

Chapter 3

Key issues in exposure assessment and risk characterization of chemical contaminants in food

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1 Introduction: key steps in risk assessment

Risk analysis has been defined within the Codex Alimentarius as a series of three activities: risk assessment being a scientific process, risk management being the result of policy interactions, and risk communication about the assessment and management decisions. Regarding the risk assessment of chemical substances in food and feed, the Codex Alimentarius adopted the terms "hazard" and "risk". "Hazard" refers to the potential of agents to cause adverse health effects, and "risk" is the probability of health effects when exposed (FAO and WHO, 2024).

The risk assessment of chemicals in food and feed is divided into four separate steps. The first step is the "hazard identification". Using data from human and animal studies, the toxicity of the chemicals is identified, which

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organs and tissues are affected, and its impact on the subject's health. In the second step, the "hazard characterization", the dose-responses of the hazards are quantified. Then the lowest dose level with adverse health effects is identified and converted into a health-based guidance level (HBGV). Relevant HBGVs are the Acceptable Daily Intake (ADI) and the Tolerable Daily Intake (TDI) (Herman J.L. and Younes M., 1999). Benchmark Dose Levels (BMDLs) can also be derived in the hazard characterization; they refer to specific adverse effects, in contrast to an ADI or TDI.

The third step is the "exposure assessment", in which dietary intake of a substance is estimated for a population or sub-populations such as infants, children, and adults, or consumers with a specific diet (e.g. vegetarians). In the fourth step, the "risk characterization", is the dietary intake compared with the HBGV in a quantitative manner. Based on that comparison, the likelihood of adverse health effects is determined (IPCS, 2009).

2 Performing exposure assessments

An exposure assessment does not depend on the toxicological data from the hazard identification and characterization, but on consumption and occurrence of substances. The HBGV is the endpoint of the hazard assessment; many publications present HBGVs, such as EFSA's opinions (EFSA Publications) and JECFA's toxicological monographs (WHO, JECFA). Many exposure assessments deal with the state of affairs of local issues, such as foods sampled in an import control which do not comply with the (EU) standards, or accidental contamination of foods produced in contaminated areas such as heavy metals in vegetables. Most of these cases are evaluated by national food safety authorities, such as Bundesinstitut für Risikobewertung (BfR) in Germany (BfR, 2024), ANSES in France (ANSES, 2024), or the Office for Risk Assessment & Research (BuRO) in the Netherlands (NVWA, 2024). Results of such national evaluations might be published in public sources and/or discussed with the European Commission and the Member States.

According to the risk analysis paradigm of the Codex Alimentarius, risk assessment is science-based, whereas risk management is policy-based. This makes risk assessors independent from the food safety policy framework, with no apparent restrictions on how to perform an exposure assessment. As a result, there are only a few general guidelines about how to perform an exposure assessment. Consequently, there are many opportunities to discuss the results. For the risk manager, this situation is unsatisfactory. A risk manager has to decide on the management options and prefers one conclusion: "safe" or "not safe"; this is to be interpreted as: "actions not needed" or "actions needed".

The dietary intake of a chemical substance is equal to the consumption quantity of the food multiplied with the concentration of the chemical in the

food. To evaluate the intake, it is to be divided by the body weight of the consumer (Annex, 1). In the current approach, a chemical substance in food does not pose a risk for the consumer when the dietary intake is less than the HBGV of that chemical substance (Annex, 2). In the European Union, the term “safe” is preferred, as it fits with article 14 of Regulation 178 of 2002, stating that unsafe food cannot be traded (Regulation (EC) No 178/2002).

3 Food consumption data

3.1 Surveys

Many data on consumers and their consumption quantities come from food consumption surveys. The drivers for such studies are diverse, such as consumer behavior, impact of cultural differences, diets and health, and economy (Wherry and Woodward, 2019). With regard to food safety, the focus is to obtain data about what foods are consumed, by whom, in what quantities, and when and where. Various techniques are used, including interviews and questionnaires, 24-hour recalls, and duplicate diets. For the evaluation of food consumption within the EU, EFSA has developed a Guidance document on sampling, assessment methodologies, tools, and quality control (EFSA, 2009, 2014). Most EU member countries follow these recommendations and have collected consumption data accordingly in the last decades. An overview of the available European surveys can be found on the EFSA website (EFSA, 2024a). There are also surveys available from other parts of the world; many of them are published in the GEMS/Food database of the WHO (WHO, GEMS/Food), or the Global Individual Food Consumption Data Tool (GIFT) databases (FAO/WHO GIFT, 2024). Other examples of food consumption surveys can be found on the Internet, such as the Canadian Food Consumption Table (Health Canada, 2017) and the USA-NHANES data set (CDC, 2024).

The data sets have different formats, e.g. due to cultural differences, different staple foods, or foods controlled by religious rules (“halal”, “kosher”). The surveys are never complete; consumption of rare foods are most likely not included. And, there is not a universal list of foods noted in all surveys. Different descriptors for food items are used. Consequently, an issue in the exposure assessment is the selection of the food items to be evaluated. There are efforts to harmonize the coding system of the list of food items, such as the FoodEx2 system of EFSA (EFSA, 2024b) but most older surveys do not refer to this coding system. Most exposure assessors still prefer to search foods by their literal name.

3.2 Databases

EFSA’s Comprehensive European Food Consumption Database: Many data sets of the EU countries are available through EFSA’s Comprehensive

European Food Consumption Database website (EFSA, 2022). This database can be approached online and contains groups (e.g. toddler, child, adult) and food items. The food items are presented at different levels, with an increasing level of detail; for example: (1) *Vegetables and vegetable products*, (2) *Leafy vegetables*, (3) *Spinach type leaves*, (4) *Spinaches and similar*. Based on the selection, the database produces a table that can be downloaded as spreadsheet (xlsx) or raw data file (csv). The tables show values for various percentiles, for all subjects and for consumers only, for a consumption quantity in grams per day or in grams per kg body weight per day, for chronic and acute exposures.

PRIMO: Another public data set from EFSA is the pesticide residue intake model (PRIMO). It is developed for the exposure assessment of pesticides and needs the user's input of a HBGV and the concentrations of a substance. Currently, versions 2, 3, and 3.1 can be downloaded as spreadsheets. In the sheets, the consumption quantities of various EU member states are included (EFSA, 2024c).

How do these consumption quantities relate to the data of EFSA's Comprehensive European Food Consumption Database? According to PRIMO_3.1, the consumption of spinach for the general Dutch population is 0.156 gram per kg body weight per day ("*chronic_consumption*", cell X169). However, using the Dutch chronic data set of 2012 in the Comprehensive database, the consumption for adults is 1.2 ± 0.91 gram per kg body weight per day for consumers only, and 0.10 ± 0.090 gram per kg body weight per day for all adults. So, the average consumption according to PRIMO falls within the range of all adults as presented in the Comprehensive database, but the numbers do not exactly match. There is no publication of how the values in PRIMO and those in the Comprehensive European Food Consumption Database were derived from the initial data of the individual consumers. Consequently, it is not quite clear how the values in PRIMO and the Comprehensive database came to be.

WHO GEMS/Food and Food Safety Collaborative Platform (FOSCOLLAB) The WHO GEMS/Food database shows a distribution of different countries of the world, divided into 17 groups. For each group, a "GEMS/Food cluster diet" is given. Values "per capita" per food category are provided. It is noted that "these diets are to be used for the assessment of chronic dietary exposure to chemicals in food, but are suitable only for estimating mean dietary exposure for the general population" (WHO, Food Cluster Diets). The website shows overviews that can be exported.

The FOSCOLLAB presents values for a series of countries, over different years, filtered by gender and age of the consumers (WHO, 2018). Its output is percentiles, quite similar to the format of EFSA's Comprehensive European Food Consumption Database. A comparison of Dutch data for spinach in the

WHO Collaborative database and in EFSA's Comprehensive database showed that the data are identical (results not shown). So, the data in both databases refer to the same surveys and were derived in a similar manner.

FAO/WHO GIFT: Another source of consumption data is the FAO/WHO GIFT online platform. It is a growing repository with access to individual consumption quantities. A series of publications is available, e.g. about the data set and the underlying surveys, and some reports based on analysis of the data. The current platform contains 62 data sets of countries in Central and South America, Africa, and the Far East that are available for download. For Europe, only data from Italy, Romania, and Bulgaria are included (FAO/WHO GIFT, 2024).

4 Establishing concentrations of chemicals in food

4.1 Sampling

The method of sampling is relevant in relation to the concentrations of chemical substances in food. Samples can be selected in various ways. For example, to perform an import control or an official control programme, samples must be taken in a random manner according to the EU legislation; only then are the results considered representative. In case of a contamination, however, "suspected" samples can be taken e.g. to look for the sources. It can be understood that concentrations in suspected samples are higher than those in randomly taken samples. So, it is important that the exposure assessor is aware of the sampling strategy that was followed, and to consider additional samples to be taken when the sampling procedure does not fit the intentions of the exposure assessment.

4.2 Detection limits

The detection limit of the chemical analysis is also a key issue in exposure assessment. If a concentration in a sample is below the detection limit, it is usually reported as "n.d." (non-detectable). They are often called "left-censored" data (Wikipedia, Censoring(statistics)). Its actual concentration will be somewhere between zero and the detection limit. The common approach then is the use of the "lower/upper bound" method. Here it is assumed that the concentration can be 0 (lower bound), and the dietary intake will also be 0. Or it is assumed that the concentration is equal to the detection limit (upper bound). One can also use a "medium bound" scenario (half of the detection limit). For official control of some contaminants, the approach that is to be used is described in the EU legislation. For example, according to Regulation (EU) 2023/915, the concentrations of PAHs are to be expressed as "lower bound" concentrations,

whereas maximum levels for dioxins and dioxin-like polychlorinated biphenyls (PCBs) refer to “upper bound” concentrations. (Regulation (EU) 2023/915). The exposure assessor, however, can deviate from these obligations, as the exposure assessment is not regulated by EU law.

The method of lower/upper bounds may lead to problems in the risk characterization. As an example: a person with a body weight of 50 kg drinks two bottles of beer per day, being a total of 600 grams. In this beer, a substance is found that is assigned an ADI of 1 ng per kg body weight per day. The concentration was below the detection limit of 100 ng per kg. Using the lower bound, intake is 0, and the beer is “safe”. Following the upper bound, the intake is $0.6 \text{ (kg beer)} \times 100 \text{ (ng/kg beer)} \div 50 \text{ (kg body weight)}$, equal to 1.2 ng per kg body weight per day. Then the ADI is exceeded, and the beer is “not safe”. It can be calculated (Annex 3) that the critical concentrations to discriminate between safe and not safe in this example are 83 ng/kg spinach ($1 \text{ ng/kg/day} \times 50 \text{ kg bw}/0.6 \text{ kg spinach}$) (Foodsafetyportal, Limit of Rejection). Consequently, the detection limit for the substance in the beer should be lower than 83 ng/kg for the exposure assessment to decide about its safety.

4.3 Series

In the food safety system, control authorities and food industries do not take one sample, but usually a series of samples. As only one number for the intake is to be compared with the HBGV, one value for the concentration has to be selected from the series. Most assessors select the highest value of the series, thus protecting all consumers. However, high values might be a statistical “outlier” (Wikipedia, Outlier) caused by errors during sampling or analysis. There are different ways to identify outliers, for example based on the values of the quartiles (Soetewey, 2020; Bobbitt, 2023), or the use of QQ-plots (Wikipedia, Q-Q plot) where a visual observation helps to find numbers that deviate from the distribution. If there is proof of errors, one has to exclude these numbers from the calculations. Such errors are usually hard to find; therefore, it is better to select high percentile values, such as the 95th or 99th percentile of the series, instead of the highest value to avoid the selection of outliers or otherwise biased values.

There are different ways to calculate percentiles; in more recent versions of MS Excel, for example one will find various pre-programmed functions. There are different acceptable methods (Rumsey, 2021), so it is possible that values of a higher percentile differ between experts. In this regard, it is important to understand that most series of concentrations are log-normally distributed, whereas many statistical functions are based on normal distributions. A transformation might then be needed. And when a series shows a different

distribution than log-normal, it could be a sign that one is dealing with a unconventional situation that needs further investigation.

Outlier example: As an example of outlier detection, a data set was taken with a series of concentrations of fipronil in eggs sampled in the period of September to November 2017 in EU member states. Details of this food safety issue are published (Miko, L., 2018; EFSA, 2018). Analysis of the data was done using the statistical package R for Windows (Version 4.2.2 of 2022) (CRAN). The data set contains 1954 samples. The series shows 707 samples above the detection limits, ranging from 0.002 mg to 2.8 mg per kg. A histogram of the data after logarithmic transformation is shown in Fig. 1. The higher percentiles based on rank are presented in Table 1.

To check for outliers, a Q-Q plot is presented for the log-transformed data. It is presented in Fig. 2. It shows that the highest value of 2.8 mg fipronil per kg (pointed to by the black arrow) deviates substantially from the log-normal

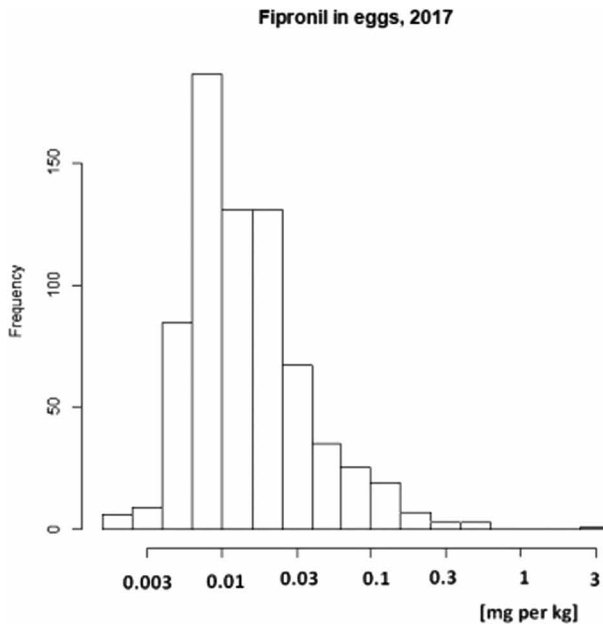


Figure 1 Histogram of concentrations of fipronil in eggs, positive samples only ($n = 707$).

Table 1 Percentiles of concentrations of fipronil in eggs, positive samples only ($n = 707$), based on their rank

[mg fipronil per kg egg]				
50 percentile	75 percentile	90 percentile	95 percentile	99 percentile
0.013	0.023	0.050	0.10	0.19

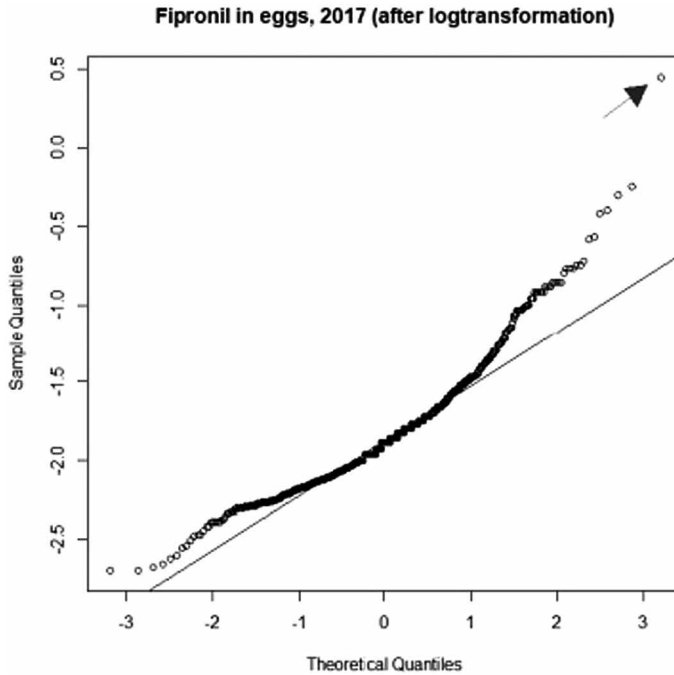


Figure 2 QQ plot of concentrations of fipronil in eggs (707 positive samples). The black arrow points to a possible outlier.

distribution and this value might be a potential outlier. Besides, it can be noticed from this figure that the values after a log transformation are still not really normally distributed, as the lower and higher values deviate systematically from the normal line.

4.4 Corrections

Before using a concentration for the dietary intake calculation, a correction might be needed for the concentration's value. There are two major items that can have a substantial influence: (1) the processing factor, and (2) the composition of the food. The processing factor refers to the differences between samples as taken and as being consumed. For example, many vegetables and fruits are sampled fresh, whereas they might be traded in cans or in a dried form. The concentrations will change during processing, e.g. by dilution in a fluid, or by mass concentration during heating and drying. Processing factors are mostly derived and published by food producers (RIVM, 2024). Unfortunately, processing factors for household and restaurants' preparations are not frequently looked for. When relevant data on processing are lacking, it should be considered to analyze the foods as consumed.

Composition might also be important for identifying the appropriate value for a concentration. As an example: the analytical results of dioxins and related compounds have to be reported per gram fat (Regulation (EU) 2023/915). To estimate exposure, it is needed to convert the concentration per gram fat into the concentration in food as consumed (wet weight). So, the concentration of dioxins in cow's milk with 3% fat equals 0.03 times the value as reported. It is also possible to estimate the concentration in a complex food on the basis of the major components. Components can be found on food labels and in food composition tables like those presented by EuroFIR (EuroFIR, 2024). For example: dioxins and related compounds are found in mozzarella cheese with 5 pg TEQ per gram fat, exceeding the EU standard of 4 pg (Regulation (EU) 2023/915). What is the concentration of dioxins in a pizza containing 30% mozzarella? The amount of mozzarella is 300 grams per kg pizza. Other ingredients do not contain relevant amounts of dioxins. The mozzarella contains 18% fat (Eatthismuch, 2024). So, the pizza contains 54 [300 × 0.18] grams of fat per kg pizza, with 5 pg TEQ from dioxins and related compounds per gram fat, equalling 270 [54 × 5] pg TEQ per kg pizza.

5 Calculating levels of exposure

5.1 Units

The units of the different variables can pose problems for an exposure assessor. For example, the "microgram" can lead to confusion. The use of its abbreviation is not consistent; many people use "µg" (the recommended symbol), but some text editors convert this automatically into "mg". Other people therefore use "ug". In North America and the UK, "mcg" is used (Wikipedia, Mikrogram). Another pitfall is the kg, as it can refer to the body weight of the consumer, or to the concentrations in the foods. Consumption quantity of foods is usually expressed in grams, whereas the concentration is per kg.

5.2 Acute or chronic intake

The consumption data in PRIMo are to be used for a chronic evaluation, whereas other data sets show data for both acute and chronic exposure. "Acute" means that health effects are evaluated within a day after a single dose or meal, whereas "chronic" refers to lifetime repeating exposure. The limit value for chronic exposure is the ADI or TDI, but for acute exposure one has to use another limit value: the Acute Reference Dose (ARfD) (European Commission, 2001) (OECD Series on Testing and Assessment, 2010). When an exposure assessment is to be made for a consignment exceeding a MRL or ML, it can be assumed that exposure will be short as the consignment is limited

and remaining foods will be rejected. To protect all consumers, it is needed to perform a realistic worst-case calculation: this is a consumer with a low body weight and a high consumption quantity (for example, the 95th percentile), with a high concentration of the chemical substance in the food item (also 95%). The probability of that situation is 0.05×0.05 , which equals to 25 persons in a population of 10 000 people (1 person in 400 consumers exceeding the ADI, being at risk). For most chemical substances, the ARfD is missing. A search in the OOFT database of the Foodsafetyportal (Foodsafetyportal, OOFT) showed a list of 5181 chemicals with an ADI or TDI; only 20 of these had also an ARfD. For the 20 chemical substances assessed, the ARfD ranged 1 to 10 times higher than the corresponding ADI or TDI, with a median ratio of 3. An ADI or TDI can be used when the ARfD is unavailable, but this approach tends to overestimate the risk by an average factor of three. So, an ADI or TDI can be used when the ARfD is missing, but this will overestimate the risk on average three times.

To evaluate chronic exposure, one should be aware that many foods are not consumed every day. Staple foods such as rice and bread are consumed frequently, but more rare items only a few times per year. The consumption frequency can be defined by the ratio between consumers vs. all subjects in the databases. As an example: according to the Dutch survey of 2012 (taken from EFSA's Comprehensive European Food Consumption Database), spinach was consumed in 2012 by 48 Dutch adolescents in a population of 870 adolescents (5.5%). So, the consumption for adolescents of spinach is on average 20 times per year. The median consumption is 81 grams per meal, equalling consumption of 3888 [48×81] grams for all adolescent consumers. For the whole population, on average this is 4.5 [$3888 \div 870$] grams per meal. So, to evaluate chronic dietary intake it is best to use median or average consumption quantities for the whole population or to correct the consumption quantity of consumers on the basis of the consumption frequency, whereas for acute exposure one should select a high percentile of consumers only.

5.3 Calculation tools

EFSA's tools for intake calculations are described by Ioannidou et al. (2021). The Food Additives Intake Model (FAIM) is developed for exposure to food additives. The tool Rapid Assessment of Contaminant Exposure (RACE) is provided for a simplified risk evaluation of chemical contaminants in food, and the Feed Additive Consumer Exposure (FACE) calculator estimates exposure to residues of feed additives. The Food Enzyme Intake Model (FEIM) model estimates dietary exposure to food enzymes. According to the paper, they all use the Comprehensive database, ... *for each individual*. The latter statement is remarkable, as the databases present summarized consumption data only.

The data from PRIMO_3.1 were copied into the online calculation tool EAST2 of the Foodsafetyportal (<https://foodsafetyportal.eu/>) for the calculation of the chronic dietary intake of chemical substances in food, for the general population. The data from the Comprehensive European Food Consumption Database are copied into the tool EAST3 (EAST, 2024). The user interfaces in both EAST tools filter the data (based on a selection of country, survey, consumer, food item) and use the numbers from the databases for calculation of dietary intake. Both tools then compare the intake with an HBGV; these are copied from the OpenFoodTox database (EFSA, 2021) and the IRIS database (US-EPA, 2025).

5.4 Monte Carlo

The calculation of the dietary intake is a "point estimate", based on one number for the consumption and one for the concentration in the food, for an average or extreme consumer. This estimate is compared with a single number for the HBGV. All values come from a range of data, and there are no fixed rules about what number to select. The tendency is to use summarized consumption quantities, and it is advised to select the higher concentrations (95th or 99th percentile) for acute exposure, with the most sensitive consumer (low body weight, most often children). One should be aware that the results will have a higher chance of exceeding the HBGV than the average situation. This can lead to the destruction of a consignment although only a small percentage of the samples will actually show the concentration that was used for the intake calculations. So, using higher percentiles gives higher intake numbers with a lower probability of happening, and a higher chance of rejection of foods that are actually safe.

To overcome the differences between a point estimate and the exposure of a population one can use "probabilistic modelling" (Wikipedia, Predictive intake modelling). It is based on a calculation where all distributions are multiplied with each other, instead of one value taken from each distribution. This is also called a "Monte Carlo" calculation. The Monte Carlo method is a class of computational algorithms that uses randomness to reach a result (Wikipedia, Monte Carlo method). For such calculations a computer is needed that reads the consumption quantities of all consumers and the concentrations of all samples. Then the computer selects a number randomly from the data, calculates the intake, giving one result. Then it selects another one, and so on, leading to a series of intakes. According to US-EPA *"a Monte Carlo analysis may be useful when ... calculations using conservative point estimates fall above the levels of concern. Or .. to disclose the degree of bias associated with point estimates ... ; or when it is necessary to rank exposure pathways, ..."*. It pleads for a "tiered approach" (EPA, 1997).

As the output of a Monte Carlo exposure calculation is a series of numbers of intakes of individual consumers, it is well suited for statistical analysis, e.g. to determine various percentiles and their probability. The exact percentage of a population exceeding the HBGV can also be identified. It is possible to relate the intake to consumers' parameters such as gender and age. Doing so, one can estimate lifelong intakes. And, by comparison of consumption data over different time periods, changes in exposure to substances can be identified, such as reported by Liem and Theelen (1997) about exposure to dioxins in the Netherlands.

Monte Carlo calculation tools on the Internet are MCRA (MCRA), XI (Foodsafetyportal, XI), and ImproRisk (State General Laboratory, 2022). Most of these tools do not include the data set with consumption quantities of individual consumers; the user has to provide this data by himself. XI is the exception; however, it contains only the consumption data of the Netherlands for the periods 2012–2016 and 2016–2019. The FAO/WHO GIFT data sets might be used in the tools, but the surveys of most EU countries are still missing in GIFT. At the moment of writing, the use of data sets from the GIFT database for Monte Carlo calculations, next to the Dutch data in XI in the Foodsafetyportal, is being explored. So it can be expected that additional tools to perform Monte Carlo calculations on the dietary intake of chemical substances in the Foodsafetyportal will become available.

6 Risk characterization: limit values

To evaluate the dietary intake, it has to be compared with a limit value for the maximal safe exposure. There are two types of such limit values: (1) HBGVs such as ADI, TDI, and ARfD and (2) BMDLs. Both types of values are derived by experts in the hazard characterization (step two of the risk assessment), and the results can be found in different publications and databases. The ADI is used to describe the maximal acceptable intake of "residues" of, for example, pesticides, additives, and veterinary drugs. For "contaminants" such as mycotoxins and environmental and process contaminants, the limit value is called a TDI. The ARfD can be used for acute exposure to both residues and contaminants.

The method of deriving HBGVs differs from that of BMDLs (Foodsafetyportal, HBGVs and BMDLs). A HBGV is based on an evaluation of all known effects, leading to a single value; usually, the lowest NOAEL is chosen (ChemSafetyPro, 2018). And, a HBGV is derived using "Safety Factors". These factors are actually extrapolation factors, which are intended to transform the NOAEL of a research study into a NOAEL for the general human population (European Medicines Agency, 2014). Doing so, the dietary intake can directly be compared with an ADI or TDI or ARfD, as it can be considered to be the

NOAEL for the most sensitive humans. On the other hand, a BMDL refers to a specific effect, such as a BMDL01 of 0.50 µg/kg bw per day for developmental neurotoxicity of lead in children, and a BMDL01 of 1.5 µg/kg bw per day for clinical effects of lead in adults (EFSA, 2010). So, BMDLs describe a specific effect in an animal or human study, which is not necessarily the most sensitive effect, without an extrapolation to the most sensitive humans. For that extrapolation, the risk characterization has to be made using a “Margin of Exposure” (MoE).

6.1 Tolerable weekly intakes and provisional tolerable monthly intakes

A TDI is set and used in the same manner as the ADI. Instead of a TDI, some contaminants have a tolerable weekly intake (TWI) or a provisional tolerable monthly intake (PTMI). When using a TWI or PTMI, it is necessary to evaluate exposure over a time period. It is recommended here not to use a “dummy TDI” (a TWI divided by 7) as some people do. As an example: a person of 60 kg body weight (bw) consumes 145 grams of spinach on a day, with 0.18 mg cadmium per kg (equal to 0.18 µg/g) of spinach. Then the intake is 26 µg [145 (g) × 0.18 (µg/g)] cadmium. This is 0.43 µg [26 µg ÷ 60 kg] per kg bw per day. The TWI for cadmium is 2.5 µg per kg bw per week (EFSA, 2013) which is equal to a “dummy TDI” of 0.36 [2.5 ÷ 7] µg per kg bw per day. The dummy TDI is exceeded. However, if the consumer eats on average three portions of spinach per week, then the intake is 78 [3 × 26] µg per week, which is 1.3 µg cadmium per kg bw per week. It can be calculated that the TWI is not exceeded as long as the consumer eats less than 6 meals (actually 5.7 meals of 145 grams) with 0.18 mg cadmium per kg spinach per week.

6.2 Selection of a limit value

In recent times deriving HBGVs is becoming rare, and more BMDLs are set. The BMDLs are limit values from a curve fit of dose-effect relations of health effects in experimental animal or human studies. In these fits one can statically calculate a minimal response of 1%, 5%, or 10%, giving a BMDL01, resp. BMDL05, or BMDL10. Consequently, one will find series of ADIs, TDIs, and ARfDs, and different BMDLs today in more recent EFSA opinions (EFSA Publications) and JECFA toxicological monographs (WHO, JECFA). These reports can contain one HBGV and/or one or more BMDLs. See for example the limit values of EFSA for total lead in Table 2.

How to select the appropriate limit value from such series? Most experts will select the most recent study, but how must one deal with both a HBGV and various BMDLs in the same opinion? It is proposed by Theelen (2024) to use

Table 2 Limit values for total lead, as taken from EFSA opinions

Opinion	Type	Value	Note
EFSA (2005)	TWI (provisional)	25 µg per kg bw per week	JECFA has established a PTWI for lead in 1986. It is set to 25 ug/kg b.w./week for infants and children on the basis that lead is accumulating in the body and an increase of the body burden of lead should be avoided. In 1993 and 2000, JECFA reconfirmed this PTWI and extended it to all age groups
EFSA (2010)	BMDL01 (Human)	1.5 µg per kg bw per day	clinical signs
	BMDL01 (Human)	0.5 µg per kg bw per day	neurology
	BMDL10 (Human)	0.63 µg per kg bw per day	clinical chemistry

Table 3 Selection of a HBGV or BMDL, when different studies and values are available

Step	
1	Select the most recent study
2	Use the HBGV when available, otherwise select the BMDLs from that study
3	Prefer BMDLs from human studies above animal studies
4	Prefer a BMDL01 over a BMDL05, and a BMDL05 over a BMDL10
5	Select the lowest value of BMDLs of the same type

distinct rules for the selection, as presented in Table 3. When following these rules, the BMDL01 of 0.5 µg per kg bw per day will be selected for the risk characterization of dietary intake of lead.

6.3 Margin of Exposure

The EFSA made the statement that the MoE for genotoxic carcinogens should be at least 10 000 lower than a BMDL10 from an animal study (EFSA, 2012). A similar type of statement for non-genotoxic substances was not made. Various EFSA Opinions demonstrate, however, that EFSA is using the MoE concept for non-genotoxic chemicals with a critical level of 100 for a BMDL10 from animal studies. Existing EFSA evaluations do, however, not make clear what the MoE should be for a BMDL01 or BMDL05 from animal studies or for BMDLs from human studies. Other critical levels for the MoE should then be used, but it is not noted what the MoE should be for the different BMDLs (EFSA, 2023). Theelen (2024) presents MoEs for the various BMDLs, shown in Table 4. These values are derived from the safety factors of HBGVs; this list is included in the

Table 4 Margin of exposure of different BMDLs

Chemical	BMDL	Study	MoE
Genotoxic	All BMDLs	Animal and human	10 000
Non-genotoxic	BMDL10	Animal	100
		Human	10
	BMDL05	Animal	30
		Human	3
	BMDL01	Animal	10
		Human	1

calculation tools of the Foodsafetyportal, leaving the user the possibility to deviate from these values.

7 Risk characterization: setting 'safe' levels

Foods are to be considered not safe for consumption when the dietary intake is above the HBGV or smaller than the MoE of a BMDL. This is not similar to the statement that adverse health effects will occur. Most toxicological experts are of the opinion that health effects cannot be excluded anymore; there is always a certain risk. That risk will usually be very small as the safety factors and the MoE leave room between the intake by the consumer and the doses for which effects are actually demonstrated in humans or animals. So, the appearance of adverse health effects is not very likely when the permissible exposure limit value is exceeded a few times.

Some toxicological experts state that there is no such thing as a "safe" level, as one cannot derive a threshold value for some adverse health effects, e.g. for carcinogenicity. For these effects limit values are set in another way; most often by a low dose linear extrapolation (Foodsafetyportal, Genotoxic carcinogens). Other experts criticize this approach, as it sometimes leads to "unreasonable conclusions" (Bolt et al., 2009). Another comment is that a NOAEL cannot be considered a real threshold between "safe" and "not safe", as hormetic dose response can lead to effects below the NOAEL (Calabrese, 2008). Although these comments are seriously debated within the scientific toxicological community, it should be concluded that the HBGVs and BMDLs are still considered the boundary values between safe and not safe exposure.

Another comment refers to the fact that a person is exposed to mixtures of chemical substances and not to a single substance. This is correct, but there are not yet unified methods on how to evaluate these mixtures. The issue here is that the effects of different substances in mixtures can be additive (equal to the sum of all substances), or synergistic (the mixture is more toxic than its components), or antagonistic (the mixture becomes less toxic) (Roell et al.,

2017). In the current situation, only additive action is taken into account for mixtures of dioxins and dioxin-like PCBs, and for a few PAHs. So, exposure to mixtures is taken care of, albeit for only a few well-defined combinations of substances.

The risk characterization deals with deterministic calculations. Many assessors use a worst-case scenario by selection of the highest concentration and largest consumption quantities. If that is "safe", all other intake levels are considered safe. The real situation is that there will always be a distribution with safe and unsafe intakes. These can only be determined using a probabilistic method such as a Monte Carlo calculation. Then the question arises, what percentage of the actual population defines a "safe" situation. For example: one consumer in 1 000 000 consumers? If so, how to evaluate an exposed population of 100 persons?

8 Conclusion

Data on food consumption of various countries in the world are available on the Internet in public databases, but these lack a unified, harmonized structure. Data on the consumption of rare foods might be missing. The description of food commodities is not yet harmonized, making the selection of the appropriate food items a challenge. EFSA's FoodEx2 is a good step in the harmonization, but its success depends on its use in the food consumption surveys of the EU member states and its ability to describe the foods in the appropriate way.

The comprehensive databases from EFSA and WHO-FOSCOLLAB contain summarized data. They present average consumption data, with a standard deviation and percentiles for population groups of different countries for the whole population and for consumers only. Doing so, the actual variation and extreme values are lost. PRIMo is based on averages of the whole population. It is not possible to compare the data of the same surveys in the different data sets, as the average values and higher percentiles are presented with little or no explanation of how these are derived.

Most data sets follow log-normal distributions; these might show other percentiles than those estimated statistically for a normal distribution (Sokal and Rohlf, 1981; Thisvsthat, 2023). Whether or not the appropriate method is used is often not clear.

An exposure assessor should be aware of the background of the occurrence data that he is using, as samples might be taken in a risk-based manner or "at random". Another issue about concentrations is the interpretation of non-detectable values. The use of "lower/upper bound" values can be helpful, but it should be checked if the LOD or LOQ is sufficiently low to discriminate between "safe" and "unsafe" concentrations. If not, an alternative analytical method should be considered.

Misunderstanding the meaning of units in an exposure calculation is a common source of calculation errors. Special attention is needed for the different notations of "micrograms". Series of consumption quantities and concentrations usually follow a log-normal distribution. Outliers should be excluded when there are reasons to conclude about possible bias; the use of higher percentiles is preferred above the single highest value. If the distribution deviates from log-normal, it could be a sign that one is dealing with a unconventional situation that may need further investigation.

Many data sets discriminate between "acute" and "chronic" consumption. For the evaluation of a short-term situation, the selection of worst-case conditions is preferred, such as higher percentiles for consumption and concentration, to protect all consumers. The dietary intake is then to be compared with the ARfD. In many cases, however, ARfDs are missing. Use of an ADI or TDI instead can be considered, but it might slightly overestimate the risk. For an estimate of long-term exposure, average data are preferred. To obtain the most reliable results for chronic dietary intake, the consumption frequency should be taken into account. If not, another overestimation is likely to occur.

The calculation with one value for consumption and one for concentration is a point estimate. Using a worst-case scenario has a higher probability of establishing safe results, but will lead to a higher chance of rejecting (and destroy) safe foods.

When the impact of the actual variation is to be known, a Monte Carlo calculation is to be considered with data of individual consumers. Monte Carlo tools that are accessible through the Internet ask the users to provide the data of individual consumers, with the exception of the Dutch data in XI (Foodsafetyportal, XI). It is very difficult to obtain this data, as no public sources are available, with the exception of the WHO-GIFT data sets.

In the hazard identification, the use of HBGVs is preferred over BMDLs, as they already include the evaluation of the relevant effects and the conversion into a human NOAEL by expert judgment. The use of BMDLs forces the assessor to select a Margin of Exposure; guidance for the appropriate MoE and on the selection of the HBGV or BMDLs from a series of values is lacking, except for the methods developed by Theelen (2024) as implemented in the Foodsafetyportal (<https://foodsafetyportal.eu/>).

When dealing with a TWI or PTMI, it is needed to define intake per week or month. The calculation of the intake should be based on the consumption frequency of the foods. For an acute assessment, however, one is dealing with a quantity per portion, so then the consumption frequency can be ignored.

The risk characterization is based on the concept of "safe" foods. A known issue here is that many people do not believe that there is such a thing as "safe" food. The exposure to mixtures and unusual dose-response relationships are

cited by (sometimes self-proclaimed) experts as reasons why a HBGV is not the limit value for the evaluation of safety of foods. Toxicological research and discussions on these topics between experts are still needed.

The issue with Monte Carlo calculations is the evaluation of an output of a series instead of a single value. In the current system of food safety exposure assessment, it is yet not defined how to evaluate the risk of a range of intakes and what number of consumers exceeding the HBGV can be considered safe.

9 The future of exposure assessment

According to the risk analysis concept of the Codex Alimentarius, exposure assessment is independent of risk management. This has led to different implementations of the calculations of dietary intake. Besides, one can notice different formats for the storage of relevant data in databases. The latter makes searching for the appropriate numbers more complicated. Consequently, results might differ, leading to discussions between experts and stakeholders. To solidify the quality of the results and to improve the transparency of the evaluations, it is recommended to better harmonize the method of exposure assessment and the selection of data. Special attention should be given to updates of data sources to guarantee consistencies between previous and present evaluations.

Most current evaluations of chemical substances in foods are point estimates, based on a limited number of data with worst-case conditions. Monte Carlo calculations are preferred for more realistic assessments; to do so, existing data sets of different countries containing the consumption quantities of individual consumers should become public. In this regard, discussions are also needed about the method of evaluation of results of Monte Carlo calculations, to define "safe" situations.

The discussions about the impact of mixtures and about how to deal with dose-response thresholds must continue, but academics should understand that clear-cut boundaries and agreements are still needed for consistent conclusions in the current global food safety system.

According to the risk analysis approach, discussion on changes and updates of the current system of exposure assessment is the responsibility of the scientific community. Risk managers should, however, join these discussions as observers to create social and legal acceptance of new developments and concepts.

10 Abbreviations

ADI	Acceptable Daily Intake
ARfD	Acute Reference Dose

BMDL	Benchmark Dose Level
CSV	comma separated values
EFSA	European Food Safety Authority
FAO	Food and Agricultural Organization of the United Nations
HBGV	Health Based Guidance Value
LOD	Limit of Detection
LOQ	Limit of Quantification
ML	Maximum Level
MoE	Margin of Exposure
MRL	Maximum Residue Level
n.d.	non-detectable
NOAEL	No Observed Adverse Effect Level
pg	picogram (10^{-12} gram)
PTMI	Provisional Tolerable Monthly Intake
TDI	Tolerable Daily Intake
TWI	Tolerable Weekly Intake
WHO	World Health Organization

11 Where to look for further information

Sources of information on exposure assessment and risk characterization of chemical substances in food are:

- Environmental health criteria, 240 (WHO 2008) Principles and methods for the risk assessment of chemicals in food. Chapter 6 Dietary exposure assessment for chemicals in food. Second edition (2020)
- Environmental health criteria, 240 (WHO 2009) Principles and methods for the risk assessment of chemicals in food. Chapter 7 Risk characterization
- FAO and WHO. 2023. Codex Alimentarius Commission Procedural Manual. Section 4 Twenty-eighth edition. Rome.
- For practical support with exposure assessment and risk characterization consulting the Food Safety Portal (<https://foodsafetyportal.eu>) is advised.

12 Annex

$$I = (C \times Q) \div bw \text{ where: } (C = C0 \times cC) \text{ and } (Q = Q0 \times cQ) \quad [1]$$

$$\text{"safe"} = (I \leq HBGV) \quad [2]$$

$$HBGV \times bw / Q \quad [3]$$

C Final concentration of substance in food as consumed [mg per kg]

Q Final consumption quantity [kg per day]

C0	Initial concentration of substance in food [mg per kg]
cC	Correction factor for initial concentration [-]
Q0	Initial consumption quantity [kg per day]
cQ	Correction factor for consumption quantity [-]
bw	Body weight of the consumer [kg]
"safe"	No adverse health effects for the consumer
I	Dietary intake of the consumer [mg chemical per kg body weight per day]
HBGV	Health Based Guidance Value of the chemical substance [mg chemical per kg body weight per day]

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