Risk Assessment of Human Exposure to Pyrethroids Through Food

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Abstract For decades, the global demand for food has been increasing as a result of population growth and changes in diets. Together with this demand, the ample use of pesticides and insecticides in every step of the production chain has grown. Pyrethroids are systemic pesticides widely used in both agriculture and veterinary. They are often found on the surface of fruits and leafy vegetables or deposited on the lipid bilayer in products of animal origin. Considering the high use of pyrethroids all around the world, the potential risks of human exposure to residues in food products are a matter of great concern. Risk assessment is the scientific basis for risk management according to various international agencies. The vast majority of pesticide residue risk assessments in food are based on the toxicological evaluation of individual compounds, but assessments of cumulative exposure to multiple residues have gained notoriety. The evaluation of the "daily intake" is of great importance for human and environment safety.

Keywords Food, Pyrethroids, Risk assessment

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According to Paracelsus, pioneer of the medical revolution of the sixteenth century, "Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy." Paracelsus' quote remains valid nowadays. Humans are subjected to high chemical daily exposure levels, thus making risk assessment of the utmost importance. Food safety is an important means to promote public health, emerging as an extremely relevant research area. Still, the dissemination of scientific information regarding food safety is not widely explored, leading us to further investigate its specifics and preferred methods of assessment. For decades, the global demand for food has been increasing as a result of population growth and changes in diets. Land for agriculture and storage options are scarce, justifying the ample use of pesticides and insecticides in every step of the production chain.

Pyrethroids constitute the majority of agricultural and veterinary pesticides and commercial household insecticides. Residues of pyrethroids are the main source of agricultural pollution and are potentially hazardous, becoming a public health concern [1].

Pyrethroids are systemic pesticides with a regulated use in food products, livestock, and livestock feed. They are often found on the surface of fruits and leafy vegetables [2] or deposited on the lipid bilayer in products of animal origin [3]. In this chapter, we will explore topics concerning the potential risks of human exposure to pyrethroid residues in food products, considering the role of population's diet in the risk assessment.

Risk assessment is the scientific basis for risk management according to various international agencies. The US Environmental Protection Agency defines the evaluation of potential outcomes of pesticides in food products through human health risk assessment as the process to estimate the nature and probability of adverse health effects in humans who may be exposed to chemicals in contaminated environmental media, now or in the future (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/overview-risk-assessment-pesticide-program). Risk assessment is also the basis of the Codex Alimentarius Commission, which through the Joint Expert Committee on Food Additives (JECFA) and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) establishes international guidelines for pesticide residues in specific food items [4].

Most international environmental protection agencies use a four-step process for human health risk assessments:

1. *Hazard identification* – aims to analyze available data on toxicity and mode of action of agents present in a particular food or group of foods which are capable of causing adverse health effects. Hazard identification is traditionally performed through observation of the effects of pesticide residues in humans and animals (domesticated and laboratory) and in vitro and structure-activity relationship analyses.
2. *Hazard characterization* – is the description of the relationship between levels or dose of the consumed residue of pesticide and the probability of development and severity of an adverse health outcome. Hazard characterization of threshold toxic effects usually constitutes reference data, such as the acceptable daily intake (ADI), for example, for a residue of a pesticide in food products.

3. *Exposure assessment* – examines the levels of pesticides in human diet, analyzing frequency and timing of contact with or consumption of food products with residues of pesticides. It estimates various factors such as age, gender, and pre-existing health conditions.
4. *Risk characterization* – examines the nature and extent of human health risks from exposure to pesticides. It indicates the overall degree of confidence in the assessment and information about populations more likely to be susceptible to pesticides.

The vast majority of pesticide residue risk assessments in food are based on the toxicological evaluation of individual compounds, but assessments of cumulative exposure to multiple residues have gained notoriety [5].

1 Human Exposure to Pyrethroids

Exposure to pyrethroids can be either occupational or nonoccupational and can occur in several ways, such as inhalation and oral and dermal routes. The majority of the population is not substantially exposed to pyrethroids via inhalation and dermal routes, as the uptake is mostly caused by manipulation of household products with pyrethroids in their formula. On the other hand, they are the major routes of exposure for agriculturists working with pesticides. Oral exposure is the primary contamination route in general population due to ingestion of food products containing pyrethroid residues [1, 6].

Ingestion of food products of vegetal origin such as fruits and vegetables usually causes more human health damage since their consumption is in a raw or a semi-processed form. Conversely, cereals and animal products are heavily processed, oftentimes through high-temperature and pasteurization processes, leading to degradation of pyrethroids [7].

Deterministic and probabilistic approaches are often employed to analyze data on food consumption and to quantitatively assess exposure [8, 9]. The deterministic model utilizes available data and does not require evaluation of uncertainty components, expressing results which can be easily elucidated. Based on results from previous studies (REFs) performed in Spain in 2016, Quijano et al. [7] a mean-estimated chronic cumulative risk assessment determined by multiplying the mean pesticide concentration in a food product by the mean or the 95th percentile of the food consumption, thus defining lower-bound and upper-bound scenarios, respectively.

The probabilistic approach quantifies variation and uncertainty, representing the data as a distribution instead of fixed values, including variance parameters. Parameters such as food consumption data, pesticide levels, body weight, and susceptible population groups (infants, expecting and breastfeeding mothers, individuals with kidney or liver disorders) are used in the probabilistic approach for higher accuracy. Monte Carlo simulation is the most commonly used approach to estimate exposure, taking into account probability distributions. Risk assessment requires an exact and systematic quantitative data analysis model, particularly

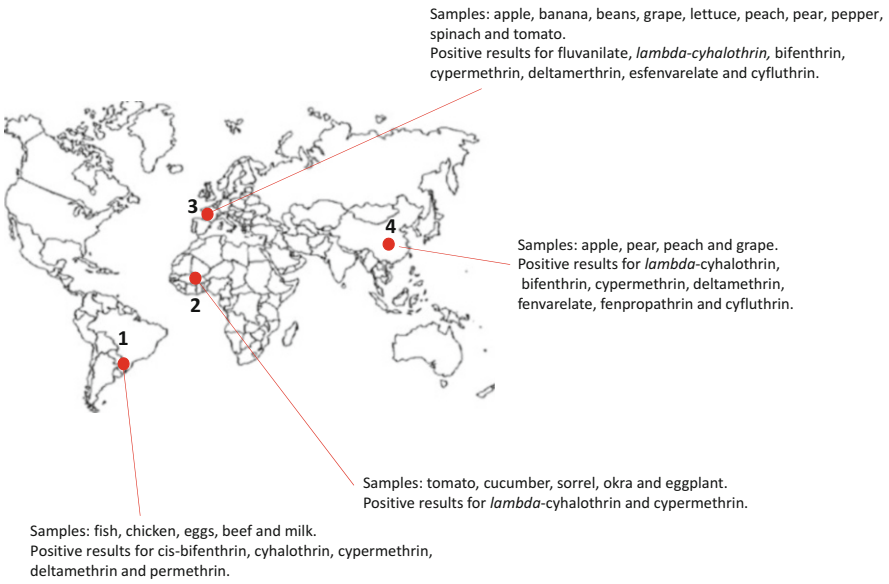

Fig. 1 Detection of pyrethroid residues in food from several continents: *1* South America [3], *2* Africa [11], *3* Europe [7] and *4* Asia [12]

when the calculated risk exceeds the acceptable values. Thus, the probabilistic model is expected to surpass the deterministic model in the near future [10] (https://www.epa.gov/expobox/exposure-assessment-tools-tiers-and-types-deterministic-and-probabilistic-assessments. Accessed 18 Apr 2019).

Global exposure to pyrethroids through food consumption is reaching alarming levels. Several studies performed in different countries reveal cases in which pyrethroids were found in food products: Dallegrave et al. [3] analyzed the presence of pyrethroid residues in food products of animal origin, finding approximately 10% of milk samples contaminated with at least five different pyrethroids. Lehmann et al. [11] analyzed food products of vegetal origin, and 8.5% of the samples had residue levels higher than the MRL for lambda-cyhalothrin, and even the acute hazard quotient (HQacute) was greater than 1, indicating risk. Quijano et al. [7] detected lambda-cyhalothrin, cypermethrin, and bifenthrin in 9, 5 and 4% of the vegetal food product samples, respectively. Zhixia Li et al. [12] reported that 30% of food products of vegetal origin showed 2, 3 or 4 different pyrethroid residues, 3% in levels higher than the MRLs. The authors also identified cypermethrin, bifenthrin, and lambda-cyhalothrin with the highest acute and chronic hazard index values (Fig. 1).

2 In Vivo Toxicity

Pyrethroids are classified in two distinct groups according to the absence (type I) or presence (type II) of a cyano group bound to the alpha-carbon in the molecule. Figure 2 depicts structures of the main type I and type II pyrethroids.

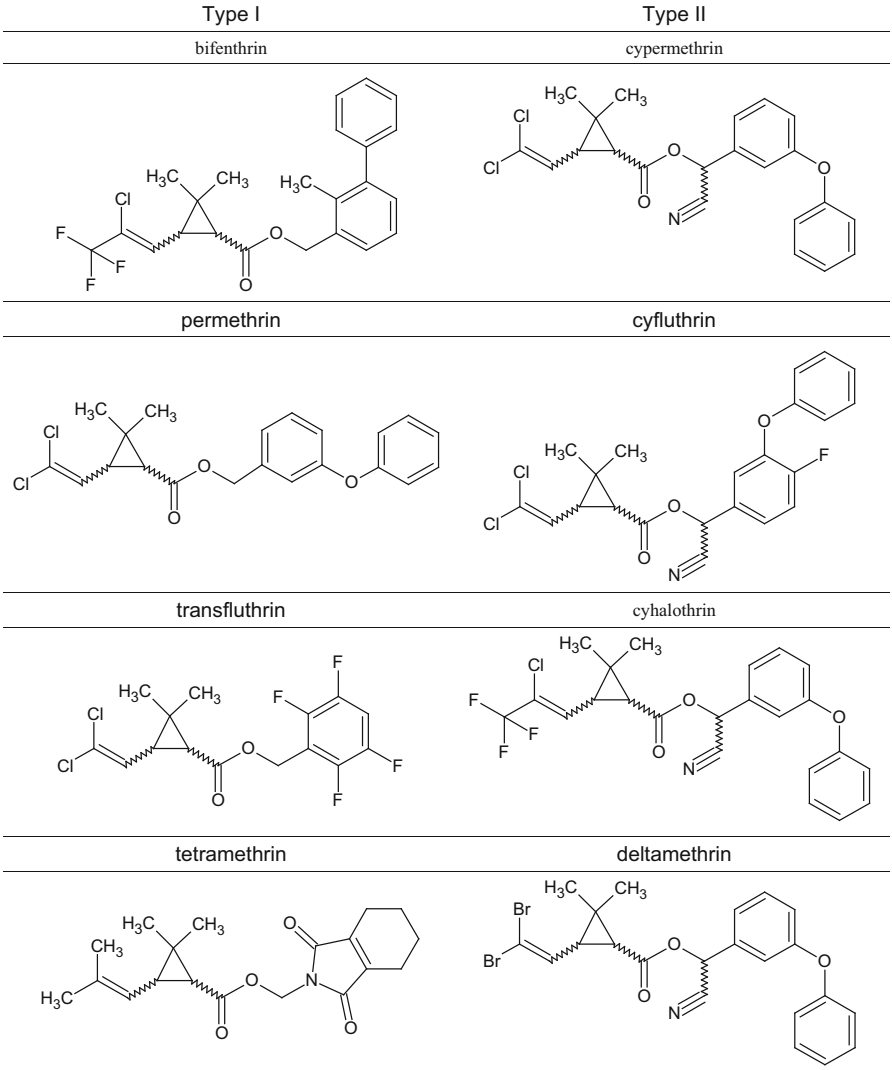

Fig. 2 Chemical structure of the type I pyrethroids (bifenthrin, permethrin, transfluthrin, and tetramethrin) and type II pyrethroids (cypermethrin, cyfluthrin, cyhalothrin, and deltamethrin)

Toxicity tests in laboratory animals revealed the occurrence of two syndromes, namely, T and CS syndromes, related to type I and type II pyrethroids, respectively. Neurotoxic symptoms caused by type I pyrethroids include shivering, irritability, high fever, comatosis, and death. Type II pyrethroids may cause salivation, involuntary movements, violent trembling, comatosis, and death. Exposure to certain pyrethroids, e.g., fempropatrin and esfenvalerate, leads to both T and CS syndromes. Mammalian toxicity is low, and specific enzymatic systems allow mammals to recover from contamination by pyrethroids in 24–48 h. Conversely, such degradation route is not present in insects, causing a higher insect toxicity [13].

3 Human Contamination

Recent research unanimously identifies ingestion of contaminated food products as the most relevant factor of human health damages caused by pyrethroids. When ingested, pyrethroids are immediately metabolized via hydrolysis of the ester, forming the corresponding carboxylic acids, oxidation and glucuronidation, and expelled in urine as conjugates. The main metabolites of pyrethroids in urine are the *cis*- and *trans*-isomers of 2,2-dichlorovinyl-2,2-dimethylcyclopropane-1-carboxylic acid (*cis*-DCCA and *trans*-DCCA) and 3-phenoxybenzoic acid (3-PBA). 3-PBA is a metabolite of various pyrethroids including fenvalerate, sumithrin, deltamethrin, permethrin, cyhalothrin, and cypermethrin. DCCA is a metabolite of permethrin, cyfluthrin, and cypermethrin. DBCA (*cis*-dibromo dimethyl vinyl cyclopropane carboxylic acid) is a metabolite of deltamethrin. 4F3PBA (4-fluoro-3-phenoxybenzoic acid) is a metabolite of cyfluthrin [14–16]. Structures of those metabolites are depicted in Fig. 3. The rapid metabolism prevents the accumulation of intact pyrethroids in plasma and blood serum; therefore, urine samples are preferred for intoxication monitoring.

Analysis of metabolites of pyrethroids in human urine has been widely used to assess the real human exposure to pyrethroids. Several studies reported the presence of metabolites of pyrethroids in human urine: 3-BPA and *cis*- and *trans*-DCCA were found in the urine of children in China [17], 3-BPA, *cis*- and *trans*-DCCA, and DBCA were found in the urine of children in Poland [18] and in Japan [19], and 3-BPA was found in the urine of children and expectant mothers in the USA [20], which was also found in the urine of expectant mothers in Japan [21].

Despite the fact that pyrethroids undergo a rapid metabolism in humans, due to its lipophilic nature, it is possible to find non-metabolized pyrethroids in breast milk. Corcellas et al. [22] reported tetramethrin, bifenthrin, λ-cyhalothrin, deltamethrin, fenvalerate, permethrin, and cypermethrin in breast milk samples in Brazil,

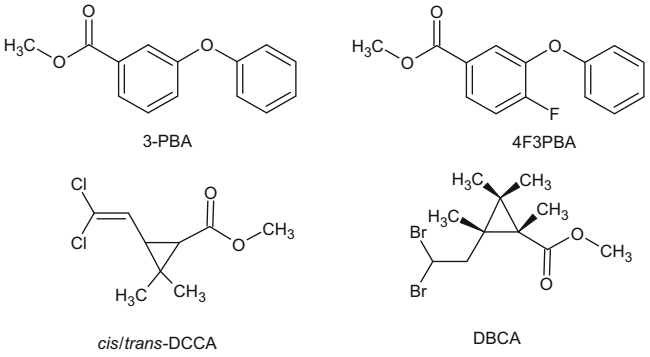

Fig. 3 Chemical structure of the pyrethroid metabolites: 3-Phenoxybenzoic acid (3-PBA), 4-fluoro-3-phenoxybenzoic acid (4F3PBA), *cis*- and *trans*-isomers of 2,2-dichlorovinyl-2,2-dimethylcyclopropane-1-carboxylic acid (*cis*-/*trans*-DCCA), and *cis*-2,2 dibromovinyl-2,2-dimethylcyclopropane-1-carboxylic acid (DBCA)

Colombia, and Spain. The presence of pyrethroids in breast milk samples is an alarming evidence of the harmful effects of pyrethroids to human health. Newborn children are the most affected by the exposure to pyrethroids due to the high dosage/body weight ratio and developing immunological system.

4 Pyrethroids and Human Health

Human health effects caused by pyrethroids can be classified as local or systemic, depending on the route of contamination and levels of exposure. Acute symptoms may include irritation of the respiratory tract (coughing and lung irritation due to inhalation of dust or aerosol particles), vertigo and headaches, nausea and vomiting, eye irritation and inflammation, and paresthesia. Studies on chronic symptoms are still very limited and oftentimes controversial [1, 14].

Epidemiological studies in men showed the impacts in male fertility related to quality the DNA of sperm and reproductive hormones. Ji et al. [23] analyzed urine and semen samples of 240 males and observed a correlation between 3-BPA metabolite levels, low concentration of sperm, and DNA damage. Toshima et al. [24] inspected urine and sperm samples of 42 males, finding a correlation between the presence of the 3-BPA metabolite and low sperm mobility. Jurewicz et al. [25] found a positive association between *cis*-DCCA and DNA damage, as well as a correlation between 3-BPA levels and sperm DNA damage in urine and semen samples of 286 males.

In women, epidemiological studies analyzed pyrethroid exposure during pregnancy. Shelton et al. [26] correlated exposure to pyrethroids during pregnancy and neurobehavioral disorders, such as autism spectrum disorders in children. Reardon et al. [27] suggested there could be an association between respiratory problems in infants and exposure of mothers to pyrethroids during pregnancy.

Research on the correlation between pyrethroid exposure and cancer are still in its infancy, and current data is still inconclusive. Nonetheless, the US EPA classified permethrin, a common insecticide and insect repellent, also used to treat lice, as "probably cancerogenic to humans" when ingested, and the International Agency for Research on Cancer (IARC) recognized potential cancerogenic risks, including permethrin, in a high-priority review list for the 2015–2019 review period (https://monographs.iarc.fr/wp-content/uploads/2018/08/14-002.pdf. Accessed 3 Mar 2019).

5 Pyrethroid Risk Assessment

The presence of pyrethroid residues on food products is a substantial risk to human health. Therefore, the levels of pesticide residues are established according to parameters such as the MRL, maximum residue limit; the ADI, acceptable daily intake; and the ARfD, acute reference dose. Those limits are determined by national and international regulatory agencies and vary according to those agencies. The

Codex Alimentarius (WHO/FAO), the US Environmental Protection Agency (US EPA), European pesticides database, Japan Food Chemical Research Foundation (JFCRF), and Agência Nacional de Vigilância Sanitária (ANVISA) are the main pesticide regulatory agencies worldwide; however, a unanimous decision regarding acceptable pesticide levels has not been reached yet. The MRL values for bifenthrin in tomatoes can range from 0.02 to 0.5 mg kg^{-1}; according to the regulatory agencies, Codex Alimentarius and European pesticides database, MRL is 0.3 mg kg^{-1}, JFCRF is 0.5 mg kg^{-1}, ANVISA is 0.02 mg kg^{-1}, and EPA is 0.15 mg kg^{-1}.

For decades, developed countries have been monitoring the levels of pesticide residues on food products. Conversely, such effort is practically nonexistent in developing countries, mainly because of the high cost involved in the analysis. Analysis of pesticide residues in food produced in Togo (Africa) [28], in Ghana (Africa) [29], and in Bolívia (América do Sul) [30] reported data on pesticide residues exceeding the MRL and ADI values, increasing the potential risks to consumers, and thus confirming the urgency on guaranteeing food safety through effective pesticide monitoring programs [11].

ADI values are estimate according to Eq. (1)

$$\mathrm{EDI}x = \frac{\sum(\mathrm{C}xy * \mathrm{FC}y)}{\mathrm{bw}} \tag{1}$$

in which

- EDIx is the estimated daily intake of pesticide x
- Cxy is the concentration of pesticide x on food item y
- bw is the body weight of the individual
- FCy is the food processing factor of food item y, as utilized by Lehman et al. [11]. The significance of FCy depends on the combination of pesticides, crops, and processes.

Diet plays an important role in pesticide risk assessment. In order to assess pesticide risks to human health, a dietary assessment method factoring history and frequency of ingestion of certain food items should be used. Moreover, regional and cultural factors should be taken into account, particularly when using national averages to estimate exposure in large countries. A wide variety of dietary survey methods exists, with each one presenting a series of advantages and disadvantages The 24-h recall method proposed by Gibson and Ferguson in 1999 [31] is an example of dietary assessment method which quantifies all food items and drinks ingested during a period of 24 h prior to the interview. Quality of data thus depends on both good memory and cooperation of the interviewee, as well as the interviewer's ability to maintain an open communication channel. The 24-h recall method is noninvasive, quick, and practical for both interviewer and interviewee.

Acute and chronic pesticide risks can be evaluated using a hazard quotient – HQ. In the case of exposure to pesticides, an HQ is defined as the ratio of the amount

of pesticide ingested and the ADI or ARfD for acute and chronic risks, respectively, as shown in Eqs. (2) and (3).

$$\text{HQacute} = \frac{\text{EDI}}{\text{ARfD}} \tag{2}$$

$$\text{HQchronic} = \frac{\text{EDI}}{\text{ADI}} \tag{3}$$

Since ADI and ARfD express the level at which no adverse effects are expected following ingestion of pesticide residues, if HQ is calculated to be less than 1, then no adverse health effects are expected as a result of exposure.

The vast majority of the studies performed in the last decade only consider individual data, to the detriment of the understanding of cumulative risks of pesticides. Daily exposure is not limited to one specific pesticide. On the contrary, people are exposed to a variety of pesticide residues via ingestion of multiple food items containing a combination of pesticide residues. Dallegrave et al. [3] found several pyrethroid residues in samples of milk, eggs, fish, chicken, and beef. In milk, there were found as many as five different pyrethroid residues. Li et al. [12] analyzed 1,450 samples of fruit, including apples, grapes, pears, and peaches. At least two and as many as four different pyrethroids of the same chemical class were detected on approximately 30% of the samples. In those cases, a simultaneous assessment including cumulative risk would therefore be preferred [7].

Pyrethroid residues of the same chemical class present similar mechanisms of action. Thus, the exposure effects and human health risks are cumulative, and a cumulative risk approach is crucial [7, 10]. Current reports referring to cumulative risk assessment of pesticide residue mostly focus on two methods, the HI and the RPF methods. Boobis et al. [32] reported data utilizing the hazard index (HI) (Eq. 4) defined by Teuschler and Hertzberg [33] as is the sum of HQs of pesticides of similar toxic effects.

$$\text{HI} = \sum\nolimits_{i}^{n} \text{HQ}i \tag{4}$$

As HI values are dependent on HQ values, HIs larger than 1.0 are not considered acceptable.

In the relative potency factor (RPF) approach, the toxic potency of each pesticide residue in the mixture is compared to that of an index chemical generating a relative measure of potency for each residue. For pyrethroids, the RPF approach is usually combined to dose additivity (when the effect of the combination is the effect expected from the equivalent dose of an index chemical) as pyrethroid, carbamate, and organophosphate pesticides present similar neurotoxicity [10, 34]. Thus, the cumulative risk is assessed as an equivalent dose or the sum of pesticide residue doses scaled by their potency relative to the index chemical [35]. The equivalent dose is then compared to reference values for ADI and ARfD. Those methods are used to assess cumulative risks related to ingestion of a food product containing

residues of different pesticides, ingestion of different food items containing residues of one specific pesticide, or ingestion of several food items containing residues of different pesticides. Other approaches can estimate cumulative risk, such as margin of exposure (MoE), the ratio of no-observed-adverse-effect level (NOAEL) obtained from animal toxicology studies to the predicted and estimated exposure dose, and cumulative risk index (CRI), the reciprocal of the HI because both are based on reference values [5, 32, 36].

Evans et al. [36] calculated cumulative risk HIs and individual risk HQs of 67 pesticides in 5-year cumulative data provided by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) for 13 different regions (Global Environment Monitoring System – Food Contamination and Assessment Programme) [37]. Presence of isomers was considered. Individual risk assessment showed an HQ larger than 1 twice only for chlorpyrifos-methyl. Cumulative risk assessment showed HIs larger than 1 for all regions. Region B, comprising Africa, Europe, and Middle East, showed a surprising HI larger than 10. Calculated HIs suggest a great contamination risk and call for broader collection and more refined treatment of data. When HI values exceed 1, HQ distributions can help in identifying the compounds with more significance to the cumulative risk and how the risk assessment model can be adjusted to incorporate those effects [36].

The European Food Safety Authority (EFSA) devised a methodology to classify pesticides into cumulative assessment groups, or CAGs. The methodology rests on the assumption that pesticides causing the same specific effects can produce cumulative toxicity – even if they do not have similar modes of action. CAGs are defined according to pesticides' chemical structure, toxicity mechanisms in mammals, and common toxic effects [38]. Cumulative risk assessment is then defined from CAG data based on hazard identification (effects specific to vulnerable populations and effects from stressor interactions) for further determination of the dose-response assessment (dose-response for sensitive populations, toxicological interactions, and combined doses of multiple stressors) and exposure assessment (multiple exposure routes and pathways, social, cultural, and economic factors that influence exposure) concluding with risk characterization (uncertainties associated with combining risks and qualitative factors affecting risk outcomes) [38]. The US Environmental Protection Agency (EPA) defined the CRA for five different classes of pesticides: organophosphates, N-methylcarbamates, s-triazines, chloroacetanilides, and pyrethrins/pyrethroids. The most recent CRA regarding pyrethroids was published in 2011 and includes a class of pyrethroids which trigger neurotoxicological effects via voltage-gated sodium ion channel through the cell membrane. All pyrethroids were classified under only one CAG, with deltamethrin as index compound (IC). The IC is selected to model the associated risk and extrapolate the estimated exposure levels in the population, thus decreasing errors and uncertainties in the risk assessment estimates. Pyrethroids with toxic potential significantly lower than IC and those with no detectable residues in monitoring were disregarded.

According to the EFSA, pesticides may cause toxic effects at multiple sites by a single mode of action. Therefore, substances can be grouped in more than one CAG. The effects considered for the establishment of reference values (ADI and ARfD) are

not necessarily representative for the CAGs, i.e., an effect observed at higher dose levels may be the specific effect relevant for grouping.

Risk assessment should consider vulnerability factors such as genetics, lifestyle, differential exposure to pesticides (including diet and distance from place of application), manufacturing processes, and recovering capacity. Moreover, food products are exposed to a myriad of pesticides and chemicals, not only to pyrethroids. For that reason, a more complete analysis employing the mixture risk assessment (MRA) approach is necessary. Even though there might be a consensus regarding cumulative risks and exposure to pesticides, the pathway to the formulation of an adequate regulation is still vague.

6 Uncertainties Associated with Exposure Assessment

Dietary exposure assessment methods are strongly affected by scientific uncertainties related to the sampling procedure which should be taken into account when interpreting the results, for example, duration of exposure, sampling sites, body weight, concentration of pyrethroid in food samples and uncertainty of the analytical techniques utilized, whether a food item or a food group has been sampled, and food processing levels. Moreover, specific characteristics of the population, such as pregnancy, breastfeeding, age, kidney or liver disorders, and hypersensibility to pesticides, are extremely important and should be carefully considered when deciding on a sampling procedure [12].

7 Perspectives

Future research efforts on the assessment of the risks related with the exposure to pesticides should focus on the analysis of total cumulative intake, considering the specifics of different population groups. The constitution of a dependable database on pesticide residues in food, water, and air is crucial to the human health and environment risk assessment. Through dietary habits, the entryway of pesticide residues into the human body, we are exposed to multiple harmful chemical substances. It is imperative that a thorough cumulative risk assessment of mixtures of pesticides is performed, providing reliable data.

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