National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

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RIVM letter report 2020-0147

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Colophon

DOI 10.21945/RIVM-2020-0147

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This investigation was performed by order, and for the account, of Ministry of Health, Welfare and Sports, within the framework of project 5.1.15 Policy advice chemical food safety

Published by:
National Institute for Public Health and the Environment, RIVM
P.O. Box 1 | 3720 BA Bilthoven
The Netherlands
www.rivm.nl/en

Synopsis

Cumulative dietary exposure to pesticides in the Netherlands

People are exposed to residues of pesticides on a daily basis through food. This often involves different pesticides. This exposure to multiple pesticides could be a risk to human health.

RIVM calculated the combined exposure to pesticides with effects on the nervous system. The calculated exposure was lower than the safe exposure level, and therefore there is no risk of adverse effects on the nervous system.

If people are exposed simultaneously to multiple pesticides, it is called cumulative exposure. Different vegetables and fruits may each contain a different pesticide. It is also possible that a single vegetable or fruit contains residues of different pesticides.

Our food also contains pesticides that may affect other organs or systems. For example, pesticides could have an adverse on the liver and/or kidney. It is not known which groups of pesticides can have these effects or other effects. Currently, the European Food Safety Authority (EFSA) is analysing this matter. As soon as a group of pesticides is identified, the cumulative exposure to this group should be calculated to assess its safety.

Keywords: cumulative exposure, food, children, adults, pesticides, probabilistic

Publiekssamenvatting

Cumulatieve blootstelling aan gewasbeschermingsmiddelen via voedsel in Nederland

Via ons voedsel worden we bijna elke dag blootgesteld aan resten van gewasbeschermingsmiddelen. Dit zijn vaak verschillende middelen tegelijk. Deze gelijktijdige blootstelling kan een risico zijn voor de gezondheid.

Het RIVM heeft berekend hoe groot de gelijktijdige blootstelling is aan gewasbeschermingsmiddelen die effecten kunnen hebben op ons zenuwstelsel. De berekende hoeveelheid is lager dan de blootstelling die veilig wordt geacht. Deze blootstelling geeft daarom geen risico op schadelijke effecten op het zenuwstelsel.

Als we meerdere middelen tegelijk binnenkrijgen, noemen we dat cumulatieve blootstelling. Verschillende soorten groenten of vruchten kunnen bijvoorbeeld elk een ander gewasbeschermingsmiddel bevatten. Het kan ook zijn dat er op één soort groente of vrucht resten van verschillende middelen zitten.

In ons eten zitten ook gewasbeschermingsmiddelen die ándere gezondheidseffecten kunnen hebben dan op ons zenuwstelsel. Ze kunnen bijvoorbeeld schadelijk zijn voor de lever en/of nieren. Het is nog niet bekend bij welke groepen middelen deze of andere effecten kunnen optreden. De Europese Autoriteit voor Voedselveiligheid (EFSA) onderzoekt dat op dit moment. Zodra zo’n groep middelen bekend is, moet de cumulatieve blootstelling daarvan berekend worden. Zo wordt bepaald of er een gezondheidsrisico is in Nederland.

Kernwoorden: cumulatieve blootstelling, kinderen, volwassenen, ouderen, gewasbeschermingsmiddelen, probabilistisch

Contents

1 Introduction

Cumulative exposure is the exposure to a group of pesticides on food that are known to have similar effects in the human body. People are exposed to multiple pesticides on food on a daily basis, because they eat various foods containing different pesticides and/or because they eat a single food containing more than one pesticide.

In 2018, RIVM calculated the cumulative exposure to residues of pesticides on foods at the request of the Dutch Ministry of Health, Welfare and Sport (VWS) for four groups of pesticides with similar toxicological effects on the nervous system or the thyroid (Boon et al., 2018). The 2018 results showed that the cumulative exposure to two groups of pesticides with a chronic effect on the thyroid and to one group with an acute effect on the nervous system was unlikely to have adverse effects. For the other group of pesticides with another acute effect on the nervous system, this could not be excluded, because the calculated exposure was only slightly lower than the safe exposure level.

Calculations in 2018 were performed based on a preliminary grouping of pesticides. This grouping was still ongoing at the time, and was finalised in 2019 by the European Food Safety Authority (EFSA, 2019c,d). The methodology to calculate cumulative exposure to pesticides on food has also been further developed since 2018 (EFSA, 2019a,b; van Klaveren et al., 2019a,b).

Use of pesticides differs between years due to, for example, the prevalence of harmful organisms and weather conditions. Therefore, exposures based on concentrations measured in a certain period should be regarded as representative for that period only. It is therefore relevant to monitor the exposure regularly. Furthermore, in 2018 the exposure was calculated based on food consumption data collected in 2002-2012, whereas currently more recent information on food consumption in the Netherlands is available.

Considering these factors, the Dutch Ministry of VWS has asked RIVM to recalculate the cumulative exposure to the two groups of pesticides with an acute effect on the nervous system using:

- Dutch food consumption data collected in 2012-2016;
- updated concentrations of pesticides on food;
- updated grouping of pesticides;
- the methodology as described in van Klaveren et al. (2019a).[1]

The cumulative exposure to pesticides with a chronic effect on the thyroid was not recalculated, because the calculated exposure was far below the safe exposure level in 2018. Even when considering the changes as indicated by the four points above, the exposure to these pesticides was expected to remain sufficiently low.

[1] EFSA (2019a) also calculated the cumulative exposure to these two groups of pesticides based on the same input data. There were some minor methodological differences between the methodology used by EFSA (2019a) and van Klaveren et al (2019a). However, these differences did not affect the exposure results.

In agriculture, pesticides[2] are used to protect agricultural crops against harmful organisms (pests) or weeds or to regulate plant growth. These pesticides contain one or more active substances that determine their effectiveness. The risk related to the exposure to pesticides is determined by these active substances. For the sake of simplicity, we use the term ‘pesticides’ when referring to these active substances. Furthermore, pesticides may be present in or on food. In this report, we use ‘on food’ meaning both ‘in and on food’.

[2] “The term 'pesticide' is often used interchangeably with 'plant protection product', however, pesticide is a broader term that also covers non plant/crop uses, for example biocides” (ec.europa.eu/food/plant/pesticides_en).

2 Calculation of cumulative dietary exposure and margins of exposure

Below we describe the input data and methodology used for calculating the cumulative exposure. The methodology described is short and not exhaustive. For a detailed description, we refer to Boon et al. (2018) and van Klaveren et al. (2019a), especially for a description of the methodology used to

- include exposure via drinking water;
- include the effect of food processing on pesticide concentrations;
- include unit variability;
- assign pesticide concentrations to
  - concentrations below the limit of quantification (LOQ), the so-called left-censored data;
  - pesticides that were not analysed in certain samples, the so-called missing values.

The methodology used by van Klaveren et al. (2019a) to calculate cumulative exposure was largely the same as the methodology used in 2018; the only methodological difference was related to concentrations assigned to pesticides belonging to a complex residue definition (see section 2.2).

Last section of this chapter describes how margins of exposure were calculated to establish if the calculated exposure levels pose a possible health risk.

2.1 Cumulative assessment groups and RPFs

Cumulative exposure was calculated for two groups of pesticides, so-called cumulative assessment groups (CAGs), with an acute effect on the nervous system:

- CAG with an acute neurochemical effect, i.e. inhibition of acetylcholinesterase activity (CAG-neurochemical)[3], including 47 pesticides;
- CAG with acute functional effects on motor division (CAG-motor division)[4], including 100 pesticides.

Pesticides included in both CAGs are listed in Annex A and B, respectively.

Cumulative exposure was calculated using the relative potency factor (RPF) approach. Using this approach, the ability for each pesticide within a CAG to cause an effect on the nervous system is expressed relative to that of a selected 'index' pesticide, resulting in an RPF for each pesticide. For example, an RPF of two means that a pesticide within a CAG is twice as potent to cause the effect as the 'index' pesticide. These RPFs were used to convert single pesticide concentrations of each

[3] CAG-neuro is equivalent to CAG-NAN, which means 'Cumulative Assessment Group - Nervous system/Acute/Neurochemical effects'.
[4] CAG-motor is equivalent to CAG-NAM, which means 'Cumulative Assessment Group - Nervous system/Acute/Motor division effects'.

sample to one cumulative concentration of each sample, which was then used to calculate the exposure. RPFs of each pesticide and for each CAG are listed in Annex A and B.

2.2 Food consumption and pesticide concentration data

Food consumption data were derived from the most recent Dutch National Food Consumption Survey (DNFCS) of 2012-2016.[5] These data include amounts of foods, including beverages, consumed per day of 4985 persons aged 1-79 years living in the Netherlands (van Rossum et al., 2018). Consumed amounts of foods and beverages were recorded on two non-consecutive days for each person.

Pesticide concentrations of 30 widely consumed commodities were included in the exposure assessment. These commodities were apple, aubergine, banana, beans with pods (e.g. French beans), broccoli, carrot, cauliflower, courgette, cucumber, head cabbage, leek, lettuce, mandarin, melon, olives for oil production, orange, peach, pear, peas without pods, pepper, potato, spinach, strawberry, table grapes, tomato, wine grapes, oats, rice, rye and wheat. Also, concentrations in foods for infants and young children, wine and olive oil were included. These commodities and foods were identical to those included in 2018 and by van Klaveren et al. (2019a).

Concentrations were obtained from the Netherlands Food and Consumer Product Safety Authority (NVWA) and based on samples collected in 2016-2018 as part of the Dutch monitoring programme and the EU-coordinated programme (EUCP).[6] Table 1 lists some summary characteristics of the samples, showing that more than 99% of the concentrations were below the limit of quantification (LOQ). Annex C and D provide an overview of the concentrations for each CAG.

Table 1 Characteristics of the samples analysed in 2016-2018 for two cumulative assessment groups (CAGs)

Characteristics	CAG-neurochemical	CAG-motor division
Number of samples analysed	3584	3584
Number of pesticides monitored	47	99[1]
Number of analyses (sample-pesticide combinations)[2]		
Total	121,955	231,524
Below LOQ	121,424 (99.6%)[3]	229,465 (99.1%)
Between LOQ and MRL[4]	469 (0.38%)	1971 (0.85%)
Above MRL	62 (0.05%)	88 (0.04%)

CAG: cumulative assessment group; LOQ: limit of quantification; motor division: acute functional effects on motor division; MRL: maximum residue level; neurochemical: acute neurochemical effect, i.e. inhibition of acetylcholinesterase activity
[1] Sulfoxaflor was not analysed in 2016-2018 (Annex B).
[2] Not all samples were analysed for all pesticides within a CAG.
[3] Percentages in brackets express number of analyses relative to the total number of analyses.
[4] MRL is the highest amount of a pesticide that is legally allowed on food.

[5] wateetnederland.nl
[6] Commission implementing Regulation (EU) 2015/595

Residue definition
Concentrations are reported according to each pesticide's legal residue definition for compliance with the maximum residue level (MRL), the so-called residue definition for enforcement and monitoring. When the pesticide is metabolised to a significant extent, such a residue definition may include one or more major metabolites of the pesticide.[7] In such cases, NVWA may report separate concentrations for the pesticide and its metabolites for each sample, and/or one concentration for the total residue definition. The concentrations for the total residue definition were used to assess the exposure. This was relevant for phosmet, pirimicarb and thiamethoxam.

However, when one of the metabolites is also a pesticide itself and, in case of a cumulative exposure assessment, has its own RPF, exposure should be calculated for each pesticide included in the residue definition. To address this, concentrations for the total residue definition were assigned to a pesticide with a probability based on its proportion in the residue definition. If no information was available, pesticides were assumed to be present with an equal probability. Assigned concentrations were corrected for the molecular weight of the pesticide, if relevant. This approach is different from the approach used in 2018, when concentrations for the total residue definition were assigned to the least potent pesticide in the residue definition.

Two important 'complex residue definitions' were dimethoate (sum of dimethoate and omethoate, expressed as dimethoate) and methomyl (sum of methomyl and thiodicarb, expressed as methomyl), referred to as 'dimethoate/omethoate' and 'methomyl/thiodicarb' respectively in the rest of this report. Omethoate and methomyl are pesticides themselves, but also major metabolites of dimethoate and thiodicarb, respectively. In the exposure assessment, concentrations of dimethoate/omethoate were assigned to either dimethoate or omethoate based on a 50% probability. If the concentration was assigned to dimethoate, it was subsequently always assumed that half of that concentration was dimethoate and half was omethoate. The same procedure was used to assign concentrations of methomyl/thiodicarb to either methomyl and thiodicarb.

2.3 Linking concentrations to foods consumed

Pesticide concentrations of 30 commodities were used to calculate exposure by linking them to consumed amounts of these commodities in the food consumption database. However, people also consume processed foods based on these commodities, such as apple juice, pizza and tomato paste. To include these foods in the calculations, the Dutch food conversion model was used. This model converts consumed amounts of processed foods to equivalent amounts of their raw ingredients (Boon et al., 2009; van Dooren et al., 1995). These conversions are based on recipe data and food conversion factors. First, consumed amounts of a food were converted to equivalent amounts of its ingredients based on recipe data, such as flour and tomato paste for a pizza. Subsequently, these consumed amounts of ingredients were converted to consumed amounts of their raw counterparts, such as

[7] Regulation (EC) No 396/2005

wheat and tomato for a pizza, using food conversion factors. As part of the conversion to raw ingredients also processing types, such as peeling, juicing or cooking, were identified for each raw ingredient. In this way, possible effects of food processing on pesticide concentrations could be included in the calculations (see section 2.4).

Concentrations for foods, such as wine, olive oil and foods for infants and young children, were linked directly to their consumed amounts in the food consumption database, as well as for raw commodities consumed as such, for example apple.

2.4 Effect of food processing and unit variability on pesticide concentrations

During food processing, such as cooking of vegetables and peeling or drying of fruit, pesticide concentrations may decrease or increase. Processing factors were used to address this. A processing factor is the ratio of the pesticide concentration in the processed food divided by the pesticide concentration in the raw commodity. We used the processing factors as used by van Klaveren et al. (2019a), which were extracted by EFSA from the EU processing factor database (EFSA, 2019a). These factors differ from those used in 2018.

Unit variability was included in the exposure assessment using the same input data as in 2018 and by van Klaveren et al. (2019a). Unit variability addresses that pesticide concentrations are analysed in homogenised samples consisting of more than one unit of a commodity (typically 12-24 units per sample). Individuals consuming just one unit may thus be confronted with higher concentrations of a pesticide than concentrations analysed in the homogenised multi-unit sample.

2.5 Cumulative exposure assessment

Cumulative exposure was calculated using a probabilistic approach, including all food consumption and concentration data simultaneously in one analysis. For a detailed description of the principles of a probabilistic approach, see Boon et al. (2018).

This approach resulted in a distribution of cumulative exposures per day and for each CAG defined by differences in consumed amounts of foods between individuals and differences in cumulative concentrations in foods. Daily exposures were divided by the corresponding individual person’s body weights. This procedure was performed 100 times using a bootstrap approach. For this, 100 food consumption and concentration databases were generated by resampling the original databases and used to calculate exposure. This resulted in 100 distributions of daily cumulative exposure levels for each CAG. For each distribution, 99th (P99) and 99.9th (P99.9) percentiles of exposure were calculated.[8] Median of the P99 and P99.9 across these 100 distributions and the 95%

[8] P99 or P99.9 of exposure is the maximum exposure level to which 99% or 99.9% of the population is exposed.

probability interval around the percentiles[9] are reported for each CAG. Also, the quartiles (P25 and P75) of the uncertainty distribution of the P99.9 were calculated to plot the uncertainty around this percentile using box plots.

Contributions of pesticide-commodity combinations, commodities and pesticides to the upper 0.1% of the total cumulative exposure distribution were calculated for each of the 100 exposure distributions and expressed as a percentage. Mean contributions across these distributions are reported. Upper 0.1% of the distribution concerns exposures equal to P99.9 and higher.[10]

Calculations were performed with the Monte Carlo Risk Assessment (MCRA) software (release 8.3) (MCRA, 2019) for four age groups: 1-6 years (n=974), 7-17 years (n=1189), 18-64 years (n=1478) and 65-79 years (n=672). These age groups address variations in exposure due to differences in food consumption patterns and consumed amounts per kilogram body weight between age groups. All exposures were weighted for small deviances in sex, age, region, level of education, urbanisation, season in which the data were collected, and day of the week. Thus, calculated exposure is representative for the total Dutch population of each age group.

2.6 Margins of exposure

Margins of exposure (MoEs) were calculated to establish whether the calculated cumulative exposure could result in a health risk (EFSA, 2020). MoE is a quantitative measure of the margin between a calculated exposure level and the dose at which no adverse effect is observed in an animal toxicity study, such as the no-observed adverse effect level (NOAEL).

In this study, MoE was calculated by dividing the NOAEL of the index pesticide by the median of the P99 and P99.9 of exposure for each CAG and all age groups. Index pesticide was oxamyl and the NOAEL was 0.1 mg per kg body weight per day for both CAGs.[11] MoEs were also calculated for the lower and upper limit of the 95% probability interval for both percentiles, and the quartiles (P25 and P75) of the uncertainty distribution of the P99.9 (see section 2.5).

MoE of at least 100 for the P99.9 is considered to be of no health concern.[12]

[9] The 95% probability interval quantifies the uncertainty of the P99 and P99.9 of exposure due to the sample size of the food consumption and concentration database. Such a confidence interval indicates that the real percentiles are within this interval with a 95% probability, and outside this interval with a 5% probability: 2.5% probability each that the real percentiles will be lower or higher than the lower or upper limit of the confidence interval, respectively.

[10] Contribution of pesticides, commodities or pesticide-commodity combinations to the exposure can be calculated for the total exposure distribution or for a certain upper percentage of this distribution, such as the upper 0.1%, 1%, 10%, 20%, etc. It is not possible to calculate the contribution at a certain point of the distribution, such as the P99.9.

[11] The safe exposure level was the no-observed adverse level (NOAEL) of the index pesticide. NOAEL reflects the dose at which no adverse effect is observed in an animal toxicity study.

[12] An MoE of 100 at the P99 of exposure in whole populations is regarded as "the threshold for regulatory consideration, as an indicative target of safety by analogy to the safety margin currently used for establishing the toxicological reference values (a factor 10 for inter-species variability and a factor of 10 for intra-species variability)" (EFSA, 2020).

3 Results

3.1 Margins of exposure

MoEs for the P99 of exposure were well above 100 for both CAGs, including lower limits of the 95% probability interval. The lowest MoE of 683 was calculated for the CAG-motor division for children aged 1-6 years. MoEs for the P99.9 are shown in Figure 1. These MoEs were also larger than 100 for both CAGs, but to a lesser extent. The youngest age group had again the lowest MoEs: 116 for CAG-neurochemical and 134 for CAG-motor division. Considering the uncertainty, MoEs for the P99.9 could be below 100 for all age groups, except for the MoE for CAG-motor division for adults aged 18-64 years (Figure 1). MoEs for all age groups and both CAGs, including lower and upper limits of the 95% probability interval, are listed in Annex E.

3.2 Contributions to the exposure

Figure 2 shows the contribution of the five **pesticide–commodity combinations** contributing most to the upper 0.1% of the exposure distribution for both CAGs for children aged 1-6 years, the age group with the lowest MoEs for the P99.9 (Figure 1). Exposure to both CAGs in the upper 0.1% was dominated by triazophos and omethoate on beans with pods, such as French beans. For the other age groups, the same pesticide–commodity combinations contributed most to the upper 0.1% for both CAGs (Annex F).

Contribution of **commodities** to the exposure to CAG-neurochemical in the upper 0.1% showed that 91% was due to the consumption of beans with pods for children aged 1-6 years. For the older age groups, this percentage varied from 92-97%. For CAG-motor division, 78% of the exposure was due to the consumption of beans with pods, followed by table grapes with 12% and spinach with 5% for the youngest age group. The same three commodities contributed most to the exposure for the older age groups; 77-82%, 3-8% and 8-14%, respectively. Other commodities contributed less than 5% to the exposure to both CAGs in the upper 0.1% of the exposure distribution for all age groups.

Pesticides contributing at least 10% to the exposure to CAG-neurochemical in the upper 0.1% for young children were triazophos with 39%, omethoate with 27% and methomyl with 16%. Corresponding pesticides for CAG-motor division were triazophos with 44%, omethoate with 28% and lambda-cyhalothrin with 20%. For the older age groups, the percentages for the same pesticides were 39-44%, 27-29% and 13-16% respectively for CAG-neurochemical and 42-48%, 28% and 18-21% respectively for CAG-motor division. Omethoate and methomyl are partly present on food due to the use of dimethoate and thiodicarb, respectively (see section 2.2).

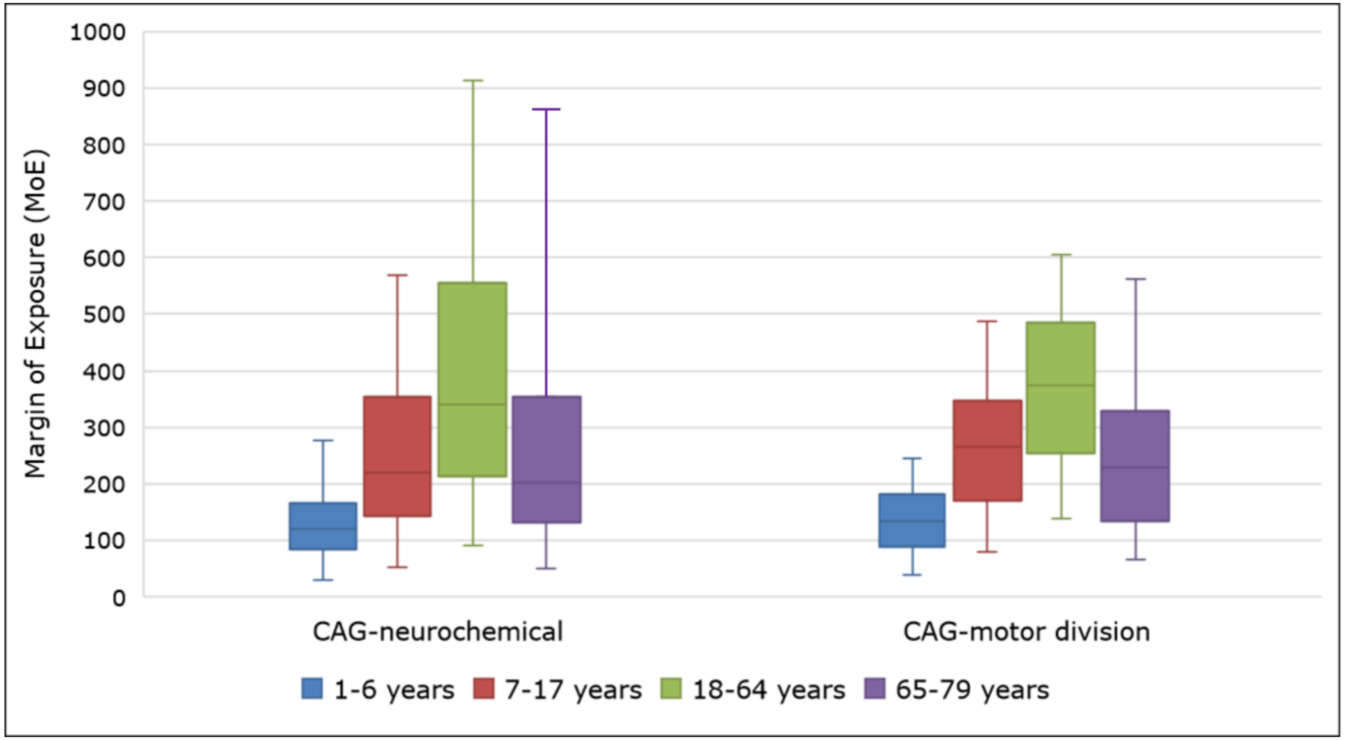

Figure 1 Boxplots of margins of exposure (MoEs) for the 99.9th percentile of exposure to two CAGs affecting the nervous system for four age groups. An MoE of at least 100 for this percentile is of no health concern. Lower and upper edges of each boxplot represent the quartiles (P25 and P75) of the uncertainty distribution for the MoE, the horizontal line in the middle of the box represents the median (P50), and the 'whiskers' above and below the box show the 95% probability interval (P2.5 and P97.5). CAG: cumulative assessment group; motor division: acute functional effects on motor division; neurochemical: acute neurochemical effect, i.e. inhibition of acetylcholinesterase activity

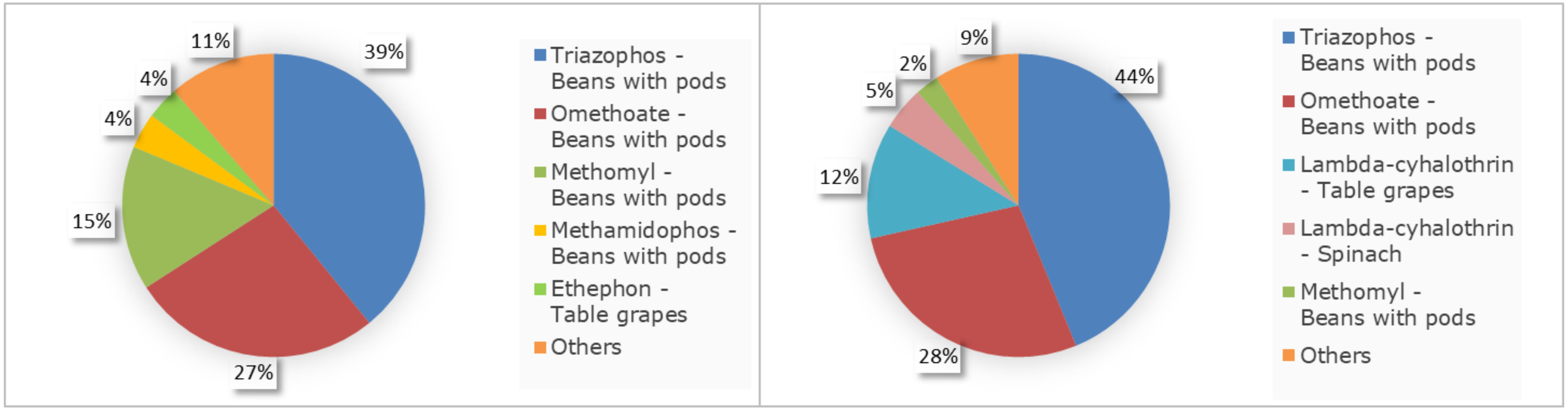

Figure 2 Contribution of the five pesticide-commodity combinations contributing most to the exposure to either CAG-neurochemical (left pie) or CAG-motor division (right pie) in the upper 0.1% of the cumulative exposure distribution for children aged 1-6 years. CAG: cumulative assessment group; motor division: acute functional effects on motor division; neurochemical: acute neurochemical effect, i.e. inhibition of acetylcholinesterase activity

4 Discussion

In this report, cumulative dietary exposure to two cumulative assessment groups (CAGs) of pesticides with an acute effect on the nervous system was calculated. This report is an update of the cumulative exposure assessment performed in 2018 (Boon et al., 2018), based on updated information on food consumption and concentration data, on pesticide grouping and, on the methodology, to calculate the cumulative dietary exposure. Below, the results of the exposure assessment are discussed.

4.1 Cumulative dietary exposure

Margins of exposure (MoE) for CAG-neurochemical were similar to those for CAG-motor division (Annex E). CAG-neurochemical includes 47 pesticides and CAG-motor division 100 pesticides (Annex A and B). All pesticides in CAG-neurochemical were also included in CAG-motor division. RPFs for 30 of these common pesticides were higher for CAG-neurochemical than CAG-motor division, and 17 pesticides had the same RPFs in both groups. These 17 pesticides included triazophos and omethoate, the two pesticides that determined largely the exposure to both CAGs (Figure 2 and Annex F). RPFs for the 53 pesticides in CAG-motor division that were not included in CAG-neurochemical were all below 1, ranging from 0.0005 to 0.2, except for endrin. Endrin has an RPF of 4 (Annex B). However, the concentration database did not include concentrations of this pesticide at or above the limit of quantification (LOQ).

These results show that a larger CAG does not necessarily result in a higher cumulative exposure as demonstrated in 2018. Cumulative exposure depends on the RPFs, the concentrations and the amounts of food consumed. Furthermore, results showed that the cumulative exposure to both CAGs was dominated by four pesticides, namely triazophos, omethoate, methomyl and lambda-cyhalothrin (Figure 2 and Annex F). Additional exposure to numerous other pesticides did not increase the exposure notably.

Cumulative exposure can result from consuming different foods containing one or more pesticides and/or from consuming just one food containing multiple pesticides. Examining the concentration database for samples with a pesticide concentration at or above the LOQ for at least one pesticide in CAG-neurochemical (n=461 out of 3584 samples analysed) showed that 399 samples (86% of all positive samples) were positive for one pesticide, 54 (12%) for two pesticides and eight (2%) for three pesticides. None of the samples contained more than three pesticides of CAG-neurochemical. Commodities with the highest number of samples containing two or three pesticides were oranges (n=28), beans with pods (n=11) and mandarins (n=10). For CAG-motor division, 1413 out of 3584 samples had a positive pesticide concentration for at least one pesticide. Of these samples, 962 (68%) were positive for one pesticide, and 311 (22%) for two, 106 (7%) for three, and 23 (2%) for four pesticides. In total, 11 samples (1%) had five up to eight pesticides with a positive concentration. Commodities with the highest number of samples containing two or more pesticides were oranges (n=95), table grapes (n=85), beans with pods (n=35), mandarins (n=34), courgette (n=26) and lettuces (n=26). One sweet pepper sample and one beans with pods sample contained eight pesticides at a concentration at or at or above the LOQ. This analysis shows that if individuals are exposed to multiple pesticides during one day, this is more likely due to the consumption of different foods containing one pesticide, and to a lesser extent of single foods containing multiple pesticides. This may especially be true for CAG-neurochemical.

As in 2018 and by van Klaveren et al. (2019a), 30 commodities and their derived foods were included in the exposure assessment. These commodities include most of the vegetable products consumed in the Netherlands, such as apple, orange, potato, wheat, cauliflower, broccoli and carrot. Pesticides may also be present on animal commodities, such as milk, eggs and meat, and their derived foods. However, as discussed by EFSA (2020), pesticide concentrations in these commodities are less frequent and at lower concentrations than in vegetable products. These products are not expected to contribute significantly to the cumulative exposure to both CAGs.

Exposure via drinking water was included in the exposure assessment by assuming that the five most potent pesticides per CAG were present in drinking water at 0.05 µg/L as in 2018 and by van Klaveren et al. (2019a).[13] This concentration equals half the drinking water standard for individual pesticides in the Dutch Drinking Water Law.[14] Use of these concentrations results in an overestimation of the exposure to both CAGs via drinking water as actual concentrations of pesticides in drinking water are lower (Swartjes et al., 2006; Boon et al., 2018). Use of the actual concentrations will result in more accurate exposure estimates. However, these concentrations are not readily available and were therefore not considered in this study.

4.2 Important contributors to exposure

About 65-70% of the exposure to both CAGs for young children in the upper 0.1% of the exposure distribution was due to the presence of triazophos and omethoate on beans with pods (Figure 2). **Triazophos** was quantified in one beans with pods sample out of 235 analysed for this pesticide. This sample was from outside the EU and had a concentration of 0.11 mg/kg, which was well above the maximum residue level (MRL) of 0.01* mg/kg.[15] As use of triazophos on beans with pods is not approved in the EU since 2007, the MRL is set at the LOQ, which is indicated by an asterisk in the legislation. This LOQ may be higher than the LOQ of an analytical method used in the laboratory for analysing pesticides.

Concentrations of **omethoate** were included in the exposure assessment via assigning omethoate to concentrations reported as

[13] Richtlijn 98/83/EG van de Raad van 3 november 1998 betreffende de kwaliteit van voor menselijke consumptie bestemd water
[14] Richtlijn 98/83/EG van de Raad van 3 november 1998 betreffende de kwaliteit van voor menselijke consumptie bestemd water.
[15] Commission Regulation (EU) 2017/626

dimethoate/omethoate (see section 2.2). Dimethoate/omethoate was quantified in two beans with pods samples out of 157 analysed for this pesticide. Both samples were from outside the EU and had a concentration of 0.12 and 1.6 mg/kg, which both exceeded the MRL of 0.02* mg/kg.[16] This MRL was in force during most of the period covered in our study. From 17 January 2018 onwards, the residue definition for dimethoate/omethoate has been changed in one definition for dimethoate and one for omethoate, both with an MRL of 0.01* mg/kg for beans with pods.[17] Use of both dimethoate and omethoate on beans with pods is not approved in the EU.

For CAG-neurochemical, also **methomyl** on beans with pods contributed more than 10% to the cumulative exposure in the upper 0.1% of the exposure distribution for young children (Figure 2). Concentrations of methomyl were included in the exposure assessment based on concentrations reported for methomyl/thiodicarb (see section 2.2). Methomyl/thiodicarb was quantified in two beans with pods samples out of 78 analysed, both from outside the EU. These concentrations were 0.0087 and 0.34 mg/kg. The MRL for this pesticide on beans with pods was 0.02* mg/kg up to 7 May 2017.[18] Currently, the MRL is 0.1 mg/kg. It is unclear whether use of methomyl is currently approved in the EU. According to legislation[18], methomyl has an MRL above the LOQ for use on beans with pods, but the EU Pesticide database[19] indicates that its use as such is not approved in the EU. Methomyl was not a risk driver for CAG-motor division, due to a 3-fold lower RPF in this CAG than in the CAG-neurochemical (Annex A and B).

For CAG-motor division, also **lambda-cyhalothrin** on table grapes contributed more than 10% to the upper 0.1% of the cumulative exposure distribution (Figure 2). This pesticide may be used in the EU on table grapes and was quantified in 27 table grape samples out of 485 analysed. All positive samples were from countries outside the EU. One of these positive concentrations, 0.28 mg/kg, was above the MRL of 0.2 mg/kg that was valid during the study period[20]. Since 26 January 2019, the MRL for lambda-cyhalothrin on table grapes has been reduced to 0.08 mg/kg.[21] Given this reduction, exposure to this pesticide through the consumption of table grapes may decrease. Spinach contributed for 5% to the exposure to this pesticide in the upper 0.1% of the exposure distribution for young children and more than 10% for the older age groups (see section 3.2). All 10 positive concentrations of lambda-cyhalothrin on spinach, out of 93 spinach samples analysed for this pesticide, were below the MRL of 0.5 mg/kg that was valid until 26 January 2019 and the current MRL of 0.6 mg/kg.[22]

Most of the cumulative exposure to both CAGs in the upper 0.1% of the exposure distribution was due to the presence of triazophos and omethoate at positive concentrations in only a few beans with pods samples. Triazophos was positive in only one sample that was analysed

[16] Commission Regulation (EU) 1097/2009
[17] Commission Regulation (EU) 2017/1135 and (EU) 2020/703
[18] Commission Regulation (EU) 459/2010 and (EU) 2016/1822
[19] ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=homepage&language=EN
[20] Commission Regulation (EU) 2017/626
[21] Commission Regulations (EU) 2018/960, (EU) 2019/50 and (EU) 2019/1015
[22] Commission Regulation (EU) 2017/626, (EU) 2018/960, (EU) 2019/50 and (EU) 2019/1015

in 2017. In 2016 and 2018, no concentrations at or above the LOQ were reported for this pesticide in any of the commodities included in the exposure assessment. Omethoate was included by assigning omethoate to concentrations reported for dimethoate/omethoate (see section 2.2). This was done in accordance with the methodology used by van Klaveren et al. (2019a). Based on this procedure, a large part of these concentrations was assigned to omethoate. Examining the concentration database, which also contains concentrations of individual pesticides belonging to complex residue definitions, showed that the presence of omethoate on foods was almost always due to dimethoate use. Due to this, the contribution of omethoate to the cumulative exposure to both CAGs is very likely lower than reported. This has very likely also resulted in an overestimation of the exposure, because the RPF for omethoate is a factor of 4 higher than that for dimethoate for both CAGs (Annex A and B). For methomyl/thiodicarb, the concentrations of individual pesticides showed that the presence of methomyl was almost always due to the use of methomyl. Use of these individual concentrations of pesticides belonging to complex residue definitions will result in a more accurate estimate of the cumulative exposure and of the contribution of these pesticides to the exposure.

4.3 Comparison with the 2018 cumulative assessment

MoEs for CAG-neurochemical were like those calculated in 2018, whereas MoEs for CAG-motor division were much lower compared to those calculated in 2018. However, results between the two studies cannot be compared due to differences in the pesticides included in both CAGs and their RPFs, and in the approach used to assign concentrations for complex residue definitions to individual pesticides.

For example, triazophos on beans with pods, the most important contributor to the exposure to both CAGs, did not contribute to the exposure to CAG-neurochemical and CAG-motor division in 2018, because it was not part of both CAGs. In 2018, pirimicarb on spinach and apple was an important contributor to the exposure to CAG-neurochemical. In the current assessment, it was not important, primarily because the RPF for pirimicarb was reduced with a factor of 20, from 0.2 to 0.01. In 2018, also methiocarb on beans with pods contributed significantly to the exposure to CAG-neurochemical. This combination was not relevant in the current assessment, because the RPF of methiocarb was reduced with a factor of 10: from 2 to 0.2.

Omethoate and methomyl, two important contributors to the exposure to both CAGs, were also not included in 2018, because concentrations of dimethoate/omethoate were assigned to the presence of only dimethoate and of methomyl/thiodicarb to the presence of only thiodicarb in 2018. It was not possible to assign one concentration to different pesticides belonging to one residue definition using probabilities; concentration was assigned to the least potent pesticide.

For lambda-cyhalothrin, RPFs were comparable between the two studies: 0.192 in 2018 and 0.2 in this study (Annex B). For this pesticide, its presence on table grapes was an important contributor to the exposure to CAG-motor division in both studies (Figure 2 and Annex F).

Pesticides included in the two CAGs with an effect on the nervous system and their RPFs were preliminary in 2018. These CAGs were finalised in 2019 (EFSA, 2019a). The finalised CAGs differ from the preliminary CAGs, because the collected information evolved over time, based on the growing experience about the information needed to establish CAGs. In addition, the finalized CAGs were updated based on updated toxicological data. It should be noted that EFSA recommends that these finalised CAGs should be regularly updated in the light of the toxicological information provided to EFSA in the context of its regulatory activities (EFSA, 2019a). This updating includes both toxicological information on pesticides that are currently in the CAGs, but also on new pesticides for which uses are requested by industry. So, the current CAGs may be adjusted in the future, which will affect exposure outcomes. Furthermore, the exposure to these groups of pesticides will also be affected by yearly changes in the use of these pesticides due to external conditions, such as the weather, or by changes in their authorisation.

4.4 Uncertainties in the exposure assessment

Uncertainty in the exposure assessment due to the limited size of the food consumption and concentration databases was quantified with 95% probability intervals (see section 2.5). The lower limits of these intervals were below 100 for all age groups and both CAGs, except for CAG-motor division for adults aged 18-64 years. This means that there is a probability that the real MoEs may be lower than 100 for both CAGs. However, the upper limits of these intervals showed that the real MoEs could also be much higher, up to 935 for CAG-neurochemical for adults aged 65-79 years. This uncertainty can be reduced by increasing the number of samples analysed for pesticides in both CAGs. As shown in Annex G, not all samples were analysed for all pesticides.

The exposure calculations included also uncertainties that could not be quantified. In 2018, these uncertainties were qualitatively evaluated, resulting in the conclusion that the MoEs were, in fact, higher than calculated. Main uncertainties contributing to this were:

- use of high pesticide concentrations in drinking water;
- use of pesticide concentrations from monitoring programmes which are likely to be biased to those commodities that are expected to contain pesticides;
- limited information on the effect of food processing on pesticide concentrations.

These uncertainties also apply to the results of our study.

In addition, as described in section 4.2, concentrations reported for dimethoate/omethoate were largely assigned to omethoate, which contributed to an overestimation of the exposure to both CAGs.

4.5 Risk characterisation

To exclude a possible health risk related to the exposure to CAGs, the MoE for the median of the P99.9 of exposure should at least be 100 (see section 2.6). In this study, these MoEs were above 100 for all age groups (Figure 1 and Annex E). The lowest MoEs were calculated for young children aged 1-6 years: 116 for CAG-neurochemical and 135 for CAG-motor division.

In 2018, the MoE for the P99.9 was 119 for young children aged 2-6 years for CAG-neurochemical (Boon et al., 2018). This MoE was deemed too close to 100 for a negligible health risk, and it was concluded that such a risk could not be excluded. It was noted that the actual MoEs were very likely higher, due to assumptions made and input data used in the exposure assessment. How much higher was not quantified.

In 2020, EFSA published an uncertainty analysis quantifying the uncertainties affecting either exposure or toxicology in the cumulative exposure assessment to both CAGs with an acute effect on the nervous system as performed by van Klaveren et al. (2019a) (EFSA, 2020). EFSA concluded that the actual MoEs were most likely 4 to 5 times higher than calculated. As stated by EFSA (2020), this overestimation is consistent with the intention to ensure that exposure calculations are sufficiently conservative. This uncertainty analysis supports our own uncertainty analysis (see section 4.4 and Boon et al., 2018) that the calculated exposure overestimates the actual exposure.

Based on these uncertainty analyses, we conclude that the calculated MoEs for both CAGs do not raise a health concern for all four age groups as actual MoEs are very likely a factor of 4 to 5 higher.

5 Conclusion and recommendation

Margins of exposure (MoEs) for the P99.9 of exposure to two CAGs with an acute effect on the nervous system are not expected to result in adverse health effects in children and adults living in the Netherlands. MoEs were all higher than 100. Furthermore, actual MoEs may even be a factor 4 to 5 higher than calculated, because of uncertainties in the calculations.

In our study, we examined only the cumulative exposure to two groups of pesticides with an effect on the nervous system. However, foods also contain pesticides, including those with an effect on the nervous system, that may affect other human systems or organs. Currently, EFSA is analysing the vast quantity of information on adverse effects of pesticides in order to identify and group pesticides according to their toxicological effect on other systems or organs in the human body. As soon as new groups of pesticides are established, the cumulative exposure to these groups should be calculated to assess their safety. This may also be relevant for the two CAGs with an effect of the nervous system, if they are adjusted based on new toxicological information. Independent of this, it is relevant to monitor the exposure regularly, due to differences in pesticide use between years and changes in pesticide authorisations.

Acknowledgements

The authors would like to thank Marcel Mengelers and Gerrit Wolterink for their valuable comments on an earlier version of this report. Gerrit Wolterink is also acknowledged for his contribution to section 4.3 about the adjustment of the CAGs since the 2018 publication.

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Annex A Overview of pesticides in CAG-neurochemical and their relative potency factors (RPFs)

Pesticide	RPF[1]	Pesticide	RPF
Acephate	0.04	Malathion	0.0029
Aldicarb	2	Methamidophos	0.33
Azinphos-ethyl	8	Methidathion	0.1
Azinphos-methyl	0.1	Methiocarb	0.2
Benfuracarb	0.055	Methomyl	0.4
Cadusafos	0.43	Monocrotophos	1
Carbaryl	0.1	Omethoate	0.4
Carbofuran	6.67	Oxamyl[2]	1
Carbosulfan	0.2	Oxydemeton-methyl	0.5
Chlorfenvinphos	0.67	Parathion	0.4
Chlorpyrifos	0.2	Parathion-methyl	0.4
Chlorpyrifos-methyl	0.01	Phenthoate	0.34
Diazinon	0.04	Phosalone	0.004
Dichlorvos	1	Phosmet	0.022
Dimethoate	0.1	Phoxim	0.077
Ethephon	0.017	Pirimicarb	0.01
Ethion	1.67	Pirimiphos-methyl	0.0067
Ethoprophos	0.11	Profenofos	0.2
Fenamiphos	0.4	Pyrazophos	2
Fenitrothion	0.076	Thiodicarb	0.2
Fenthion	0.1	Tolclofos-methyl	0.0071
Fonofos	0.5	Triazophos	8.33
Formetanate	0.2	Trichlorfon	0.01
Fosthiazate	0.19		

CAG: cumulative assessment group; neurochemical: acute neurochemical effect, i.e. inhibition of acetylcholinesterase activity

[1] RPF is the potency of a pesticide to cause an effect on the nervous system relative to the index compound. RPF has no dimension.

[2] Index pesticide

Annex B Overview of pesticides in CAG-motor division and their relative potency factors (RPFs)

Pesticide	RPF[1]	Pesticide	RPF
2, 4-D	0.0013	Fonofos	0.025
Abamectin	0.067	Formetanate	0.1
Acephate	0.0013	Fosthiazate	0.019
Acetamiprid	0.01	Glufosinate	0.001
Acrinathrin	0.1	Heptachlor	0.2
Aldicarb	1	Imidacloprid	0.0043
Amitraz	0.1	Indoxacarb	0.002
Azinphos-ethyl	8	Lindane	0.017
Azinphos-methyl	0.05	Malathion	0.0001
Benfuracarb	0.05	Mepiquat	0.0031
Bifenthrin	0.0029	Metaldehyde	0.0033
Cadusafos	0.004	Methamidophos	0.1
Carbaryl	0.01	Methidathion	0.025
Carbofuran	0.33	Methiocarb	0.2
Carbosulfan	0.02	Methomyl	0.133
Chlorfenvinphos	0.67	Milbemectin	0.01
Chlormequat	0.01	Monocrotophos	0.25
Chlorpropham	0.002	Omethoate	0.29
Chlorpyrifos	0.01	Oxamyl[2]	1
Chlorpyrifos-methyl	0.0013	Oxydemeton-methyl	0.053
Clothianidin	0.0005	Parathion	0.057
Cyfluthrin	0.1	Parathion-methyl	0.059
Cyfluthrin, beta-	0.05	Penflufen	0.002
Cyhalothrin, lambda-	0.2	Permethrin	0.00067
Cypermethrin	0.005	Phenthoate	0.34
Cypermethrin, alpha-	0.043	Phosalone	0.004
Cypermethrin, beta-	0.1	Phosmet	0.0044
Cypermethrin, zeta-	0.01	Phoxim	0.02
Deltamethrin	0.1	Pirimicarb	0.01
Diazinon	0.04	Pirimiphos-methyl	0.00067
Dichlorvos	0.013	Profenofos	0.00053
Dicofol	0.0067	Pymetrozine	0.008
Dieldrin	0.1	Pyrazophos	0.22
Dimethoate	0.005	Pyrethrins	0.005
Dinotefuran	0.001	Pyridate	0.0025
Emamectin	0.1	Spirotetramat	0.001
Endosulfan	0.033	Sulfoxaflor[3]	0.004
Endrin	4	Tefluthrin	0.2
Esfenvalerate	0.031	Tembotrione	0.0005
Ethephon	0.0002	Tetramethrin	0.0032
Ethion	1.67	Thiacloprid	0.032
Ethoprophos	0.02	Thiamethoxam	0.001
Fenamiphos	0.27	Thiodicarb	0.02
Fenitrothion	0.008	Thiram	0.02
Fenpropathrin	0.0067	Tolclofos-methyl	0.0005

Pesticide	RPF[1]	Pesticide	RPF
Fenthion	0.096	Triadimefon	0.05
Fenvalerate	0.005	Tri-allate	0.0017
Fipronil	0.04	Triazophos	8.33
Flufenacet	0.013	Trichlorfon	0.01
Fluvalinate, tau-	0.01	Ziram	0.0067

CAG: cumulative assessment group; motor division: acute functional effects on motor division
[1] RPF is the potency of a pesticide to cause an effect on the nervous system relative to the index compound. RPF has no dimension.
[2] Index pesticide
[3] Sulfoxaflor was not analysed in 2016-2018.

Annex C Overview concentrations of pesticides in CAG-neurochemical

See PDF document 2020-0147 Annex C

Annex D Overview concentrations of pesticides in CAG-motor division

See PDF document 2020-0147 Annex D

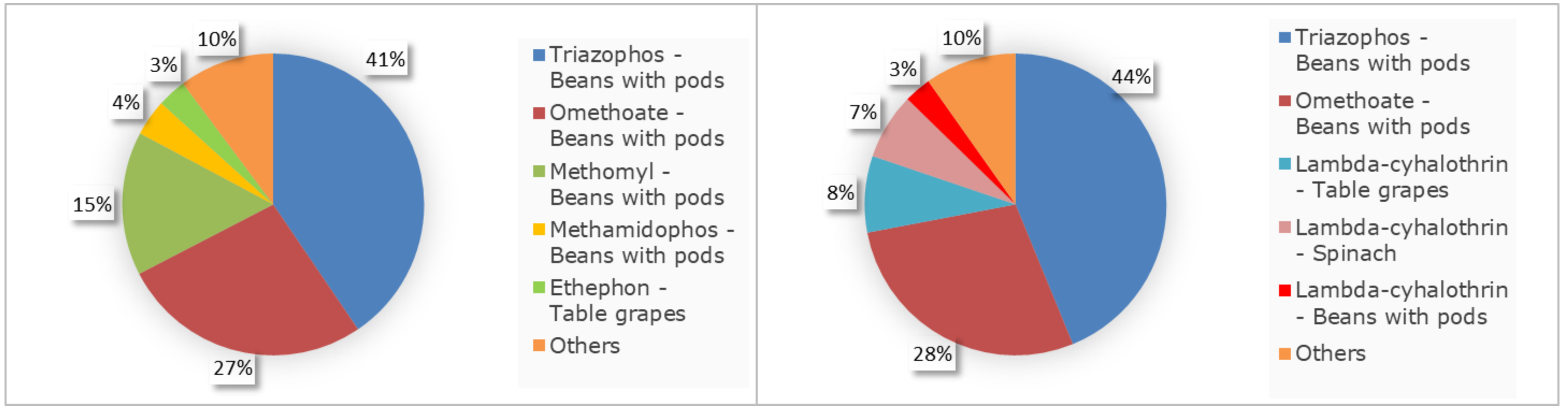
Annex E Margins of exposure for the P99 and P99.9 of exposure to either CAG-neurochemical or CAG-motor division for four age groups

Age (years)	Margins of exposure[1] for two exposure percentiles	
	P99	P99.9
CAG-neurochemical[2]		
1-6	702 (503 - 864)	119 (29 - 276)
7-17	1430 (983 - 1854)	220 (53 - 569)
18-64	2297 (1595 - 3157)	339 (90 - 913)
65-79	2168 (1153 - 3204)	201 (51 - 864)
CAG-motor division[3]		
1-6	683 (552 - 889)	134 (38 - 244)
7-17	1360 (1065 - 1781)	265 (79 - 488)
18-64	1873 (1520 - 2476)	373 (138 - 605)
65-79	1789 (1222 - 2274)	230 (65 - 561)

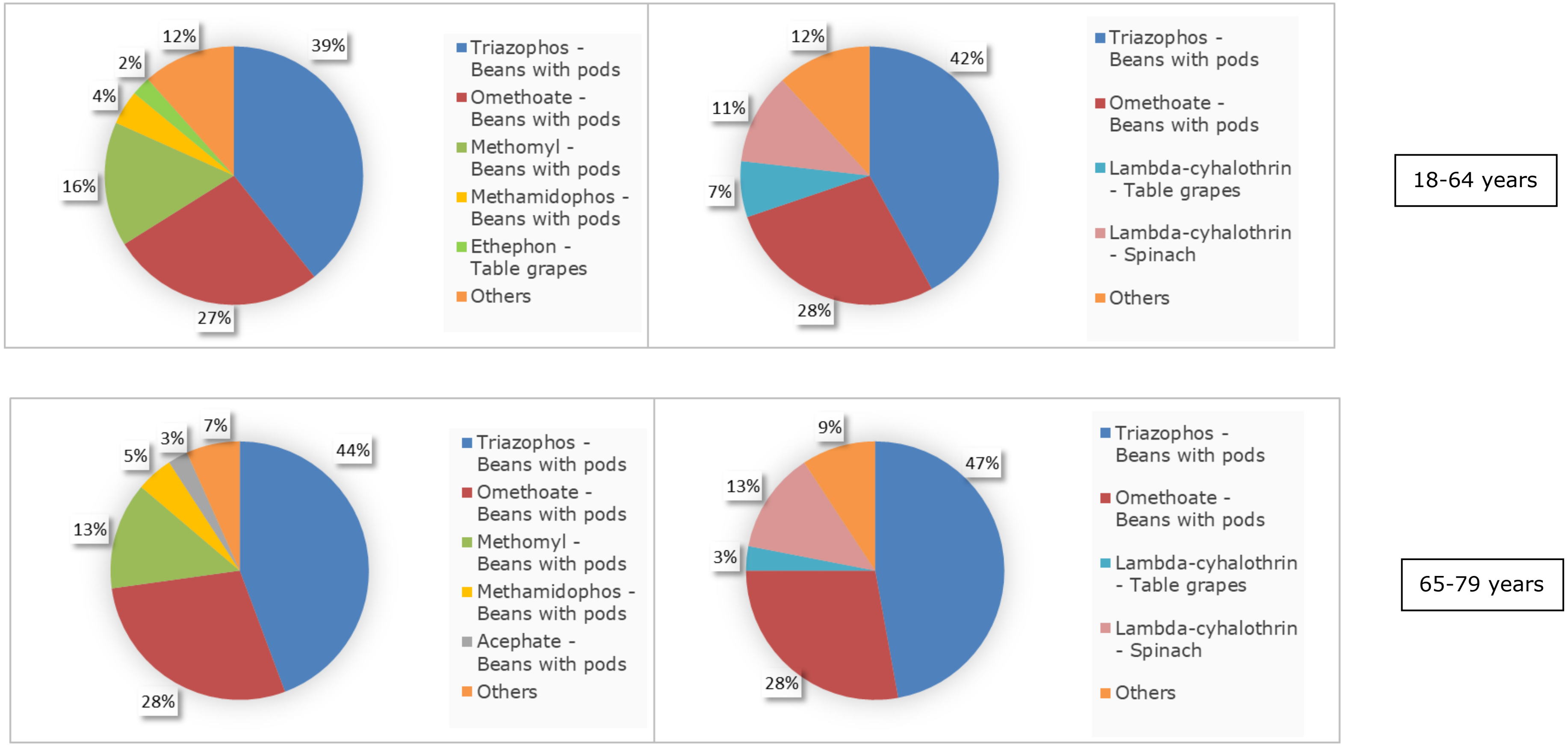
CAG: cumulative assessment group; motor division: acute functional effects on motor division; neurochemical: acute neurochemical effect, i.e. inhibition of acetylcholinesterase activity; P99: 99th percentile of exposure; P99.9: 99.9th percentile of exposure

[1] Margin of exposure (MoE) is the ratio between the no-observed adverse effect level (NOAEL) of the index pesticide and the percentile of exposure (see section 2.6). MoE has no dimension.

Annex F Contribution of the five pesticide-commodity combinations contributing most to the exposure to either CAG-neurochemical (left pie) or CAG-motor division (right pie) in the upper 0.1% of the cumulative dietary exposure distribution for children aged 7-17 years, and adults aged 18-64 and 65-79 years

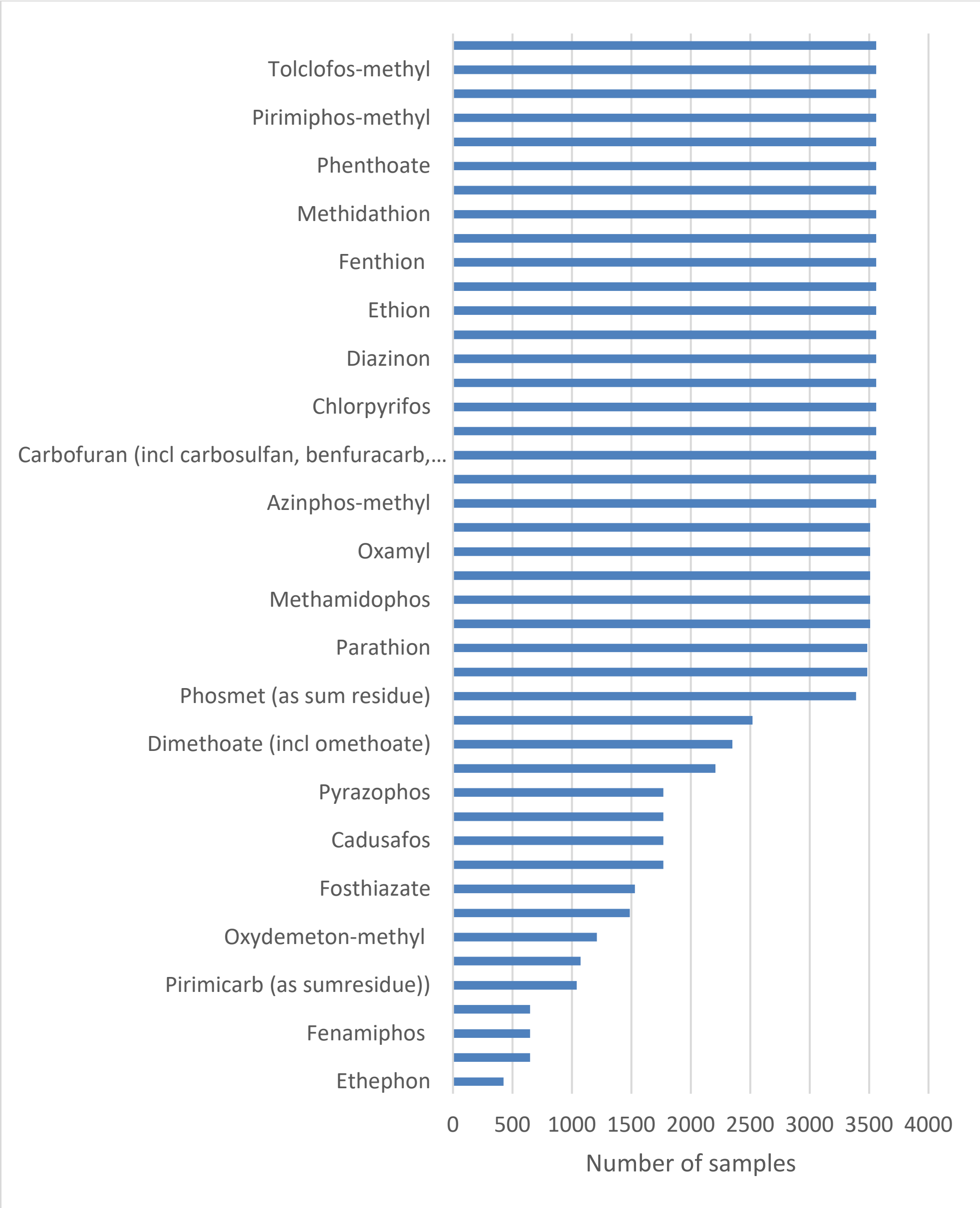


7-17 years



CAG: cumulative assessment group; motor division: acute functional effects on motor division; neurochemical: acute neurochemical effect, i.e. inhibition of acetylcholinesterase activity

Annex G Number of analysed samples per pesticide



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