisation, indicating that individuals may be exposed to chlorpropham residues above the ADI on single days. Although the probability for the long-term exposure to exceed the ADI on subsequent days is low and therefore insignificant for the German population, it is recommended to continue the analysis of chlorpropham at a high level to provide a complete picture of the exposure situation.

Both halfenprox and tricyclazole were found in one food commodity only (herbal infusions and rice grain, respectively) but the long-term dietary exposure for the German population (P99.9) exceeded the TTC for genotoxicity as both commodities represent frequently consumed foods. For halfenprox no further toxicological information concerning its genotoxicity are available while for tricyclazole at European level no toxicological reference values have been established so far owing to missing data on *in vivo* genotoxicity[31] (p.8). Although the TTC for genotoxicity is already a very conservative approach in assessing the dietary risk, currently no conclusions on the dietary risk can be drawn for both compounds.

Copper is an element naturally occurring in many foods. The P99.9 of the exposure distribution represented 83% of the ADI value derived for copper in European plant protection legislation. Main contributors to the dietary exposure via foods were wheat (34.9%) and cacao (18.6%). However, the current assessment only considered residues in foods, whereas drinking water poses an additional source for copper. Average exposure data for copper from drinking water are not applicable as the major sources are copper plumbings in individual households themselves. The EFSA Scientific Committee on Food (SCF) derived an upper level (UL) for the daily copper intake of 5 mg/d for adults, with lower ULs for children while pregnant women were excluded from the UL[32] (p.209). For an average adult of 65 kg bodyweight this UL would equal 0.077 mg/kg bw/d, which is approximately half of the ADI value derived for copper as pesticide. Owing to the missing information on drinking water, the current exposure assessment on copper is only indicative. Although the ADI is nearly completely utilised by the contribution from foods (83%) at P99.9, the UL derived by the SCF might be exceeded (~160%) for adults. In view of the lower or non-applicable ULs for the vulnerable subpopulations children and pregnant women, further investigation on the copper exposure in the German population is recommended, especially in combination with drinking water.

Acute Dietary Risk Assessment

For the short-term dietary exposure assessment the 1st tier screening identified 196 compounds (including compounds for which no ARfD is necessary) and the 2nd tier screening additional 84 compounds below the 10% ARfD criterion (P99.9). The short-term exposure of 14 compounds in the 2nd screening tier without established toxicological reference values was below the TTC for genotoxicity of 0.0025 μg/kg bw/d (P99.9). Based on the results of both screening tiers, an acute public health concern for the German population was not identified for residues of these substances (SI).

A refined short-term dietary exposure assessment was conducted for 14 compounds (Table 3). For mirex and pirimiphos-ethyl, no exceedance of their toxicological reference values was

Table 2. Results of the refined long-term probabilistic modelling

Active substance	*Toxicological reference value*[28]	*Refined run % of toxicological reference value or exposure in μg/kg bw and day when no ADI/ARfD is available; in parenthesis: modelling range of the probabilistic assessment (lower bound 2.5% and upper bound 97.5%)*					*Composition of foods contributing to the P97.5 of the exposure distribution*[a]
		P90	*P95*	*P99*	*P99.9*	*P99.99*	
Chlorpropham	ADI: 50 μg/kg bw/d	1.4% (< 0.1–1.4)	4.7% (< 0.1–4.7)	10% (0.5–10)	40% (3.6–40)	74% (14–170)	100% Potato
Chlorpyrifos	ADI: 1 μg/kg bw	4.8% (3.4–7.0)	6.2% (4.5–8.9)	10% (8.1–15)	21% (17–30)	30% (24–44)	35.6% Pears (excluding juice) 20.7% Apple (excluding juice) 13.2% Grapes 11.8% Banana 5.9% Peach < 5% other foods (individually)
Copper	ADI: 150 μg/kg bw	38% (36–39)	44% (43–46)	59% (57–62)	83% (76–89)	135% (96–183)	34.9% Wheat 18.6% Cacoa 7.0% Potato < 5% other foods (individually)
Diazinon	ADI: 0.2 μg/kg bw/d	0.7% (< 0.1–1.1)	1.8% (0.2–2.9)	7.5% (0.9–13)	23% (2.4–48)	53% (4.9–93)	93.8% Pineapple 6.2% Grapefruit
Dimethoate and Omethoate	ADI: 1 μg/kg bw/d (Potency factor of 3 used for Omethoate)	3.2% (2.0–5.3)	5.9% (3.1–11)	11% (5.7–22)	15% (8.6–30)	18% (11–37)	70.6% Potato 9.2% Spinach 5.6% Cherry (excluding juice) < 5% other foods (individually)
Dimethylvinphos	No ADI available	< 0.0025 μg/kg bw (n.c.)	< 0.0025 μg/kg bw (n.c.)	< 0.0025 μg/kg bw (n.c.)	< 0.0025 μg/kg bw (n.c.)	< 0.0025 μg/kg bw (n.c.)	100 % Wine grapes (Wine)
Dithiocarbamates[b]	ADI: 6 μg/kg bw/d (based on Ziram, reflecting the most potent dithiocarbamate)	8.4% (7.8–9.5)	10% (9.7–12)	17% (15–20)	32% (26–42)	55% (42–73)	53.3% Pears (excluding juice) 9.4% Apricots (excluding juice) 6.6% Apples (excluding juice) 6.5% Table grapes < 5% other foods (individually)
Hexachlorobenzene	No ADI available TDI: 0.16 μg/kg bw[47]	0.9% (0.8–1.0)	1.1% (1.0–1.2)	1.6% (1.4–1.8)	2.2% (2.0–2.8)	3.3% (2.4–6.4)	35.9% Bovine milk 26.3% Butter 17.4% Fish (seafish) 13.3% Goat milk < 5% other foods (individually)
Imazalil	ADI: 25 μg/kg bw/d	6.3% (1.4–9.7)	15% (1.9–15)	33% (4.0–33)	46% (7.4–46)	52% (10–75)	84.0% Potato 12.1% Banana 1.5% Apple (excluding juice) < 1% other foods (individually)

Table 2. (Continued)

Active substance	Toxicological reference value[28]	Refined run % of toxicological reference value or exposure in μg/kg bw and day when no ADI/ARfD is available; in parenthesis: modelling range of the probabilistic assessment (lower bound 2.5% and upper bound 97.5%)					Composition of foods contributing to the P97.5 of the exposure distribution[a]
		P90	P95	P99	P99.9	P99.99	
Maleic hydrazide	ADI: 250 μg/kg bw	1.2% (0.1–3.3)	3.1% (0.2–9.0)	6.4% (0.2–20)	8.8% (0.4–27)	11% (0.5–39)	97.2% Potato 2.8% Bulb onion
Prochloraz	ADI: 10 μg/kg bw/d	0.2% (< 0.1–0.5)	0.4% (0.2–0.8)	0.8% (0.4–1.8)	2.2% (1.2–4.9)	4.0% (2.1–8.2)	86.9% Pineapple 11.2% Lemon < 1% other foods (individually)
Tricyclazole	No ADI available	0.0057 μg/kg bw (0.0035–0.0094)	0.0075 μg/kg bw (0.0046–0.013)	0.014 μg/kg bw (0.0082–0.022)	0.036 μg/kg bw (0.020–0.060)	0.058 μg/kg bw (0.032–0.099)	100% rice

Abbreviations: n.a., not available; n.c., not calculated, only one positive sample reported. [a]For the composition of foods contributing to the upper end of the exposure distribution the P97.5 was selected instead of the P99.9. At very higher percentiles like the P99.9, the contribution of foods becomes unpredictable since individual exposures are often driven by randomly selected single high residue/high consumption combinations. At a P97.5, foods with overall high consumption and high residue concentrations are selected more frequently, allowing more robust estimates on their contribution to the exposure. [b]Dithiocarbamates were analysed for CS_2 as representative marker. To refer to a toxicological reference value, Zineb was selected as critical case. The following factor was taken into account ($CS_2 \times f$ = Parent equivalents): Ziram: $f = 2.0$.

identified. Residues of mirex and pirimiphos-ethyl are unlikely to present an acute public health concern for the German population.

Chlorpropham, cyhalothrin (excluding lambda-cyhalothrin), deltamethrin, ethephon, hexachlorobenezene and imazalil resulted in short-term dietary exposures below their respective ARfDs at the P99.9. Based on this percentile it is unlikely that residues of these substances present an acute public health concern for the German population. However, taking into account the ranges of modelling uncertainty, the extreme upper end (P99.99) of the exposure distribution exceeded the respective ARfDs or the TDI for hexachlorobenzene. The probability for such an exceedance is low and therefore insignificant for the German population but cannot be fully excluded for all combinations of large portions and high residues. It is recommended that the analysis of these compounds in monitoring is maintained at a high level to assess the future exposure situation. Hexachlorobenzene is a persistent organic pollutant according to the Stockholm Protocol.[33] Its use is globally banned, but owing to the long environmental half-life times accumulation especially in fish, fatty tissues and milk is inevitable. It is recommended to reduce its occurrence as far as technically possible.

For chlorpyrifos, the refined short-term dietary exposure indicated a nearly complete utilisation of the ARfD with 99% (P99.9) with an exceedance of 104% of the ARfD taking into account the upper range of modelling uncertainty. Also, the 1st and 2nd tier runs for chlorpyrifos indicated no significant influence of < LOQ values, showing utilisations of the ARfD of 90% and 114%, respectively. The higher ARfD utilisation in the 2nd tier run compared with the 1st tier run is based on the high variability of the short-term exposure modelling without upper/lower bound estimation of the modelling range for screening. The refined short-term exposure for dimethoate and omethoate, which are closely rated compounds and were assessed for their cumulative dietary risks[34] (p.18), gave a lower average utilisation of the ARfD with 21%. However, the upper range of the modelling uncertainty at the P99.9 represented 280% of the ARfD, indicating a high variability in the results. This variability may have been increased by single samples exceeded the MRLs and also the ARfD based on the IESTI-concept. Random selection of residue concentrations measured in such samples during probabilistic modelling would results in total exposure levels highly above levels based on MRL-compliant samples. For both compounds highest food contributors to the short-term exposure were broadly spread as these substances are frequently found in monitoring samples. For chlorpyrifos, apples excluding juice (42.2%), pears (30.6%), bananas (9.9%) and peaches (7.6%) contributed mostly to the total exposure while for dimethoate and omethoate potatoes (26.1%), cherries excluding juice (18.3%), spinach (12.6%) and barley (10.2%) were the main contributors. Taking into account the range of modelling uncertainty, residues of chlorpyrifos and cumulative exposure to dimethoate and omethoate in foods may present an acute public health concern for the German population. A general reduction strategy for residues of these compounds in foods is recommended.

The refined assessment for chlorobromuron indicated a short-term dietary exposure below the TTC for genotoxicity of 0.0025 μg/kg bw (P99.9). Based on the TTC approach it is unlikely that residues of chlorobromuron present an acute public health concern for the German population.

For dimethylvinpos, halfenprox and tricyclazole the short-term dietary exposure (P99.9) was above the TTC for genotoxicity of 0.0025 μg/kg bw used as a conservative surrogate in absence of specific toxicological data. Each compound was found in one food commodity only (wine, herbal infusions and rice grain, respectively); however these commodities represent frequently consumed foods. For diemethylvinphos and halfenprox no further toxicological information concerning its genotoxicity are available

Table 3. Results of the refined short-term probabilistic modelling

Active substance	*Toxicological reference value (Reference: 28 unless noted otherwise)*	*Refined run % of toxicological reference value or exposure in μg/kg bw and day when no ADI/ARfD is available; in parenthesis: modelling range of the probabilistic assessment (lower bound 2.5% and upper bound 97.5%)*					*Composition of foods contributing to the P97.5 of the exposure distribution[a]*
		P90	*P95*	*P99*	*P99.9*	*P99.99*	
Chlorobromuron	No ARfD available	0 (n.c.)	0 (n.c.)	0 (n.c.)	< 0.0025 μg/kg bw (n.c.)	0.010 μg/kg bw (n.c.)	100% Celeriac
Chlorpropham	ARfD: 500 μg/kg bw	< 0.1% (< 0.1- < 0.1)	0.1% (< 0.1–0.4)	1.1% (0.5–4.3)	11% (3.6–36)	76% (14–170)	58.3% Potato41.7% Kale
Chlorpyrifos	ARfD: 5 μg/kg bw	1.3% (< 0.1–1.3)	3.8% (0.2–3.8)	20% (0.9–21)	99% (7.0–104)	264% (23–422)	42.2% Apples (excluding juice)30.6% Pears (excluding juice)9.9% Banana7.6% Peach3.0% Grapes < 2% other foods (individually)
Cyhalothrin (excl. lambda-cyhalothrin)	ARfD: 2.5 μg/kg bw assuming gamma-cyhalothrin only	< 0.1% (0- < 0.1)	0.3% (< 0.1–0.7)	1.9% (1.0–3.8)	8.2% (4.3–27)	189% (9.9–402)	47.6% Kale30.3% Lettuce11.6% Spinach < 5% other foods (individually)
Deltamethrin	ARfD: 10 μg/kg bw	< 0.1% (< 0.1- < 0.1)	< 0.1% (< 0.1–0.2)	1.6% (0.7–3.1)	16% (7.2–40)	72% (18–348)	52.3% Rice32.5% Maize < 5% other foods (individually)
Dimethoate and Omethoate	ARfD: 10 μg/kg bw (Potency factor of 6 used for Omethoate)	< 0.1% (< 0.1%-0.2)	0.3% (0.1–0.9)	3.8% (2.0–23)	21% (15–280)	68% (32–569)	26.1% Potato18.3% Cherry (excluding juice)12.6% Spinach10.2% Barley8.8% Bovine meat < 5% other foods (individually)
Dimethylvinphos	No ARfD available	0 (n.c.)	0 (n.c.)	0 (n.c.)	0.015 μg/kg bw (n.c.)	0.038 μg/kg bw (n.c.)	100 % Wine grapes (Wine)
Ethephon	ARfD: 50 μg/kg bw	< 0.1% (< 0.1–0.4)	0.3% (0.2–1.1)	2.0% (0.9–8.1)	14% (3.1–70)	53% (7.3–197)	53.6% Tomato19.7% Grapes6.3% Apples (excluding juice)6.3% Cherry (excluding juice)5.5% Wheat < 5% other foods (individually)
Halfenprox	No ARfD available	0 (n.c.)	0 (n.c.)	0 (n.c.)	0.0071 μg/kg bw (n.c.)	0.013 μg/kg bw (n.c.)	100% Herbal infusions
Hexachlorobenzene	No ARfD available TDI: 0.16 μg/kg bw[47]	1.2% (1.1–1.3)	1.8% (1.7–2.0)	3.8% (3.4–4.6)	13% (8.7–22)	39% (16–107)	38.3% Fish (seafish)29.6% Bovine milk10.1% Butter8.3% Goat milk5.3% Rice < 5% other foods (individually)
Imazalil	ARfD: 50 μg/kg bw	0.3% (< 0.1–1.2)	0.8% (< 0.1–3.5)	4.3% (0.4–16)	23% (3.2–64)	141% (8.1–182)	42.0% Banana19.1% Apples (excluding juice)16.6% Potato7.6% Lemon5.9% Orange (excluding juice) < 5% other foods (individually)
Mirex	No ADI available RfD: 0.2 μg/kg bw/d[48]	0 (n.c.)	0 (n.c.)	2.25 (0.6–3.7)	12% (6.9–17)	30% (11–39)	100% Fish (seafish)
Pirimiphos-ethyl	No ARfD, ADI only: 0.2[49]	0 (n.c.)	0 (n.c.)	0 (n.c.)	22% (n.c.)	45% (n.c.)	100% Wheat grain
Tricyclazole	No ARfD available	0 μg/kg bw (0–0)	0 μg/kg bw (0–0.0031)	0.062 μg/kg bw (0.033–0.11)	0.37 μg/kg bw (0.17–0.62)	1.4 μg/kg bw (0.40–2.0)	100% rice

Abbreviations: n.a., not available; n.c., not calculated, only one positive sample reported. [a]For the composition of foods contributing to the upper end of the exposure distribution the P97.5 was selected instead of the P99.9. At very higher percentiles like the P99.9, the contribution of foods becomes unpredictable since individual exposures are often driven by randomly selected single high residue/high consumption combinations. At a P97.5, foods with overall high consumption and high residue concentrations are selected more frequently, allowing more robust estimates on their contribution to the exposure.

while for tricyclazole at European level no toxicological reference values have been established so far owing to missing data on the *in vivo* genotoxicity[31] (p.8). Although the TTC for genotoxicity is already a very conservative approach in assessing the dietary risk, currently no conclusions on the dietary risk can be drawn for these compounds.

CONCLUSIONS

The risk for the German population, which might arise from the acute and chronic dietary exposure of pesticide residues, was assessed by a two-step screening approach followed by refinement, if necessary. The probabilistic model used provides full consideration of all foods eaten within a day for the estimation of the total exposure. However, short-term exposure results are difficult to compare with the IESTI-methodology. Single samples containing residue concentrations, which would exceed the ARfD based on the IESTI, may become insignificant only affecting the high percentiles of the exposure distribution above the P99.9. Also, the model is sensible to foods with a high percentage of detected residues in combination with a low number of total samples. Owing to the random selection of data, residue concentrations above the LOQ are overrepresented, also resulting in an overestimation for the total exposure. As final result, for 693 of 700 compounds a chronic or acute public health concern was unlikely for the German population. On the other hand, the refined assessments indicated that the short-term exposures for chlorpyrifos and for dimethoate and omethoate, assessed for their cumulative dietary risks, may present an acute public health concern for the German population. A general reduction of chlorpyrifos, dimethoate and omethoate residues in foods is recommended.

For copper the current assessment is only indicative, because drinking water as a major source of exposure was not yet taken into account. The ADI value derived for copper used as pesticide was nearly completely utilised by the exposure via foods, whereas the UL derived by the SCF might even be exceeded. Further investigations of the exposure of copper in the German population, especially under consideration of drinking water, are recommended before final conclusions on the dietary consumer risk can be drawn. However, the results already indicate that the long-term dietary exposure for copper might exceed tolerable levels and further reduction might be inevitable.

Dimethylvinphos, halfenprox and tricyclazole exceeded the TTC for genotoxicity either in the long- or short-term dietary exposure. As information to exclude a genotoxic potential for these compounds is not available, the dietary risk assessment remains inconclusive.

By applying available probabilistic methodologies, an important aspect is added to the dietary consumer risk assessment by consideration of the total daily consumption, especially for the short-term dietary exposure. Using the advantageous general features of probabilisitic assessments like the distribution of exposures amongst multiple individuals and the variability in food consumption, a more comprehensive assessment of the dietary exposure can be achieved. Another beneficial aspect is the application of the TTC concept, improving the interpretation of results for compounds where adequate toxicological reference values are not available. Further investigations on chronic and acute cumulative risks arising from compounds with similar targets of toxicity are required in the future to improve the assessment of dietary risks for consumers exposed to pesticide residues.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DISCLAIMER

The material presenting is original research, has not been published previously and has not been submitted for the publication elsewhere while under consideration.

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Probabilistic cumulative dietary risk assessment of pesticide residues in foods for the German population based on food monitoring data from 2009 to 2014

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ABSTRACT

Cumulative dietary risks for the German population owing to pesticide residues in foods were assessed using food monitoring and consumption data. Based on grouping principles for cumulative assessment groups (CAG) as defined by the European Food Safety Authority, probabilistic modelling gave cumulative long- and short-term dietary exposures relevant to the nervous and thyroid system. Compound specific toxicological reference values were considered to assess the total margins of exposure (MoEs) for each CAG, allowing an assessment of the cumulative dietary consumer risk. For the German population, no public health concerns were identified for 6 of 11 CAGs. For three CAGs high uncertainties remained, since MoEs were less than the usually required threshold of 100 for the upper confidence interval of the modelling uncertainty. For two CAGs relevant to the nervous and thyroid system, possible health risks cannot be excluded with the selected approach. Most potent risk drivers were chlorpyrifos and the group of dithiocarbamates (expressed as propineb). For regulatory decisions on possible cumulative dietary health risks the limitations of the published approaches and the absence of harmonized data sources for robust refinements have to be considered. Future research to reduce this high uncertainty is considered necessary in this area.

1. Introduction

In the regulatory framework of plant protection products the safety of consumers regarding residues of pesticidal active substances in foods is a crucial requirement for authorization. The assessment of dietary risks to consumers addresses the long- and short-term exposure using the National Estimated Daily Intake (NEDI) (Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food), 1997) and the International Estimated Short-Term Intake (IESTI) concept, respectively, as defined by the World Health Organization (WHO) and the Food and Agricultural Organization (FAO) (Food and Agriculture Organization of the United Nations (FAO), 1999). Both concepts rely on single substances, taking into account either the average daily consumption of all foods for the long-term exposure estimation or a single large portion of one specific food commodity for the short-term exposure estimation. However; in reality consumers are exposed to a variety of pesticides via different food items consumed within one day or even within one meal. The established concepts lack consideration of the simultaneous exposure to residues of multiple active substances in food (cumulative exposure).

When two or more pesticides induce similar toxicological effects, co-exposure could result in increased health risks compared to the individual compounds. . Various frameworks on cumulative risk assessment (CRA) have been proposed or are developed by European or international organizations, such as the European Food Safety Authority (EFSA), the WHO, the International Programme on Chemical Safety (IPCS) and the Organization for Economic Cooperation and Development (OECD) (Kienzler et al., 2016). However; the lack of agreed and sufficiently specific and applicable technical guidance is considered the major obstacle for a consistent and adequate implementation of a harmonized approach for cumulative risk assessment (Solecki et al., 2014).

CRA scenarios are currently not implemented in the regulatory process for the approval of pesticide active substances or the setting of maximum residue levels (MRLs) on European level. National implementations of CRA in authorization procedures have been introduced e.g. in Germany (Bundesanzeiger, 2017; Stein et al., 2014), but it is limited to short-term effects soley based on active substances present in the respective plant protection product under evaluation. On European level, EFSA has the mandate to develop an overarching guidance document on the harmonization of risk assessment methodologies for human health and ecological risk assessment of chemical

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Abbreviations

ADI	Acceptable Daily Intake
aHI	adjusted Hazard Index
BVL	Bundesamt für Verbraucherschutz und Lebensmittelsicherheit
CAG	Cumulative Assessment Group
CRA	Cumulative Risk Assessment
EFSA	European Food Safety Authority
EsKiMo	Ernährungsmodul im Kinder-und Jugendgesundheitssurvey
EU	European Union
FAO	Food and Agricultural Organization
ICPS	International Programme on Chemical Safety
IESTI	International Estimated Short-Term Intake
LOQ	Limit of quantification
MCRA	Monte Carlo Risk Assessment software
MoE	Margin of Exposure
MRL	Maximum Residue Level
NEDI	National Estimated Daily Intake
NOAEL	No Observed Adverse Effect Level
NVS II	German Nutrition Survey II
OECD	Organization for Economic Cooperation and Development
P	Percentile
RAC	Raw Agricultural Commodity
US EPA	United States Environmental Protection Agency
VELS	Nutrition survey to determine the food intake of babies and infants for the estimation of the exposure with pesticide residues
WHO	World Health Organization

mixtures across regulatory sectors within the next years (European Food Safety Authority (EFSA), 2016).

Based on food monitoring data from market samples, the cumulative exposure of consumers to pesticide residues can be assessed retrospectively (Boon et al., 2008; Jardim et al., 2018). A similar approach was used in the current work based on German food consumption and food monitoring data.

2. Material and methods

2.1. Grouping and index concept for hazard data

The CRA considered the grouping concept for cumulative assessment groups (CAGs) as defined by the EFSA PPR Panel (EFSA: Panel on Plant Protection Products their Residues (PPR), 2013), based on the common toxicological impact on specific tissues or organs, irrespective of the structural relationship of the substances. Dose addition is adopted as the default assessment concept unless there is evidence that response addition or interaction is more appropriate (European Food Safety Authority (EFSA), 2013; Scientific Committee on Health and Environmetal Risks (SCHER), 2012).

EFSA's concept of CAGs defines four levels of detail based on common general target organs or systems (CAG level 1), specific phenomenological effects (CAG level 2), a common mode of action (CAG level 3) and finally a common mechanism of action (CAG level 4). Currently, only level 2 CAGs for the nervous and the thyroid system have been published. The specific chronic and acute phenomenological effects defined for the nervous system are: motor division, sensory division, autonomic division and neuropathological changes (chronic only). For the thyroid system only chronic effects on the parafollicular C-cells or the calcitonin system and for effects on follicular cells and/or the thyroid hormone (T3/T4) system were defined.

The NOAELs derived by EFSA (EFSA: Panel on Plant Protection Products their Residues (PPR), 2013) were used to normalize the exposure for each compound included in the respective CAG against an index compound. The index compound represents a mathematical denominator to generate a common basis for adding the cumulative toxicological effect on the target organ system. When a compound induces multiple specific toxicological effects within one CAG, the overall lowest NOAEL was used for the current CRA. For example, lambda-cyhalothrin may have chronic effects on the autonomic system both via piloerection (NOAEL: 1.8 mg/kg bw per day) and via salivation (NOAEL: 2.5 mg/kg bw per day), thus the lower NOAEL of 1.8 mg/kg bw per day was used for the assessment (see Supplemental Information for CAG composition and NOAELs). This approach represents an adjusted hazard index concept (aHI) (Stein et al., 2014). One exception was made for residues of dimethoate and its metabolite omethoate. Since both compounds are very closely related and share the same mode of toxicity, the sum of dimethoate and its metabolite omethoate (total dimethoate) was used in the CRA. For the calculation, total dimethoate equivalents were calculated for each sample based on potency factors for omethoate of 3 (chronic) or 6 (acute) (European Food Safety Authority (EFSA), 2006).

Relative potency factors, as previously used by the United States Environmental Protection Agency (U.S. Environmental Protection Agency (EPA), 2003) for specific chemical groups, have not been published within the EFSA concept. Such higher tier approaches were introduced into more recent guidance documents (U.S. Environmental Protection Agency, 2016) as one of three options (Option 3) for refinement, depending on the level of detailed knowledge on toxicity and exposure.

For the decision on dietary health risks, the limitations of the selected EFSA approach have to be considered. In the absence of detailed mechanistic data for refinement, an overall margin of exposure (MoE) (World Health Organization (WHO), 2009b) to the NOAEL of the index compound of at least 100 was selected to exclude dietary risks with the same default safety factors usually applied to derived acceptable daily intake values and acute reference doses (World Health Organization (WHO), 2009a).

2.2. Occurrence data

The occurrence data was obtained from the German Food Monitoring conducted between 2009 and 2014, providing representative information for pesticide residues in foods including detailed information on analytical methodologies used and the corresponding quantification limits achieved (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL), 2011, 2012, 2013, 2014, 2015, 2016). Starting in 2009, a six year sampling period was conducted focused on estimating the dietary exposure for the German population to pesticides (Sieke et al., 2008a; b). Depending on the variability of residues expected in foods on the market, the number of samples varied: at least 188 samples were collected for commodities with high variability (e.g. most fresh fruit and vegetables) and 94 samples for commodities with low variability (processed products like fruit juices). The numbers of samples were based on the tolerance criteria according to Conover (Conover and Iman, 1982), allowing estimation of mean or high residues (97.5th percentile) with a precision corresponding to the default laboratory uncertainty of 50%. In addition, the importance of foods in the diet was considered. Commodities frequently eaten were sampled once within three years (like apples or oranges) while commodities rarely eaten only once within six years (e.g. Brussels sprouts). For active substances with complex residue definitions including multiple analytes, total parent compound equivalents were calculated on the basis of each individual sample.

The coverage of CAGs by the monitoring data was very high (see supplemental information). For most plant commodities, at least 95% of the individual compounds for each CAG were analysed per food. In animal matrices the rate of analysis was lower, but due to the overall low transfer of pesticide residues into food commodities of animal origin, the resulting underestimation is expected to be insignificant. For compound/commodity combinations without any measured results, a general LOQ of 0.01 mg/kg was assumed.

2.3. Consumption data

Consumption data for the German population were obtained from three different surveys.

The VELS study (Heseker et al., 2003) was conducted in 2003 and covered the daily consumption of children aged 6 months up to 4 years (n = 816) with three consecutive day weighed/estimated food records repeated after 3–6 months (4–8 weeks for children < 1 year).

In the EsKiMo study (Mensink et al., 2007, Stahl et al., 2009), conducted by the Robert Koch-Institute and the University of Paderborn in 2006, children aged 6–17 years were surveyed. The daily consumption was recorded by using a consecutive 3-day food protocol on 1234 individuals for the sub-group of 6–11 years and by a 4-week food frequency questionnaire for the sub-group of 12–17 years. Only the data on a daily basis for 6–11 years old children were used.

Adults ages 14–80 years were covered by the German Nutrition Survey II (NVS II), which was conducted by the Max Rubner-Institute between November 2005 and December 2006 (Brombach et al., 2006; Krems et al., 2006) utilising various sampling techniques to measure the daily consumption. For the cumulative exposure assessment, the consumption data collected in two EPIC-SOFT (S. Voss et al., 1998) assisted recall interviews per individual were used (2 × 24 h interviews for 13926 individuals with one to 6 weeks interval), allowing consideration of the consumption pattern on a daily basis.

Between the three surveys used the age groups of 5 years and of 12 and 13 years are not covered by consumption data. Since the closest age groups available were consistent in their consumption pattern, an exceptional different diet is not expected for the missing population.

The consumption data from all three surveys (VELS, EsKiMo and NVS II) were reverted into their respective raw agricultural commodities (RACs), as defined in Annex I of Regulation (EG) No. 396/2005 (European Union (EU), 2005). The VELS study already included this conversion, whereas for EsKiMo and NVS II conversions were conducted primarily based on recipe data from the German Nutrient Data Base (Max Rubner-Institut (MRI)). For all foods eaten, both the contribution of RACs to complex foods (e.g. percent tomato in Pizza Napoli) and the yield for each processing step (e.g. juicing, baking, cooking, and peeling) were addressed. Finally, RACs contributions from all reported food items consumed within one day were aggregated into one of 115 RAC consumption equivalents like “wheat grain” or “tomato” (see supplementary information). The use of RAC consumption equivalents represents a strong overestimation of the exposure, since it assumes that all residue present in the raw commodity is transferred into the consumed part. For fruit juices, consumption data from direct consumption or as ingredients in composite foods were also referred back to the RAC, but kept as separate commodities (e.g. “apple, excluding juice” and “apple juice”) due to the very large portion sizes. Especially for juices, the combination of RAC based consumption equivalents with occurrence data for juice as consumed results in a slight overestimation of the exposure.

2.4. Probabilistic modelling

For assessing the total cumulative exposure to a CAG, residues for all active substances in this group have to be linked to the daily food consumption for each individual. To cope with such a plethora of combinations, the Monte-Carlo Risk Assessment software (MCRA, Version 8.1 for VELS and EsKiMo and MCRA, Version 8.2 for NVS II) was selected, developed by the Dutch National Institute for Public Health and the Environment (RIVM) and Biometris, Wageningen University & Research (de Boer WJ et al., 2015). The major advantage of MCRA is compliance with the “Guidance on the use of probabilistic modelling for pesticides” issued by the European Food Safety Authority (EFSA) (EFSA Panel on Plant Protection Products and their Residues (PPR), 2012) and with the latest developments of CRA in the EU.

For the cumulative exposure assessment the way of considering samples with residues being below the analytical limit of quantification (LOQ) is of high importance. Since dose additivity is assumed for the CAG, the sum of LOQs may significantly influence or even supersede the estimated exposure based on quantified residues. The sensitivity of LOQs was characterized by performing three different scenarios for the probabilistic modelling. Residues below the limit of quantification were either expressed as the numerical LOQ value itself or as zero, representing the pessimistic and optimistic approach according to EFSA's Guidance on probabilistic modelling or additionally as 0.5 × LOQ.

The cumulative exposure was calculated individually for each consumption survey. For the short-term exposure estimation, the probabilistic runs were based on 1.000.000 iterations for the VELS and EsKiMO studies using MCRA 8.1 and on 100.000 iterations for the NVS II study with MCRA 8.2. The switch to MRCA 8.2 with a lower number of maximum iterations became necessary for the NVS II study, since the previous version was not capable of handling such an amount of data. In the long-term exposure modelling, the randomly selected consumption value for a single day is substituted by an estimated mean value, taking into account both the portions size and the frequency of consumption (see chronic modelling below). In the modelling, occurrence data for each compound of the CAG was normalised based on the NOAEL of the index compound selected for this group. The combined exposure of all compounds of a CAG represents the total cumulative daily exposure.

To assess possible adverse health effects, the MoE was calculated by dividing the NOAEL of the index compound with the 99.9th percentile (P99.9) of the exposure distribution. The P99.9 was originally proposed as regulatory threshold by the US EPA for acute probabilistic modelling (U.S. Environmental Protection Agency - Office of Pesticide Programs, 2000) and also discussed on EU level. In absence of a commonly agreed regulatory threshold, the P99.9 was also considered for chronic effects but can be considered as very conservative. To allow a more flexible interpretation of the results, MoEs for additional percentiles were calculated (P50, P90, P95, P99 and P99.99, see supplemental information).

A bootstrapping procedure was conducted for chronic and acute LOQ × 0 scenarios involving 100 resampling cycles of 10.000 iterations each to describe the uncertainty. A bootstrapping procedure uses multiple runs with a limited number of iterations to describe the uncertainty around the outcome due to variability in the data and the random sampling uncertainty (Efron, 1992; Efron and Tibshirani, 1993). For other scenarios the uncertainty was not calculated since LOQs dominated the overall exposure. From the generated bootstrapping distributions, the interval between the 2.5th and 97.5th percentile for the target percentiles indicates the lower and upper confidence interval, respectively. A large confidence interval reflects to high variability in the input data and therefore high uncertainty for the prediction of exposure percentiles.

Chronic modelling: Since all consumption data were collected for single days, the estimation of the long-term dietary exposure requires adjustment of the consumption data to address varying consumption frequencies over days or weeks. By using the MCRA built-in Logistic Normal-Normal model, which was tested and recommended for a realistic “right-tail assessment” (van Klaveren et al., 2012), a significant overestimation of the long-term exposure was avoided. The principle idea of LNN is based on the use of a frequency model for the consumption by logistic regression, which is combined into a bivariate normal distribution with a random individual effect for the food amount (Tooze et al., 2010).

Acute modelling: For the short-term exposure modelling, unit-to-unit variability was taken into account by considering variability factors as used in the IESTI methodology. In the European Union default variability factors of 5 or 7 are used for commodities with unit-weights ≥25 g (European Food Safety Authority (EFSA), 2007) while within Codex Alimentarius, a general variability factor of 3 is used since 2003 (Food and Agriculture Organization of the United Nations (FAO), 2003). In the probabilistic model, variability factors were generated for each sample by using a beta-distribution with mean values corresponding to the EU default factors of 5 or 7. Theoretical lower and upper limits were 0 and 10, respectively, the latter based on the number of units usually collected for a food monitoring sample of medium sized commodities. Unit-weights were obtained from the IESTI based German NVS II-model (Federal Institute for Risk Assessment (BfR), 2011). For processed or mixed commodities (IESTI Case 3) or for small-sized commodities with unit weights below 25 g/piece (IESTI Case 1) consideration of a variability factor is unnecessary.

To support interpretation of the long- and short-term exposure results, the compounds, food commodities and risk drivers (compound/commodity combinations) contributing at least 10% to the total exposure distribution and to the P97.5 were identified (see supplemental information). The P97.5 was preferred over the P99.9 used for dietary risk assessment, because it provides a more robust estimate for the upper end of the cumulative exposure distribution. Risk drivers at the higher percentiles were unstable towards reproducing the results for the short-term exposure.

3. Results and discussion

3.1. Chronic neuropathological effects and chronic effects on the parafollicular C-cells or the calcitonin system of the thyroid

For these two CAGs the cumulative exposure (see Table 1, Table 2 and Fig. 1) resulted in MoEs of 100 or more for the P99.9 for all three scenarios. A public health concern for these CAGs was therefore considered unlikely for the German population.

3.2. Chronic motor division, chronic effects on the sensory system and acute or chronic effects on the autonomic system

For these CAGs the conservative LOQ × 1 and LOQ × 0.5 scenarios indicated cumulative exposures below MoEs of 100 while the LOQ × 0 scenarios were well above MoEs of 100 for all sub-populations (best estimate MoEs 246–4876). The MoEs for the LOQ × 1 and LOQ × 0.5 scenarios were directly proportional to the factor of two (mean: 2.0; σ = 0.23; min.: 1.65; max.: 2.54; see supplemental information), indicating very high sensitivity to non-quantified residues. The large gap in best estimate MoEs between the LOQ × 0.5 and LOQ × 0 scenarios (factor of 2.9–60) suggests that the actual probability of finding residues at or above the LOQ for compounds of these CAGs is very low. Principally, LOQ × 0 scenarios tend to underestimate the true exposure due to an unknown amount of residues below the LOQ. However, an opposing factor used in the current model is the use of RAC based consumption data, overestimating the true exposure. Especially for acute and chronic autonomic effects, commodities only consumed after processing (maize, potatoes and rice, see supplemental information) had a high impact on the upper end of the exposure distribution. Typically, these commodities are subject to processing techniques like

Table 1
MoEs for nervous system level 2 CAGs based on the P99.9

CAG level 2	Index Compound (NOAEL)	Consumption survey	Margin of Exposure (MoE) – best estimates		
			LOQ × 1	LOQ × 0.5	LOQ × 0 (uncertainty range)
Motor division – acute	Deltamethrin (1 mg/kg bw)	VELS	15	39	272 (76–395)
		EsKiMo	28	51	180 (145–360)
		NVS II	33	63	517 (301–814)
Motor division – chronic	Deltamethrin (1 mg/kg bw)	VELS	11	22	1000 (815–1227)
		EsKiMo	13	26	1568 (1413–1874)
		NVS II	23	43	2311 (2061–2656)
Neurochemical effects – acute	Oxamyl (0.1 mg/kg bw)	VELS	21	29	331 (16–443)
		EsKiMo	25	53	273 (61–410)
		NVS II	3	32	586 (120–772)
Neurochemical effects – chronic	Oxamyl (1.69 mg/kg bw)	VELS	6	11	83 (66–97)
					Refined: 86 (66–117)
		EsKiMo	7	12	54 (42–65)
					Refined: 191 (148–220)
		NVS II	11	21	158 (127–197)
					Refined: 232 (185–282)
Neuropathological effect – chronic	Indoxacarb (4 mg/kg bw)	VELS	211	398	1797 (1341–2400)
		EsKiMo	240	461	3802 (2985–4711)
		NVS II	405	775	4460 (3195–5888)
Effects on the sensory system - acute	Deltamethrin (1 mg/kg bw)	VELS	23	41	281 (41–484)
		EsKiMo	34	61	233 (96–435)
		NVS II	42	581	695 (288–1035)
Effects on the sensory system - chronic	Deltamethrin (1 mg/kg bw)	VELS	22	43	287 (217–354)
		EsKiMo	26	49	581 (458–682)
		NVS II	40	78	806 (653–951)
Effects on the autonomic system – acute	Deltamethrin (1 mg/kg bw)	VELS	13	33	292 (161–637)
		EsKiMo	37	86	246 (138–606)
		NVS II	49	81	739 (508–1456)
Effects on the autonomic system - chronic	Deltamethrin (1 mg/kg bw)	VELS	22	43	2545 (1682–3268)
		EsKiMo	26	52	2902 (2420–3341)
		NVS II	43	83	4876 (4170–5583)

NOAEL: No observed adverse effect level.
CAG: cumulative assessment group.
LOQ: Limit of quantification.

Table 2
MoEs for thyroid system level 2 CAGs based on the P99.9

CAG level 2	Index Compound (NOAEL)	Consumption survey	Margin of Exposure (MoE) – best estimates		
			LOQ × 1	LOQ × 0.5	LOQ × 0 (uncertainty)
Effects on the parafollicular C-cells or the calcitonin system - chronic	Fenbuconazole (3 mg/kg bw)	VELS	179	344	1599 (1229–2240)
		EsKiMo	245	488	3479 (2177–4390)
		NVS II	397	765	4189 (3048–5345)
Effects on follicular cells and/or the thyroid hormone (T3/T4) system – chronic	Fenbuconazole (5.7 mg/kg bw)	VELS	10	17	58 (47–72)
		EsKiMo	12	23	93 (73–120)
		NVS II	20	37	121 (88–157)

NOAEL: No observed adverse effect level.
CAG: cumulative assessment group.
LOQ: Limit of quantification.

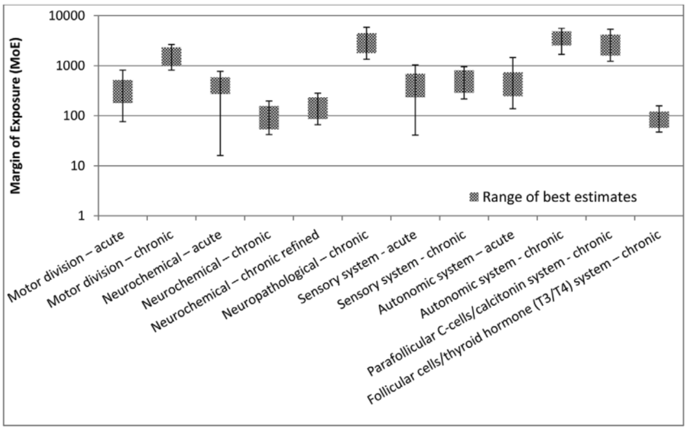

Fig. 1. Total best estimate MoE ranges for the LOQ × 0 scenario (VELS, EsKiMo and NVS II), including their overall minimum lower (P2.5) and maximum upper (P97.5) uncertainty ranges.

milling/fractionating, peeling or polishing, reducing residue concentrations significantly (Scholz et al., 2016).

Additionally, for chronic effects on motor division or the sensory system, dithiocarbamates were the main risk driver. The group of dithiocarbamates consists of several active substances (e.g. methiram, mancozeb, propineb or ziram) which are all analysed with a common moiety analytical method based on the release and determination of total carbon-disulfide (CS_2). The total CS_2 cannot be attributed to a specific active substance and many plants (e.g. onions or brassicacea) already contain natural sources of CS_2 pretending false positive findings (Perz et al., 2000). It was therefore assumed that the whole CS_2 originated from the dithiocarbamate with the lowest NOAEL within the CAG, although this represents a vast overestimation of the true risk.

Taking into account the overall low probability of residues above the LOQ for these CAGs, a substantial contribution of theoretical residues below quantification limits to the cumulative exposure seems unlikely. In contrast, the overestimation of the cumulative exposure by the conservative approaches used is expected to overcompensate the underestimation in the LOQ × 0 scenarios. Taking into account these factors, public health concerns for CAGs based on chronic motor division, chronic effects on the sensory system and acute or chronic effects on the autonomic system were considered unlikely for the German population.

3.3. Acute motor division, acute neurochemical effects and acute effects on the sensory system

For these CAGs best estimate MoEs were below 100 for the conservative LOQ × 1 and LOQ × 0.5 scenarios and above 100 for the LOQ × 0 scenarios. However, considering the lower and upper uncertainty range, cumulative exposures below a MoE of 100 were identified also in the LOQ × 0 scenarios for younger and/or older children (VELS and EsKiMo survey).

In the CAG for acute effects on motor division, the analysis of active substances contributing most to the cumulative exposure (see supplemental information) identified multiple compounds, namely deltamethrin, triadimenol, lambda-cyhalothrin and dithiocarbamates (expressed as ziram). Corresponding food commodities were apples, lettuce, pears, pineapple, rice and spinach. The P97.5 of the exposure was driven by compound/commodity combinations of deltamethrin/rice, dithiocarbamates (expressed as ziram)/pears, lambda-cyhalothrin/spinach, oxamyl/peppers and triadimenol/pineapple. Some foods with high contributions like rice or pineapple require processing such as cooking or peeling before consumption, probably lowering the real exposure. Also, the dithiocarbamate group measured as total CS_2 showed high contributions to the cumulative exposure. As discussed above, the assumption that all CS_2 residues originating from the dithiocarbamate with the lowest NOAEL within the CAG, represents an overestimation of the true risk.

For acute neurochemical effects, the confidence intervals of the uncertainty analysis were large showing lower and upper MoEs from 16 to 772. Best estimate MoEs were all above the threshold of 100 for all population groups (273–586). At the P97.5, total dimethoate contributed most to the cumulative exposure (69.5–72.3%). Most contributing food commodities were cherries, spinach, barley and potatoes. Total dimethoate was the only risk driver at the P97.5 present in spinach (up to 28.9%), cherries (up to 21.2%) and potatoes (up to 13%). In the German 2010 food monitoring, total dimethoate equivalents were found above legal limits in spinach (one sample) and in cherries (three samples), posing an acute public health concern *per se* (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL), 2013). Analysis of nine individual person-days around the P99.9 (drill-down) indicated total dimethoate as the main risk driver in 7 cases. Associated foods were potatoes (6 out of 9) and cucumbers (1 of 9), which are normally consumed with higher daily large portions than spinach and cherries. Also, methomyl in strawberries and pirimicarb in spinach contributed to the P99.9.

Also for the CAG on acute effects on the sensory system, confidence intervals of the uncertainty indicated MoEs below 100 for children (MoEs of 41–96). The best estimate MoEs were 281–695. Compounds contributing most to the P97.5 were deltamethrin (37.6–53.8%) and total dimethoate equivalents (35.9–51.9%). A broad range of food commodities was identified as a potential source of exposure: barley, cherries, maize, potatoes, rice and spinach. The main risk drivers were deltamethrin in maize and rice (17–32.6% contribution) and total dimethoate equivalents in cherries and spinach (10.6–33.9% contribution). The drill-down (P99.9) indicated total dimethoate as the main risk driver (6 × potatoes, 1 × spinach), followed by two person-days with deltamethrin in rice.

In summary, for all three CAGs the total cumulative exposure is either overestimated (motor division) and/or dominated by compounds representing a public health concern by themselves (total dimethoate equivalents in the CAGs for neurochemical effects and effects on the sensory system). Currently, no harmonized approach for refinements of cumulative risk assessments has been implemented. Databases on the influence of processing are still under preparation in the EU. In parallel, advanced concepts for the assessment of combined toxicological effects at higher tiers are developed e.g. in the EuroMix project (EuroMix, 2018). Without such a refinement, no final conclusion on the cumulative dietary risk arising from these CAGs can be drawn.

3.4. *Chronic neurochemical effects and chronic effects on follicular cells and/or the thyroid hormone (T3/T4) system*

The cumulative exposure for substances exhibiting chronic neurochemical effects and chronic effects on follicular cells and/or the thyroid hormone (T3/T4) system resulted in best estimate MoEs below the threshold of 100 (P99.9) for nearly all scenarios (see Table 1 & Table 2) tested.For the CAG referring to chronic neurochemical effects, best estimate MoEs for the LOQ × 0 scenario were 83 for younger children (confidence interval: 66–97), 54 for older children (confidence interval: 42–65) and 158 for the general population (confidence interval: 127–197). The most contributing compound to the P97.5 was chlorpyrifos (81.8–89%), followed by total dimethoate equivalents (13.3%). Relevant food commodities were citrus fruits (oranges: 18.2–54.6%; mandarins: 24.4–33%, grapefruit: 21.6%), pears (26.1%) and potatoes (14.8%). A significant risk driver was only identified for the group of 6–11 years old children with chlorpyrifos in oranges (52.5%). Within this CAG, chlorpyrifos residues in citrus fruits tend to have a large influence on the cumulative exposure. Chlorpyrifos is a non-systemic compound, which is primarily located on the inedible peel of citrus fruits (European Food Safety Authority (EFSA), 2014). For chlorpyrifos, data showing a peel-pulp ratio of 0.08 was available for mandarins (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL), 2013). Mandarins have a very thin peel, making it a conservative basis to extrapolate this factor to all citrus fruits. A refined calculation was conducted, taking into account the peel-pulp ratio for citrus fruits. Consequently, the age groups of 6–11 and 14–80 years resulted in significantly higher best estimate MoEs (P99.9): 191 instead of 54 and 232 instead of 158, respectively. All corresponding confidence intervals were also higher than the MoE threshold of 100.

However, for young children aged 6 months up to 4 years, the best estimate MoE increased only marginally in the refined calculation (from 83 to 86). The highest impact for the young children was identified for chlorpyrifos in pears (40.9%) and for total dimethoate equivalents in potatoes (22.3%), both unaffected by the citrus refinement.

For the CAG covering substances with chronic effects on follicular cells and/or the thyroid hormone (T3/T4) system, best estimate MoEs of 58 were calculated for younger children (confidence interval: 47–72), of 93 for older children (confidence interval: 73–120) and of 121 for the general population (confidence interval: 88–157) for the LOQ × 0 scenario (P99.9). The exposure (P97.5) was nearly exclusively driven by dithiocarbamates expressed as propineb (contribution: 94.8–96.6%). Food commodities with the highest contribution were apricots (12%), head cabbage (12–20.5%), lettuce (10.7%) and pears (27.5–66.7%). Consequently, dithiocarbamates (expressed as propineb) in pears were the only major risk driver (36.5–66.1%). Again, the assumption that all CS_2 originates from propineb induces a vast overestimation of the true cumulative exposure. For example, plant protection products containing propineb are currently not registered in Germany (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL), 2017). According to the German Food Monitoring, 50–58% of all samples tested were produced in Germany (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL), 2011, 2012, 2013, 2014, 2015, 2016) and have probably not been treated with propineb at all. Based on the available data, no refinement can be conducted allowing consideration of propineb as active substance *per se*. This would require the use of substance-specific analytical methods for the group of dithiocarbamates instead of the CS_2 common moiety method.

4. Conclusion

In this conservative estimate of the cumulative exposure for the German population the dietary CRA indicated no public health concerns for 6 of 11 Level 2 CAGs. For three CAGs (acute motor division, acute neurochemical effects and acute effects on the sensory system) high uncertainties remained and for two CAGs (nervous system: chronic neurochemical effects; thyroid system: chronic effects on follicular cells and/or the thyroid hormone (T3/T4) system) best estimate MoEs of 100 to exclude cumulative health risks were not reached. The findings for the CAG on chronic neurochemical effects are in line with previous findings for French pregnant women, for which also a significant cumulative risk was identified (de Gavelle et al., 2016).

It became apparent that CAGs as currently defined by EFSA and the use of food monitoring data limit the options for further refinement. For the CAGs, the highest tier supported by toxicological data is based on common specific phenomenological effects. Information on more sophisticated modes or mechanisms of action is not available for most compounds. Research on new grouping approaches of chemicals and their interactions in complex mixtures is on-going (see e.g. https://www.euromixproject.eu). More advanced grouping principles would allow the usage of relative potency factors based on mechanistic data instead of phenomenological NOAELs. Until then, the CRA performed here has to be considered as a conservative estimate of the group toxicity. Especially for large CAGs like effects on follicular cells and/or the thyroid hormone (T3/T4) system or future CAGs related to effects on the liver, full understanding of influences on adverse outcome pathways is required for profound refinements.

Also, the use of food monitoring data probably involves cases, where single compoundspose public health concerns *per se* and may influence the cumulative exposure of CAGs significantly (e.g. dimethoate and omethoate). For retrospective assessments, it is of high importance to identify the main sources of exposure. Singular contributers may suggest a public health concern for the whole CAG, but are much easier to manage than a group of compounds all adding equally to the cumulative dietary exposure. For example, MRLs for chlorpyrifos, being one of the main risk drivers in the CAG for chronic neurochemical effects to the nervous system, were revised in 2016 in the EU to reduce possible dietary risks for consumers. This change is not yet reflected in the food monitoring data from 2009 to 2014 used here.

Another challenge identified for future CRAs is the need of robust, harmonized processing information to consider residues measured in RACs from food monitoring programs also in foods as consumed. Although collections of processing factors for pesticides are available (Scholz et al., 2016), common agreement on quality criteria and their implementation in higher tier exposure modelling are required to enable harmonized regulatory decisions.

Finally, it became obvious that the use of CS_2 as a common analytical marker for dithiocarbamates is unsuitable for CRAs. After complete conversion into CS_2, all information on the active substances present in the food commodity is lost. Also, various natural sources for CS_2 in fruits and vegetables may result in false positive findings and in an overestimation of the true pesticide concentration. Although the analytical common moiety method for CS_2 is well established in many enforcement laboratories, development of new compound specific methods to be used in food monitoring programs would allow consideration of the dithiocarbamate group in refined CRAs.

For regulatory decisions on possible cumulative dietary health risks, conceptual limitations of the published approaches and the absence of harmonized data sources for robust refinements have to be considered. Future research to reduce the high uncertainties both in the hazard characterization and in the exposure estimation for cumulative risk assessments is considered necessary.

Disclaimer

This Paper presents the opinion of the author and not necessarily the regulatory views of the BfR.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2018.09.010.

Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.fct.2018.09.010.

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4.1 Additional considerations on sensitivity parameters for the cumulative exposure

In addition to the results presented in this publication, an analysis of the sensitivity of individual compounds and foods within a CAG was conducted. For all diets used, the contribution of substances towards the upper exposure distribution was characterised as percentage of the total exposure. In addition, it was investigated if the total cumulative exposure was primarily based on a single compound or resulted from a combination of multiple compounds. To answer this question, the “maximum cumulative ratio” (MCR) [59] was used, which describes the total cumulative exposure divided by the compound specific exposure (expressed in toxicological equivalents). Consequently, MCR values close to 1 result from an exposure of a single compound while higher numbers represent a mixture of multiple components contributing additively. The MCRA software [60] provides in-built log-normal bivariate plots for MCRs and pie-charts to display the sensitivity of each substance to the total exposure. For all chronic assessments, the contribution of foods to the upper percentiles of the total exposure distribution was quantified. In acute scenarios, the randomly selected variability factors introduced to much variation for the contribution to estimate robust contribution percentages.

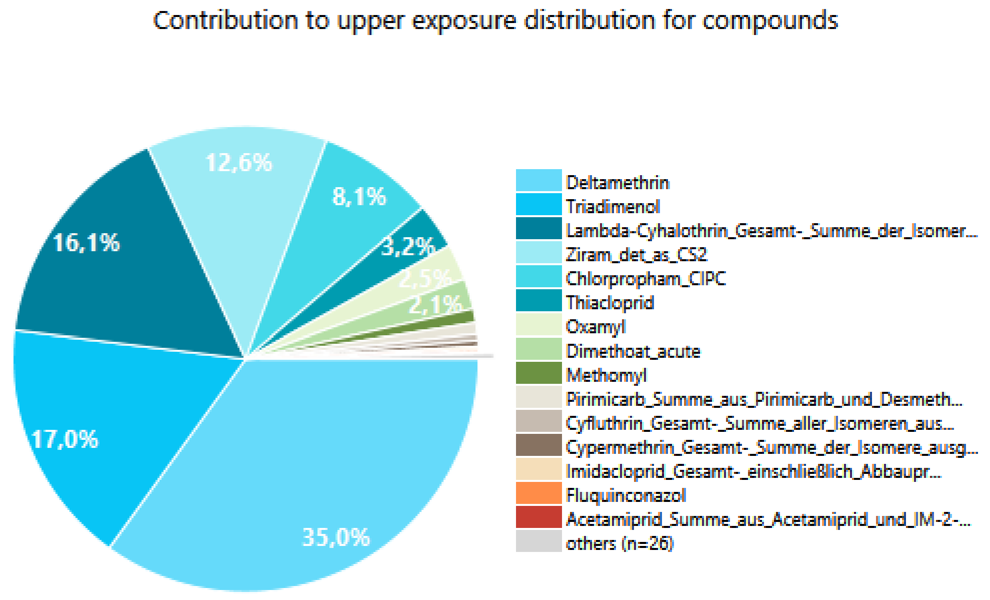
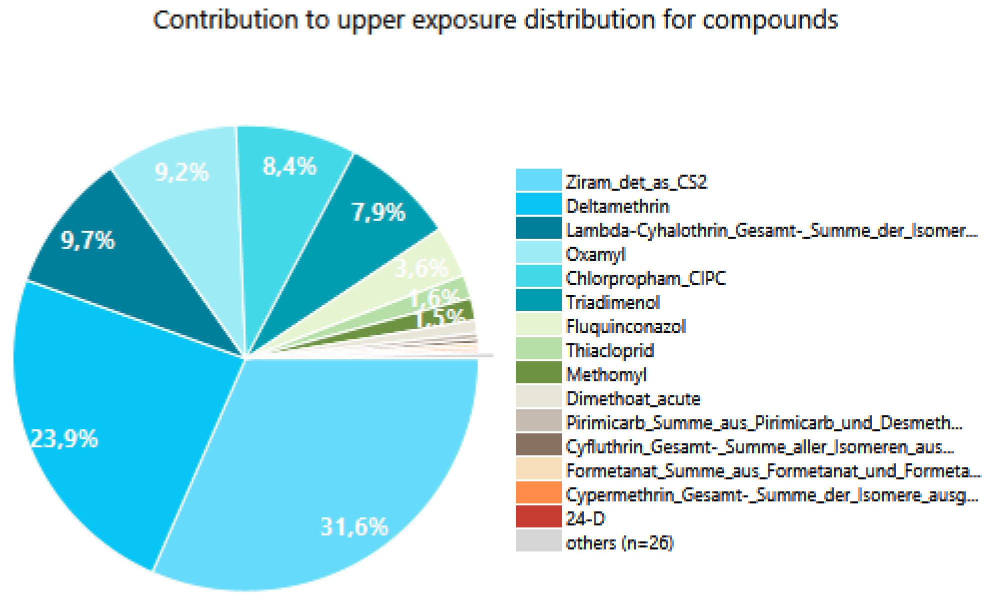
In the following, more detailed analysis for all CAG with potential public health concerns (nervous system: chronic neurochemical effects; thyroid system: chronic effects on follicular cells and/or the thyroid hormone (T3/T4) system) or with high uncertainties not allowing conclusions on the absence of public health concerns (acute motor division; acute neurochemical effects and acute effects on the sensory system) are presented:

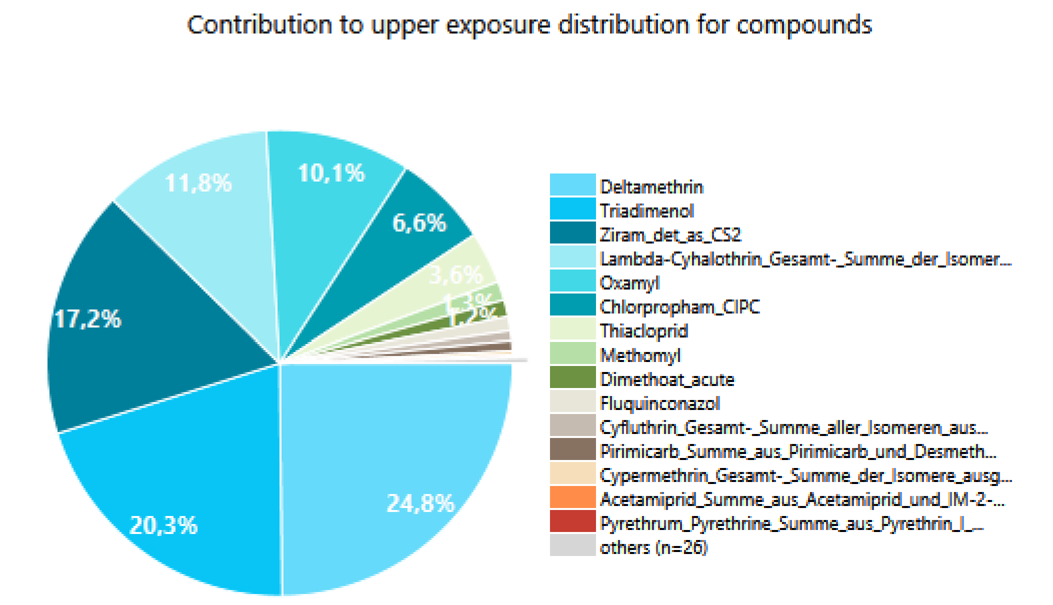
4.1.1 Nervous system: acute motor division

Contribution of compounds to the upper exposure distribution

For this CAG, the main contribution of compounds (≥10%) was driven by five substances (deltamethrin, lambda-cyhalothrin, oxamyl, triadimenol and CS_2 calculated as Ziram). The exposure resulting from the sum of these compounds represented over 75% of the total exposure at the P99.9.

Table 1: Contribution of compounds to the P99.9 of the total cumulative exposure distribution for acute effects on the motor system

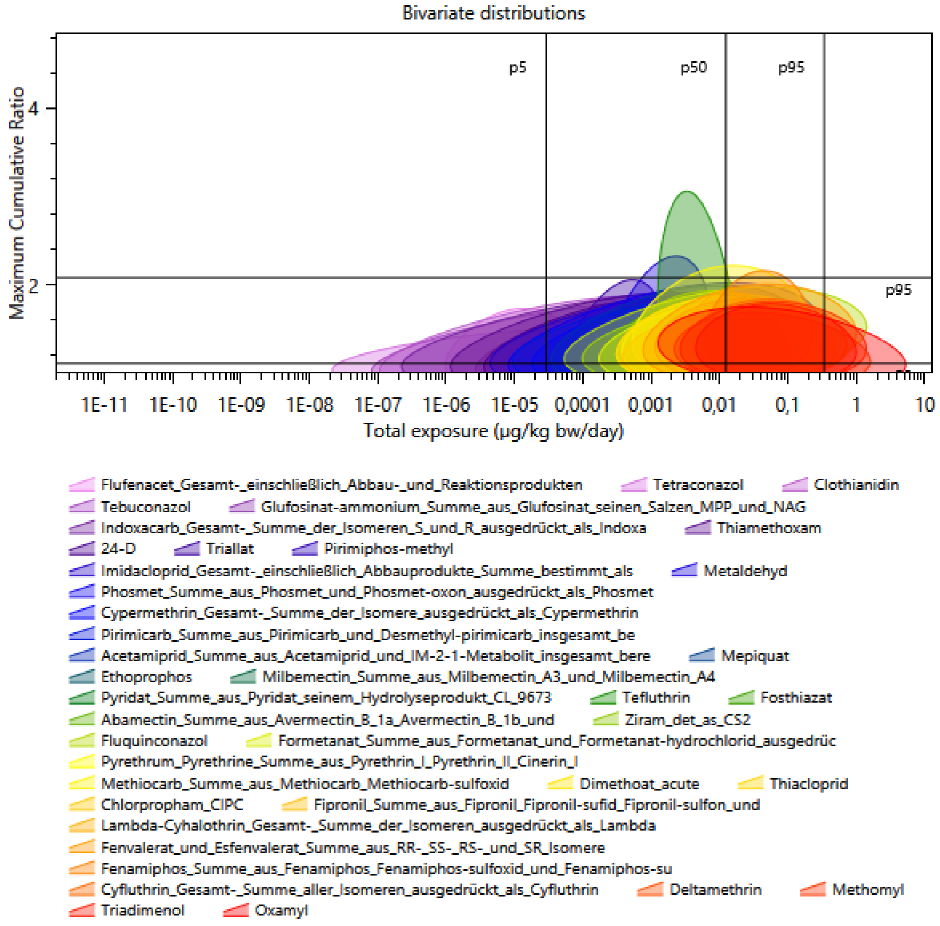
Survey	Contribution of compounds
VELS	
EsKiMo	

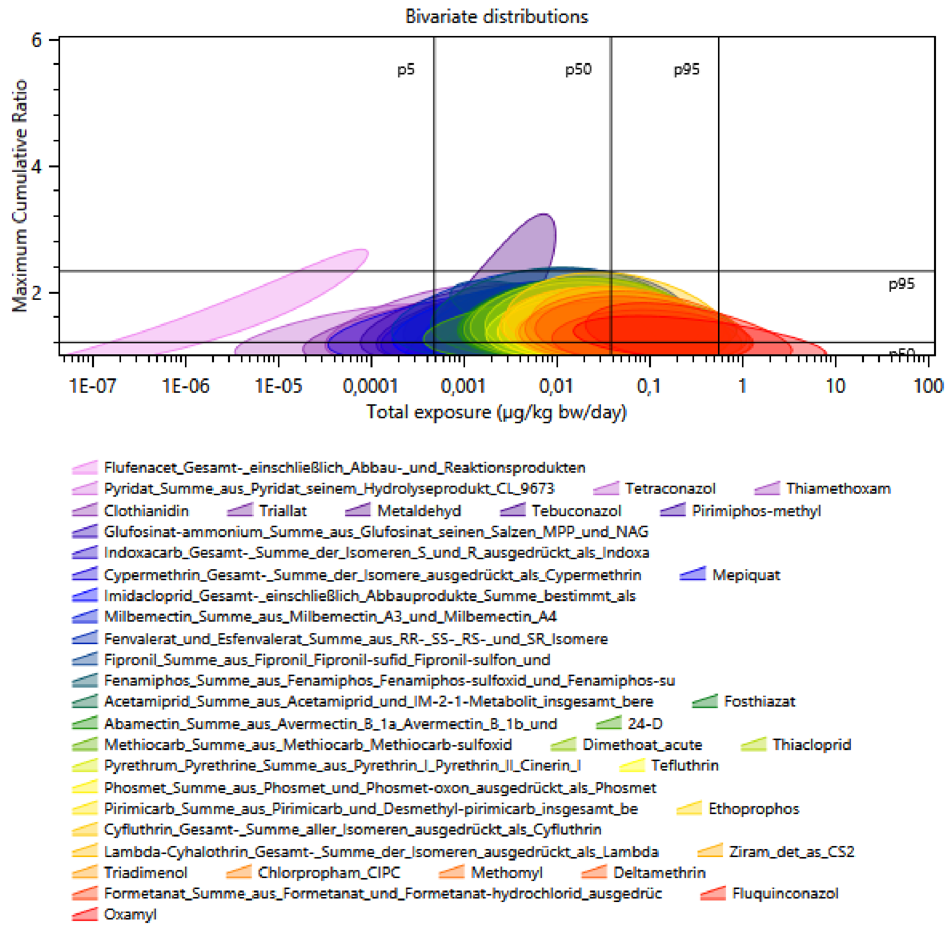
Survey	Contribution of compounds
NVS II	

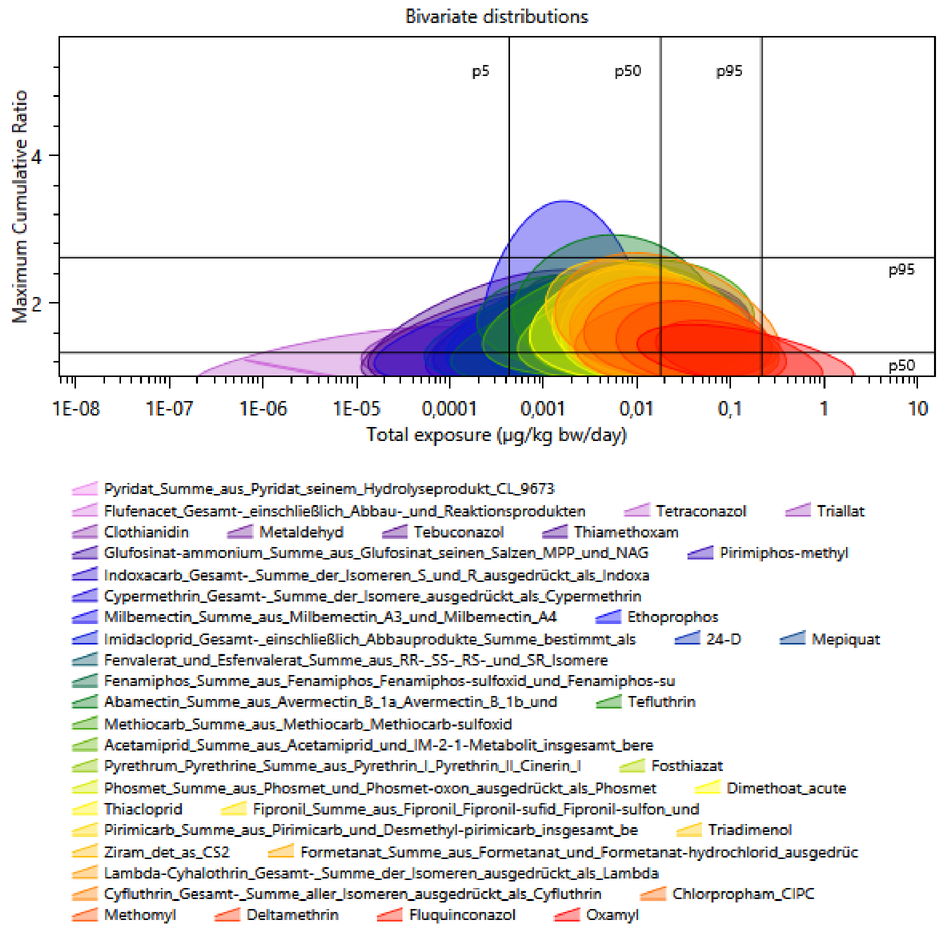
Maximum cumulative ratios

In view of multiple components contributing to the upper end of the total exposure distribution, the MCR becomes of high interest to identify possible additive correlations. The analysis of the MCRs revealed, that in most cases only up to two compounds are responsible for the total exposure. The P95 MCR was slightly above 2 and was reached in the middle of the total exposure distribution (around the P50). At the upper end, the total exposure was dominated by oxamyl. Although several compound could potentially add to a cumulative effect, the main driver was still a single compound. The results confirm the publications conclusion, since oxamyl was found in the German food monitoring at concentrations in some sample posing an acute health risk per se.

Table 2: Maximum cumulative ratios of compounds for acute effects on the motor system

Survey	Maximum cumulative ratios (bivariate)
VELS	

Survey	Maximum cumulative ratios (bivariate)
EsKiMo	

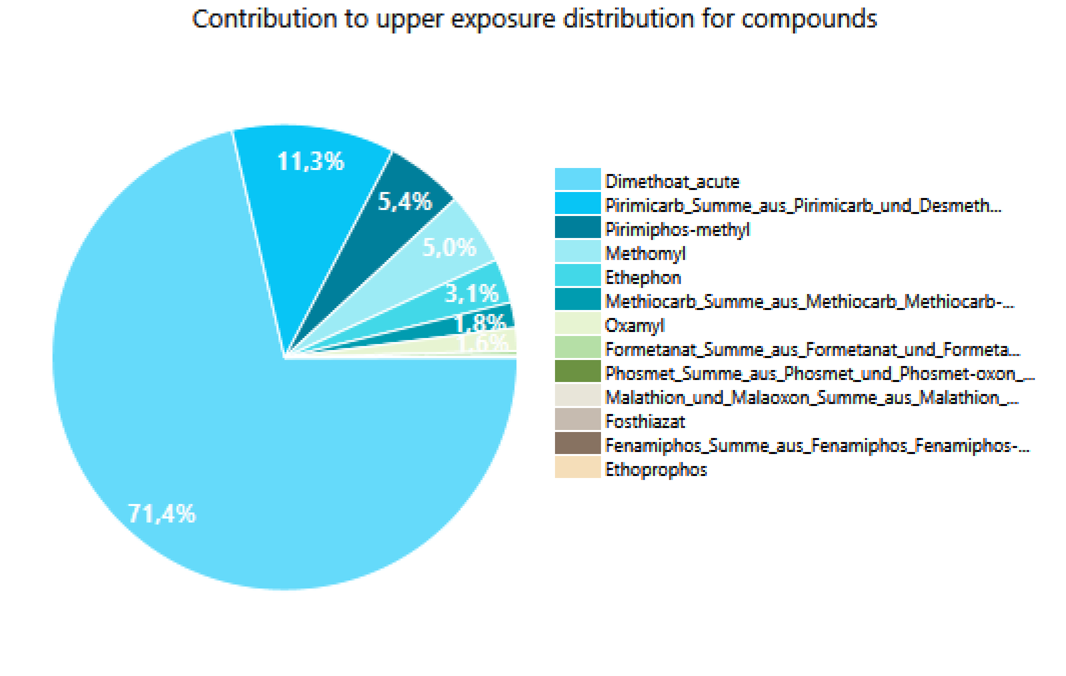
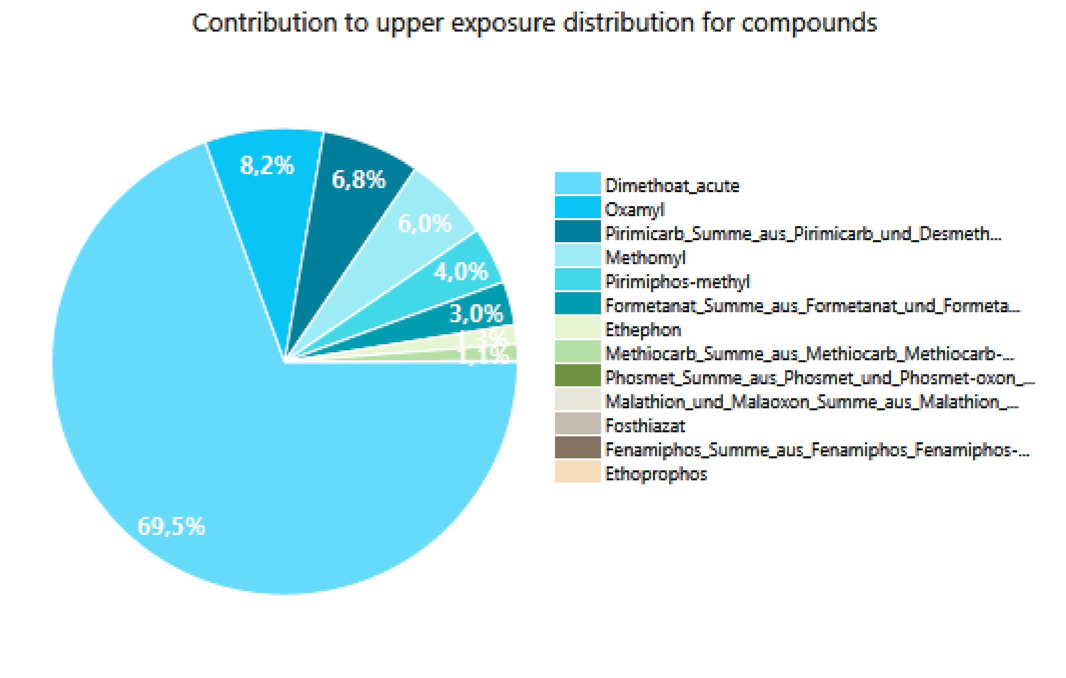
Survey	Maximum cumulative ratios (bivariate)
NVS II	

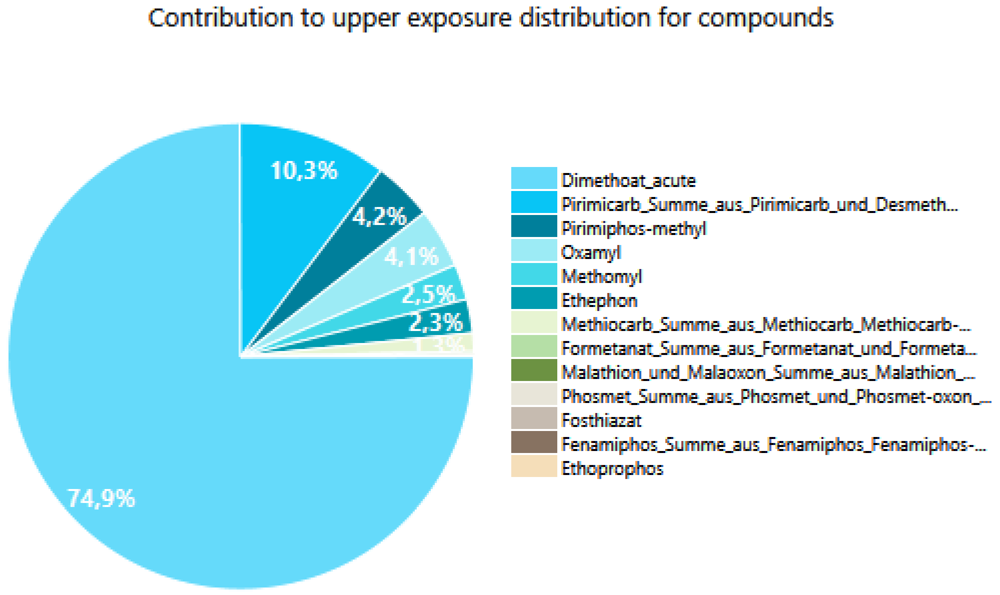
4.1.2 Nervous system: acute neurochemical effects

<u>Contribution of compounds to the upper exposure distribution</u>

In this group, the total exposure at the P99.9 was mostly caused by the sum of dimethoate and its metabolite omethoate. The only other main contributor was pirimicarb, adding up to 11.3% to the total exposure.

Table 3: Contribution of compounds to the P99.9 of the total cumulative exposure distribution for acute neurochemical effects

<table>
<tr><th>Survey</th><th>Contribution of compounds</th></tr>
<tr><td>VELS</td><td>
</td></tr>
<tr><td>EsKiMo</td><td>
</td></tr>
</table>

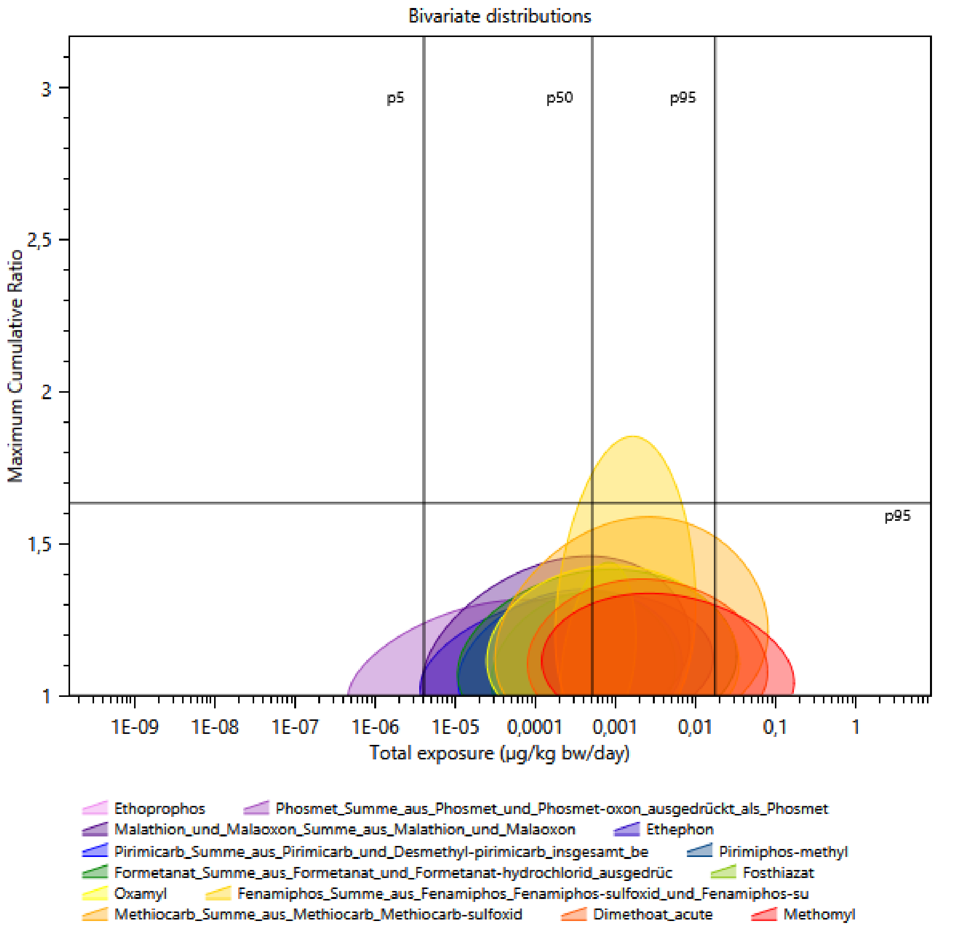
Survey	Contribution of compounds
NVS II	

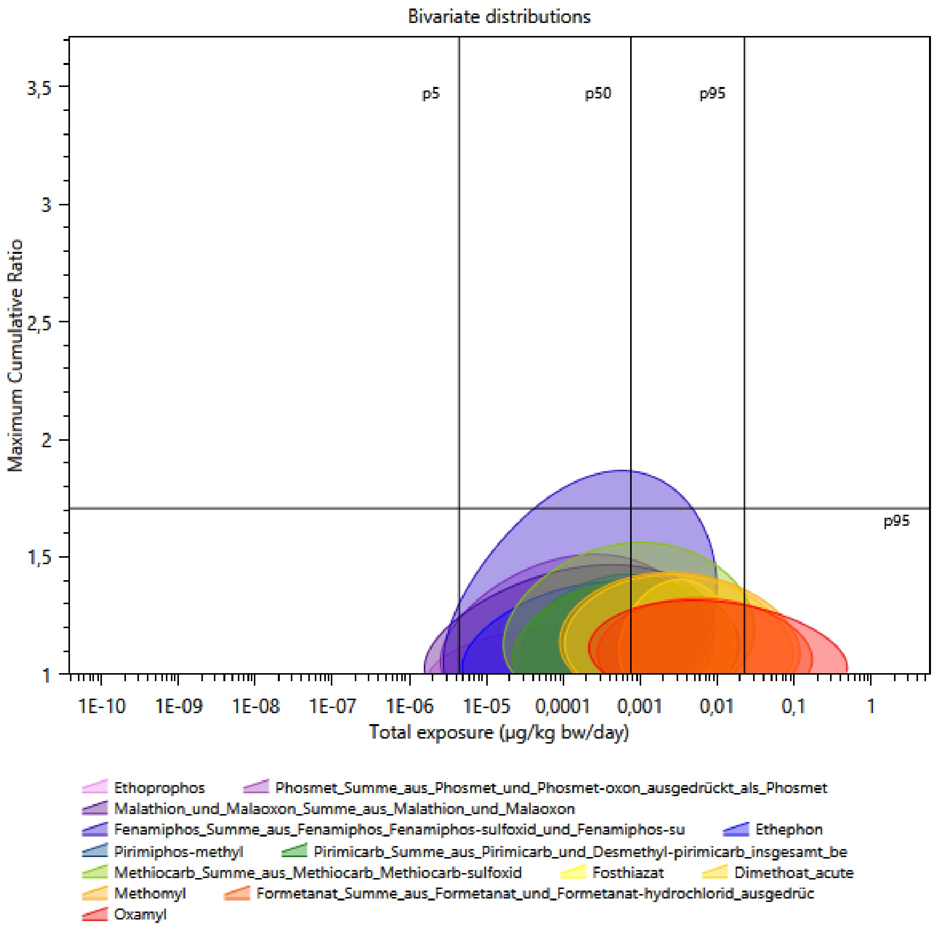
Maximum cumulative ratios

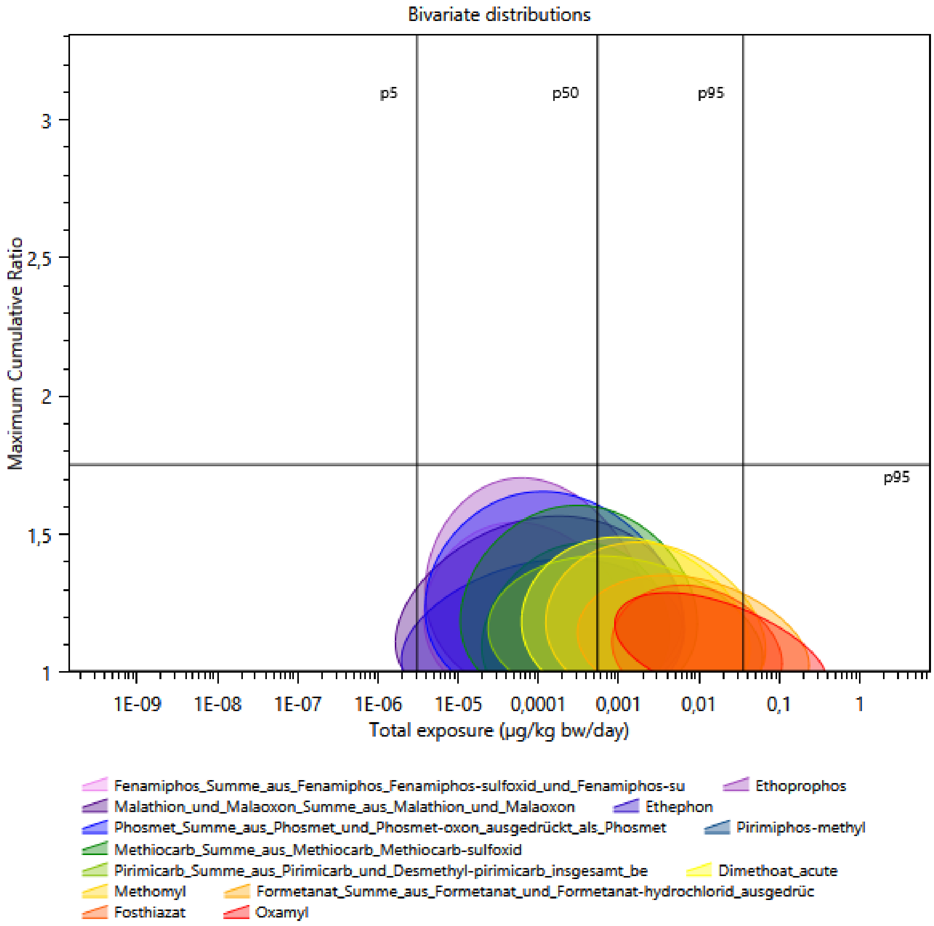
The MCR analysis also showed the sum of dimethoate and omethoate as one of the main contributors to the upper end of the total exposure distribution, however peak exposures were caused by methomyl. This discrepancy to the percent contribution may occur due to strong differences in the detection frequencies. While dimethoate is found very often in a broad range of foods, methomyl is detected rarely. Consequently, dimethoate residues are selected more often by the probabilistic model and show much higher contribution to the P99.9. However, when methomyl get randomly selected, its exposure equivalent is higher than for sum of dimethoate and omethoate.

In view of possible additive effects from multiple compounds, MCRs were below 2 for all age groups investigated. An increased dietary risk from the CAG compared to single compounds was not identified.

Table 4: Maximum cumulative ratios of compounds for acute neurochemical effects

Survey	Maximum cumulative ratios (bivariate)
VELS	

Survey	Maximum cumulative ratios (bivariate)
EsKiMo	

<table>
<tr><th>Survey</th><th>Maximum cumulative ratios (bivariate)</th></tr>
<tr><td>NVS II</td><td>
</td></tr>
</table>

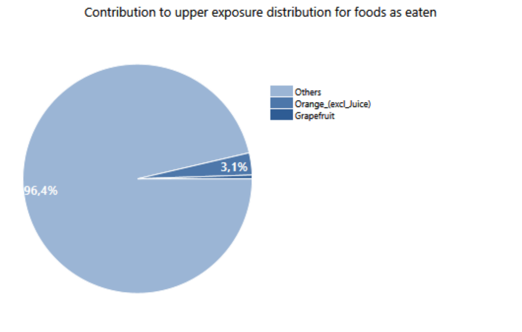
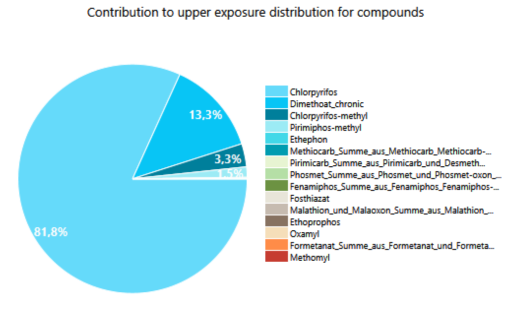
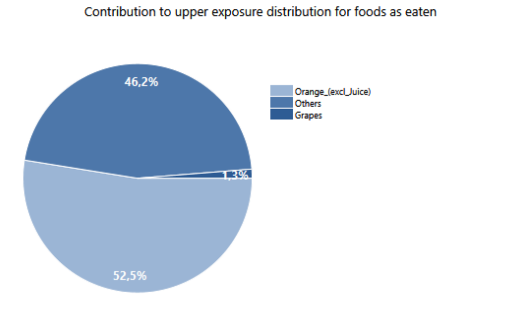
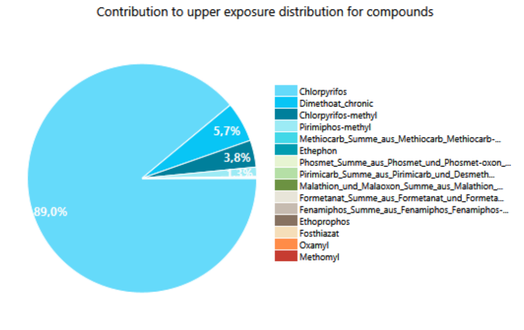
4.1.3 *Nervous system: chronic neurochemical effects*

Contribution of compounds and foods to the upper exposure distribution

The contribution of individual substances was dominated by chlorpyrifos, which represented more than 81.8% of the total exposure at the P99.9 for all age groups investigated. The only other compound with a significant contribution (≥10%) was the sum of dimethoate and omethoate.

Also for the foods, the contribution to the total exposure mainly originated from citrus fruits, namely oranges and grapefruit. Especially chlorpyrifos was frequently found in citrus fruits. It should be noted, that the penetration of chlorpyrifos through the inedible citrus peel is very limited. A refined assessment of this aspect is discussed in the corresponding publication.

Table 5: Contribution of compounds and foods to the P99.9 of the total cumulative exposure distribution for chronic neurochemical effects

<table>
<tr><th>Studie</th><th>Contribution of foods</th><th>Contribution of compounds</th></tr>
<tr><td>VELS</td><td>
</td><td>
</td></tr>
<tr><td>EsKiMo</td><td>
</td><td>
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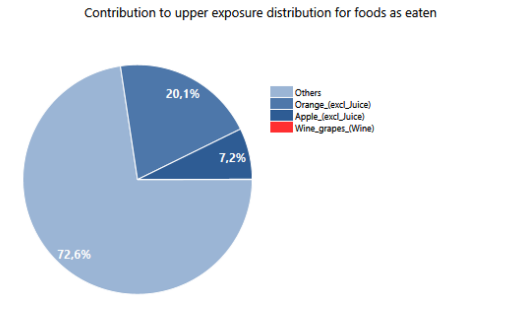
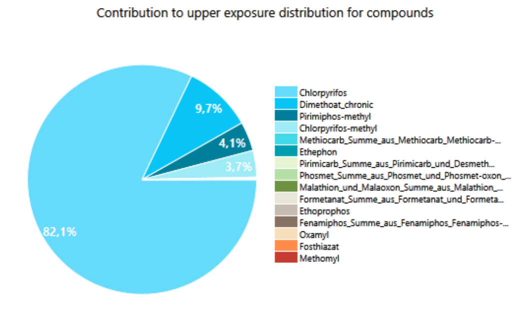
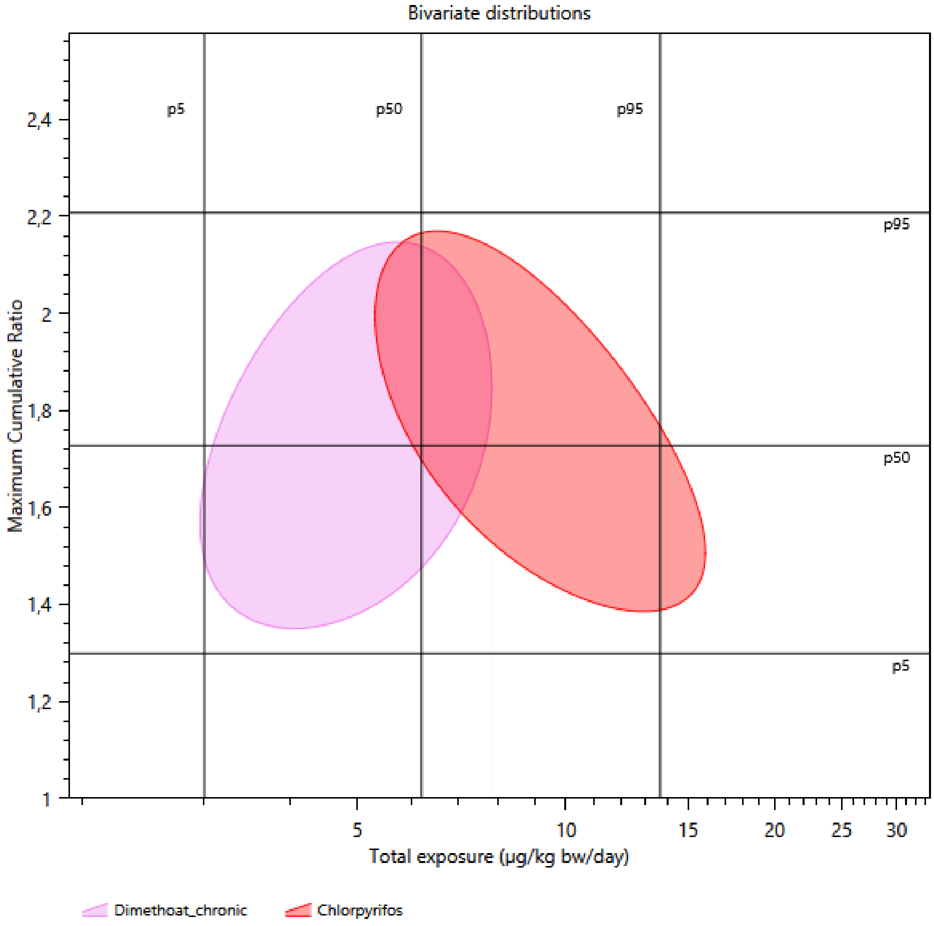
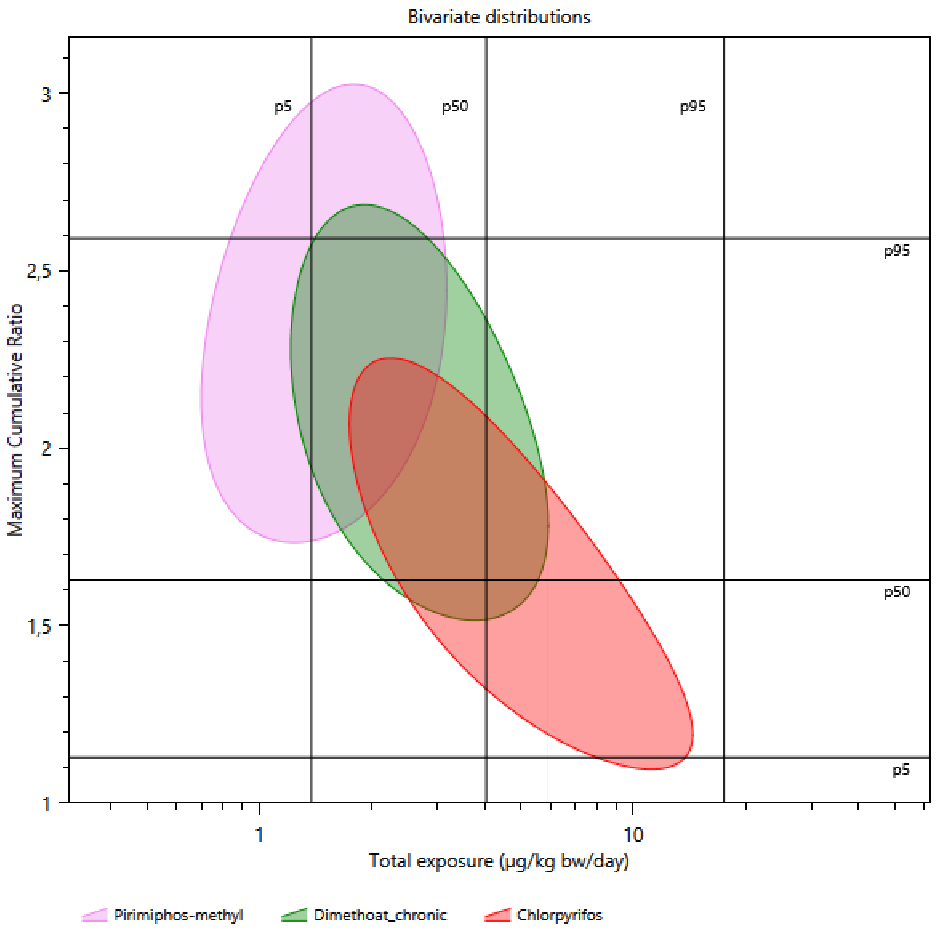
<tr><td>NVS II</td><td>
</td><td>
</td></tr>
</table>

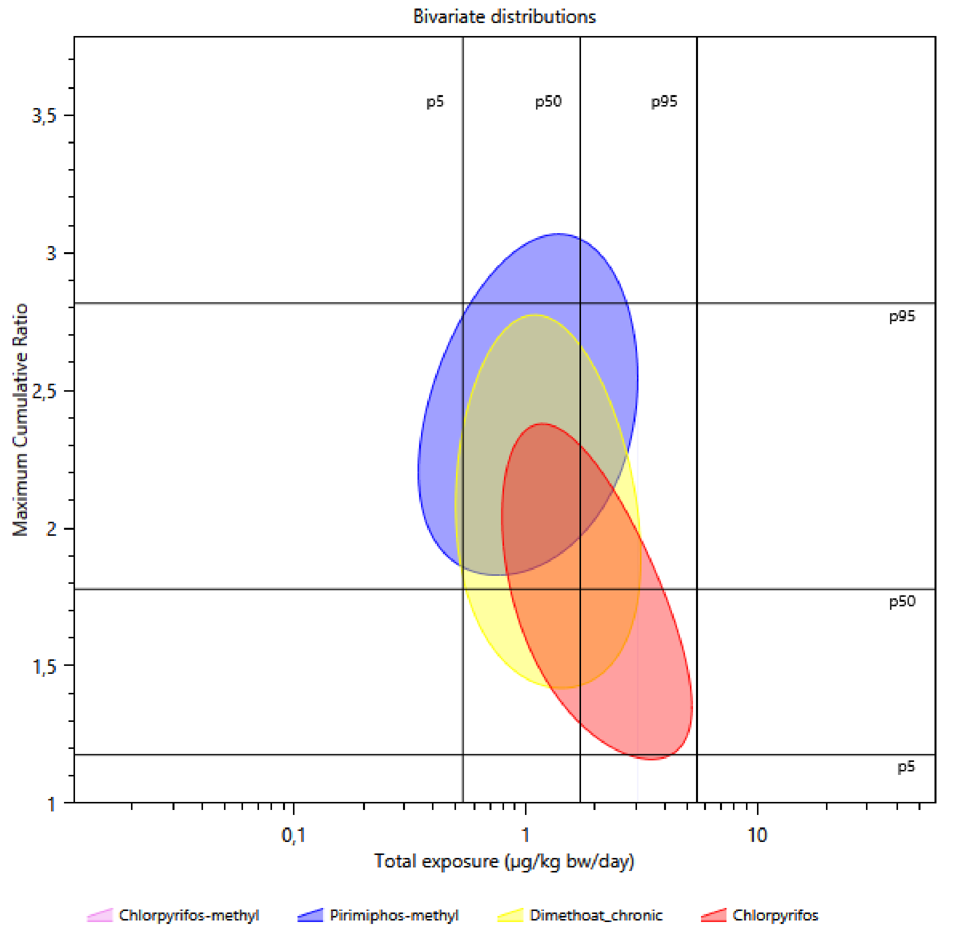
Maximum cumulative ratios

In correspondence to the results for the percent contribution, the upper end of MCRs are dominated by chlorpyrifos. With increasing exposure, the MCRs becomes closer to 1, indicating that this compound represents the major residue for the upper percentiles. At lower percentiles of the total exposure distribution, also dimethoate and pirimiphos-methyl add significantly and at levels comparable to chlorpyrifos, since MCRs between 2 and 3 were identified.

Table 6: Maximum cumulative ratios of compounds for chronic neurochemical effects

Survey	Maximum cumulative ratios (bivariate)
VELS	

Survey	Maximum cumulative ratios (bivariate)
EsKiMo	

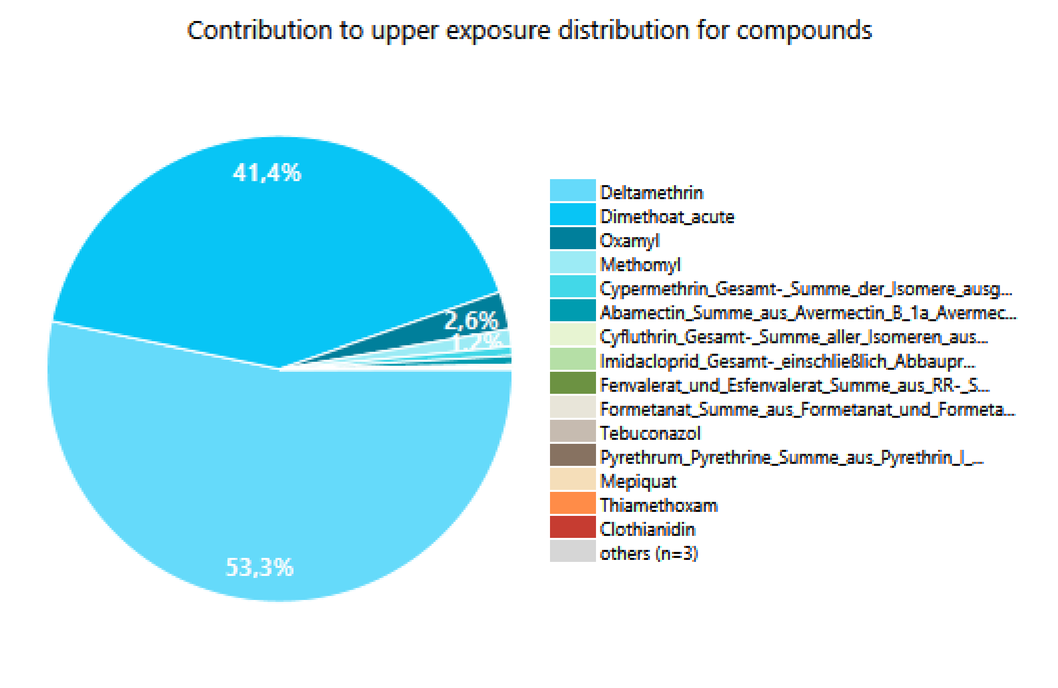
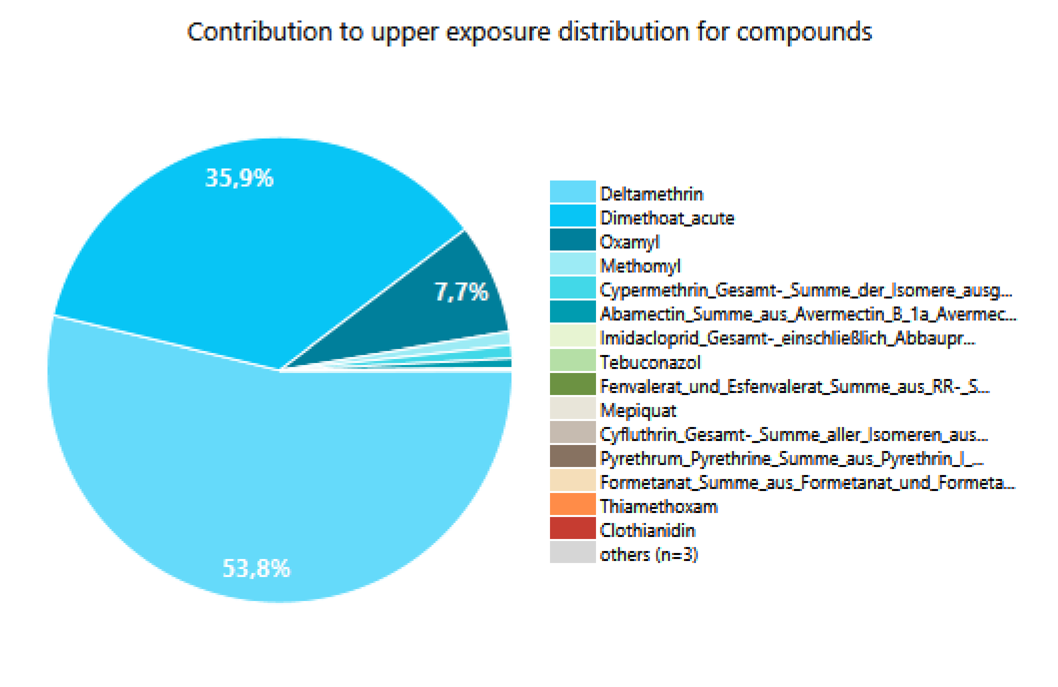
Survey	Maximum cumulative ratios (bivariate)
NVS II	

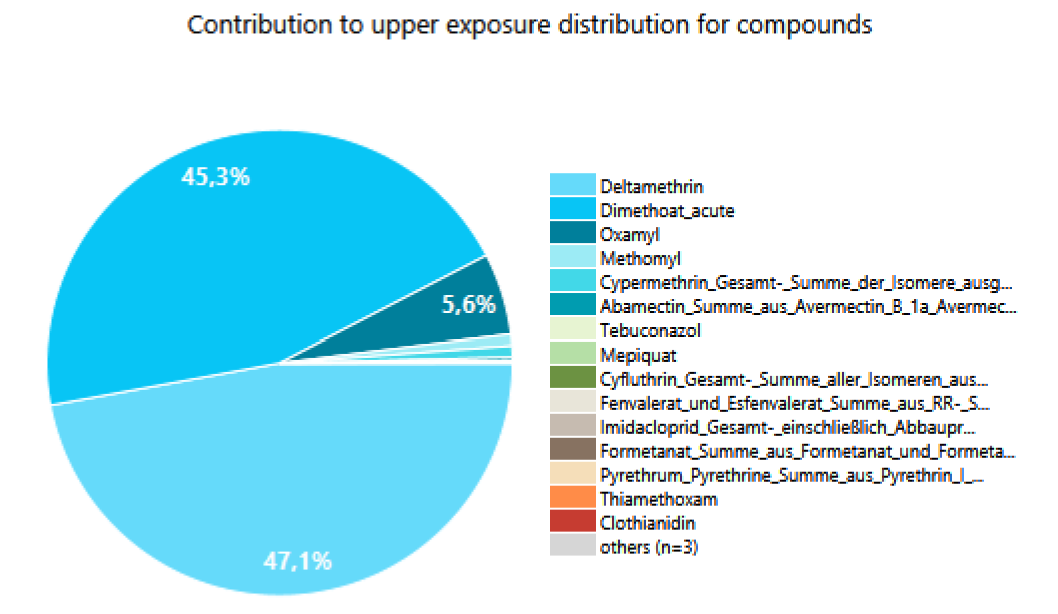
4.1.4 Nervous system: acute effects on the sensory system

Contribution of compounds to the upper exposure distribution

In this CAG, three compounds nearly complete gave the total exposure at the P99.9. Thereof, deltamethrin and the sum of dimethoate and omethoate represented the major part with 35.9-53.8% contribution each. The third compound was oxamyl, adding 2.6-7.7%.

Table 7: Contribution of compounds to the P99.9 of the total cumulative exposure distribution for acute effects on the sensory system

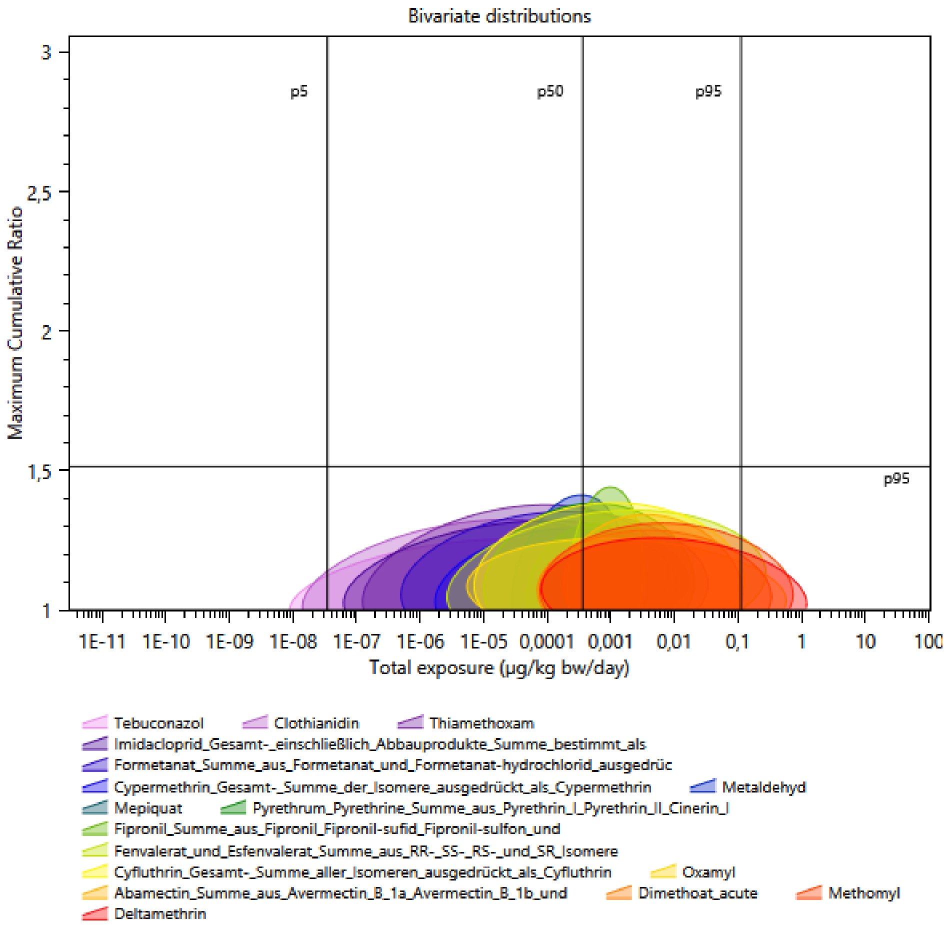
<table>
<tr><th>Survey</th><th>Contribution of compounds</th></tr>
<tr><td>VELS</td><td>
</td></tr>
<tr><td>EsKiMo</td><td>
</td></tr>
</table>

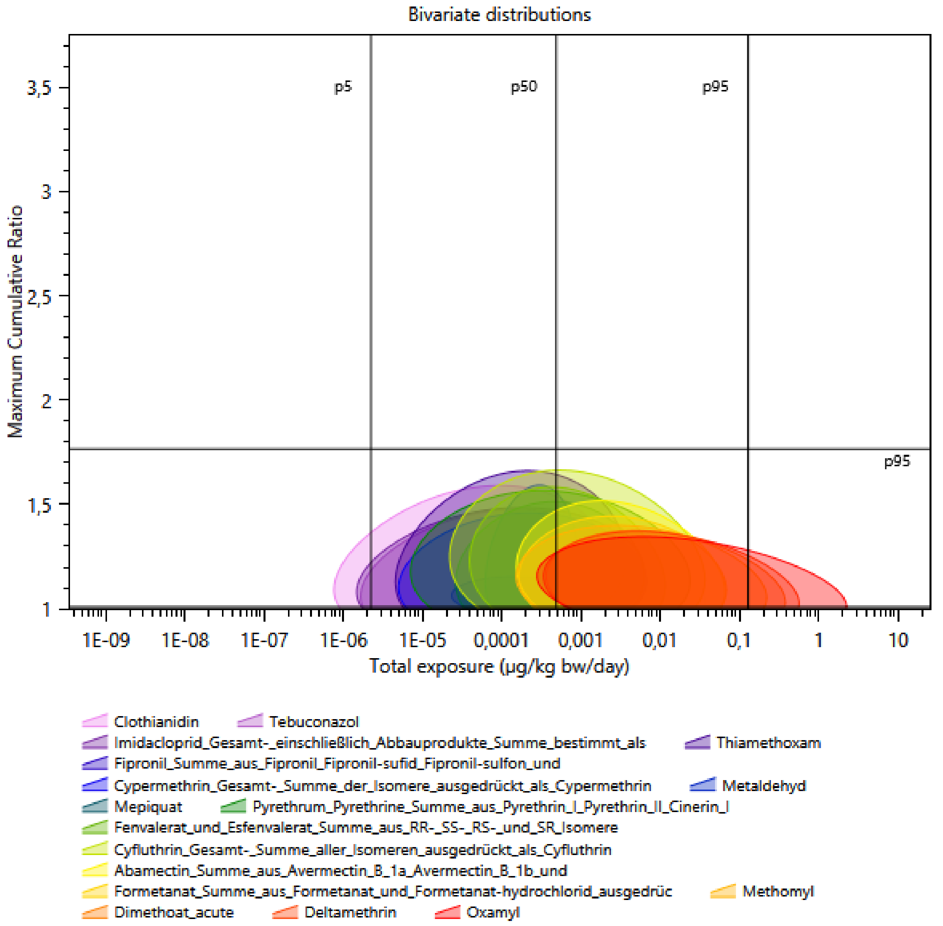
Survey	Contribution of compounds
NVS II	

Maximum cumulative ratios

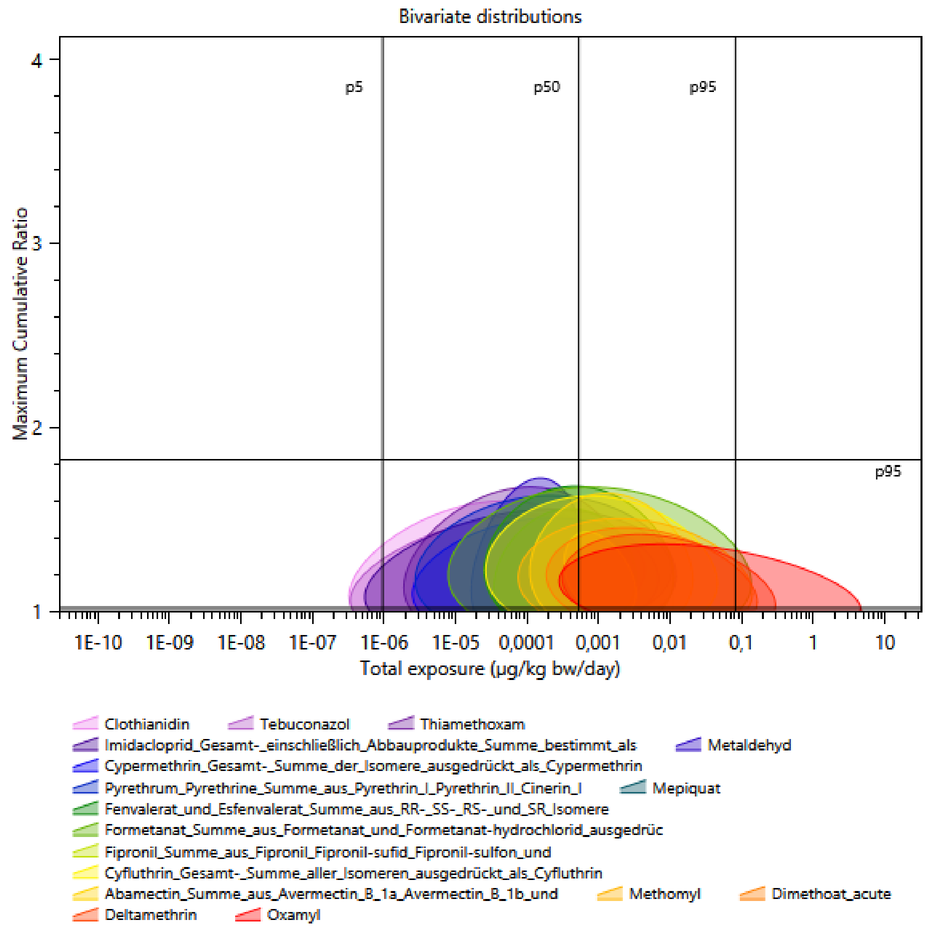
For the CAG, all three sub-populations showed very little additive effects with MCRs all below 2. At the upper percentiles, oxamyl gave the highest sensitivity to the total exposure for the EsKiMo and NVS II survey, while in VELS deltamethrin was the driving compound.

Table 8: Maximum cumulative ratios of compounds for acute effects on the sensory system

Survey	Maximum cumulative ratios (bivariate)
VELS	

<table>
<tr><th>Survey</th><th>Maximum cumulative ratios (bivariate)</th></tr>
<tr><td>EsKiMo</td><td>


</td></tr>
</table>

<table>
<tr><td>Survey</td><td>Maximum cumulative ratios (bivariate)</td></tr>
<tr><td>NVS II</td><td>
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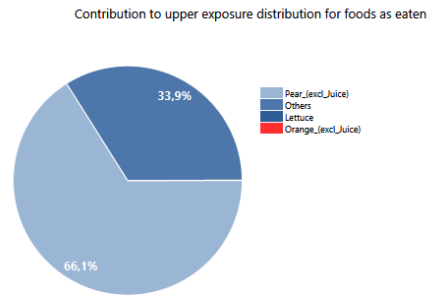
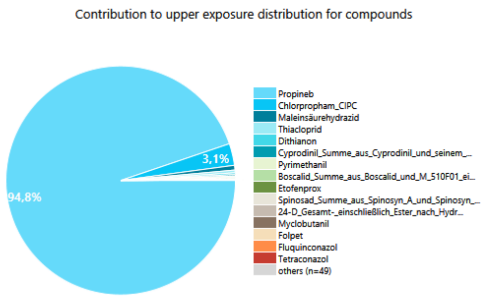
</table>

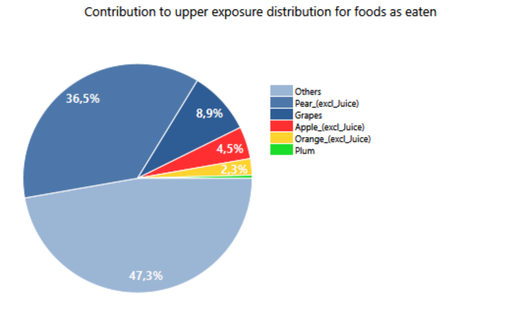
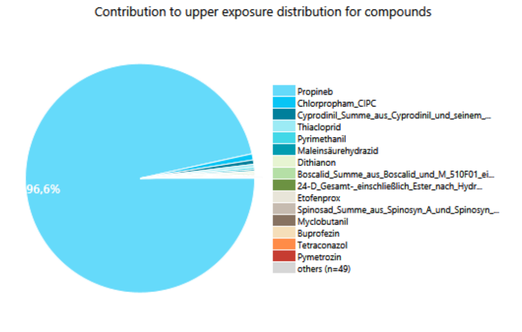
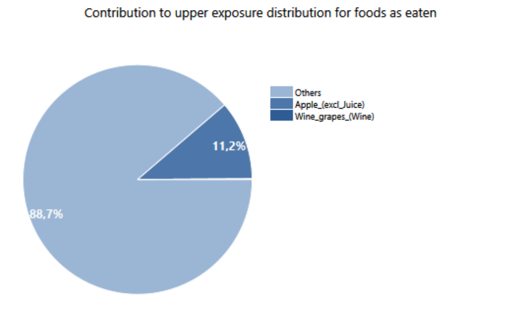
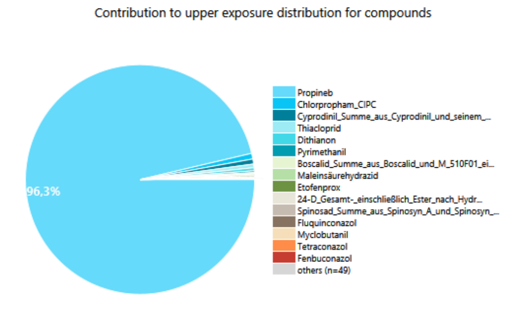
4.1.5 Thyroid system: chronic effects on follicular cells and/or the thyroid hormone (T3/T4) system

<u>Contribution of compounds and foods to the upper exposure distribution</u>

In this CAG, residues of CS_2 calculated as propineb nearly completely represented the total exposure with over 94% for all consumer groups. The most sensitive foods were apples, pears, grapes and lettuce.

Table 9: Contribution of compounds and foods to the P99.9 of the total cumulative exposure distribution for chronic effects on follicular cells and/or the thyroid hormone (T3/T4) system

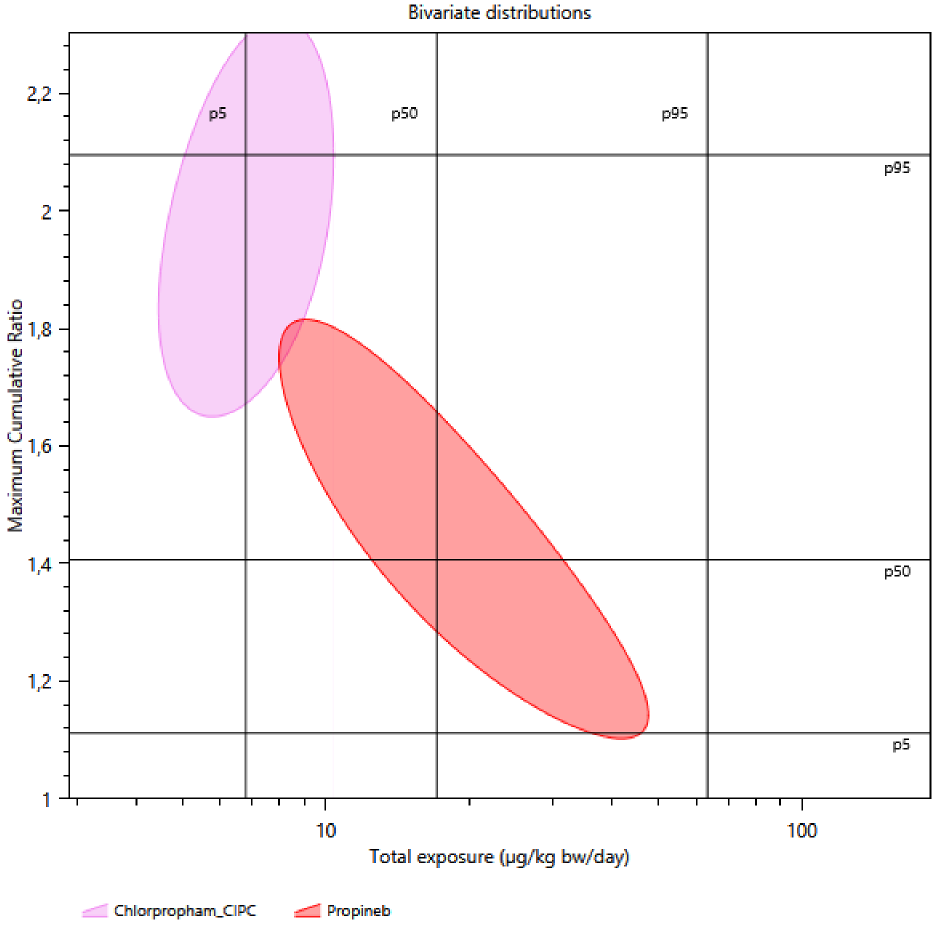
<table>
<tr><td>Studie</td><td>Contribution of foods</td><td>Contribution of compounds</td></tr>
<tr><td>VELS</td><td>
</td><td>
</td></tr>
</table>

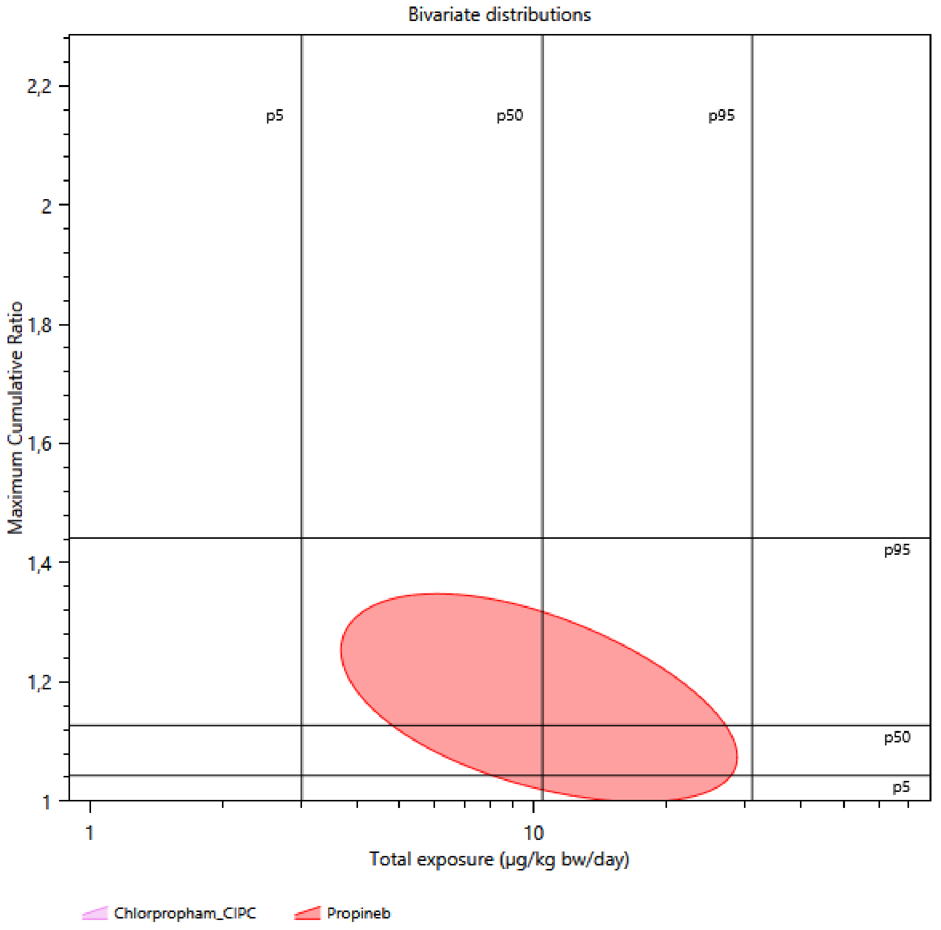
<table>
<tr><th>Studie</th><th>Contribution of foods</th><th>Contribution of compounds</th></tr>
<tr><td>EsKiMo</td><td></td><td></td></tr>
<tr><td>NVS II</td><td></td><td></td></tr>
</table>

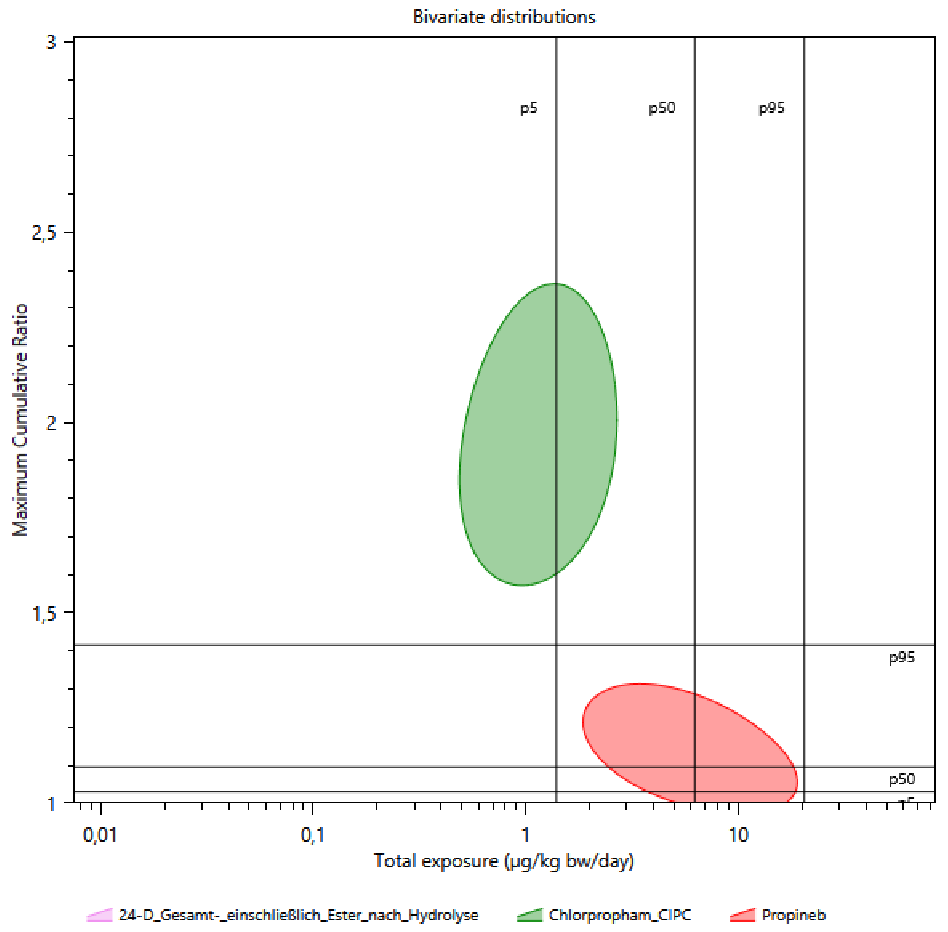
Maximum cumulative ratios

In view of the CS_2 calculated as propineb dominating the total exposure at the upper percentiles, also the MCRs were nearly completely based on this substance with values close to 1. At the lower end of the distribution, also chlorpropham was identified to contribute to the total cumulative exposure.

Table 10: Maximum cumulative ratios of compounds for chronic effects on follicular cells and/or the thyroid hormone (T3/T4) system

Survey	Maximum cumulative ratios (bivariate)
VELS	

Survey	Maximum cumulative ratios (bivariate)
EsKiMo	

Survey	Maximum cumulative ratios (bivariate)
NVS II	

4.1.6 Summary

It became evident, that the upper percentiles of the total exposure distribution are mainly driven by single compounds instead of a mixture of components. For all CAGs, multiple substances with significant average contributions (≥10%) were identified at the P99.9, however the MCR analysis showed that their simultaneous occurrence in the diet is very unlikely and does not affect the risk. Rarely, more than two substances add to the total risk and in such cases these additive effects relate to more central parts of the exposure distribution between the P25 and the P75.

5 Part 3: Identification of a pesticide exposure based market basket suitable for cumulative dietary risk assessments and food monitoring programmes

Reference

C. Sieke, 'Identification of a pesticide exposure based market basket suitable for cumulative dietary risk assessments and food monitoring programmes', Food Addit. Contam. Part A, pp. 1–15, Mar. 2020, doi: 10.1080/19440049.2020.1737334 [63]

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Authors contribution

Christian Sieke: Conceptualisation, analysis, software, visualisation, writing – original draft

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Identification of a pesticide exposure based market basket suitable for cumulative dietary risk assessments and food monitoring programmes

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ABSTRACT

Consideration of cumulative dietary risks is a requirement in the European legislation for setting maximum residue levels for pesticides. Current cumulative exposure assessment methodologies strongly rely on representative occurrence data from food monitoring programmes. This study provides a sensitivity analysis, utilising (i) European consumption data expressed as raw agricultural commodity (RAC) equivalents from 23 different countries as published by the European Food Safety Authority and (ii) all maximum residue levels established for pesticides under European Regulation (EC) No 396/2005. Based on two different degrees of conservatism, market baskets consisting of 16 or 41 RACs, respectively, were identified, covering the majority of the total chronic and acute daily exposure. The coverage of the exposure by these market baskets was tested by comparison of cumulative probabilistic exposure assessments for the German population using all food commodities and those using the reduced sets. It was demonstrated that ≥85% of the total chronic exposure is already covered by 16 RACs, while 41 RACs are required to reach a similarly satisfying coverage of the total acute exposure. Results from this study support resource efficient modelling of complex cumulative assessment scenarios and may help to improve the design of food monitoring programmes with respect to a more efficient assessment of potential consumer risks.

ARTICLE HISTORY
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KEYWORDS
Pesticide; exposure; monitoring; cumulative; risk

Introduction

In regulatory frameworks for pesticides a shift from single substance evaluations towards the assessment of complex mixtures and multiple residues in foods takes place. In the European Union (EU), consideration of "cumulative and synergistic effects, when the methods to assess such effects are available" is a mandatory request when setting maximum residue levels (MRLs) for pesticide residues in foods and feeds under Regulation (EC) 396/2005 (EU 2005). However; a harmonised methodology to address the cumulative risk for consumers has not yet been implemented and is still under scientific development. To accelerate this process, large research projects like EuroMix (EuroMix 2018) were funded by the European Commission (EC) to improve the knowledge both on mixture toxicity and on methodologies to estimate the cumulative exposure to multiple components.

Mixture toxicity is often related to specific adverse outcome pathways (AOPs) (OECD 2017) and therefore strongly linked to the toxicological properties of each component in the mixture. A common approach is the grouping of potentially relevant components into cumulative assessment groups (CAGs), for example based on their capability to induce similar toxicological effects e.g. to target organs (PPR 2013) or by their structural relationship like sharing the organophosphorus moiety (EPA 2006).

From an exposure assessment point of view, the individual modes of toxicity and the grouping of components are of low relevance for the dietary risk assessment methodologies. In all cases, occurrence data for each component of interest is correlated with information on the amount of food consumed in a specific timeframe. The underlying data and the principles in the exposure models used are mostly unaffected by the size of CAGs or by the AOP they are based on. However; with increasing complexity of models, computational capacity becomes the most limiting factor, both in time and in cost. Currently,

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Supplemental data for this article can be on the publisher's website.

most dietary exposure models addressing multiple residues like MCRA (van der Voet et al. 2015) or DEEM (EPA 2014) are based on probabilistic approaches. The general aim is the generation of an exposure distribution for the population group of interest, from which specific percentiles are selected for decision making (e.g. percentile 99.9) (EPA 2000). The data sources used in such models are typically food consumption surveys and results from representative food monitoring programmes. Especially the latter provide a large potential for optimisation of the sampling design to enable a focused and efficient modelling of cumulative dietary risks. Since these programmes have not been optimised in regard to the sensitivity of analysed matrices for the consumer exposure, sampling resources and computation capacities could be invested with maximum benefit.

In Europe, the food monitoring for pesticide residues is organised both on national level (e.g. Germany (Bundesministerium für Ernährung und Landwirtschaft 2015)) and in an EU-wide coordinated control programme (European Parliament and the Council of the European Union 2018). The underlying scientific concepts for the Germany Food Monitoring (Sieke et al. 2008a, 2008b) and for the EU Annual Coordinated Control Programme (EFSA 2015b) focus on a food basket covering a high percentage of the average daily consumption. Although this concept ensures coverage of important foods eaten frequently, it contains no substance related information on its sensitivity for the dietary risk assessment. The contribution to the total daily dietary exposure from highly consumed food commodities like cereal grains or meat could be much lower than for less consumed foods due to different residues concentrations. Especially for cumulative risk assessments based on probabilistic modelling, the upper percentiles of exposure distributions are driven by a very limited range of food commodities. For example, the cumulative dietary risk to organophosphorus and carbamate insecticides was mainly driven by 6 different raw food commodities each, representing 73% to 89% of the total exposure (Boon et al. 2008). In view of the plethora of possible combinations between foods and residue components, consideration of all possible cases would require high efforts and very broad, detailed data but often with only very limited impact on the final result.

In the current work, the sensitivity of raw food commodities for cumulative dietary risk assessments was determined considering the pesticide MRLs established in the European Union. Based on the results, a prioritisation of foods in monitoring programmes is suggested, which allows to focus on key commodities and to identify less relevant commodities which could be omitted from the programmes. Also, in view of future approaches to establish MRLs on the basis of cumulative effects, knowledge of key commodities may help to increase the practicability.

Material and methods

In the first step, a sensitivity analysis was conducted for the contribution of all raw food commodities to the long- (chronic) and short-term (acute) daily exposure. The results were expressed as percentages of the total exposure via all food items and as percentages of the compounds' health based guidance values (HBGVs), namely the acceptable daily intake (ADI) or the acute reference dose (ARfD), as derived by EFSA in the assessment for the approval of active substance into Annexe I of the European Regulation (EC) 1109/2007 (The European Parliament and the Council of the European Union). The information was obtained from the Pesticide Database of the European Commission (European Commission (COM)). Data management was performed with Microsoft EXCEL while all model calculations were performed using R Software (R Core Team 2019).

Consumption data

Consumption data were obtained from the EFSA raw primary commodity (RPC) model (Dujardin and Kirwan 2019). The EFSA RPC model is based on 51 dietary surveys from 23 different European countries, representing a total of over 26 million consumption records covering 111 sub-populations. Within the EFSA RPC model, consumption data were transformed into their respective raw primary commodity equivalents according to Annexe I of Regulation (EC) 396/2005, based on recipe data and under consideration of processing effects by using yield factors. The complete daily consumption of a given commodity from all sources was obtained by aggregating all entries to one single raw commodity equivalent per commodity and survey. The RPC model provides statistical parameters (e.g. mean, median and selected percentiles) for the consumption of each raw food item per survey, based either on the total population (including non-consumers) or on consumers only (individuals with a daily portion size >0). In both datasets, consumption is expressed either on a "g per day" or "g per kg bodyweight and day" basis, from which the latter was used for direct comparison with HBGVs.

From the RPC model, the "total population" was considered to calculate the relative contribution of each commodity to the chronic exposure as suggested for predicting the dietary exposure of pesticide residues (Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food) 1997). For the acute exposure, consumption data for "consumers only" were considered. This approach reflects the procedure to derive large portions in the "International Estimate of Short-Term Intake" (IESTI) approach (FAO 1999; EFSA 2015a) which is broadly used in pesticide regulatory frameworks.

Occurrence data and toxicological information

The maximum concentration of pesticides allowed in food commodities according to Regulation (EC) 396/2005 as well as corresponding HBGVs were obtained from the European Commission's Pesticide Database (date: 31.07.2019) (European Commission (COM) 2019). MRLs set at the limit of quantification (LOQ) were considered at the numeric value of the LOQ. Compounds without established MRLs have not been considered in the calculation. Also, MRLs normally address residue components according to the residue definition for enforcement purposes, primarily selected to ensure easy and cost-efficient analysis. For risk assessment purposes, it may be necessary to considered the presence of additional residue components with toxicological relevance. The ratio between these two approach is commonly described as a conversion factor (CF) (EFSA Panel on Plant Protection Products and their Residues 2016), which may be used to extrapolate from analytical enforcement results to the residue relevant for the exposure assessment. However, since CF are very limited in their availability, differences in the residue definitions for enforcement purposes and for risk assessment were not taken into account.

For considering the sensitivity of individual foods to the cumulative exposure, ADI and ARfD values are expected to provide a conservative estimate of the risk involved. Both HBGVs are established at the lowest "no observed adverse effect level" (NOAEL) multiplied by a safety factor (typically 100). When this lowest NOAEL is related to the toxicological effect of the CAG, the individual toxicity is directly addressed. When another toxicological effect provides the lowest NOAEL, the sensitivity is even overestimated.

Sensitivity analysis model

In the current work, a model was used to address the sensitivity of each food commodity to the total long- or short-term exposure. The sensitivity was expressed either by the relative contribution to the total daily exposure or by the utilisation of health based guidance values for each commodity.

The relative contribution to the total daily exposure was expressed in percent and calculated as the ratio between the exposure arising from each individual raw food commodity and the total mean exposure from all raw food commodities (Equation 1). For each individual commodity, the mean consumption ("mean approach") and the percentile P97.5 (or the next lower available percentile P90, P75 or mean, if the P97.5 was not available in the RPC model), were used ("high approach"). This calculation was performed for each consumption survey and each pesticidal active substance, providing a large overall distribution of relative contributions from all active substances per food commodity.

$$Rel.contribution\ food\ X(\%) = 100 \times \frac{(Mean\ or\ high)Consumption_{Foodx} \times Occurrence_{Foodx}}{\sum_{Food1}^{n} Mean\ Consumption_{Foodn} \times Occurrence_{Foodn}} \quad (1)$$

In addition, the utilisation of HBGVs by the exposure for individual food commodities (Equation 2) was calculated. The mean and high approach for the "total population" was assessed against the ADI, while only the high approach based on "consumers only" was assessed against the ARfD. Compounds with a very limited range of uses could result in high relative contributions of single food commodities to the total daily exposure. However, their relevance becomes low when only a very minor percentage of the ADI value is utilised. On the other hand, single combinations of commodity and MRL may already result in acute exposures close to the ARfD although the contribution to the long-term total exposure is minor. The calculations were performed for each survey and for each pesticidal active substance.

$$Contribution\ HBGV\ food\ X(\%) = 100 \times \frac{(Mean\ or\ high)Consumption_{Foodx} \times Occurrence_{Foodx}}{HBGV} \quad (2)$$

For both approaches, summary statistics were applied to the total distributions of the relative contributions to the exposure and of the utilisations of HBGVs. Based on the reporting frequency in the RPC model, total distributions consisted of 455 up to 56000 individual results. When HBGVs have not been established or were not considered necessary, only the relative contribution to the exposure was calculated. All food commodities either posing a significant contribution to the total daily exposure or utilising a significant percentage of the HBGVs were taken into account to derive an overall market basket.

Reassessment of cumulative risks from pesticide residues in food

Based on the overall market baskets derived by the model, the impact of the reduced number of food commodities on probabilistic cumulative dietary exposure assessments was investigated. In 2018, the cumulative exposure against pesticide residues was estimated for three German sub-populations based on food monitoring data in 115 commodities (Sieke 2018). The cumulative assessment groups were obtained from EFSA and referred to chronic and acute effects to the nervous and thyroid system (PPR 2013). It should be noted that recently the CAGs for the nervous and thyroid system (Crivellente et al. 2019a, 2019b) have been updated. However; to estimate the relative coverage of the total diet under realistic conditions, the exact composition of the CAG is not expected to make much difference and therefore adaption to the new CAGs was not performed.

The datasets from the 2018 calculation were directly used for recalculations with the full range of commodities and with the reduced market basket. All scenarios were newly calculated with the MCRA 8.2 software version released in the meantime to identify differences solely based on the food selection, not on changes of the algorithm. Results for the reduced market baskets were expressed in terms of percentage of the exposure of the whole market basket for selected percentiles (percentile 50, 90, 95, 99, 99.9 and 99.99).

Due to the high percentage of non-detects in food monitoring, two different approaches were selected. For each CAG the limit of quantification (LOQ) was either used as such or substituted by zero. The calculations were based on German consumption data for children (0.5–4 years) (Heseker et al. 2003) and the general adult population (14–80 years) (Brombach et al. 2006; Krems et al. 2006; Max Rubner-Institut (MRI) 2016), however, for the latter the size of the database did not allow computation of the acute CAG for neurotoxic effects on the motor system ("motor division").

Results

The results of the model were evaluated by calculating the mean, median, 90th, 95th and 97.5th percentile and the maximum for the contribution of each food commodity and scenario (see supplemental information). Generally, a contribution of ≥10% was considered sufficiently significant to affect the outcomes of total exposure estimations. From the calculated statistical figures, the 95th percentile (P95) was selected to provide a robust upper-bound estimate of the relevance of each food commodity. In addition, the 97.5th (P97.5) was selected to correlate to the degree of conservatism involved in the IESTI concept to address potential cases relevant for acute exposure scenarios.

Total population

For the total population, contributions from individual food commodities to the overall exposure for each compound ranged from close zero up to 60% for the P95 and P97.5 (Tables 1 and 2). In total, 12 food commodities were identified as

Table 1. Total population chronic contribution (95th percentile of the results, descending).

Commodity	Mean approach – % Contribution	Mean approach – % ADI	High approach – % Contribution	High approach – % ADI	Number of combinations
Cow milk	50.9	45.1	102.5	88.4	53244
Oranges	19.2	18.2	70.2	74.9	56376
Apples	19.2	19.7	57.5	67.2	56376
Sugar beet roots	16.8	16.8	42.0	44.6	56376
Wine grapes and similar	18.0	<10	67.6	26.4	56120
Wheat grain	21.8	15.2	40.0	31.1	56840
Sugar canes	12.7	12.5	29.9	33.1	56376
Tomatoes	15.1	<10	41.2	24.9	56376
Potatoes	10.0	<10	22.3	19.3	56492
Table grapes and similar	<10	<10	27.4	17.2	55144
Head lettuces	<10	<10	21.3	10.7	55290
Mandarins and similar	<10	<10	14.4	15.7	54432
Banana	<10	<10	12.2	14.0	56260
Olives for oil production	<10	<10	13.4	12.3	56260
Pears	<10	<10	12.8	12.5	56376
Strawberries	<10	<10	11.6	10.5	56376
Barley grains	<10	<10	11.9	<10	56235
Pig fresh meat	<10	<10	10.6	<10	53012
All other commodities	<10	<10	<10	<10	variable

Table 2. Total population chronic contribution (97.5th percentile of the results, descending).

Commodity	Mean approach – % Contribution	Mean approach – % ADI	High approach – % Contribution	High approach – % ADI	Number of combinations
Cow milk	60.1	77.6	125.6	154.5	7752
Oranges	31.9	31.9	115.7	127.8	53244
Apples	28.9	35.2	86.1	119.2	56376
Wine grapes and similar	30.0	14.5	119.5	60.1	56376
Sugar beet roots	23.0	35.6	65.5	94.5	56120
Wheat grain	32.4	27.2	58.6	54.8	56376
Sugar canes	15.1	24.3	36.3	63.0	56840
Tomatoes	23.7	13.3	63.4	37.9	56376
Potatoes	15.3	15.3	33.4	36.9	56376
Head lettuces	11.0	<10	47.2	22.2	56492
Table grapes and similar	<10	<10	44.2	30.7	55290
Olives for oil production	12.3	<10	23.6	29.2	55144
Mandarins and similar	<10	<10	23.7	30.7	56260
Banana	<10	<10	22.1	26.8	54432
Pig fresh meat	<10	<10	19.0	27.3	56260
Pears	<10	<10	21.7	20.7	53012
Strawberries	<10	<10	20.6	19.5	56376
Bovine fresh meat	<10	<10	16.2	22.6	56376
Barley grains	<10	<10	22.4	10.6	53128
Peaches and similar	<10	<10	16.6	16.3	56235
Oat grain	<10	<10	16.7	14.4	55890
Durum wheat grain	<10	<10	16.0	15.0	55257
Sunflower seeds	<10	<10	15.0	14.8	56840
Spinaches	<10	<10	17.5	10.7	56376
Rice grain	<10	<10	12.1	12.3	55775
Maize grain	<10	<10	12.6	11.8	56840
Carrots	<10	<10	12.2	11.4	56724
Rye grain	<10	<10	13.1	10.0	56260
Chicken fresh meat	<10	<10	10.0	12.0	55257
Crisp lettuces	<10	<10	21.2	<10	53012
Teas leaves, dry and/or fermented, and similar	<10	<10	11.5	<10	44620
Rapeseeds	<10	<10	11.5	11.2	55031
Pineapples	<10	<10	10.5	<10	56376
Coffee beans, green	<10	<10	10.1	<10	54805
All other commodities	<10	<10	<10	<10	Variable

major contributors to the exposure in the mean approach (descending order: cow milk ≤61.4%, oranges <60.1%, sugar cane ≤32.4%, apples ≤31.9%, sugar beet roots ≤30.0%, wine grapes ≤28.9%, potatoes <23.7%, wheat grain ≤23.0% head lettuce ≤15.3%, tomatoes ≤15.1% and olives for oil production ≤12.3%). Taking also into account the individual chronic HBGVs for each pesticide, only nine food commodities remained at the P95 and P97.5 which were major contributors to the exposure and utilised the ADI by 10% or more (descending order: cow milk ≤77.6%, apples ≤35.9%, sugar beet roots ≤35.6%, oranges ≤31.9%, wheat grain ≤27.2%, sugar cane ≤24.3%, potatoes ≤15.3%, wine grapes ≤14.5% and tomatoes ≤13.3%).

In the high approach, which calculates the percentage of a large daily portion size versus the mean daily consumption, 18 food commodities were identified with more than 10% contribution (Table 1) for the P95 and 34 food commodities for the P97.5 (Table 2). The RPC model expresses all food consumptions in terms of their raw agricultural commodity equivalents. Highly processed foods or ingredients like white sugar, hard cheese or olive oil show exceptionally high sensitivity in the calculation, since yield rates are low and therefore high amounts of raw commodity are used to prepare the processed food. Of the major contributors to the exposure, 16 food commodities at the P95 and 28 food commodities at the P97.5 also resulted in utilisations of the ADI of 10% or more.

Consumers only

When only consumers of a food are considered, the contribution of portion sizes to the total daily consumption would give unrealistic results, since the frequency of consumption is not considered anymore. The sensitivity of rarely consumed food commodities would be overestimated in comparison to frequently eaten food commodities. Thus, only the sensitivity against HBGVs is calculated to identify food commodities utilising a large percentage of the compound specific ADI or ARfD value. The aim is to address consumers with high consumption frequencies and consumers of single large portions.

For the mean approach, only 9 food commodities were identified (see Table 3) utilising the ADIs by 10% or more (in descending order: nettle ≤37.7%, oranges ≤37.4%, cow milk ≤21.7%, mandarins ≤15.9%, apples ≤14.3%, wheat grain ≤12.4%, quinces ≤11.9%, sugar beet roots ≤10.7% and lamb´s lettuce ≤10.1%). The high approach resulted in a total of 14 food commodities for the P95 and 38 food commodities for the P97.5 with at least 10% ARfD utilisation.

Table 3. Consumer only HGBV contribution (95th and 97.5th percentile of the results, descending).

Commodity	Mean approach – % ADI		High approach – % ARfD		Number
	P95	P97.5	P95	P97.5	
Oranges	18.0	37.4	54.2	125.2	53460
Cow milk	13.1	21.7	33.8	53.4	50949
Mandarins and similar	<10	15.9	21.9	50.3	46656
Apples	<10	14.3	29.6	47.9	53946
Sugar beet roots	<10	10.3	21.0	42.2	53946
Nettle	17.3	37.7	20.3	40.6	2430
Wheat grain	<10	12.4	14.9	31.2	54390
Wine grapes and similar	<10	<10	13.4	22.8	52704
Table grapes and similar	<10	<10	13.6	20.5	51240
Grapefruits	<10	<10	<10	20.0	43254
Oat grain	<10	<10	<10	19.7	47922
Strawberries	<10	<10	10.2	19.6	53460
Bilberries	<10	<10	<10	19.6	11155
Banana	<10	<10	<10	19.2	53835
Tomatoes	<10	<10	12.0	18.9	53460
Sugar canes	<10	<10	12.0	18.4	53946
Sour cherries	<10	<10	<10	17.6	26675
Pineapples	<10	<10	<10	17.1	47045
Pears	<10	<10	10.2	16.5	51516
Barley grains	<10	<10	<10	16.3	49389
Peaches and similar	<10	<10	10.0	15.8	51030
Olives for oil production	<10	<10	<10	15.4	53835
Durum wheat grain	<10	<10	<10	15.1	54390
Lamb's lettuces	<10	10.1	<10	14.1	13095
Head lettuces	<10	<10	<10	14.0	47045
Potatoes	<10	<10	<10	12.8	54057
Cherries (sweet)	<10	<10	<10	12.3	46075
Quinces	<10	11.9	<10	12.1	4860
Cranberries	<10	<10	<10	11.9	28674
Spinaches	<10	<10	<10	11.7	47045
Lemons	<10	<10	<10	11.6	52974
Plums	<10	<10	<10	11.6	46075
Sorrel	<10	<10	<10	11.2	3888
Goat fresh meat	<10	<10	<10	10.6	458
Melons and similar	<10	<10	<10	10.4	39285
Crisp lettuces	<10	<10	<10	10.2	32980
Beans (with pods) and similar	<10	<10	<10	10.2	50440
Watermelons and similar	<10	<10	<10	10.0	32010
All other commodities	<10	<10	<10	<10	variable

Consolidated market basket

Based on the analyses for the total population and for consumers only, all food commodities with high sensitivity (≥10%) towards the total daily consumption or to the exposure were identified (Table 4). For the P95, 16 food commodities with high sensitivity were identified whereas for the more conservative P97.5 this was a total of 41 food commodities. Normally, all commodities with significant contributions to the total daily diet are also significant commodities in terms of exposure. Exceptions are tea leaves, rape seeds and coffee beans. Although these foods may add more than 10% to the total

Table 4. Consolidated market basket of commodities contributing significantly to the total daily diet and dietary exposure (95th and 97.5th percentile of the results, alphabetic order).

	P95							P97.5							
Commodity	TP Mean ≥10% cont.	TP Mean ≥10% ADI	TP High ≥10% cont.	TP High ≥10% ADI	CO Mean ≥10% ADI	CO High ≥10% ARfD	Market basket inclusion	TP Mean ≥10% cont.	TP Mean ≥10% ADI	TP High ≥10% cont.	TP High ≥10% ADI	CO Mean ≥10% ADI	CO High ≥10% ARfD	Market basket inclusion	Remarks
Apples	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Banana	×	×	✓	✓	×	×	✓	×	×	✓	✓	×	✓	✓	
Barley grains	×	×	✓	×	×	×	×	×	×	✓	✓	×	✓	✓	
Beans (with pods) and similar	×	×	×	×	×	×	×	×	×	×	×	×	✓	✓	2
Bilberries	×	×	×	×	×	×	×	×	×	×	×	×	✓	✓	2, 5
Bovine fresh meat	×	×	×	×	×	×	×	×	×	✓	✓	×	×	✓	
Carrots	×	×	×	×	×	×	×	×	×	✓	✓	×	×	✓	
Cherries (sweet, sour)	×	×	×	×	×	×	×	×	×	×	×	×	✓	✓	2
Chicken fresh meat	×	×	×	×	×	×	×	×	×	✓	✓	×	×	✓	
Coffee beans, green	×	×	×	×	×	×	×	×	×	✓	×	×	×	×	1
Cow milk	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Cranberries	×	×	×	×	×	×	×	×	×	×	×	×	✓	✓	2, 5
Goat fresh meat	×	×	×	×	×	×	×	×	×	×	×	×	✓	✓	2
Grapefruits	×	×	×	×	×	×	×	×	×	×	×	×	✓	✓	2
Lamb's lettuces	×	×	×	×	×	×	×	×	×	×	×	✓	✓	✓	4
Lemons	×	×	×	×	×	×	×	×	×	×	×	×	✓	✓	2
Lettuces (head, crisp)	×	×	✓	✓	×	×	✓	✓	✓	✓	✓	×	✓	✓	
Maize grain	×	×	×	×	×	×	×	×	×	✓	✓	×	×	✓	
Mandarins and similar	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Melons and similar	×	×	×	×	×	×	×	×	×	×	×	×	✓	✓	2
Nettle	×	×	×	×	✓	✓	✓	×	×	×	×	✓	✓	✓	5
Oat grain	×	×	×	×	×	×	×	×	×	✓	✓	×	✓	✓	4
Olives for oil production	×	×	✓	✓	×	×	✓	×	×	✓	✓	×	✓	✓	
Oranges	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Peaches and similar	×	×	×	×	×	✓	✓	×	×	✓	✓	×	✓	✓	
Pears	×	×	✓	✓	×	✓	✓	×	×	✓	✓	×	✓	✓	
Pig fresh meat	×	×	✓	×	×	×	×	×	×	✓	✓	×	×	✓	
Pineapples	×	×	×	×	×	×	×	×	×	×	✓	×	✓	✓	
Plums	×	×	×	×	×	×	×	×	×	×	×	×	✓	✓	2
Potatoes	✓	×	✓	✓	×	×	✓	✓	✓	✓	✓	×	✓	✓	
Quinces	×	×	×	×	×	×	×	×	×	×	×	✓	✓	✓	4
Rapeseeds	×	×	×	×	×	×	×	×	×	✓	×	×	×	×	1
Rice grain	×	×	×	×	×	×	×	×	×	✓	✓	×	×	✓	
Rye grain	×	×	×	×	×	×	×	×	×	✓	✓	×	×	✓	
Sorrel	×	×	×	×	×	×	×	×	×	×	×	×	✓	✓	2, 5
Spinaches	×	×	×	×	×	×	×	×	×	✓	✓	×	✓	✓	
Strawberries	×	×	✓	✓	×	✓	✓	×	×	✓	✓	×	✓	✓	
Sugar beet roots	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	3
Sugar canes	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	×	✓	✓	3
Sunflower seeds	×	×	×	×	×	×	×	×	×	✓	✓	×	×	✓	
Table grapes and similar	×	×	✓	✓	×	×	✓	✓	×	✓	✓	✓	✓	✓	
Teas leaves, dry and/or fermented	×	×	×	×	×	×	×	×	×	✓	×	×	×	×	1
Tomatoes	✓	×	✓	✓	×	✓	✓	✓	✓	✓	✓	×	✓	✓	
Watermelons and similar	×	×	×	×	×	×	×	×	×	×	×	×	✓	✓	2, 4

(*Continued*)

Table 4. (Continued).

Commodity	P95 TP Mean ≥10% cont.	P95 TP Mean ≥10% ADI	P95 TP High ≥10% cont.	P95 TP High ≥10% ADI	P95 CO Mean ≥10% ADI	P95 CO High ≥10% ARfD	P95 Market basket inclusion	P97.5 TP Mean ≥10% cont.	P97.5 TP Mean ≥10% ADI	P97.5 TP High ≥10% cont.	P97.5 TP High ≥10% ADI	P97.5 CO Mean ≥10% ADI	P97.5 CO High ≥10% ARfD	P97.5 Market basket inclusion	Remarks
Wheat grain (common, durum)	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Wine grapes and similar	✓	×	✓	✓	×	✓	✓	✓	✓	✓	✓	×	✓	✓	
All other commodities	×	×	×	×	×	×	×	×	×	×	×	×	×	×	2

Remark 1: no inclusion, only relevant in terms of contribution to the total daily consumption but not in terms of exposure.
Remark 2: inclusion, potentially relevant for short-term exposure.
Remark 3: primarily consumed as white sugar, which does not contain quantifiable residues. No consideration necessary.
Remark 4: extrapolation from other commodities according to EU Guidance for Extrapolation possible.
Remark 5: only relevant based on single RPC diets like infants or specific European regions.
✓: relevant.
×: not relevant.
TP: Total population.
CO: Consumers only.

exposure, related residues are too low to represent a significant utilisation of HBGVs. Also, sugar cane and sugar beet are consumed primarily as highly processed white sugar, for which residue concentrations are normally negligible (Scholz et al. 2018). In view of estimating the dietary exposure, these raw commodities can be considered as irrelevant.

For some commodities separately listed in the EFSA RPC model (e.g. bilberries and strawberries) only one common code exists in the Regulation (EC) No 396/2005 and the respective MRL applies to all sub-commodities. Aggregation to one representative commodity is therefore possible.

Recalculation of previous cumulative exposure assessments

Chronic CAGs

The coverage of the total exposure by the reduced market baskets was generally higher for the upper percentiles of the exposure distribution relevant for decision making like the P99.9. Since lower percentiles represent the background exposure consisting of a plethora of foods with multiple active substances, the outcome is strongly affected by any reduction of the number of commodities. In contrast, the upper percentiles are mainly driven by single food commodity and compound combinations, which remain unchanged as long as sensitive pairings are still considered.

Based on the strongly reduced P95 market basket, the median coverage of the exposure calculated for the total market basket was less than 70% for the 50th percentile, but increased to 85–89% for the 99.9th percentile (Figure 1). The results were in the same order of magnitude for all 11 CAGs considered for the chronic cumulative exposure. The impact of the LOQ scenario was low. Although absolute exposures differed strongly due to the high amount of "<LOQ" values substituted by zero in the "LOQx0" scenario, the relative change by the reduction of food items was identical for both approaches.

As expected, the percent coverage for the larger P97.5 market basket was higher, ranging from 82–89% for the 50th percentile up to 89–94% for the 99.9th percentile (Figure 2). The LOQx1 scenario generally resulted in a higher coverage of the

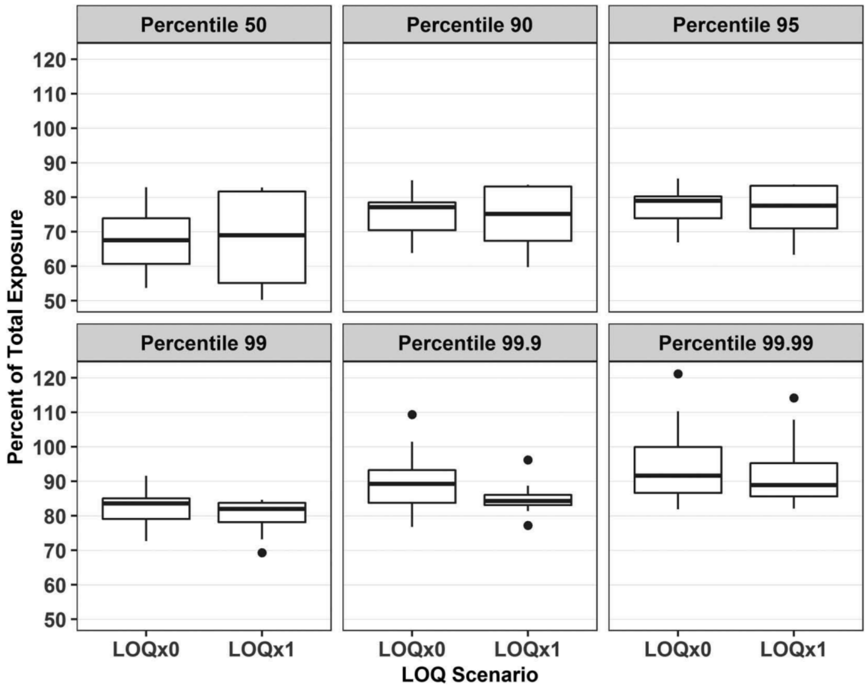

Figure 1. Percent chronic exposure based on P95 market basket relative to the total market basket.

total exposure than the LOQx0 scenario. However, the differences were still small with less than 10% deviation between both scenarios.

Acute CAGs

The recalculation of acute scenarios for the CAGs showed a much lower coverage of the total exposure for the reduced P95 market basket (Figure 3). For the LOQ×0 scenario, the 50th and 90th percentile of the exposure distribution represented less than 60% of the total exposure. Median levels for higher percentiles like the 99.9th percentile were below 70%, suggesting a significant underestimation of the total acute exposure based on the 16 food commodities selected. The LOQ×1 scenario gave more robust results, showing coverages of the total exposure above 80% for all scenarios.

The larger P97.5 market basket also takes into account food commodities, which potentially utilise a significant part of the ARfD (Figure 4). Consequently, the coverage of the total acute exposure was much higher with >90% for the 90th to 99.9th percentiles. The 50th percentile again resulted in a low coverage of <70% of the total acute exposure.

One deviation was observed for the CAG on acute effects on the autonomic system, which gave less than 60% coverage of the total exposure at higher percentiles like the 99.9th. Detailed investigation of the risk drivers in this group revealed, that the combination of oxamyl in peppers represents a main contributor to the exposure, which is not covered by the P97.5 market basket. In the underlying German monitoring data used for the probabilistic modelling, three samples with oxamyl residues above the LOQ were reported, two of them exceeding the established MRLs by a factor of up to 25. The sample with the highest residue already resulted in an exposure above the ARfD for oxamyl per se (BVL 2011). An additional calculation of the P97.5 market basket plus peppers resulted in an increased coverage of the total exposure of 73.7% at the 99.9th percentile (Figure 5), demonstrating the high sensitivity of the probabilistic cumulative exposure calculation for these two non-MRL compliant samples.

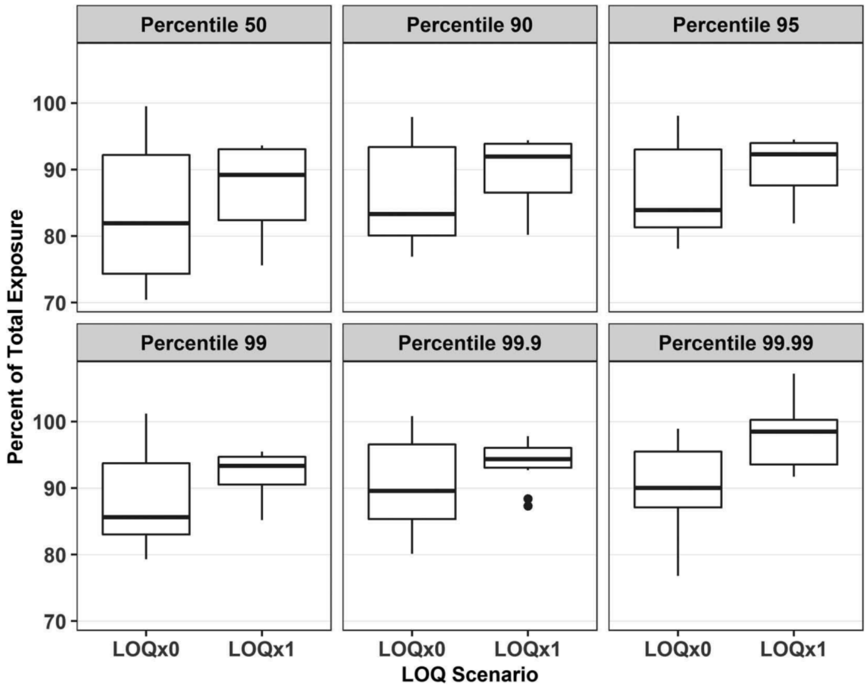

Figure 2. Percent chronic exposure based on P97.5 market basket relative to the total market basket.

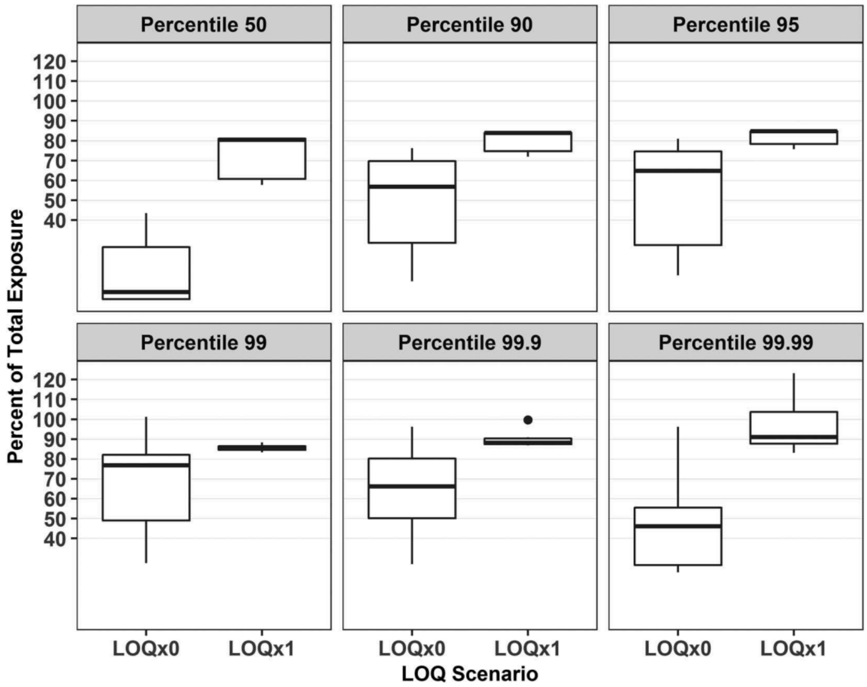

Figure 3. Percent acute exposure based on P95 market basket relative to the total market basket.

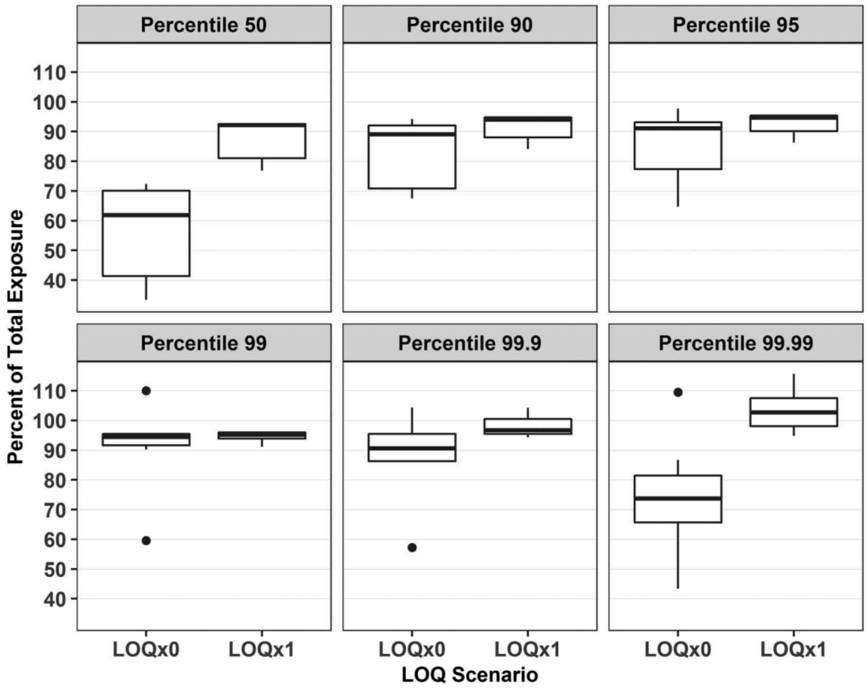

Figure 4. Percent acute exposure based on P97.5 market basket relative to the total market basket.

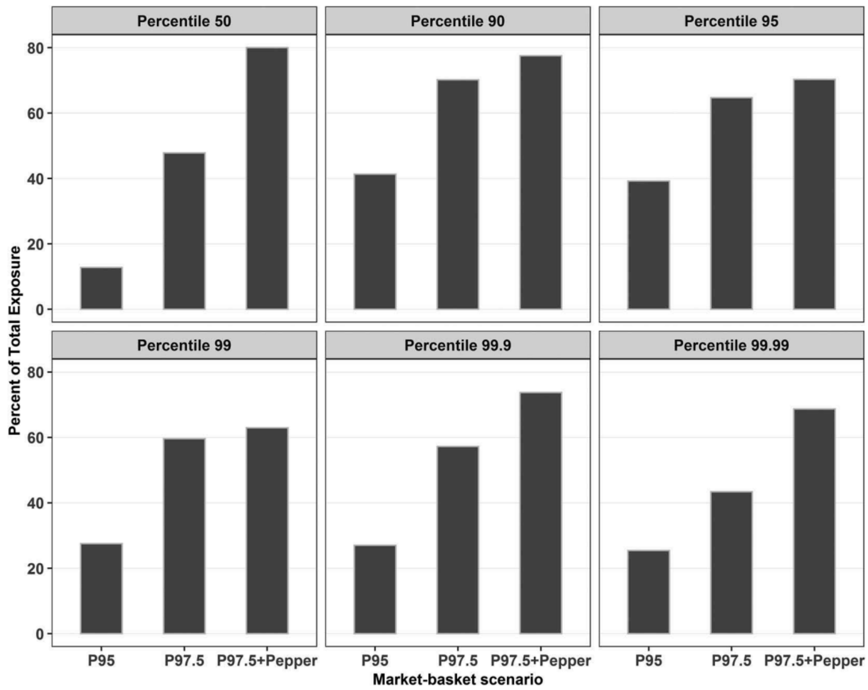

Figure 5. Impact of peppers to the acute cumulative exposure for the CAG on motor division effects to the nervous system (LOQx0 scenario).

Discussion

The current assessment has demonstrated that for probabilistic cumulative exposure calculations a strongly reduced number of raw food commodities still covers the majority of the total exposure. For chronic scenarios, where single high findings level out for the long-term exposure, already the small P95 market basket consisting of 16 raw food commodities gave a coverage of ≥85%. However, also short-term cumulative effects are relevant and may already be induced by single compound-commodity combinations. Only the larger P97.5 market basket provides a sufficiently high coverage of the total short-term exposure (≥90%) to address this scenario. Under practical conditions, the coverage is likely to be even higher than calculated, since possible extrapolations between closely related commodities, as they are currently accepted in the EU (e.g. wheat to rye grain or tomatoes to aubergines) (EC 2017), have not been considered yet.

Consequently, when using exposure based market baskets, resources can be focused to improve the robustness and the sample size of residue data for the key commodities identified. Additional information like processing factors or information on the agricultural use can be implemented in the modelling to improve the outcome. Finally, technical resources for the modelling itself in terms of computing power and time could be redirected to put more emphasis on a broader range of subpopulations or add factors like non-dietary exposure pathways or benchmark-dose modelling of HBGVs.

In the European multi-annual control programme for pesticides (EC 2019), currently 30 plant and 6 animal food commodities are considered for the years 2020 to 2022. From the P95 market basket, all commodities except mandarins are already scheduled for analysis in the EU. In comparison to the P97.5 market basket, significant differences exist. Beans with pods, cherries, goat meat, lemons, maize grain, mandarins, pineapples, plums and sunflower seeds gave a significant contribution to the total exposure, but are currently not part of the monitoring programme. Also lamb´s lettuce, quinces and watermelons were identified as relevant, but residues in these commodities can be extrapolated from lettuce, apples/pears or melons, respectively, and do not necessarily require specific sampling. Additionally, bilberries, cranberries, nettle and sorrel, which were identified as relevant contributors to the exposure for single populations reported in the EFSA RPC model, are not covered by the EU coordinated control programme. In contrast, kiwi fruits, dry beans, aubergines, broccoli, sweet peppers, cultivated fungi, head cabbage, bovine liver and chicken eggs are included in the current monitoring programme, although the contribution of these commodities is too low to influence the total long- or short-term cumulative exposure significantly at the upper percentiles.

The European multi-annual control programme for pesticides primarily relies on the Pesticide Monitoring Programme designed by EFSA (EFSA 2015b), which ranked food commodities from multiple European Member States according to their proportions in terms of the total daily consumption. The 30 food items identified by this approach represented up to 74% of the daily consumption. However; the contribution of food items to the daily consumption is not necessarily related to their total exposure. Food commodities with large portion sizes but diminutive residues might falsely be identified as relevant while food commodities with small portion sizes but high residues might be omitted. In terms of exposure, the P95 market basket based on 16 raw food commodities already covers a higher percentage of the total exposure (≥85%) than the 30 food commodities suggested by EFSA.

Although the proposed market baskets already represent a refinement in view of consumer exposure assessment, it became obvious that the rate of non-MRL compliant samples may have a high sensitivity to the upper percentiles of the exposure distribution. Frequent findings of residues resulting in potential exceedances of the ARfD *per se*, like oxamyl in peppers, require consideration both in cumulative exposure modelling and in establishing monitoring programmes.

It needs to be mentioned that the current sampling approaches for pesticide residues in monitoring programmes are a hybrid between the purposes of estimating the consumer exposure and identifying potential MRL violations. For example, the Pesticide Monitoring Programme designed by EFSA or the

Pesticide data programme in the USA (USDA 2019) both rely on foods which are highly consumed, especially by vulnerable sub-populations like infants and children. The focus is normally based on the raw/fresh commodity, while processed foods are only considered following simple transformations like cooking, freezing or juicing. The selection criteria are solely the contribution to the diet, not the sensitivity towards the exposure of pesticide residues. Another approach is followed for market baskets used in total diet studies (TDS). These kind of studies allow measurement of the average exposure by analysis of representative samples for the majority of foods consumed. Again, the selection of food items follows the principle to cover a high percentage of the daily consumption, but in contrast to food monitoring programmes the food list is amended by specific food items with high contribution to the exposure. For example, in the second Fresh TDS (Sirot et al. 2009) 51 additional foods have been identified adding significantly to the exposure. The main advantage of a TDS is the good approximation to the true average dietary exposure, since effects like industrial processing, blending or the composition of complex foods is already taken into account. However, total diet studies also have the drawback that their design is limited to measure mean residues and to estimate the chronic dietary exposure. It does not allow assessments on the acute dietary exposure or on the MRL compliance of individual samples (European Food Safety Authority/FAO/WHO 2011).

The newly proposed exposure based market basket keeps the principles of the established monitoring programmes to assess both the dietary exposure and the MRL compliance, but was amended with the relevance of each food towards the exposure. Exposure based market baskets might be helpful when in future cumulative and synergistic effects have to be taken into account for establishing legal limits for pesticide residues as demanded by EU legislation (EU 2005). Since consumer protection is the key intention for such a requirement, the range of commodities for which interaction between active substances needs to be regulated could be drastically reduced.

In summary, the exposure based market baskets identified in the current work allow better priorisation of raw food commodities for food monitoring programmes. While the current design of the European food monitoring relies on the contribution of each food to the daily consumption only, a more focused layout becomes possible when potential residue concentrations and HBGVs are taken into account additionally. In parallel, the proposals allow more resource efficient approaches both for cumulative and single compound based exposure assessments and provide a quantitative estimate of the uncertainties arising from a limited set of foods.

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Disclaimer

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6 Results and discussion

In view of the complete work, the results for each of the three aspects add consistently to characterise the dietary risk towards pesticide residues for the German population. Within this context, it is important to compare the model results with other studies conducted previously or after publication of the papers to conclude on the realism and quality of the findings. In the following parts, the outcome of the single substance evaluation, the cumulative dietary exposure assessment and the proposed market-basket will be discussed in view of comparable studies. Direct conclusions concerning the consumer risk for single substances and cumulative effects can be obtained from the respective papers presented above.

6.1 Evaluation of individual substances

The population based estimate the dietary exposure of the German population towards pesticide residues was the first national approach considering the full range of available food consumption and occurrence data from representative monitoring programmes. Previously, only acute dietary risks were characterised commodity-wise based on findings in individual samples as outlined in the Annual Reports on the German food Monitoring Programme by the BVL. Also EFSA, who provides the Annual Report on the European Coordinated Control Programme, limits its consumer risk assessment to acute risk based on individual samples, but additionally contains a deterministic chronic dietary exposure assessment using the PRIMo model [64].

Studies investigating the total daily exposure for individual substances using population based approaches are scarce for Europe, proving a very limited database to compare the results in the current work with.

In 2009, Boon et al [65] estimated the acute dietary exposure to captan and tolylfluanid, using a previous version of MCRA (6.1) in combination with five consumption surveys from Europe (CZ, DK, IT, NL and SE). The occurrence data were obtained from national food programmes in the respective countries conducted in the years 2002-2003. Model parameters included processing information for both compounds and variability factors of 7 and 5 for medium and large sized commodities. Also, results from food monitoring programmes below the reporting limit were considered as “zero”. The selected approach was comparable to the 2nd Tier screening used in the first publication for the German population from 2018 presented above, however the underlying consumption and concentration data differed. At the P99.9 estimated captan exposure levels were 1.5-11 g/kg bw for the five surveys investigated by Boon et al. In the 2018 German assessment, the exposure was estimated at 27.9 µg/kg bw (9.3% of the ARfD of 300 µg/kg bw), being approximately 2.5 times higher. For tolylfluanid, exposure levels estimated by Boon et al were 1.1-2.22 µg/kg bw at the P99.9. The calculation for the German population stopped at Tier 1 (LOQ×1), with 4.9 µg/kg bw (1.6% of the ARfD of 250 µg/kg bw), which was already considered as insignificant in terms of a potential dietary consumer risk. In summary, the 2009 analysis for five European consumption survey and the 2018 calculation for the German population were not identical but at least comparable, taking into account the potentially strong impact of the deviating consumption and residue database.

A second study investigating the exposure of the Belgian population was published in 2011 by Claeys et al [66]. Based on 2008 surveillance data from Belgium, the chronic exposure for adults was estimated arising from the consumption of fruits and vegetables. Also, a Monte-Carlo based probabilistic assessment was conducted, aiming at the P97.5 as decision criterion for potential dietary consumer risks. However, the scope of compounds was limited to 10 pesticides with detection frequencies between 2.4-12.7% in the samples analysed. The LOQ values were handled in a lower (LOQ×0), middle (LOQ×0.5) and upper bound (LOQ×1) scenario. Results were reported for the middle scenario with highest identified exposure levels for chlorpropham and imazalil, representing 21.9% and 22.9% of the ADI at the P97.5, respectively. For comparison, the Tier 2 assessment (LOQ×0) for the German population, which was estimated for the P95 and P99, gave values of 9.8 and19% of the ADI for chlorpropham and of 21% and 46% for imazalil, respectively. Again, the methodology and data used to assess the dietary exposure for the Belgian population was different to the newer approach from 2018 for German consumers. Nevertheless, the percentages of the ADI values for the two main compounds were in the same order of magnitude.

In view of the limited information on the consumer exposure from modelling results, a second source of information to conclude on the validity of the approach can be found in total diet studies (TDS). For Germany, the BfR MEAL-study [67] will be the first total diet study to directly compare the modelled results within this work with measured values for the total dietary exposure. Unfortunately, the pesticide module of the MEAL-study is still on-going. However; pesticide exposure via foods was also investigated in the French TDS2 and the results summarised in the corresponding study report [68]. The French TDS2 included analysis of 283 pesticides in 194 individual food items. The selected foods covered over 90% of the diet for adults and children in France. In total, 1235 composite samples were collected from 2007 to 2009 and 37% showed detectable pesticide residues. Total diet studies measure the average presence of analytes in foods as consumed and provide the most realistic estimate of the true dietary exposure. Ideally, the estimated exposure from exposure models should be above the results from total diet studies to be sufficiently conservative but as close as possible to be realistic.

To draw conclusions on the quality of results for the dietary risk assessment of single compounds presented in the first part of this work, comparison between the modelled exposure and the measured exposure in the French TDS2 can be used. Since the total diet study already represents a best estimate approach for the chronic exposure, the results for the 12 compounds with a refined long-term risk assessment from Part 1 are taken into account.

Table 11: Comparison of results from the modelled dietary exposure for the German population with the measured exposure of children and adults in the French Total Diet Study 2

Compound	**Modelled long-term exposure at the P95 and the decision relevant P99.9 (% HBGV)**	**Measured exposure in the French TDS2 (% HBGV, upper bound mean/ P95)**
Chlorpropham	P95: 4.7 P99.9: 40	Children: 0.7 / 1.7 Adults: 0.5 / 1.0
Chlorpyrifos	P95: 6.2 P99.9: 21 (Note: ADI considered for the German population was 0.001 mg/kg bw)	Children: 1.5 / 3.0 Adults: 1.3 / 2.3 (Note: ADI considered in French TDS was 0.01 mg/kg bw)
Copper	Not compared due to high background exposure	
Diazinon	P95: 1.8 P99.9: 23	Children: 82.1 / 157.4 Adults: 66.7 / 112.3
Dimethoate & Omethoate	P95: 5.9 P99.9: 15	Children: 0.7 / 1.7 Adults: 0.5 / 1.0

Compound	Modelled long-term exposure at the P95 and the decision relevant P99.9 (% HBGV)	Measured exposure in the French TDS2 (% HBGV, upper bound mean/ P95)
Dimethylvinphos	Not analysed in TDS2	
Dithiocarbamates (expressed as Ziram eq.)	P95: 10 P99.9: 32 (Note: ADI considered for the German population was 0.006 mg/kg bw)	Children: 32.6 / 67.6 Adults: 23.3 / 42.1 (Note: ADI considered in French TDS was 0.007 mg/kg bw)
Hexachlorobenzene	P95: 1.1 P99.9: 2.2 (Note: TDI considered for the German population was 0.00016 mg/kg bw)	Children: 13.9 / 27.5 Adults: 12.9 / 23.1 (Note: ADI considered in French TDS was 0.0008 mg/kg bw)
Imazalil	P95: 15 P99.9: 46	Children: 4.8 / 10.3 Adults: 3.4 / 6.1 (Note: ADI considered in French TDS was 0.025 mg/kg bw)
Maleic hydrazide	Not analysed in TDS2	
Prochloraz	P95: 0.4 P99.9: 2.2	Children: 2.6 / 5.9 Adults: 3.0 / 6.1
Tricyclazole	Not analysed in TDS2	

In comparison, the refined modelling of the long-term exposure for the German population was above the exposure levels measured in the French TDS2 study for three compounds, namely chlorpropham, dimethoate & omethoate and imazalil. For copper no comparison was made, since the other significant exposure sources like drinking water were not considered in the modelling and the results were considered as indicative only. Three other components (dimethylvinphos, maleic hydrazide and tricyclazole) have not been investigated in the French TDS2.

Chlorpyrifos exposure was considered in both studies and the estimated percentage of the ADI-value modelled for the German population was approximately ten times higher at the P99.9; however under consideration of a 10-fold lower ADI-value which was lowered in the meantime. Absolute exposure concentrations per kg bodyweight were nearly identical. It needs to kept in mind, that the monitoring data used in the probabilistic modelling and the samples for the French TDS2 were collected in different years and that consumption patterns between Germany and France differ. In view of the involved variabilities, the excellent correlation of the results was observed.

Diazinon exposure in the French TDS2 was identified above the respective HBGV for the upper bound, while the modelling for Germany resulted in a much lower exposure representing only 23% of the ADI value at the P99.9. It needs to be taken into account that the approval of diazinon expired and the last date of usage in France was stated to be the 1st of December 2008. The German monitoring data used for the probabilistic modelling covered the years 2009-2014, explaining much lower occurrence values for this analyte.

Dithiocarbamates represents a whole group of chemical compounds which are analysed via the common moiety CS_2. This parameter is not exclusively linked to the presence of pesticide residues but also occurs naturally for example in brassica species. It becomes very difficult to distinguish between plant protection use and background levels without more specific methods of analysis aiming for the specific active substances themselves. This issue was addressed both in the French TDS2 report and in the first paper on the probabilistic modelling for single compounds presented here. Also, the French TDS2 struggled with relatively high LOQ values due to which no residues were detected in 95 food items analysed. The consumer exposure was primarily based on LOQ levels and the knowledge of broad use of dithiocarbamates in specific crops. In contrast, the refined modelling for the German population solely relied on measured concentrations and substituted all below LOQ values with zero. Although the exposure in the French TDS2 was slightly higher in the upper bound estimate, it represents a very conservative approach since a large percentage of foods potentially contained residues at concentrations much lower than the LOQ. Although results for the modelling approach were slightly below measured exposure levels in the French TDS2, it can still be concluded that the model provides a conservative overestimation of the true expose for this group of chemicals without being unrealistic.

Hexachlorobenzene in a persistent organic pollutant and enriches especially in fatty tissues of marine animals. This food group was poorly represented in the German monitoring data and it seems very likely that the exposure is underestimated by the modelling approach, since potentially sensitive foods were not analysed.

Prochloraz is also one compound where the European approval expired End of 2011. Consequently, residues in the French TDS2 are expected to be higher than in the German food monitoring programme. Surprisingly, no detectable residues were found in the TDS2 and the consumer exposure was estimated on basis of the LOQ values. In the German food monitoring programme, a total of 17119 food samples were analysed for prochloraz, with 192 findings at or above the LOQ. The refined modelling results are therefore based on truly measured concentrations instead of assumed values at the quantification limit. This case is similar to dithiocarbamates, where high exposure levels were estimated in the French TDS2 based on the LOQ, but a much lower exposure is probably present in reality. The modelling results for the German population are slightly lower for prochloraz than in the TDS2, but in view of the usage of truly measured results in the modelling sufficiently conservative.

In summary, the probabilistic modelling for the German population correlated well with the estimated exposure levels based on the French TDS2. Especially for active substances still approved in the European Union or recently expired, the probabilistic modelling provided sufficiently conservative results above the TDS2 finding but still close enough to be considered as realistic. To eliminate the additional bias by comparing different consumption patterns of the German and the French population, future results of the BfR MEAL study should also be compared to the modelling results to conclude on the quality of the assessment.

6.2 Evaluation of cumulative risks

For the assessment of cumulative dietary risks according to EFSA CAGs, no previous works have been published for the European Union. After publication of the results for the German population, a comparable assessment was conducted 2019 by EFSA in combination with revisiting and updating the CAGs from 2013. Although minor modifications to the composition of the CAGs and the NOAELs for several substances were made, the new EFSA assessments provide a good basis to compare the results for the German population with.

Methodology

After publication of the cumulative dietary risk assessment for the German population presented above, EFSA revisited their CAGs for neurotoxicity and effects on the thyroid system [46], [47]. While the principles for grouping remained mainly unchanged, the range on compounds characterised for their toxicological potency towards the specific effects was enlarged and the uncertainty for their inclusion into corresponding CAGs was assessed. In parallel, the cumulative dietary exposure based on monitoring data was estimated for the nervous system and the thyroid system using two different computing tools. The Dutch RIVM provided scientific reports on the cumulative exposure for the nervous system [69] and the thyroid system [70] using the MCRA software (Version 8.3), which was also used for the work presented here. EFSA conducted comparable studies assessing the cumulative dietary exposure via a Monte-Carlo based model using SAS software [71], [72].

Both approaches were intentionally conducted using identical data to compare the methodologies and the performance of the software involved. The studies relied on occurrence data from the official European pesticide monitoring programmes in 2014, 2015 and 2016, which covered drinking water and 30 raw primary food commodities of plant and animal origin. Consumption data were obtained from the EFSA RPC model also used and described in publication number three cited above. Thereof, 10 consumption surveys were selected (adults: Belgium, Czech Republic, Germany and Italy; toddlers: Denmark, Netherlands and United Kingdom; other children: Bulgaria, France and Netherlands) to provide a representative overview on the European population. In addition to the approach taken here for the German population in 2018, full use of information on compound specific processing factors published was made [23]. Also, the handling of left-censored data differed by using a Tier I conservative calculation with ½ of the LOQ for all samples and a less conservative calculation with ½ of the LOQ adjusted by estimated agricultural use frequencies.

In the following, the results for the German NVS II survey used in the current work from 2018 and by EFSA from 2019 are directly compared based on the P99.9, which was selected as decision criteria by all authors. Due to differences in the methodology and data used, the closest scenarios to each other are the LOQ×0.5 scenario used in this work and the Tier 1 scenario by EFSA (½ LOQ). In addition, the scenarios with the lowest level of conservatism (LOQ×0 vs. Tier II) are compared. The results for all calculation were expressed as the MoE to a lead compounds NOAEL. For several compounds refined NOAELs were derived by EFSA during the CAG updates in 2019. Although the selection of the lead compound does not have an influence on the MoE, the potency of single compounds is weighted differently for the total exposure.

In addition to the dietary modelling, comprehensive assessments on the involved uncertainties using expert elucidation techniques were provided by EFSA for both cumulative effects analysed [73], [74].

Results for the nervous system

For the nervous system, two of the CAG were investigated by EFSA concerning their cumulative dietary exposure, namely effects associated with brain and/or erythrocyte acetylcholinesterase inhibition (CAG-NAN) and effects associated with functional alterations of the motor division (CAG-NAM). In terms of the 2013 CAG, these effects translate into CAGs for neurochemical and motor division effects. For both CAGs, only the acute cumulative dietary exposure was estimated by EFSA. Additional considerations on the variability factor were made in tier I and II, introducing different degrees of conservatism. In tier I, variability factors were taken into account by applying a beta-distribution around the default values used in the EFSA Pesticide Residue Intake Model

(PRIMo) [64]. These values are variability factors of 7 for medium sized units between 25 g/piece and 250 g/piece and factors of 5 for large sized commodities above 250 g/piece. In the less conservative tier II, the beta-distribution was shaped around a mean variability factor of 3.6 as identified by EFSA in 2005 [57].

Table 12: Comparison of results from the cumulative dietary risk assessment on the nervous system based on the German population

Scenario and software	MoE Best estimate	MoE uncertainty range	Top contributors (≥10%)
Acute brain and/or erythrocyte acetylcholinesterase inhibition - LOQ×0.5 vs. Tier I scenario			
CAG acute neurochemical effects, Sieke (2018), MCRA	61	Not calculated	Not calculated
CAG-NAN, EFSA (2019), SAS	22	26.4-36.6	Carbofuran (tomatoes): 28%
CAG-NAN, van Klaveren et al (2019), MCRA	22	18-27	Not calculated
Acute brain and/or erythrocyte acetylcholinesterase inhibition - LOQ×0 vs. Tier II scenario			
CAG acute neurochemical effects, Sieke (2018), MCRA	586	120-772	Dimethoate total (spinach): 29% Dimethoate total (spinach): 13%
CAG-NAN, EFSA (2019), SAS	92.4	72.9-116	Chlorpyrifos (apples): 27% Chlorpyrifos (wine grapes): 11%
CAG-NAN, van Klaveren et al (2019), MCRA	95	73-120	Chlorpyrifos (apples): 30% Chlorpyrifos (wine grapes): 12%
Acute motor division - LOQ×0.5 vs. Tier I scenario			
CAG acute motor division, Sieke (2018), MCRA	63	Not calculated	Not calculated
CAG-NAM, EFSA (2019), SAS	48.7	44.5-53.8	No drivers ≥10%
CAG-NAM, van Klaveren et al (2019), MCRA	49	46-53	Not calculated
Acute motor division - LOQ×0 vs. Tier II scenario			
CAG acute motor division, Sieke (2018), MCRA	517	301-814	Oxamyl (peppers): 27% Deltamethrin (rice): 20%)
CAG-NAM, EFSA (2019), SAS	170	128-216	No drivers ≥10%
CAG-NAM, van Klaveren et al (2019), MCRA	171	127-211	No drivers ≥10%

Although based on food monitoring data from different years, it becomes clear that tendencies of the two approach are identical. In view of the variabilities involved, the LOQ×0.5 and tier I scenarios provided the same results, with MoE below 100. While for neurochemical effects EFSA results were approximately three times higher (MoE 22 vs. 61), motor division effects gave nearly the same result (MoE 49 vs. 63). A general observation was also, that for the high percentiles single compounds drove the total exposure instead of a mix of multiple components. For the EFSA CAG-NAN and -NAM, single substances contributed by 78-80 % to the total dietary exposure at the P99 [73]. These findings correspond to the results for the German population, where MCRs were below 1.5 for the upper percentiles of the exposure distribution.

For the less conservative LOQ×0 and tier II scenarios, the 2018 cumulative dietary risk assessment provided 3-5 times lower results than estimated by EFSA in 2019. Apart from different concentrations in the monitoring programmes used as occurrence data, systematic deviations could occur from the handling of <LOQ values and processing factors.

The direct utilisation of a certain percentage of LOQ values as residue concentrations based on the agricultural use frequency as used by EFSA should result in a higher exposure than estimated in the 2018 approach, which substituted all <LOQ values with zero. EFSA conducted a sensitivity analysis of their LOQ approach and identified that “the imputation of left-censored data has a limited impact on the outcome of the assessment. This finding is consistent with the expectation that MOETs at the 99.9th percentile of the acute exposure distribution are primarily driven by samples with quantifiable findings.” [66] (Remark: “MOETs” refers to Margin of Exposure total”). Consequently, the differences in the approach to address left-censored data seems to have minimal impact on the scenario with the lowest conservatism. For the LOQ×0.5 and tier I scenarios, the effect might be stronger and depends on the frequency of measured residues versus LOQs. If residues were found more often and at substantially higher concentrations than the LOQ, these quantified results will dominate the upper percentiles of the total exposure distribution. The small additional contribution of LOQs would not affect the overall outcome significantly. However, detailed analysis of the sensitivity for the more conservative scenario was not conducted.

Another difference is the implementation of processing information in the newer EFSA assessments. When compound specific information on food processing was available, these processing factors were incorporated into the modelling, which normally introduces further refinement and a reduction of the calculated exposure. EFSA investigated, how strong the MoE will be affected under the assumption that all processed foods without compound specific processing factors would not contain residues. This approach was chosen to estimate the upper limit contribution of processed foods eaten. It was shown that the MoE would increase by a factor of 1.6-2.5 in such a scenario. However, also the conclusion was drawn “that processing factors were not available for important risk drivers, such as chlorpyrifos in apple juice and wine, and omethoate in olive oil” [72]. The biggest difference of the European to the German monitoring programme design is the sampling of such sensitive foods with a large consumption but significantly lower residues compared to the raw commodities. Consequently, in the German monitoring, pesticide residues in juices (apple, orange, pear), wine and olive oil – all of them issued as highly sensitive in the EFSA assessment - were directly measured and not extrapolated from their raw commodities with processing factors. In parallel, the consumption data used in the 2018 assessments for juice, wine and olives per individual were not aggregated with other foods like raw fruits or processed commodities. This strategy allows direct correlation of analytical data for these commodities with the consumed amounts reported in German consumption surveys. In EFSA´s RPC model used for the 2019 cumulative assessments, all sources were translated into a single RAC equivalent per commodity, including e.g. juices and wine. It seems that the complete conversion of all foods into their RACs added a very high level of conservatism to the cumulative dietary risk assessment compared to the 2018 approach, which preserved the information on juices, wine and olive oil.

This high level of conservatism was also identified in the corresponding overall characterisation of the cumulative risk [73]. Taking into account all sources of uncertainty and conservatism, the true median MoE for the EFSA assessment was expected to be 4-5 times higher than expressed by the models. In view of this uncertainty analysis, the 2018 assessments for the German population are still conservative (3.0-6.2 higher MoEs), but closer to the actual exposure. In addition, it was identified that residues of chlorpyrifos in apples above the established MRLs contributed significantly to the total exposure of the group. Since these findings occurred in sampling years not considered in the 2018 assessment for the German population, the more critical median MoE in the EFSA assessment can be explained.

Results for the thyroid system

For the thyroid system, two chronic CAG comparable to the 2013 definition of cumulative assessment groups were also used in the 2019 EFSA cumulative dietary exposure studies [70], [71]. The groups relate to hyperthyroidism and on effect on C-cells hypertrophy, hyperplasia and neoplasia. Included compounds and the corresponding NOAELs mostly correspond to the former CAGs of effects on follicular cells and/or the thyroid hormone (T3/T4) system and effects on C-cells, respectively. Since both CAG related to chronic effects, no consideration of the short-term dietary exposure becomes necessary and consequently no variability factors are required. The approaches to address the impact of left-censored data was similar to the acute cumulative dietary risk assessment presented above, using a tier I and II scenario with different degrees of conservatism. In the following table, the outcomes for the German population of the 2018 cumulative dietary risk assessment described within this work and 2019 EFSA calculations are summarised.

Table 13: Comparison of results from the cumulative dietary risk assessment on the thyroid system based on the German population

Scenario and software	**MoE Best estimate**	**MoE uncertainty range**	**Top contributors (≥10%)**
C-Cells - LOQ×0.5 vs. Tier I scenario			
Sieke (2018), MCRA	765	Not calculated	Not calculated
EFSA (2019), SAS	259	205-313	Thiram (apples): 33 % Thiram (lettuce): 18 % Thiram (wine grapes): 17 %
van Klaveren et al (2019), MCRA	303	270-325	Not reported
C-Cells - LOQ×0 vs. Tier II scenario			
Sieke (2018), MCRA	4189	3048-5345	No drivers ≥10%
EFSA (2019), SAS	2290	1210-3250	Thiram (wine grapes): 29 % Thiram (apples): 22 % Thiram (lettuce): 18 %
van Klaveren et al (2019), MCRA	2241	1496-2868	Thiram (wine grapes): 32 % Thiram (apples): 20 % Thiram (lettuce): 17 %
Hyperthyroidism - LOQ×0.5 vs. Tier I scenario			

Scenario and software	MoE Best estimate	MoE uncertainty range	Top contributors (≥10%)
Sieke (2018), MCRA	37	Not calculated	Not calculated
EFSA (2019), SAS	57.4	52.9-61.1	Ziram (apples): 18 % Ziram (oranges): 15 %
van Klaveren et al (2019), MCRA	58	55-61	Not reported
Hyperthyroidism - LOQ×0 vs. Tier II scenario			
Sieke (2018), MCRA	121	88-157	No drivers ≥10%
EFSA (2019), SAS	301	255-324	Bromide ion (wheat): 18 % Ziram (wine grapes): 12 %
van Klaveren et al (2019), MCRA	266	228-302	Bromide ion (wheat): 19 %

Especially for effects on C-cells, differences in the MoE between the 2018 and 2019 cumulative dietary estimations can be observed. The MoE in 2018 for the German population was 2-3 times higher than in the EFSA projects. The main reason may be found in the new CAG composition and the risk driving active substance thiram in the 2019 assessment. The NOAEL for this compound was lowered in the 2019 revision of the CAG from 7.31 mg/kg bw per day to 1.5 mg/kg bw per day. Since thiram is one member of the very frequently found dithiocarbamate group quantified via the common parameter CS_2, its impact on the upper percentiles of the exposure distribution is strong. Consequently, the much higher total exposure equivalent for this CAG (≙lower MoEs) identified by EFSA compared to the 2018 assessment for the German population can be explained by this change of the toxicological database. Again, as for effects on the nervous system, wine grapes and apples were identified as sensitive commodities but the transfer into wine and juice could not be fully quantified by EFSA. Since dithiocarbamates are very susceptible to hydrolysis, normally no quantifiable residues of these compounds are found in processed commodities. In summary, both assessments showed MoEs well above 100 for C-cell effects, which was considered as decision criterion to exclude potential cumulative dietary risk.

For hyperthyroidism, exposures calculated in the 2018 assessment for the German population were generally higher than in the EFSA assessments from 2019. Again, this is primarily related to the revisited CAGs. Dithiocarbamates expressed as propineb were the major contributor to the upper percentile in the 2018 assessment, representing more than 90% of the total exposure. The effect specific NOAEL for this compound was raised from 0.18 mg/kg bw in 2013 to 0.74 mg/kg bw in 2019. This increase of the NOAEL by a factor of 4 is expected to pose a strong decreasing impact on the total exposure – a difference nearly reached in comparison to the EFSA results (MoE 2.2-2.5 higher). Another change in the CAG composition was made by the inclusion of the bromide ion, which is a naturally occurring element in all foods and may be present in very high natural background concentrations. Consequently, it was also identified as one of the risk drivers in the 2019 EFSA assessments but was not taken into account in the 2018 assessment for the German population. These two major changes of the CAG have opposing effects on the total exposure. Since the NOAEL for the bromide ion is relatively high with 12 mg/kg bw, its inclusion into the CAG affects the total exposure less than the increase of the NOAEL for propineb, probably explaining the overall higher outcome for the 2018 assessment by a factor or 2-3.

6.3 Exposure based food monitoring market-basket

The development of an exposure based market-basket was proposed for the first time in context with food monitoring programmes on pesticide residues. Previous approaches like for the German food monitoring [10], [11] or the European Coordinated Control Progamme [75] identified food items based on their percentage of the total daily consumption. The aspect, that highly consumed foods may contain negligible residue concentrations whereas potentially high contaminated commodities could contribute significantly to the total exposure already with small portion sizes was not addressed systematically in any of these previous designs.

The concept of considering exposure aspects in addition to portion sizes is already common for designing food lists in total diet studies. In the Guidance document towards a harmonised Total Diet Study approach by EFSA, FAO and WHO [76] it was stated that “...foods that could be significant sources of specific contaminants...will assure that the main contributors to exposure for the chemical substances under investigation (contaminants and/or nutrients) are included; otherwise the TDS might underestimate the exposure”. For example, in the French TDS2 [77], additional foods were included into the food list by applying one criterion established by the WHO Codex Alimentarius Commission in its Procedural Manual for maximum limits in foods or food groups contributing significantly to the tolerable daily or weekly intake [78]. The selected criterion defines foods or food groups as relevant, if they contribute approximately 5% or more to the tolerable intake in two or more consumption diets. This criterion is not linked to the amount of food consumed itself, but to the contribution of a chemical to the total exposure. Alternatively, another criterion was established by WHO considering foods as significant contributor, when they contribute at least 10% of the tolerable intake based on a single diet.

The development of an exposure based food market-basket for pesticide residues was not solely focussed on a realistic measurement of the true consumer exposure like a TDS but also aimed at conducting a monitoring of residues to control MRL compliances of raw agricultural commodities. Consequently, the MRLs also formed the basis for estimating the contribution to the exposure for the monitoring market-basket, representing an upper-bound approach compared to the suggest contribution criterion by WHO. In view of these more conservative input parameters, the lower 5% contribution criterion established by WHO, as used for the French TDS, becomes too low to identify potential contributors. Therefore, the higher 10% contribution criterion to a single diet was selected to reflect to to the generally more conservative parameter selection.

Although the identified commodities were primarily assessed in view of the potential contribution to a cumulative dietary risk assessment, the same considerations are also valid for population based exposure assessments of single substances. In practice, further refinement of the market-basket will become necessary before implementation.

The methodology for the identification of potential contributors to the exposure was always based on the RAC, not the edible form of the commodities. Especially for highly processed commodities like sugar beets or sugar cane, which are not consumed in an unprocessed form, the residue transfer into edible portion becomes negligible and consequently their inclusion into monitoring programmes could be omitted. Also, some foods are consumed at significant amounts as juice. As recognised in the EFSA assessments on the cumulative dietary risk, the influence of juice consumption on the total exposure will be overestimated, when no appropriate processing factors are available for refinement. In contrast, the German monitoring data already analysed the major juices, allowing significantly more realistic estimations of the consumer exposure. In view of the sensitivity of these commodities in population based exposure assessments, individual analysis of raw commodities and juice is generally recommended. Even the availability of compound specific processing factors for all juices would not solve this overestimation, since blending effects with untreated lots cannot be taken into account by such factors. Finally, it became obvious in all three papers presented in this work, that single samples with residues potentially posing a public health concern per se may have a strong impact on population based consumer risk assessments. In the planning of food monitoring programmes for pesticide residues, inclusion of critical combinations know from surveillance systems like the European Rapid Alert System needs to be carefully considered when not covered by the commodities already included in the proposed market-baskets.

6.4 Limitations

The approach selected in the current work involves several limitations, especially regarding the representativeness of the data and the capability to allow prognosis of the results to future scenarios.

The selected data are linked to specific consumption habits and residue patterns found in foods. While the overall consumption behaviour between 2008 and 2015 was shown to be relatively stable for the German population based on the NVS II study in combination with the National Nutrition Monitoring (NEMONIT) [79], the regulatory situation of plant protection products and consequently the residues remaining on foods may change very quickly. Even in the short period between completion of the first and second part of this work and its publication, significant changes to the risk driving compounds chlorpyrifos and dimethoate/omethoate were initiated by the European Commission to ensure consumer safety. While the typical period for approval of active substances is between 10 to 15 years [2], extensions of their use pattern and the necessity to establish new MRLs for additional commodities is an on-going process in the EU. In parallel, active substances are frequently re-assessed and may potentially not be approved under Reg. (EU) 1107/2009 anymore. Thus, authorisations in all European Memberstates have to be withdrawn after a period of grace and also MRLs will be lowered respectively. In principle, a frequent update of the calculations presented here needs to be implemented to ensure best consideration of the current residue situation on the market and to allow the utilisation of the results for prospective risk assessment scenarios. Typically, the completion of the food monitoring market basket every three years in the EU and every six years in Germany represents a new set of occurrence data and also suits as a possible interval for performing such a task.

But also consumption data involve limitations regarding their representativeness. First, several age groups of the German population have not been covered by the VELS-, EsKiMo- or NVS II-surveys used. Especially infants below 6 months and elderly people above 80 years are currently not addressed by this consumption data. Also, ethnic minorities or sub-populations with special consumption behaviours like vegetarians or vegans are not specifically considered. New consumption data may probably address these sub-populations in the future and allow estimations on the exposure for single compounds or for cumulative effects. Second, in order to align the occurrence data with the consumption data, all foods eaten were converted into their raw agricultural commodity equivalents. This approach represents a strong simplification of the daily consumption pattern and affects the estimate of the true exposure. Comprehensive information on substance specific processing factors would allow the inclusion of effects to residue concentrations on the level of each food consumed. However; these kind of data are available only for a small number of compounds covering the minority of processed foods consumed. On this topic, research and data collection is still ongoing and future assessments will include more and more aspects of food processing. Finally, for the German population, no study data have yet been generated to measure the true dietary exposure towards pesticide residues. A good tool for benchmarking the performance of the selected models would be the BfR MEAL-study. This study represents the first German total diet study and includes a specific module for pesticide residues and measurement of the related consumer exposure. Results for the BfR MEAL-study have not been finalised, but after their publication comparison of modelled results with the measured dietary exposure would allow an estimate of the quality and realism of the probabilistic methodology used.

Another aspect is the limitations of computing power itself to perform such complex calculations. Especially very large consumption surveys like the NVS II-study in combination with food monitoring results from six years touch the computation limit of the probabilistic model for large CAGs. The coverage of the theoretical number of combinations by the number of computable iteration was low and did not always allow robust reproduction of results for the upper percentiles. Here, a higher number of iterations would generate more reliable results especially for the acute cumulative assessments and could reduce the variation. In the future, it depends on improvements of the software and the computing power, if more complex calculations become possible or if only food commodities with high sensitivity towards the dietary exposure will be considered.

Finally, the proposed exposure based market-baskets for pesticide residues consider the current regulatory situation and the consumption data available for the assessment. Any modification to MRLs or the completion of new consumption data renders previous calculations on the sensitivity of raw food commodities as obsolete. Therefore; a recalculation of the sensitivity assessment will also be required frequently and should be conducted before the start of a new monitoring cycle. Also, the proposed approach is vulnerable against food commodities illegally put on the market, which may exceed established MRLs. Here, risk management decisions are required to define the desired protection goal (e.g. by considered twice or triple the MRL in the analysis). This aspect does not affect the developed tool itself, but is necessary to make it work with the established regulatory framework for pesticide residues in the EU.

7 Conclusions

For the first time a representative dietary risk assessment of pesticide residues for the German consumers was conducted using population based approaches to address single compounds as well as cumulative effects on the nervous and thyroid system. For all scenarios, the complete daily consumption via all food items was considered on individual level for children and adults, which represents a higher tier compared to the deterministic exposure models currently used in regulatory practice.

Comparison of the models results for single compounds with findings from previous studies conducted in other European Memberstates and with the French Total Diet Study 2 showed good correlation of the results, suggesting a realistic estimation of the consumer exposure. In summary, for 693 compounds included in the probabilistic modelling, the estimated dietary exposure was unlikely to present a chronic or acute public health concern for the German population. Potential consumer risks were identified for chlorpyrifos and the combination of dimethoate and omethoate. Both compounds were re-assessed on European level in the meantime and MRLs in plant and animal commodities have been lowered significantly. The dietary exposure of copper was also high, however due to the plethora of exposure sources, the modelling results are only indicative and more complex tools are required to conclude on the dietary consumer risk. For three compounds (dimethylvinphos, halfenprox and tricyclazole), crucial information on their toxicological properties are missing and consequently the dietary risk assessment remained inconclusive.

The probabilistic modelling of the cumulative dietary exposure was the first work considering CAGs as proposed by EFSA in a population based approach by using the full range of food monitoring and consumption data available for Germany. In a comparable modelling approach recently published by EFSA itself, good correlation of the findings was observed although occurrence data were collected in different years and the CAGs had been revisited in the meantime. It became obvious, that the exposure for the CAGs on chronic (German population) and acute (EFSA) neurochemical effects (erythrocyte acetylcholinesterase inhibition) and chronic hyperthyroidism were below or near a MoE of 100 at the P99.9, which was selected as decision criterion in both studies. All approaches for assessing the cumulative acute dietary risk for neurochemical effects identified single compounds as the driving contributor to the total exposure at upper percentiles instead of a complex mixture of components. This effect was also confirmed with respect to chronic CAGs for the German population, which showed MCRs well below 2. However; no detailed analysis of the exposure drivers has been reported in the EFSA studies for comparison. In the end, the study for the German population as well as the EFSA approach represent the first systematic estimation of the cumulative dietary risk for the EU. In view of the complexity of the models, many sources of uncertainties need to be taken into account. This aspect was not yet addressed in the modelling for the German population, but EFSA provided a first estimate on the conservatism of the results. It was concluded that the certainty to not reach the threshold for regulatory consideration was between 80% to >99% for effects on the nervous system and between 85% and >99% for thyroid effects.

In general, all the results for single compounds and cumulative assessment groups rely on residue patterns found in the monitoring data and may change over the years in parallel to the authorised plant protection products. Therefore, frequent re-assessment of the dietary exposure for the German population becomes necessary. Also, in the future, results from the BfR MEAL-study will provide additional information on the true exposure of consumers to pesticide residues.

The improve these future re-assessments, the knowledge from the modelling was considered to propose an exposure based market-basket for the monitoring of pesticide residues in foods. In contrast to previous food monitoring designs, which primarily identified relevant commodities based on their contribution to the daily consumption, the potential concentrations of analytes in foods were taken into account and their sensitivity towards the consumer exposure was estimated. Depending on the desired degree of conservatism, a set of 16 or 41 raw food commodities were identified covering the total dietary exposure by >85%. Based on this new market-basket, occurrence data generated for this limited set of foods will allow estimations of the consumer exposure covering the majority of the total daily intake. In the next step, implementation into the regulatory process becomes necessary to refine the current concept for the German food monitoring for pesticide residues.

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9 Abbreviations

ADI	Acceptable daily intake
BfR	Bundesinstitut für Risikobewertung (German Federal Institute for Risk Assessment, www.bfr.bund.de)
BVL	Bundesamt für Verbraucherschutz und Lebensmittelsicherheit
CAG	Cumulative assessment group
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
EsKiMo	Ernährungsmodul im Kinder- und Jugendgesundheitssurvey (KiGGS)
EU	European Union
FAO	Food and Agricultural Organisation of the United Nations
HBGV	Health based guidance value
IESTI	**I**nternational **E**stimate of the **S**hort-**T**erm **I**ntake
JMPR	Joint Meeting on Pesticide Residues (WHO/FAO)
LOQ	Limit of Quantification
MCR	Maximum cumulative ratio
MRL	Maximum residue limit
NEMONIT	Nationales Ernährungsmonitoring
NOAEL	No observed adverse effect level
NVS II	Nationale Verzehrstudie II (German Nutrition Survey II)
OECD	Organisation for Economic Co-operation and Development
PPP	Plant protection product
RAC	Raw agricultural commodity
RIVM	Rijksinstituut voor Volksgezondheid en Milieu
TDS	Total diet study
VELS	**V**erzehrsstudie zur **E**rmittlung der **L**ebensmittelaufnahme von **S**äuglingen und Kleinkindern für die Abschätzung eines akuten Toxizitätsrisikos durch Rückstände von Pflanzenschutzmitteln
WHO	World Health Organisation of the United Nations

10 List of Tables