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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.

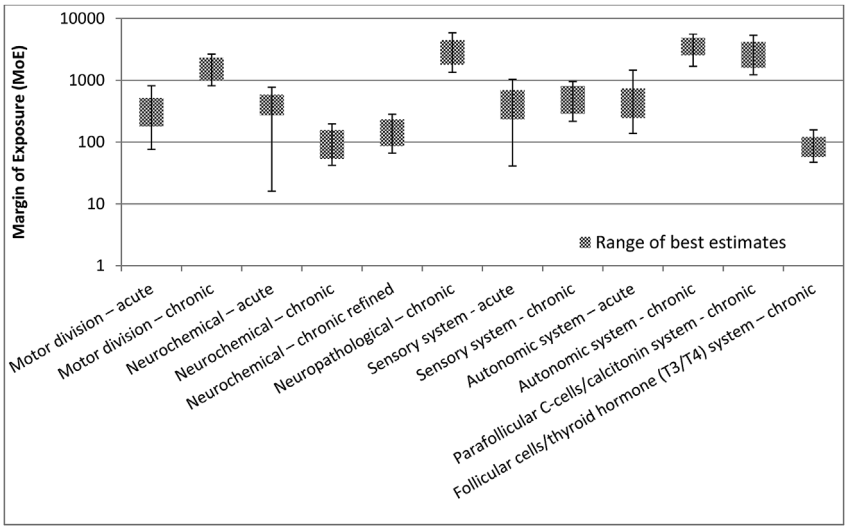

Fig. 1. Total best estimate MoE ranges for the LOQ × 0 scenario (VELS, EsKiMo and NVS II), including their overall minimum lower (P2.5) and maximum upper (P97.5) uncertainty ranges.

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

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Transparency document

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