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Approaches for cumulative dietary risk assessment of pesticides☆

Eloisa D Caldas

Strategies to estimate the risks from dietary exposure to multiple pesticides have been developed since the 1980s, based on the dose-addition of substances within a mixture with similar biological activity that differ in their potencies. In this paper, the different strategies to estimate the exposure and characterize the cumulative risks are presented and discussed, and some studies conducted in the last three years are reviewed. The main challenge is to define a cumulative assessment group (CAG), which depends primarily on a sound and high-quality toxicological database. Owing to the complexity of the process, harmonization has not yet been reached among regulatory agencies, and the process is not used for setting maximum residue levels. Most studies conducted around the world have shown potential health risks from cumulative exposure only when very conservative assumptions are used in the assessment.

Address
University of Brasília, Faculty of Health Sciences, Laboratory of Toxicology, 70910-900 Brasilia, DF, Brazil

Corresponding author: Caldas, Eloisa D (eloisa@unb.br)

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Introduction

Food consumption is the major source of exposure to pesticides and other chemicals by the general population, and dietary risk assessment studies are necessary to identify exposure scenarios that could pose a potential health concern [1]. In most cases, the assessment is conducted separately for each chemical; however, in real life, humans are co-exposed to various chemicals in the diet, including multiple pesticide-active ingredients [2]. The concern about human exposure to chemical mixtures was first raised during the 1980s and guidelines for conducting cumulative assessment were further published by the United States Environmental Protection Agency (USEPA) [2] and the European Food Safety Authority (EFSA) [3].

The concept of cumulating substances with similar biological activity that differ in their potencies was applied by the USEPA in identifying pesticides that cause common toxic effects by the same mechanisms of toxicity (common mechanism group) [2]. Further, the EFSA proposed cumulative assessment groups (CAG) based on common toxic effects and/or target organs, regardless of the mechanism/mode of action [4,5]. It is a consensus between the two agencies that the dose-addition approach should be taken for cumulative exposure, which assumes that no interaction among the compounds within the mixture is expected at low levels of exposure [2,3].

Although the European Parliament and the Council require that the cumulative effects of pesticides be considered when maximum residue levels (MRLs) are adopted (EC 396/2005), this regulation has not been yet implemented in the region, except for some initiatives in some countries [3,6]. USEPA does not use cumulative assessments to set MRLs; however, if a cumulative assessment identifies risks of concern, it might be used to guide mitigation for food uses, which may lead to changes in MRLs and/or canceling registrations/revoking MRLs (Michael Doherty, USEPA, *personal communication*).

The identification of pesticides for inclusion in a CAG is driven mainly by their toxicological profile and that of their metabolites. Some pesticides may be excluded from a group if they contribute only marginally to the cumulative risk, due to low or negligible exposure level (low detection rate in monitoring, nonregistered pesticides) and/or have a poor toxicological database [5]. Hence, the number of compounds included in a CAG may vary among studies and agencies.

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The objectives of this work were to review the main approaches used for estimating the risks from the exposure to multiple pesticide residues in the diet, to discuss their limitations and uncertainties, and to summarize the results of some studies conducted in the last three years.

Cumulative assessment group

Cumulative assessment group based on common mechanism/mode of action

Table 1 shows the main known CAGs based on common mechanism/mode of action, and it includes compounds of the same chemical and pesticide class that are structurally similar [5]. The USEPA CAG for organophosphorus insecticides is one of the largest groups, including 33 pesticides and metabolites [7] (Table 1). The agency has a separate CAG for the N-methyl carbamates [8], also inhibitors of acetylcholinesterase (AChE), unlike the EFSA, which established a CAG for AChE inhibition in the brain and/or erythrocytes that includes both pesticide classes [9], an approach also used by some authors [10,11].

With the exception of the chlorotriazine CAG, for which the compounds assumed to be of equal potency for neuroendocrine effects, an index compound (IC) was selected for each CAG (Table 1). The IC is typically the compound within the CAG with the highest-quality toxicological database, statistical robustness of the findings, evidence of dose–response relationship, and consistency in the occurrence of the specific effect across genders, species, and studies [2,9]. However, different ICs can be chosen for a given CAG depending on the database available at the moment of the assessment. For example, the IC for the organophosphorus CAG set by the USEPA is methamidophos, but other authors have used acephate, chlorpyriphos, or phosmet (e.g. [11–15]). The choice of the IC may indeed impact the outcome of the assessment. Using acephate as the IC, Caldas et al. found the cumulative intake of pesticides by the Brazilian population to be about 10 times higher compared with methamidophos as IC, when the CAG includedboth AChE inhibitors (N-methyl carbamates and the organophosphorus) [10]; also for the Brazilian population, Jardim et al found similar results when the CGA included only the organophosphorus compounds [12]. Boon and van Klaveren [15] also reported different cumulative intakes for AChE inhibitors for the Dutch population, using acephate or phosmet as IC, with levels using phosmet about twofold higher. In these cases, the approach selected by risk managers should consider the uncertainties involved in the IC choice.

The mechanism/mode of action of adverse effects that are relevant to humans are, however, not always known or completely elucidated, which may limit the number of pesticides included in the CAGs and potentially underestimate the risk [16].

Cumulative assessment group based on common effect on target organ/system

When the grouping is based on a common target organ/system toxicity, many chemicals included in a CAG may not share the same mechanism/mode of action, leading to more uncertainties, and can be considered a conservative approach [5]. In most cases, the mechanism/mode of action of the substances within the group is not available or can be assumed dissimilar [3,4].

Table 2 shows the CAGs based on the common effects for pesticides, mainly developed by the EFSA. Two CAGs were established by the EFSA [20] for the triazole fungicides: cranium–facial malformation to the fetus and hepatoxicity for chronic exposure. It was concluded that the cranium–facial malformation is probably due to a common mechanism of toxicity (inhibition of embryonic CYP-26 degradation of retinoic acid) [20]. More recently, the EFSA [21] established two new CAGs for cranium–facial alterations (Table 2) that include pesticides and metabolites other than from the triazole class, such as organophosphorus insecticides, dithiocarbamate fungicides, and the herbicide 2,4-D. Twenty-nine compounds were common to both cranium–facial alteration CAGs.

Table 1

CAG of pesticides based on common mechanism/mode of action with the respective IC.

CAG (number of pesticides)	Common mechanism/mode of action	Ref.
Organophosphorus (33) *IC (acute)= methamidophos*	Inhibits the enzyme AChE by phosphorylating	[7]
N-methyl carbamates (10) *IC (acute)=oxamyl*	Inhibit AChE by carbamylation	[8]
Organophosphorus (36) and N-methyl carbamates (11) *IC (acute): oxamyl IC (chronic): omethoate*	Brain and/or AChE inhibition	[9]
Pyrethrins/pyrethroids (17) *IC (acute) = deltamethrin*	Interaction with the voltage-gated sodium channels	[17]
Chloroacetanilides (acetochlor, alachlor, and butachlor) *IC (chronic)= alachlor*	Generation of reactive metabolite that leads to cytotoxicity and regenerative proliferation in the nasal epithelium	[18]
Chlorotriazines (atrazine, propazine, simazine, and metabolites)[a]	Disruption of the hypothalamic–pituitary gonadal axis by altering the levels of luteinizing hormone	[19]

[a] Assumed to be of equal potency for neuroendocrine effects, and no IC is needed.

Table 2

CAG of pesticides based on common effect on a target organ/system with the respective IC.

CAG (number of pesticides)	Ref.
Triazoles:	[20]
Acute effect on the fetus: cranium–facial malformation (7)	
IC = fluzilazole	
Chronic effect: hepatoxicity (4)	
IC = cyproconazole	
Cranium–facial alterations (acute, women of child-bearing age)[a]	[21]
Alterations due to abnormal skeletal development (39)	
Head soft tissue alterations and brain neural tube defects (41)	
Effects on nervous system (acute):	[23]
Functional alterations of the motor division (119)	
IC (acute): oxamyl; IC (chronic): emamectin benzoate	
Functional alterations of the sensory division (101)	
IC (acute): oxamyl; IC (chronic): endrin	
Functional alterations of the autonomic divisions (101)	
IC (acute): oxamyl; IC (chronic): methamidophos	
Histological neuropathological changes in neural tissues (19)	
IC (chronic): emamectin	
Effect on thyroid (chronic)[a]	[24]
Hypothyroidism (128)	
Hypertrophy, hyperplasia, and neoplasia (17)	
Liver steatosis (144)	[22]
IC (chronic) = flusilazole	

[a] No IC was established, use of MOET approach.

Indeed, most CAGs based on target organ/system toxicity include a large number of pesticides, as shown in Table 2, with compounds from different chemical and pesticide classes. The liver steatosis CAG proposed by Crepet et al [22] contains 144 compounds, three of the four CAGs for the effects on the nervous system contain over 100 compounds [23], and 128 compounds were included in the hypothyroidism CAG [24].

Colnot et al. [25] emphasized that only studies with sufficient quality that show unambiguous adverse effects of human relevance should be considered for a target organ toxicity CAG. Furthermore, the adverse effect needs to exhibit a dose–response relationship and be consistent with other changes related to the disease development. The authors questioned the large number of CAGs (level-2 subgroups) for liver toxicity proposed by the EFSA in 2016 (a total of 129 substances in 15 CAGs), since several CAGs are liver changes that are the consequence of phenomenological effects covered by other CAGs within the group. This point was also raised by Foster et al. [26], who proposed an approach that reduces to six the number of CAGs for liver toxicity. Colnot et al. [25] outlined a flow scheme for the grouping of substances into a target organ toxicity CAG. The approach resulted in a reduced number of CAGs for the liver, which, according to the authors, may lead to a faster, scientifically sound, and more consistent assignment of substances, without affecting consumer safety.

Moxon et al. [27] reviewed and refined the approach taken in 2016 by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) for defining a CAG for reproductive/developmental toxicity. From the 129 pesticides scrutinized by ANSES, 124 were found to have at least one effect on the system and were included in one or more of the nine specific-effect CAGs (including effects on mating, effects on reproductive organs, fetal alterations, and effects on postnatal development). The reproductive/development system is challenging, mainly because the effects occur through different phases of the reproductive cycle, affecting various life stages, from embryo to adult, in different ways. The authors highlighted some key points that need to be evaluated in the reproductive/development studies, including the influence of the parental/maternal systemic toxicity on the endpoint and the time course of the parental toxicity.

The EFSA has been conducting a systematic uncertainty analysis when proposing a CAG based on effects or target organ/system toxicity [7,20,22,23]. In general, the lowest uncertainty can be achieved when knowledge on an adverse outcome pathway is available and mode of action for the chemicals is known [5]. For example, the sources of uncertainty related to the CAGs for effects on the nervous system include the slope and shape of the dose responses, the contribution of metabolites and degradation products, the adequacy of the dose-addition model, and the inter- and intraspecies differences in toxicological sensitivity [7]. The CAG for functional alterations of the motor division was addressed using weight of evidence and expert knowledge elicitation, and active substances were allocated in subgroups of varying levels of evidence. This approach was not necessary for the CAG for brain and/or erythrocyte AChE inhibition, as this mode of action is clear for organophosphorus and N-methyl carbamate insecticides [7].

Cumulating the residues within a cumulative assessment group

One approach to cumulate the residues within a CAG is to normalize the residue of each compound in relation to the IC of the group, by calculating the relative potency factor (RPF [2]). The RPF of a chemical p is the ratio between the toxicity point of departure of the IC (benchmark dose lower confidence limit [BMD_L], no observed–adverse-effect level [NOAEL]) and that of the chemical p. Ideally, the RPF should be based on BMD_L from studies with the same species and similar study design (duration of the study) [2,25]. The RPFs are then used to convert the concentration of the chemicals within the CAG into equivalents of the IC. For example,

if an apple sample contains three pesticides belonging to a CAG (p1, p2, and p3), the cumulative residue in the sample, expressed as the index compound (CR_{IC}), is the sum of the residue of each pesticide (R_p) multiplied by its RPF_p (Equation 1)

$$CR_{IC} = R_{p1} \times RPF_{p1} + R_{p2} \times RPF_{p2} + R_{p3} \times RPF_{p3} \quad (1)$$

Exposure assessment

Dietary exposure to multiple pesticides can occur via the consumption of a food portion containing multiple residues, as the food crop was treated with different pesticides, and/or different foods that were treated with different pesticide products [12]. The cumulative exposure (concentration X food consumption/body weight) is estimated as for single substances, involving similar uncertainties related to the data used in the assessment.

The exposure is estimated by deterministic methods, using defined levels for each parameter (mean, median, highest) or probabilistic methods, where all the values in the dataset are considered to generate an exposure distribution. The probabilistic assessment uses Monte Carlo simulation models running in statistical tools such as Statistical Analysis System (SAS®), Monte Carlo Risk Assessment (MCRA) developed by the Dutch National Institute for Public Health and the Environment, or @ risk® Software Package (add-in tool for Microsoft Excel). While the deterministic approach shows a single-exposure outcome, the probabilistic approach provides different scenarios for risk managers, which are associated with a quantitative measure of uncertainty (lower and upper boundary of the uncertainty interval) at each percentile of the exposure distribution. In general, the 95th or higher percentiles are used to characterize the cumulative risk, but in most cases, the 99.9th percentile (P99.9) is used by regulatory agencies [3,5,7,28].

Uncertainty in the concentration data is related to the sampling procedure, the analytical method, and a limited number of analyzed samples; low sensitive methods increase the uncertainty over the actual residue scenario [12]. Most pesticide residue monitoring data show a large number of left-censored data, that is, samples with no residues detected (below the analytical method limit of detection [LOD]) or quantified (below the limit of quantification [LOQ]) [12,29–31]). Approaches to deal with these data include considering the levels < LOD/LOQ as zero (optimist), as ½ LOD/LOQ, or at the LOD/LOQ (pessimist). The approach taken may depend on the registration status of the pesticide, the likelihood of finding the residue in a food, and the level of conservativeness taken by the risk assessor [3]. The pessimistic approach is very conservative and most likely leads to an overestimation and an unrealistic exposure scenario [32]. When available, processing factors are applied to the residue data to estimate the residues in the food-as-eaten (cooked, peeled) as a tool for exposure refinement [3].

When consumption and body weight data are available, cumulative exposure can be conducted for different age groups within a population (infants, adolescents, and adults) or for specific population groups, such as women of child-bearing age. Ideally, consumption data should reflect individual consumption and body weight information of a given population, obtained in national surveys, and the data are disintegrated into the raw commodities analyzed in the residue monitoring programs [3,12,22,31,33].

Characterizing the cumulative risk from pesticides

When RPFs are estimated, the risk characterization may be expressed as percentage of the IC health-based guidance values (HBGV), Acceptable Daily Intake (ADI) for chronic or Acute Reference Dose (ARfD) for acute exposure. Risk may exist when the cumulative exposure is higher than the HBGV (> 100%) [10,12,31,32]. Alternatively, risk can also be assessed by estimating the margin of exposure (MOE), which is the ratio between the point of departure (NOAEL or BMD_L) of the IC and the cumulative exposure; risk may exist when the MOE is lower than a certain threshold [8,33]. For pesticides, a MOE of 100 is usually used as a threshold for risk management consideration [28].

One method used to characterize the cumulative risk from pesticides that precludes the selection of an IC and the application of RPF is the combined margin-of-exposure (MOET), which is the reciprocal of the sum of the reciprocals of the individual MOEs [3]. This method was applied by the EFSA using a probabilistic model (SAS®) for the cranium–facial alterations [21], effects on the nervous system [23], and thyroid effect [24] CAGs; MCRA was also used in the last two assessments. For the cranium–facial alterations, in addition to 100, a MOET threshold of 500 was also considered due to the severity of the effect [21].

Crepet et al [22] proposed a statistical method (sparse nonnegative matrix underestimation) that combines exposure and hazard information to identify relevant mixtures of chemicals belonging to the liver steatosis CAG. Following various exposure scenarios for nine European countries, the study identified 15 out of the 144 pesticides included in the CAG to be prioritized for further investigation, including toxicological studies to better elucidate the mechanism/mode of action responsible for the steatosis effect.

Another approach to characterize the cumulative risk from pesticide exposure (and other chemicals) is the

Hazard Index (HI), which can be used for a mixture of chemicals, regardless of the class, mechanism/mode of action, or target organ/system toxic effects [3]. The HI is calculated by summing up the individual hazard quotient (HQ = exposure/HBGV) of the pesticides to which a population is exposed, normally identified based on the residue data. A potential risk is identified if the HI is higher than 1.

Boberg et al. [16] proposed a web-based tool for cumulative risk assessment using the HI approach (www.chemicalmixturecalculator.dk). The database includes hazard and exposure (Danish data) estimates for more than 200 chemicals in food and the environment, including pesticides, mycotoxins, phthalate, and heavy metals. The pesticides were classified in CAGs for effects on hematological system, kidney, liver, nervous system, developmental and reproductive system and thyroid, and each CAG was divided into subgroups (levels) for different effects within each organ/system. The authors defined the term 'Derived Tolerable Dose' for each CAG, mainly based on experimental in vivo data for the compounds in each group, which is the HBGV used to estimate the HQ in the study.

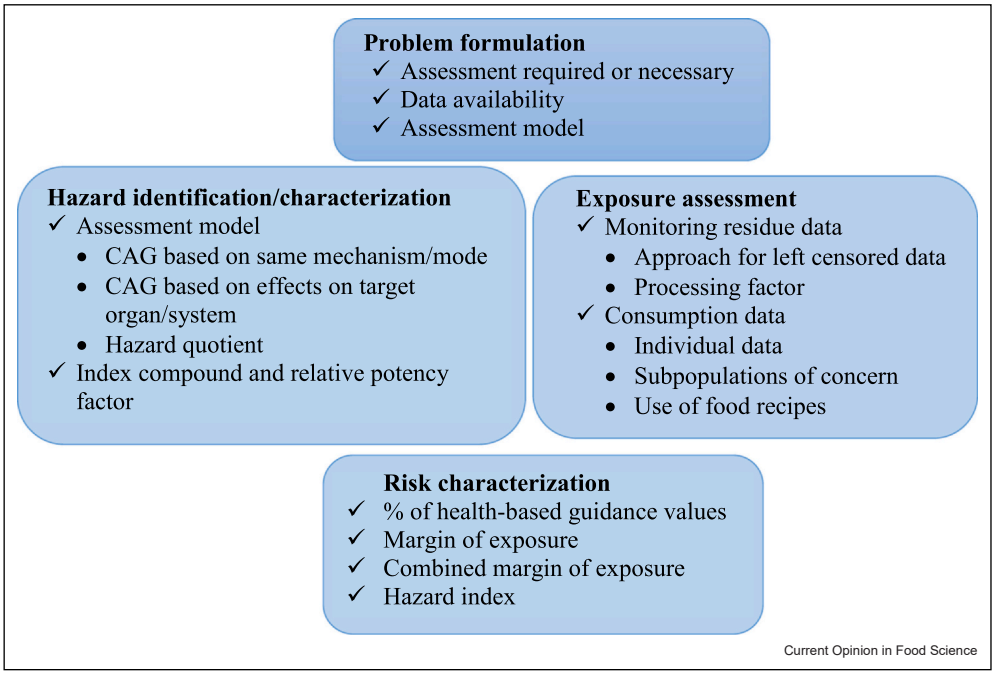
The three approaches to characterize the cumulative risk discussed in this paper have limitations and advantages. The use of RPF requires the selection of an IC for a given CAG, which can be challenging mainly when the CAG is based on effects on target organ/system, where the consistency of the occurrence of the effects across the studies may not always be evident. This is especially true when a large number of pesticides is included in the CAG, as discussed previously, and for this reason, the EFSA has used the MOET approach. On the other hand, the HI approach is much simpler and faster to implement, and can include compounds across different silos (e.g. phthalates and other chemicals); however, it is based on the assumption that a dose-addition of effects occurs with compounds that have different toxicological mechanisms and act on different organs/systems, which is not biologically plausible.

Figure 1 summarizes the different approaches for conducting cumulative dietary risk assessment of pesticides discussed in this paper. The process may start with a problem formulation, when a number of aspects are considered, including whether the assessment is required or necessary, and the availability of the data (hazard and exposure assessment), which may define the assessment model used [5].

Studies conducted worldwide

The assessment of the potential risks from the cumulative exposure to pesticide residues has been the object of various studies around the word in the last 20 years, using different approaches. Most studies were conducted in Europe (e.g. [6,13–15,20–24,32–37]). Few

Figure 1



Frameworks for conducting cumulative dietary risk assessment of pesticides.

Table 3

Cumulative dietary risk assessment of pesticides published in the period of 2020–2022.

Consumption and body weight data	Residue data	Method	Results	Ref.
Data from nine European countries 5–11 and 18–60 years old	Monitoring data from 2010 to 2014 126 pesticides in 204 crops	CAG: liver steatosis Probabilistic (MCRA) Chronic exposure RPF	MOE at P95, Optimistic: 503–6500 Pessimistic: 7–20	[33]
Data for different age groups in Europe 1–64 years old	Monitoring data from 2014 to 2016 30 crops < LOQ = zero or ½ LOQ when at least one positive result	CAGs 1. Brain and/or erythrocyte AChE inhibition, 2. Functional alterations of the motor division Probabilistic (SAS®)	Acute MOET at P99.9 1. Toddlers and children: 40–59 Adults: 92–124 2. Toddlers and children: 63–89 Adults: 141–176	[23]
Data from 14 European countries, women-of- child-bearing-age population	Monitoring data from 2017 to 2019 36 raw commodities, olive oil, wine, and drinking water	CAGs: 1. Abnormal skeletal development 2. Head soft tissue alterations/ brain neural tube defects Probabilistic (SAS®)	Acute MOET at P99.9 1. 69.9–209 2. 168–238	[21]
2011–2015 Denmark Dietary survey: 4–6 years old 15–75 years old	Monitoring data from 2012 to 2017 314 pesticides, 200 crops	Deterministic, HI Mean residues < LOQ = zero < LOQ= ½ LOQ	Chronic HI: Children: 0.09–0.46 Adults: 0.03–0.16	[36]
FAO/WHO database general population	3406 samples of 13 food commodities in 2019 Chronic: median residues	CAG: triazoles Deterministic, HI	Chronic HI: 1.83×10^{-3}	[38]

studies have been conducted outside Europe, mainly in China (e.g. [11,38]) and Brazil (e.g. [10,12,31]).

Most studies were conducted using the probabilistic approach for estimating the cumulative exposure, mainly using MCRA. In many studies, the authors estimated the exposure using the optimistic and the pessimistic approach for the left-censored data (e.g. [6,33]). Potential risks are only seen when the pessimistic approach (censored data at LOD/LOQ level) is applied, as shown by Sprong et al. [33] for the liver steatosis CAG (Table 3). Although the authors applied the pessimistic approach only for registered pesticides, they most likely overestimated the exposure and the risks. The concentration data used in the study contained 135 of the 144 pesticides included in the CAG, of which 126 were present in at least one sample analyzed; over 99% of the samples had no detected residues [33].

Table 3 shows the results of the assessments conducted by the EFSA for the two CAGs for effects on the nervous system, with the MOET at P99.9 ranging from 40 to 89 for children and toddlers and from 92 to 176 for adults [23]. Taking into account all identified uncertainties, it was concluded that the MOET for the brain and/or erythrocyte AChE inhibition CAG was not below the threshold for regulatory consideration (100) and considered not of health concern, with a certainty that exceeds 99% for adults, 90% for children, and at least 80% for toddlers. For the functional alterations of the motor division CAG, the certainties were 99% for adults and at least 95% for children and toddlers [23].

In the cumulative acute assessment conducted by the EFSA for the craniofacial alterations for the women-of-child-bearing-age population (abnormal skeletal development and head soft tissue alterations/brain neural tube defects) [21], the MOET was higher than 100, but lower than 500 (Table 3), which may indicate potential health risks for a certain percent of the population. These conclusions were reached when some conservative assumptions were taken (tier 1), including imputing a concentration in water of 0.1 μg/L for the most potent approved pesticides (against a concentration of 0.05 μg/L in tier 2) and unit-to-unit variability of 5 or 7 (against a fixed value of 3.6 in tier 2) [21].

Most studies conducted in Denmark used the deterministic HI approach (e.g. [34–37]). In the study conducted by Jensen et al. [36], the mean concentration used for chronic exposure was estimated assuming levels < LOR (limit of reporting, similar to LOQ) equal to zero (optimistic approach), to ½ LOR, or the smallest mean of either the second approach or 25 times the optimistic approach. In all cases, the HIs were below 1 (Table 3), indicating no potential risk to the studied population. The same conclusion was reached by previous studies conducted in the country [34,35,37]. Although the HI is a conservative approach for including all pesticides in the cumulative assessment, regardless of the toxicological profile, the HI is normally very

low, and no potential risks are identified. This is expected as it normally reflects the mean exposure (mean concentration x mean consumption) in the deterministic chronic assessment, compared with when a CAG is considered in a probabilistic approach, when percentiles of exposure, which are higher than the mean, are used in the risk characterization (Table 3).

All the studies shown in Table 3 used national consumption data, except for Cui et al. [38] in China, in a study that used the Food and Agriculture Organization/World Health Organization (FAO/WHO) consumption database (Global Environment Monitoring System–-Food Contamination Monitoring and Assessment Programme [GEMS]/Food) to estimate the cumulative risks to the triazole CAG (deterministic approach, Table 3). The database includes the GEMS/Food Consumption Cluster Diets for chronic exposure, which reflect food availability, not food consumption. Although the FAO/WHO Joint Meeting on Pesticide Residues uses these data to conduct chronic dietary risk assessment at an international level, they are not related to individual countries, but to 17 clusters that include different countries [1]. Furthermore, the Cluster diets refer to the general population and not to any specific age group, although the authors estimated the risks for children. The authors also conducted acute cumulative assessment for children and adults (not shown in Table 3), although this assessment is only relevant for women of child-bearing age, as the critical effect is cranium–facial malformation in the fetus (Table 2).

Concluding remarks

A number of approaches on cumulative dietary risk assessment for pesticides have been proposed in the last few decades, but this is a complex process, and a harmonized procedure has not yet been achieved among different risk assessors. A major challenge relies on the availability of sound toxicological data to define the CAGs, and the scientific judgment of the studies, which may differ among the experts. So far, only retrospective cumulative assessment has been conducted by regulatory agencies and implementation of this process during pesticide registration and MRL setting needs a thorough discussion between risk assessors and managers, as it can have important impacts on availability of products for pest management and food trade. Most studies conducted around the world have shown low potential health risks from cumulative exposure to pesticides.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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- •• of outstanding interest

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