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EVALUATION OF HUMAN HEALTH RISKS ASSOCIATED WITH PESTICIDE DIETARY INTAKE - AN OVERVIEW ON QUANTITATIVE UNCERTAINTY ANALYSIS

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Abstract

The probabilistic estimation and the risk analysis of the exposure to pesticides through the ingestion of plants and food products is an important task for ensuring informed decision making and appropriate consumer protection. Monte Carlo-based methods are powerful tools in this regard, allowing for the empirical estimation of the distribution of exposure values, as well as for carrying out a corresponding uncertainty analysis. Such findings are important for assessing the exposure risk for multiple categories of the general population, divided by age groups, body weight, food consumption etc. The general model used for determining the exposure allows for a detailed assessment and analysis of the distribution of exposure values along a determined range, and of the probabilities of occurrence for acute and chronic exposure levels, while also accounting for potential uncertainties in the input parameters. Researchers in the related fields propose various probabilistic approaches using several distribution shapes to estimate each parameter of the model. Furthermore, the related literature contains a series of guidelines for carrying out the aforementioned tasks, for various types of data with a wide assortment of distributions. Consequently, this study presents a general framework and characterization of exposure as a result of food consumption, as well as common practices for carrying out an assessment of exposure levels, with an emphasis on significant related work from the state-of-the-art in the field. The findings of the present study indicate that probabilistic approaches are powerful tools for aiding the regulatory decision-making process in the case of acute or chronic dietary exposure.

Key words: exposure, fruits and vegetables, Monte Carlo analysis, pesticide residues, probabilistic modeling

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1. Introduction

In order to provide and ensure safe fruits and vegetables for consumers and to protect human health, monitoring programs often involve measuring and comparing the pesticide residues with established maximum residue levels (MRLs). The data retrieved by the continuous monitoring programs at national and

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international levels can be further used to assess dietary exposure, an important indicator for risk and benefit analysis (Kettler et al., 2015; Sieke et al., 2018). Estimating the values and distributions of such indicators, as well as understanding the related uncertainties in risk analysis constitutes important bases for providing transparent, meaningful information to support decision making in the related areas regarding food consumption. Health risks associated with pesticide dietary intake are usually carried out for single components even if usually the human exposure occurs for more than one component (such as when multiple pesticides are used concurrently). Traditionally, in order to assess the risk of human exposure, individual exposure values can only be estimated simultaneously if the components have the same toxicological endpoints and similar action mechanisms (Boon et al., 2008; Kettler et al., 2015). The assessment of uncertainties in probabilistic risk assessments compared to classic deterministic methods has the potential to provide more in-depth estimations of the required levels of consumer protection as identified in real-world situations.

Probabilistic modeling techniques have been receiving increased attention in risk assessment since they allow the analysis of both uncertainty and variability (Boon et al., 2008; Ferrier et al., 2006; Kim et al., 2013; van der Voet and Slob, 2007). Since in most cases a direct analytical solution is either too complex or unavailable, simulation methods such as Monte Carlo analysis constitute a viable way of carrying out probabilistic modeling to quantify both uncertainty and variability. Monte Carlo-based approaches are frequently used to perform quantitative uncertainty analysis applied for risks associated with pesticide residues by dietary intake. One frequently-encountered problem in existing uncertainty analysis approaches is that certain key sources of uncertainty such as experimental errors or modeler subjectivity are ignored (Dubus et al., 2003). Given this background, the key objectives of this paper are:

- understanding the main context and concepts used in exposure assessments for human health risk analysis;
- providing an overview of the quantitative uncertainty analysis of pesticide residues in food considering deterministic and probabilistic modeling approaches, as well as of the steps in performing probabilistic modeling and characterizing the uncertainty and variability;
- providing some practical examples of Monte Carlo simulations as part of probabilistic modeling to identify the risks to human health posed by pesticide residues in fruits and vegetables.

2. Assessing exposure to pesticides in food products

2.1. Exposure and human health risks from pesticide residues in food

Exposure assessment is defined by United States Environmental Protection Agency (USEPA, 2002) as *"the process of estimation or measurement of the magnitude, frequency, and duration of exposure to an agent, along with the number and characteristics of the population exposed. During the process it's necessary to describe and identify the sources, routes, pathways and uncertainty factors."*

Three pathways were identified in assessing human exposure to pesticide residues in food (Cozma et al., 2017; Preda et al., 2012; USEPA, 1992):

- *Inhalation* (e.g. pesticide vapors, dust, or spray particles);
- *Dermal contact* (i.e. direct contact with pesticide residues on the contaminated surfaces of various objects or food products);
- *Ingestion* (i.e. consumption of food or drinking water contaminated with pesticide residues).

Depending on their chemical and physico-chemical properties, pesticide residues, once ingested along with contaminated food, are partially absorbed by the gastrointestinal tract, causing several toxic effects in various organs (Fig. 1). Considering the potential behavior of pesticides in the human body, it can be concluded that the intestines, the liver and the bile are the organs most exposed to pesticides. However, pesticides may also transported to other organs through blood and lymph, potentially affecting their normal functions (Chedik et al., 2017; Genuis et al., 2016; Singh et al., 2017; USEPA, 2004).

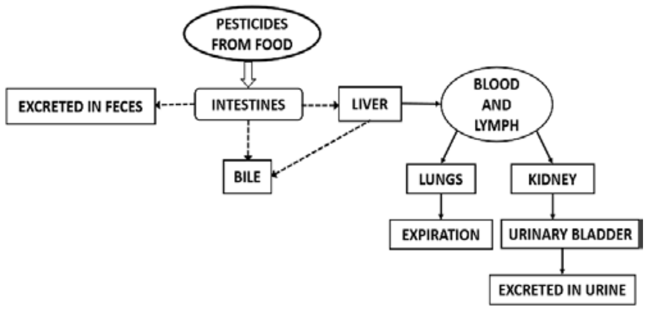

Fig. 1. Routes of absorption, distribution and excretion related to the human exposure to pesticide from food (adapted after Singh et al., 2017)

Given that the intestines have the primary role of absorbing nourishing elements from food, they are also responsible for absorbing toxic compounds along with them (Chedik et al., 2017; Genuis et al., 2016). According to the study conducted by Chediket al. (2017), approximately 81.4% of pesticides (the percentage of predicted intestine-permeant molecules being high for the triazines, followed by the carbamates, organophosphorus pesticides, miscellaneous pesticides and the pyrethroids) are absorbed by the intestines with a high yield (96%) and once a chemical has entered the bloodstream, it is rapidly distributed throughout the body. Of the total amount of pesticides absorbed and distributed to the various organs, only a small part is eliminated through sweat or urine, while the rest accumulates into the body causing irreversible organ damages (Genuis et al., 2016).

2.1.1. Acute and chronic exposure

Some of the many adverse health problems caused by acute or chronic exposure resulting from the ingestion of food products contaminated with different levels of pesticide residues are presented in Fig. 2.

Studies on animals demonstrated that the acute effects appear in less than 24 hours, usually after one-time contact with high levels of pesticide residues, while prolonged exposure to low levels of pesticide causes the appearance of chronic effects in various organs. The main factors influencing acute or chronic exposure to pesticides are the frequency and duration of exposure, the level of exposure and the toxicity of the pesticides that are taken into consideration in the risk assessment process (Cozma et al., 2017; Roșca et al., 2017). As shown in Fig. 2, the toxic effects of acute exposure are quite different from those caused by chronic exposure, manifesting particularly as discomfort and body malaise. Chronic exposure has much more serious effects, potentially causing irreversible damages and even death (Nicolopoulou-Stamati et al., 2016).

The majority of studies conducted to establish the potential effects of pesticides had a particular interest in the evaluation and management of the human health risks caused by the presence of pesticides, especially in food products. The risk posed by pesticides is closely related to their toxicity, the amount ingested, inhaled or absorbed, the route and duration of the exposure and also by the number and types of pesticides to which humans are exposed concurrently (Boobis et al., 2008; Moretto et al., 2017; Sexton et al., 2012; Stoleru et al., 2016). Because it is not possible to change the inherent toxicity of pesticides and also successfully use them for the desired purpose, it is necessary to take a series of measures to prevent or to reduce as much as possible the human exposure to these types of substances (Boobis et al., 2008).

2.1.2. Cumulative risk assessment

The cumulative risk was defined for first time by the Environmental Protection Agency of United States - USEPA (USEPA, 2002) as "*the risk of a common toxic effect associated with concurrent exposure by all relevant pathways and routes of exposure to a group of chemicals that share a common mechanism of toxicity*". The World Health Organization (WHO) through the International Program on Chemical Safety considered the term "cumulative" as inadequate and recommended its replacement with "combined exposure to multiple chemicals". Thus, taking into account the positions of the USEPA and WHO organizations, in European pesticide regulations the phrasing "cumulative risk assessment" is considered equivalent to "combined exposure to multiple pesticides" (EFSA, 2013).

Considering the reports published by national and international agencies regarding the methods for the cumulative risk assessment of pesticides in food, it can be emphasized that no general framework was yet established (Boobis et al., 2008). Each proposed framework has a common purpose, specifically to identify the fundamental elements and basic principles for assessing the cumulative risk due to the simultaneous ingestion of multiple pesticides.

Developmentally, these frameworks use two approaches for the assessment of the cumulative risk of pesticides (Moretto et al., 2017):

- the first approach involves the evaluation of the potential health effects of singular pesticide categories, considering a hypothetical population and exposure;
- according to the second perspective, the assessment of cumulative risk consists in the identification and consideration of all potential pesticides that can induce observed negative effects to a certain category of population.

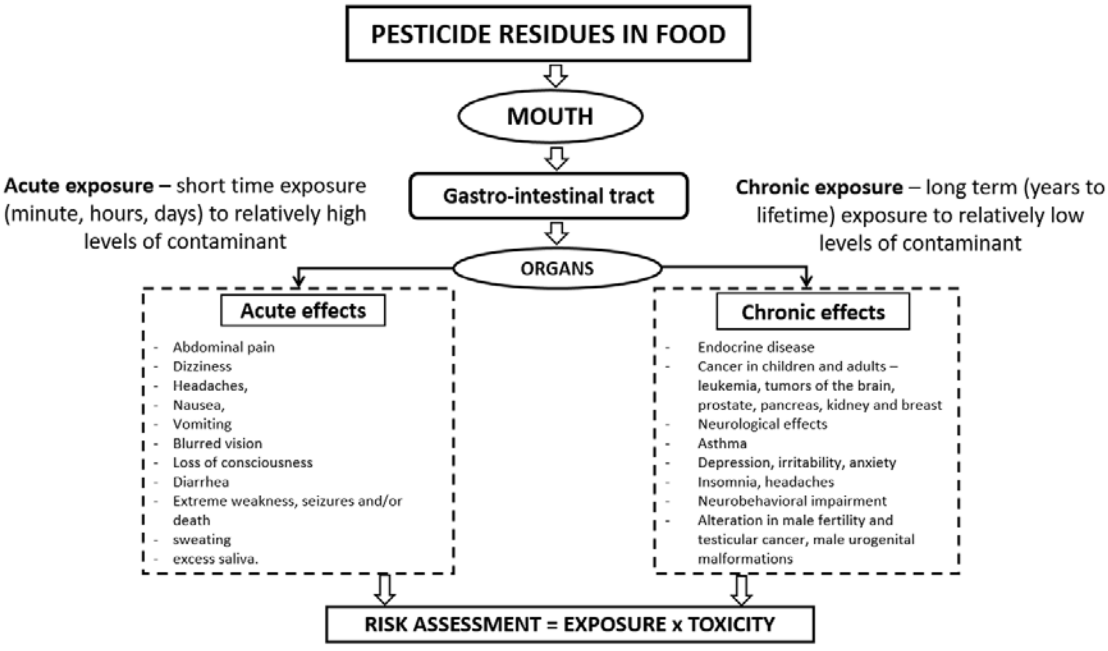

Fig. 2. Acute and chronic effects to human health caused by exposure to pesticide residues from food

The majority of cumulative risk assessment methods and methodologies were developed based on the first approach, which involves the assessment of the potential effects caused by a category of pesticides (Moretto et al., 2017; Sexton et al., 2012). The cumulative risk assessment framework proposed and described by USEPA in "*Guidance on Cumulative Risk Assessment of Pesticide Chemicals that Have a Common Mechanism of Toxicity*" involves 10 distinct steps (Fig. 3), which must be taken into account for the organization and explanations of the decision-making process (USEPA, 2002).

The cumulative risk assessment process is complex, summing up the individual risks of pesticides based on some criterion related to their effects and properties. Starting from this principle, a variety of methods were developed only for the "*cumulative risk of pesticide chemicals that have a common mechanism of toxicity*" (Boobis et al., 2008). The most frequently-applied methodologies consider factors such as the hazard index, adjusted hazard index, cumulative risk index (CRI), reference point index (RPI), combined margin of exposure (MOET), toxic equivalency factor (TEF), potency equivalency factor(PEF) or relative potency factor (RPF). These methodologies were developed based on the reference points (e.g. points of departure or PODs) or the reference values (e.g. acceptable daily intake, ADI, acute reference dose, aRfD), also considering several uncertainty factors (Boobis et al., 2008; Sexton, 2012). The methods and methodologies specified above are widely discussed in both EFSA and USEPA official documents (EFSA, 2013; USEPA, 2007), and in many studies conducted for cumulative risk assessment caused by the presence of pesticides in fruits and vegetables (Boobis et al., 2008; Moretto et al., 2017; Sexton, 2012). However, according to Regulation (EC) No. 396/2005 on maximum residue levels (MRLs) of pesticides in food and feed *"….in view of human exposure to combinations of active substances and their cumulative and possible aggregate and synergistic effects on human health, MRLs should be set after consultation of the European Food Safety Authority…"* (Regulation (EC), (2005). Taking into account MRL settings, two possible scenarios are known for cumulative risk assessment: acute and chronic exposure. These scenarios are briefly discussed in Boobis et al. (2008) work.

2.2. Quantitative uncertainty analysis of pesticide residues: an overview on current methods

2.2.1. Essentials of deterministic and probabilistic modeling approaches

Additives such as artificial dyes, artificial flavors, emulsifiers, nitrites or pesticides such as insecticides, fungicides or rodenticides are added to crops and food products in order to preserve their quality or for pest control, respectively. These chemicals have various adverse effects on human health, thereby requiring that a series of policies, laws and regulations be implemented in order to minimize the toxicity of food products.

One way of detecting the extent to which these substances pose a threat to consumers is to conduct risk studies which focus on exposure assessment (Boon and van der Voet, 2015). In this context, various exposure models are employed in order to estimate the amount of potentially-harmful chemical intake via food by the human population. Dietary exposure assessments can be performed using various risk analysis tools capable of carrying out a wide range of tasks, such as lower tier or higher-tier (probabilistic) analyses, or the determination of short-term intake or long-term exposure (Stephenson and Harris, 2016).

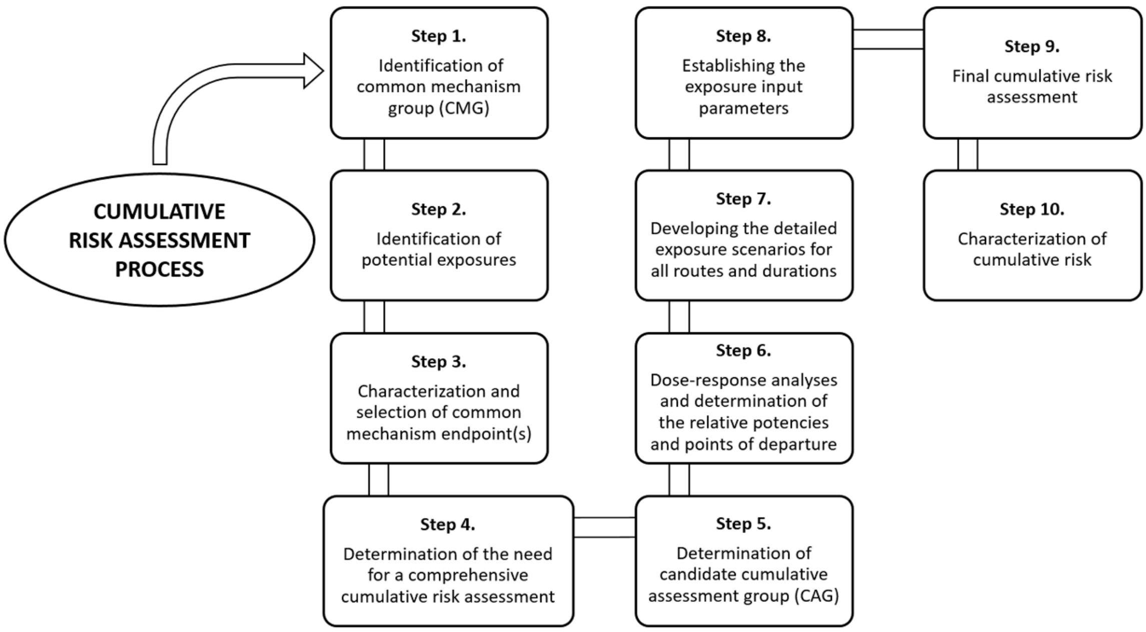

Fig. 3. Cumulative risk assessment framework of the Common Assessment Group (CAG) proposed by USEPA (USEPA, 2002)

The main risk analysis tools for estimating exposure to pesticide residues via dietary intake and their respective approaches are included in Table 1.

An accurate risk assessment is based firstly on *experimental methods* focused on identifying chemical residues in food (for example by means of High Performance Liquid Chromatography (HPLC) and Liquid chromatography mass spectrometry (LC–MS/MS) methods) and, secondly, on *statistical methods* which involve deterministic and probabilistic modeling.

Higher-tier approaches must be considered when more precision in the exposure estimation is necessary. These models are also referred-to as probabilistic models (Boon and van der Voet, 2015). In the past, deterministic models were frequently applied due to their ease-of-use, since they involve solving simple equations and models using standardized methods. These models use fixed values and combine a single high-level consumption event with a single measured residue value providing a single output (in other words a single point estimate of exposure). Unfortunately, this is often insufficient for real-world scenarios. Conversely, a probabilistic approach also takes into account the variability and uncertainty of the model parameters, thus significantly increasing the complexity of the related methodologies. The outputs of a probabilistic method are provided in the form of distributions of risk / exposure levels, considering the food consumption data amongst individuals within a population (He et al., 2015). Furthermore, a probabilistic model can also be used to estimate the dietary exposure by taking into account the variation of the exposure induced by the variation in consumption patterns among individuals (Boon and van der Voet, 2015). Some of the typical characteristics of probabilistic approaches are presented in Fig. 4, while Fig. 5 illustrates the main informational resources available for developing probabilistic assessments.

2.2.2. Steps in performing probabilistic modeling

A Monte Carlo simulation is *"a technique for characterizing the uncertainty and variability in exposure estimates by repeatedly sampling the probability distributions of the exposure equation inputs and using these inputs to calculate a range of exposure values"* (USEPA, 2001). A Monte Carlo simulation may be used to assess acute (or short-term) exposure related to acute toxicity which covers a period of up to 24h, and chronic (long-term) exposure related to chronic toxicity which covers a longer period of time. The simulation may also account for variations and uncertainties in the input data (food consumption data, pesticides residue levels and body weight) (Jensen et al., 2008). Food consumption data are usually obtained from nationwide dietary surveys carried out for a given population (e.g. Freshfel Consumption Monitor estimates a value of 167.62 g/capita/day fruit consumption in 2012) (FRESHFEL, 2014; Hlihor et al., 2016). Pesticide residue data may result from a monitoring program, from experimental studies or from total diet surveys during a period of time and from different commodities (fruits, vegetables, etc.).

The body weight of a population is typically divided into subgroups, most commonly according to gender and age. For example, the average body weight for the population in Europe was estimated as being 70.8 kg for adults (Walpole et al., 2012), and 23.1 kg for children (age group, 3 to < 10 years) (EFSA, 2012; Hlihor et al., 2016). Exceptional cases exist however, such as pregnant women, unborn babies and infants, which are more vulnerable to pesticide residues (EFSA, 2012). Eq. (1) provides an example of a frequently used and effective model for the determination of both acute and chronic exposures (Hlihor et al., 2016):

Dietary exposure = concentration of pesticide residues detected in food (mg/kg) x food consumption rate (or food intake) (kg/person/day)/body weight (kg) (1)

Table 1. Available risk analysis tools for estimating exposure to pesticides residues via dietary intake

Risk analysis tools	***Approach***	***Reference***
European Food Safety Authority (EFSA) Pesticide Residue Intake Model (PRIMo)	deterministic	EFSA (2006) https://www.efsa.europa.eu/en/applications/pesticides/tools
German NVS-II and VELS models	deterministic	BfR (2012)
Pesticide residues and acute risk assessment -the USEPA approach	deterministic	US Environmental Protection Agency (USEPA)
Equations for the national estimate of short-term intake (NESTI) (CRD's acute consumer risk assessment spreadsheet version)	deterministic	http://www.hse.gov.uk/pesticides/topics/pesticide-approvals/pesticides-registration/data-requirements-handbook/consumer-exposure.htm
World Health Organization (WHO) Global Environment Monitoring System (GEMS/Food) consumption cluster diets - IEDI (International Estimated Daily Intake) model	deterministic	WHO/FAO (2014)
Dutch National Institute for Public Health and the Environment (RIVM) Monte Carlo Risk Assessment (MCRA) probabilistic tool	probabilistic	van der Voet et al. (2014)
Dietary Exposure Evaluation Model (DEEM) for probabilistic dietary exposure	probabilistic	USEPA https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/deem-fcidcalendex-software-installer

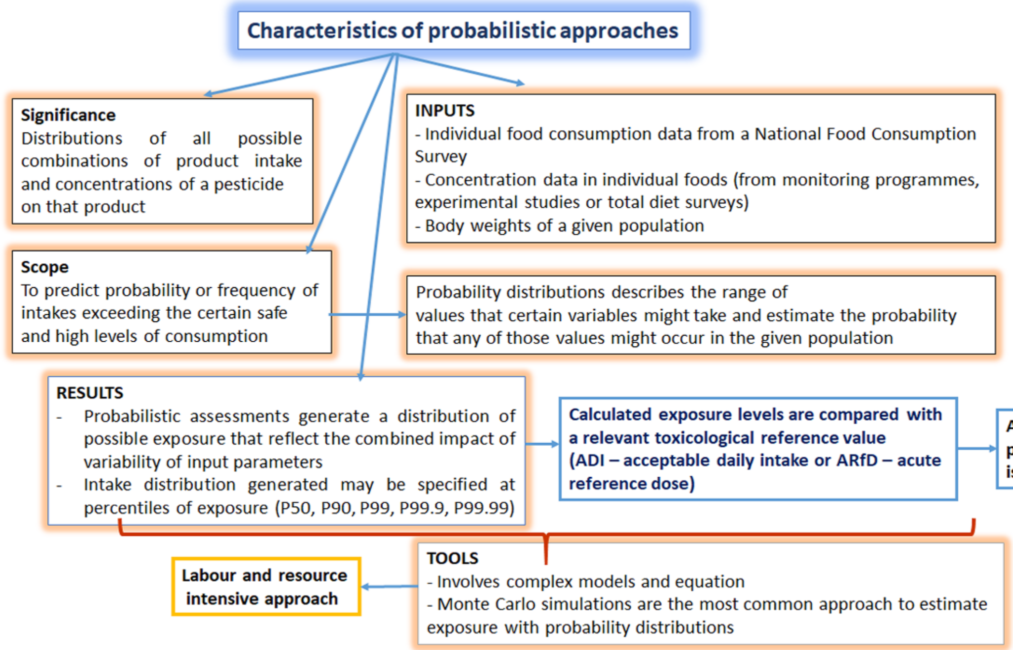

Fig. 4. Typical characteristics of probabilistic approaches

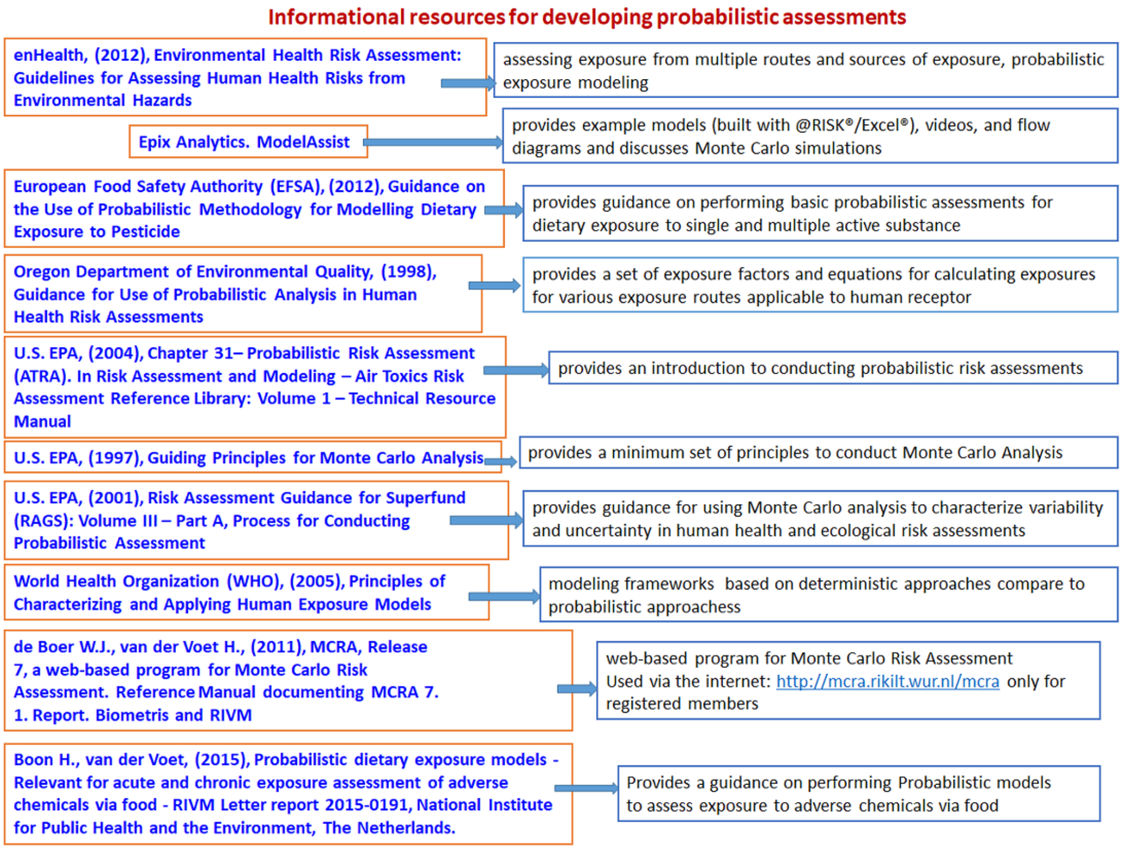

Fig. 5. Informational resources for developing probabilistic assessments (updated upon https://www.epa.gov/expobox/exposure-assessment-tools-tiers-and-types-deterministic-and-probabilistic-assessments)

Essentially, a dietary exposure model combines food consumption data with the concentrations of pesticides residues detected in the related food category, considering the body weight of a given population (Fig. 6). The results in terms of *intake* expressed in *mg/kg body weight/day* are then compared to a relevant guidance value of the category of food in question. The default, deterministic manner of exploiting this model is to directly determine exposure based on singular values of the input parameters. This is the simplest and most basic approach. Conversely, in a probabilistic approach, the goal is to determine (or at least estimate) the distribution of the exposure as a random variable, considering that some or all of the input parameters are also random variables with known distributions. A potentially-useful result in this regard is the determination of the probability to occur or to exceed pesticide exposure reference values or toxicological references values, namely, ADI (acceptable daily intake), aRfD (acute reference dose) and cRfD (chronic reference dose). Several extensions may be added to the basic model such as (EFSA, 2012):

- **processing factors**, which account for changes in the nature and quantity of pesticide residues during processing of agricultural products (including peeling, juice preparation, cooking, storage, freezing etc.);
- **variability factors**, used to measure the variation of pesticide residues among individual product units;
- **food conversion factors**, used for the conversion of compound foods consumed as recorded in dietary surveys into their individual products (e.g. transforming the consumption of apple juice, apple pie into apples);
- **units of measurement**, used to divide the quantities of food recorded in dietary surveys into individual articles for certain commodities.

The output distribution generated by the Monte Carlo simulation may be expressed by mean, 90th, 95th, 97.5th, 99th or 100th percentiles of intake (for example, P95 which corresponds to 5 µg/kg bw per day means that 95% of the population has an exposure of 5 µg/kg bw per day or less). A challenging issue in Monte Carlos analysis is to select appropriate distributions for the parameters of the model. The distributions types should be chosen by taking into account the characteristics of the variable (e.g. continuous or discrete, the range and boundary values of the variable, whether the distribution is skewed or symmetrical etc.). If a proper distribution cannot be selected, bootstrapping techniques may be applied to generate the form of the distribution (Lipton et al. 1995). A series of tables with parameters and associated distributions are reviewed by Binkowitz and Wartenberg (2001), Ferrier et al. (2006), Lipton et al. (1995) etc.

2.2.3. Characterizing uncertainty and variability in dietary exposure assessment

WHO/IPCS (World Health Organization/International Program on Chemical Safety, 2008) defines uncertainty as *"imperfect knowledge concerning the present or future state of an organism, system, or (sub-) population under consideration"*. In other words, uncertainty arises due to a lack of information about a variable, various relationships among variables, inputs, the type of the model, exposure scenarios (Kettler et al. 2015). On the other hand, variability is defined as *"a quantitative description of the range or spread of a set of values"* (USEPA, 2011). A clear description of the two terms is presented in Fig. 7.

4. Case studies

In order to estimate the risk of exposure to pesticide residues detected in different categories of food on human health, various probabilistic models/methods, many of which are based on Monte Carlo simulations, analysis, and bootstrapping, may be used.

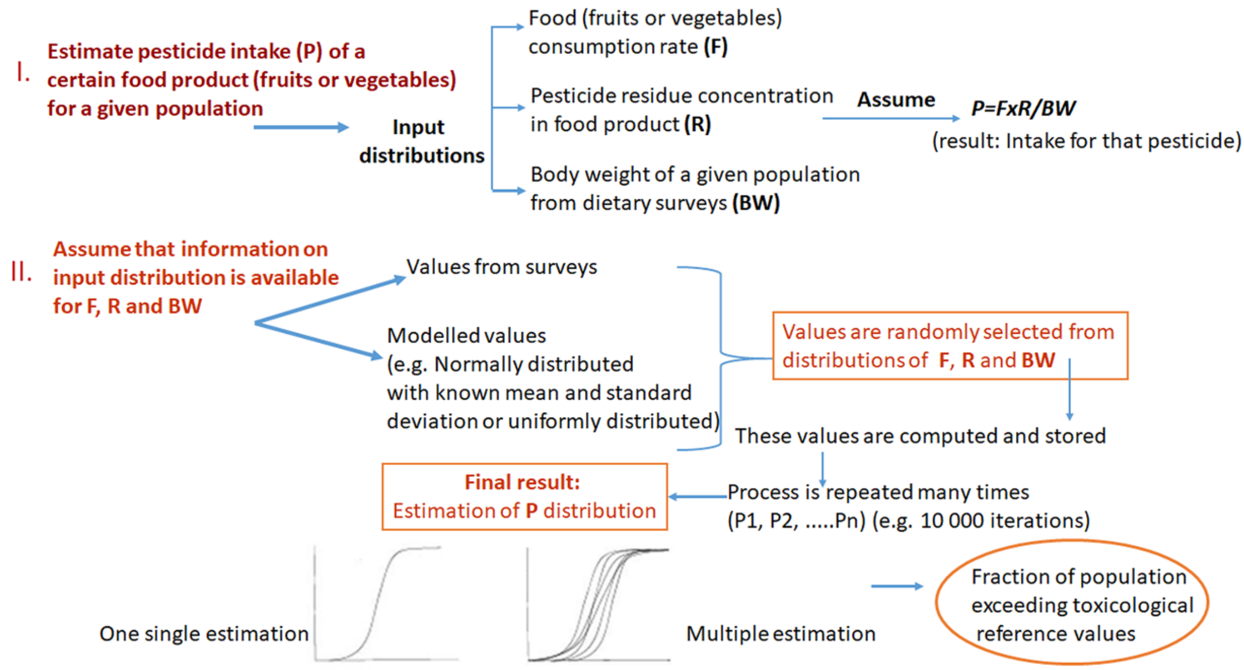

Fig. 6. Monte Carlo method to estimate pesticide intake for a given population (updated upon Ferrier et al., 2002)

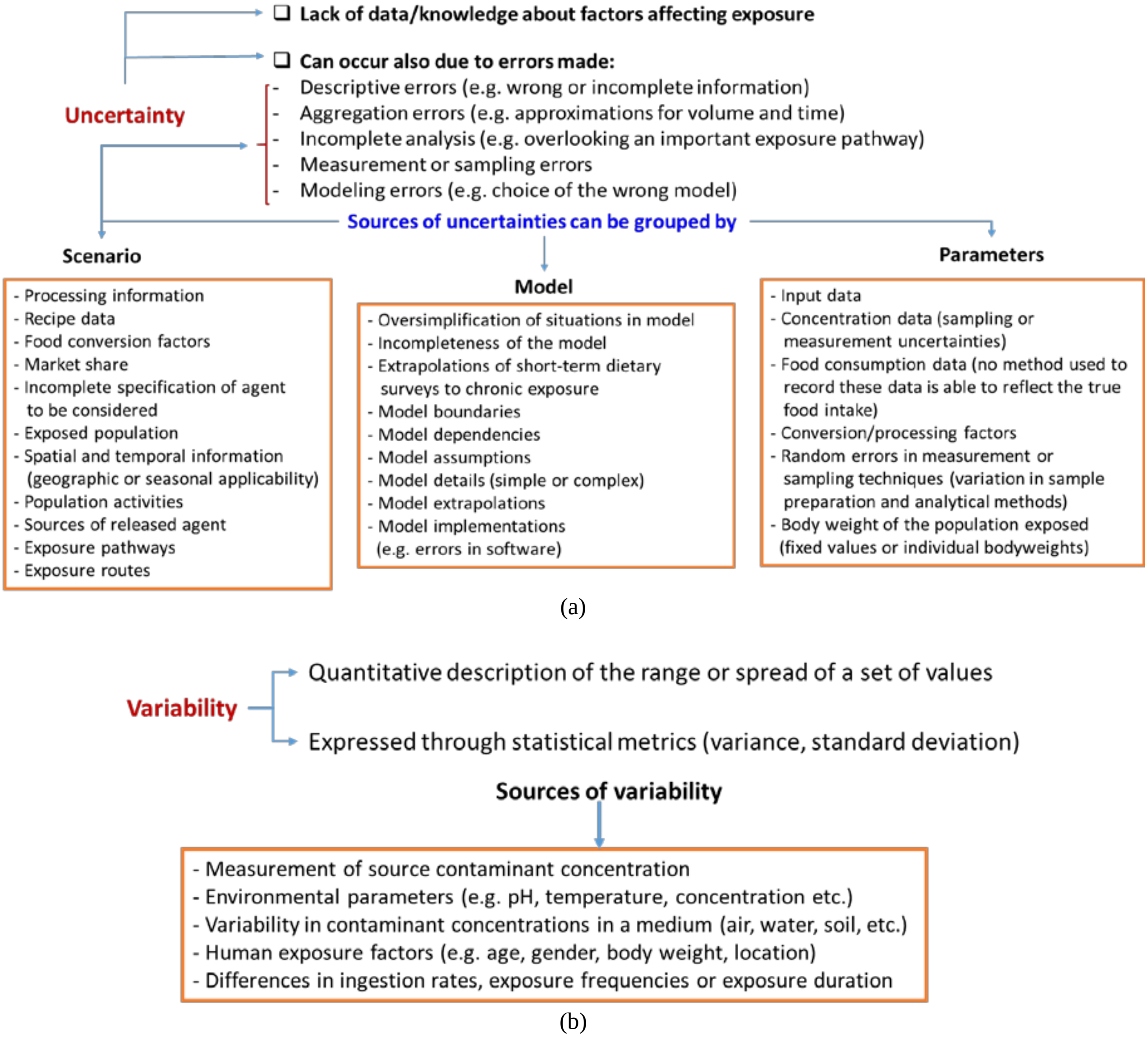

Fig. 7. The main characteristics of (a) uncertainty and (b) variability
(adapted upon: https://www.epa.gov/expobox/uncertainty-and-variability; Kettler et al., 2015)

These methods were applied in numerous studies for the estimation of cumulative risk, acute ingestion dose and/or chronic dietary exposure induced by the presence of pesticide residues in fruits and vegetables (Table 2). Multiple authors from the related literature apply various probabilistic modeling methods in order to analyze and overcome uncertainties in risk assessments (Chen et al., 2017; Huan et al., 2016; Jensen et al., 2008). In a deterministic risk assessment, Huan et al. (2016) showed that the estimated short-term intakes (ESTIs) of carbofuran were between 1199.4% and 2621.9% of the acute reference doses (aRfD), while the rates were between 985.9% and 4114.7% when using probabilistic assessment, further indicating that between 4.2-7.8% of subjects present unacceptable acute risk of exposure to carbofuran-contaminated cowpeas from five provinces.

In this study, all estimations are based on conservative assumptions. Jensen et al. (2008) compared the results of deterministic and probabilistic methods for the assessment of the chronic risk of exposure to dithiocarbamate for Danish adults and children, and found nearly the same mean value: 0.08 μg/kg bw/day and 0.22 μg/kg bw/day corresponding to 0.16% and 0.44% of the ADI of 50 μg/kg bw, respectively. At the P99.9% percentile, the intakes for adults and children were 0.35 μg/kg bw/day (0.70% of the ADI) and 0.76 μg/kg bw/day (1.5% of the ADI), respectively. The authors concluded that using the probabilistic approach instead of the deterministic one in the calculation of the chronic intake provides insights on the exposure at different percentiles. The highest intake was estimated to be 2.35 μg/kg bw/day (4.7% of the ADI) for both adults and children.

The investigations of Blaznik et al. (2016), Boon et al. (2008, 2009), Jensen et al. (2009) involved the probabilistic approach of MCRA cumulative risk assessment for organophosphorus compounds present in various fruits and vegetables. Blaznik et al. (2016) concluded that for the schoolchildren from thirty-one primary schools, apples, bananas, oranges and lettuce had the most significant contribution to the total acute pesticide intake. Furthermore, the results indicated that the exposure to organophosphorus and carbamate pesticides is not a health concern with the assessed dietary patterns of fruit and vegetable consumption.

Table 2. Summary of some studies that used the probabilistic models/methods for the risk assessment of pesticides in food

Model/ method used	***Pesticides***	***Age of population***	***Body weight***	***Type of food***	***Percentiles of exposure***	***Exposure***	***Reference***
MCRA - Cumulative risk assessment	Organophosphorus insecticides (OPs) Carbamates	1-68 years	12-107 kg	Different fruits and vegetables	P99.9	23 µg/kg bw/d for OPs 0.64 µg/kg bw/d for carbamates	Boon et al. (2008)
MCRA - Chronic dietary exposure using a probabilistic approach	Glyphosate	Children: 2-6 years Adults: 19-30 years	Children: 14.5 kg Adults: 75.2 kg	Different fruits and vegetables processed or not	P99.9	Children 0.64-4.49 µg/kg bw/d Adults 0.17-2.89 µg/kg bw/d	Stephenson and Harris (2016)
Chronic and acute exposure risks using Monte Carlo sampling method	Carbofuran	Children: <=11 years Youngster: 12-18 years Adult: 18-60 years Elder: >60 years	Children: 21.2 kg Youngsters: 45.9 kg Adults: 62.5 kg Elders: 58.5 kg	Cowpea	P99.9	*Chronic* 1.7%, 1.2%, 1 % and 1.1% of EDIs to ADIs *Acute* 2462.4%, 1533.1%, 1266.4%, 1199.4% of ESTIs to aRfDs	Huan et al. (2016)
Cumulative acute exposure using MCRA 7.1	Organophosphorus esters and carbamates	Schoolchildren: 11-12 years	41.5 kg	24 fruits and vegetables	P99.99	32 µg/bw/day	Blaznik et al. (2016)
Probabilistic exposure assessment using bootstrap method and Monte Carlo sampling	Chlorothalonil	General population: > 1 year	53.2 kg	cucumber, celery, pepper, leaf lettuce, kidney bean and tomato	P99.9	3.353-383.58 µg/kg bw/d	Zhang et al. (2016)
Acute and chronic intake estimation using MCRA 4.0	Dithiocarbamates expressed as carbon disulfide (CS2)	Children: 4-6 years Adults: 15-75 years	Children: 22 kg Adults: 74 kg	26 commodities of fruits and vegetables	P99.9	*Daily acute intake* - children: 28.2 µg/kg bw/d - adults: 11.2 µg/kg bw/d *Chronic Intake* - children: 0.76 µg/kg bw/d - adults: 0.35 µg/kg bw/d	Jensen et al. (2008)
Cumulative acute exposure using MCRA 6.1	Chlorpyriphos and Methamidophos as index compounds	Children: 4-6 years General population: 4-75 years	Children: 22 kg for General population - not available data	Different fruits, vegetables and cereals	P99.99	Children: 5.8 % of aRfD General population: 2.6% of aRfD Children: 115% of aRfD General population: 46% of aRfD	Jensen et al. (2009)
Probabilistic estimation of the exposure using the MCRA 3.5	Dithiocarbamates expressed as carbon disulfide (CS2)	less than 1 year (newborn) up to 110 years	3 kg up to 200 kg (mean of 53.1 kg)	Fruits, vegetables, beans (dry, without pods) and rice (polished)	P99.99	1.32 and 1.84 µgCS2/kg bw/d	Caldas et al. (2006)
Cumulative dietary exposure using MCRA Release 6.0 and 6.1	Organophosphorus pesticides	Children: 2 - 6 years	not available data	91 different raw agricultural commodities	P99.9	19 – 27 µg/kg bw/d	Boon et al. (2009)
Dietary exposure estimation based on a Monte Carlo simulation using the @Risk program	Chlorpyrifos	3 to 65 years	M: 19.25-70.61 kg F: 18.77-60.79 kg	packaged red pepper powders	P95	M: 0.052-0.083 µg/kg bw/d F: 0.051-0.074 µg/kg bw/d	Kim et al. (2013)
	Cypermethrin					M: 0.024-0.039 µg/kg bw/d F: 0.023-0.033 µg/kg bw/d	

Note: MCRA - Monte Carlo Risk Assessment programme; M - male; F - female

Boon et al. (2008, 2009) conducted two surveys considering the probabilistic approach. In the first one, the authors reported the acute cumulative exposure to organophosphorus insecticides (OPs) and carbamates in the Dutch population and young children (1-6 years), according to their respective diets. Spinach contributed most to the exposure to OPs in both age groups, followed by oranges and mandarins. Also, according to the results, about 3% of the composite samples analyzed for OPs and 0.2% for carbamates contained combinations of these pesticides. In the second study, the authors focused on the diet of Dutch children aged 2 to 6, exposed to toxic compounds from fungi and organophosphorus pesticides. The results of the risk assessment indicated that four compounds exceeded the relevant health based limit values (HBLV), namely dioxins, deoxynivalenol (DON), ochratoxin A (OTA) and nitrate. For two compounds, acrylamide and aflatoxin B1, the margin of exposure (MOE) was estimated below 10,000.

Jensen et al. (2009) assessed the cumulative acute exposure of the Danish population to 25 organophosphorus and carbamate pesticide residues, as a result of the consumption of fruit, vegetables and cereals. The authors used the relative potency factor (RPF) approach to normalize the toxicity of the various organophosphorus and carbamate pesticides to the two index compounds, chlorpyriphos and methamidophos. Their results showed a cumulative acute exposure of 1.8% and 0.8% of the acute reference dose (aRfD) for 100 μg kg^{-1} body weight (bw) day^{-1} of chlorpyrifos as an index compound, at the P99.5 for children and adults. When the authors used methamidophos as the index compound, the cumulative acute intakes were 31.3% and 13.8% of the aRfD of 3 μg kg^{-1} body weight (bw) day^{-1} at P99.9 for children and adults.

When applying MCRA for chronic dietary exposure of glyphosate using a probabilistic approach, Stephenson and Harris (2016) estimated that the ADI ranged from 0.03% to 0.90%, depending on whether optimistic or pessimistic hypotheses were made in the calculations. The health risk of chlorothalonil residues to two consumer groups via vegetable exposure was found low by Zhang et al. (2016), and the level of residual chlorothalonil was below the aRfD.

A swift probabilistic risk assessment (sPRA) model was developed by Kim et al. (2013) in order to obtain information on exposure to food hazards before performing complex full-scale risk assessment. The case study was conducted on residual pesticides in red pepper powder. Risk of dietary exposure to hazards was quantitatively estimated by the sPRA model, and the risk of residual pesticide in red pepper powder in Korea was found to be very low. A risk assessment on dithiocarbamate pesticides was carried out by Caldas et al. (2006) using the Monte Carlo Risk Assessment software tool (MCRA 3.5). Daily intakes at the highest percentiles for the general population reached a maximum of 2.0 μg CS2/kg body weight per day (upper band of the 95% confidence interval at P99.99). Tomato, rice, apple and lettuce were found to have contributed the most to the intake.

Duan et al. (2016) conducted a study on monitoring the presence of pesticides groups such as organophosphates, carbamates and pyrethroids in cowpea. The estimated daily intakes (EDIs) were assessed as 9.15-72.89% of ADI, while the probabilistic modeling demonstrated that the exposure to triazophos exceeded the ADI at P99.9.

5. Conclusions

The worldwide application of probabilistic modeling for human health risk assessments indicates an increased interest of researchers, stakeholders and risk managers in methods for the analysis and handling of uncertainties generated by the dietary intake of pesticide residues from consumed food products. In this regard, the main route of exposure is by ingestion of pesticide residues available in food crops due to their widespread availability.

This paper focused on highlighting the importance of probabilistic methods which show a significant potential to provide a more thorough analysis of exposure and health risk, considering the importance of these factors in providing consumer protection in real- world scenarios. Furthermore, the analysis of uncertainty and variability is important to ensure proper and transparent decision-making in the food industry and to raise consumer awareness on food safety issues.

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