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SCIENTIFIC REPORT OF EFSA

Overview of the procedures currently used at EFSA for the assessment of dietary exposure to different chemical substances[1]

European Food Safety Authority[2, 3]

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ABSTRACT

The health impact of chemical hazards in food is estimated by comparing dietary exposure to toxicological levels of concern. Exposure assessments combine data on concentrations of a chemical substance present in food with the quantity of those foods consumed. Some guidance documents have been produced over the last ten years at international level that describe the current state-of-the-art of methodologies for dietary exposure assessment with little harmonisation across disciplines. A number of different methods exist ranging from quick worst-case estimations to refined methods aimed at assessing actual exposure. As the accuracy of dietary exposure assessments increases, the cost of undertaking the assessments also increases. An EFSA opinion affirms that exposure assessment has to be conservative and that a stepwise approach should be used commensurate with specific needs. However, some of the methodological differences among Panels are not fully justified by the specific requirements of the class of substances under evaluation. There is potential to further harmonise the way exposure is estimated with the availability of more refined and accurate food consumption information in EFSA. To improve chemical concentration data statistically based sampling frames could be developed in collaboration with Member States for their monitoring programs and a coordinated approach of using data from Total Diet Studies could be promoted. There is a need to further harmonise the screening methods used across Panels and the modelling of high consumers for calculating chronic exposure using individual data and summary statistics. It is suggested to always consider children, and in particular toddlers, since they are often at the high end when calculating exposure. It is considered useful to explore the use of probabilistic dietary exposure assessments on a more routine basis in case refinements are needed, of cumulative exposure assessment for all metabolically or structurally related chemical substances, and to test statistical methodologies for the estimation of usual intake from short-term dietary data.

KEY WORDS

Exposure, chemicals, harmonisation, food consumption, screening, acute, chronic.

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SUMMARY

The potential health impact posed by the presence of chemical hazards in food is estimated by calculating the likelihood that the consumer will be exposed to a substance and to quantify the extent of such exposure in relation to health based guidance values. Exposure assessments combine data on concentrations of a chemical substance present in food with data on the quantity of those foods consumed. Some guidance documents have been produced over the last ten years at international level that describe the current state-of-the-art of methodologies for dietary exposure assessment. Exposure assessments are often performed according to the fit-for-purpose principle with the consequence that there is little harmonisation across disciplines with each having their own agreed international guidelines.

A number of different methods exist to combine or integrate consumption estimates with chemical concentration data, ranging from quick worst-case estimations to refined methods aimed at assessing actual exposure. The selection of the method usually depends on a number of factors, including the purpose of the assessment (target chemical substance, population group, degree of accuracy required, etc.) and, above all, the availability of information. In general, it is considered neither cost-effective nor necessary to collect detailed food consumption and concentration data for every hazardous substance. A stepwise or tiered approach in which the initial steps rely on conservative screening methods is commonly used to minimise estimation costs and focus resources on the most important issues for which there is a potential health concern. The stepwise approach to dietary exposure assessment is such that as the accuracy of dietary exposure assessments increases, the cost of collecting adequate data and human resources needed to undertake the assessments also increases.

The described approach has been adopted by EFSA for its risk assessments. In particular, an EFSA opinion on exposure assessment clearly affirms that exposure assessment has to be conservative and that a stepwise approach should be used. However, different procedures are currently used in the dietary exposure assessment of the different classes of chemical substances at EFSA. Three different approaches can be distinguished. A tiered approach is used by the ANS Panel and Pesticides Unit when evaluating additives and pesticides. Conservative screening methods without a tiered approach are applied by other Panels when evaluating pre-regulatory chemicals (CEF, FEEDAP and NDA Panels, ANS Panel when evaluating nutrient sources). Only the CONTAM Panel, supported by the DCM Unit, is using a more refined exposure model based on individual food consumption data on a routine basis.

Some of these methodological differences are not fully justified by the specific requirements of the class of substances under evaluation. Among the Panels using only screening methods it might be opportune to question why a stepwise approach has not been consistently implemented to harmonise as much as possible the approaches in EFSA. Also the different screening methods used within EFSA are not fully harmonised. The methods based on model diets are the most commonly used for screening among the Panels (ANS, CEF and FEEDAP Panels). The screening method used to estimate exposure to pesticides is the only method based on summary food consumption data from different countries.

Historically, the safety of food additives and residues of pesticides and the risk posed by chemical contaminants have been evaluated on the basis of single-chemical and single-exposure pathway scenarios. Risk assessors examined each chemical exposure scenario separately. Although different chemicals may act by the same mechanism and produce the same effect, consideration has rarely been given to the potential additive or synergistic toxicological effects of multiple chemicals. Currently in EFSA, cumulative exposure assessments of structurally and metabolically similar substances are only being discussed for contaminants, pesticides and flavourings.

For substances requiring further refinement beyond screening methods or conservative estimates of exposure, a probabilistic analysis to capture variability in exposure can be conducted. In EFSA,

probabilistic distributional analysis is not performed on a routine basis. Only the CONTAM and PPR Panels have started to consider the possibility to perform ad-hoc probabilistic exposure assessments.

Estimates of usual intake - average intakes modelled over long periods - are needed for use in chronic exposure and risk assessments. Different statistical methodologies are currently available for the estimation of usual intake from short-term dietary data, none of them being a widely recognised standard. No EFSA Panel is currently using a technique for the estimation of usual exposure.

There is potential to further harmonise the way exposure is estimated in EFSA by the different Panels. With the availability of more refined and accurate food consumption information in EFSA summary statistics from new databases could be used for Tier 2 calculations when evaluating additive exposure and to crosscheck and validate all standard portions and model diets used in EFSA's exposure calculations. To improve the validity of the chemical concentration data used in calculating exposure statistically based sampling frames could be developed in collaboration with Member States for their monitoring programs and data submitted using the Standard Sample Description (SSD) format to capture important sampling details. A coordinated approach of using more statistically validated data from Total Diet Studies could be promoted as a complement to monitoring programs.

There is a need to further harmonise the screening methods used across Panels and the modelling of high consumers for calculating dietary exposure using individual data and summary statistics. It is suggested to always consider the children population, and in particular toddlers, since they are often at the high end when calculating exposure. It is considered important to expand probabilistic dietary exposure assessments on a more routine basis in case refinements are needed, to explore cumulative exposure assessment for all metabolically or structurally related chemical substances, and to test statistical methodologies for the estimation of usual intake from short-term dietary data.

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BACKGROUND AS PROVIDED BY EFSA

The levels of chemical substances in food are an important aspect of food quality and safety. These components may constitute a health hazard when overall intakes are too high. Dietary exposure assessment is therefore a crucial component of risk assessment.

EFSA's Scientific Panels perform risk assessment for a variety of chemical substances. The assessment of exposure to hazardous substances, or the estimation of intake for substances with potential beneficial effects, is performed within the risk assessment process.

Different procedures are currently used in the assessment of exposure to the different (classes of) chemical substances within the remit of EFSA. Some of these differences are justified by the specific requirements. In the case of chemicals, some of the differences may be the result of the class of chemical substances under evaluation whereas others are just due to the different assumptions made to compensate for the lack of food consumption and/or occurrence data. Therefore, a fundamental step in order to refine current procedures to accurately calculate exposure is the availability of representative and accurate food consumption and occurrence information at EU level.

It is a long-term objective of EFSA to, as much as possible, harmonise exposure assessment across the different (classes of) substances through the development of standardised methodologies.

TERMS OF REFERENCE AS PROVIDED BY EFSA

The Dietary and Chemical Monitoring (DCM)[4] Unit is requested to describe the procedures currently used in the assessment of exposure to the different classes of chemical substances within the remit of EFSA. A critical evaluation should be performed in order to evaluate if existing differences are justified by the specific requirements of the class of substances under evaluation. The different assumptions made to compensate for the lack of food consumption and/or occurrence data should also be discussed in order to identify possible areas of improvement in the EFSA strategy for data collection.

[4] Formerly the Data Collection and Exposure Unit

EVALUATION

1. Introduction

Risk assessment is the mainstay of EFSA's activities. To conduct a risk assessment, the hazard is described and the health impact identified. Public exposure to the hazard is ascertained and the health impact of the risks posed by ingesting the hazardous substance at these exposure levels is evaluated. A critical element in the conduct of a risk assessment is therefore the exposure assessment, i.e. the estimation of the likelihood that the consumer will be exposed to a substance and to quantify the extent of that exposure, when it occurs. To do so, exposure assessments combine data on concentrations of a chemical substance present in food with data on the quantity of those foods consumed. To be able to combine these different types of data it is necessary to consider standardisation of associated metadata, in particular harmonisation of the food description.

Exposure assessments are most often conducted at the general population level, but subgroups can also be explored that show particular exposure patterns, e.g. due to a high level of consumption or particular physiological or pathological conditions. The methodology can equally be applied to harmful as well as beneficial effects of substances that are naturally present in food (including macro- and micronutrients), food additives, food supplements, contaminants and residues, including pesticides and veterinary drug residues. Assessments can be made either for acute or chronic exposure, where acute exposure is estimated for a period of up to 24 hours while chronic (long-term) exposure covers the average daily exposure over several years or an entire lifetime.

The main objective of this report is to provide an overview of the procedures currently used for the assessment of dietary exposure to the different (classes of) chemicals within EFSA's work program and to evaluate them with regard to the sources of chemical concentration and food consumption data used. To put this into perspective, the report will initially present the state of the art for exposure assessment methodology with a particular emphasis on issues in relation to suitable concentration and food consumption data and the methods used to combine them in an exposure assessment. In the following part, the actual assessment methods used within the different Panels of EFSA are described. In addition, general recommendations concerning the different types of data sources and the methods for the assessment of dietary exposure at EFSA are given. The present report is focused on harmful and beneficial chemical substances whereas biological agents, e.g. micro-organisms, are not considered. The assessment of animal exposure to chemicals is as well not considered.

2. State of the art exposure assessment methodology

Exposure assessment, as part of the risk assessment process, is defined as the qualitative and/or quantitative evaluation of the likely intake of biological, chemical or physical agents via food as well as exposure from other sources if relevant (WHO, 1997a). Some guidance documents have been produced in the last ten years at international level that describe the current state-of-the-art of methodologies for dietary exposure assessment. A comprehensive review of the assessment of exposure to chemicals via food, including nutrients, was published by Kroes et al. (2002). More recently, guidance documents have been published by EFSA and the World Health Organization (WHO). EFSA issued two opinions of the Scientific Committee, the first referring to internationally accepted guidelines on how exposure assessments can be conducted in the various areas covered by EFSA (EFSA, 2005a) and the second providing guidance on how to address uncertainties in dietary exposure assessments (EFSA, 2006).

Exposure assessments are often performed according to the fit-for-purpose principle with the consequence that there is little harmonisation across disciplines with each having their own agreed international guidelines. A comprehensive monograph reviewing the methods used in each area was published by WHO based on a consultation on dietary exposure assessment of chemicals in food held in Annapolis in 2005 (WHO, 2009).

In the area of contaminants and natural toxins a workshop organised by the Food and Agriculture Organization of the United Nations (FAO) and WHO in 2000 described how to combine occurrence data from various origins to calculate exposure (WHO, 2000). Acute and long-term exposure assessments of pesticide residues in food are based on guidelines published by WHO (WHO, 1997b). Methods are described for estimating long-term exposure to residue levels, such as the Theoretical Maximum Daily Intakes (TMDI) and the Estimated Daily Intakes (EDI), and short-term exposure, such as the International estimated Short Term Intake (IESTI). FAO/WHO have also published guidelines for the experts of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) to assess exposure to food additives (FAO/WHO, 2003). In this area, the use of the Budget method is recommended and illustrated in detail. If necessary, refined assessments are performed with increasing accuracy using simple distributions or probabilistic techniques. For well-defined population subgroups, like e.g. vegetarians and breastfeeding mothers, even more elaborate methods can be used like the duplicate portion technique or biomarkers to confirm the relevance or applicability of results derived from previous estimates. Most of the above mentioned methods are currently used in EFSA opinions and are presented in details in chapter 3.

The accuracy of any exposure assessment will ultimately depend on the precision in the two calculation inputs – chemical concentration and food consumption.

2.1. The concentration of chemicals

A central aspect in the assessment of exposure is the concentration of the chemicals in food as consumed. Depending on the purpose of the exposure assessment (pre-regulation or post-regulation) chemical concentration data can originate from:

- experimental data provided by applicants (pre-regulatory exposure assessment)
- legislated Maximum Permitted Levels (MPLs), Maximum Residue Levels (MRLs) or usage levels as reported by manufacturers;
- monitoring and surveillance programs;
- estimation from mathematical modelling;
- a Total Diet Study (TDS).

The representativeness of the data will vary according to the measurement method, whether it is based on estimated levels or actual analytical results, the sampling strategy and the market coverage.

2.1.1. Experimental data provided by applicants

In the framework of pre-regulatory exposure assessment (e.g. pesticides) the primary source of residue data in foods are the supervised trials. These data must be submitted by the applicants in support of the registration of a pesticide. The trials are usually performed by a manufacturer and simulate a maximum registered use scenario. The trials are designed to determine the maximum residue concentration that may be present in food or feed at the earliest point at which these food commodities could enter into commerce and are used to establish legally enforceable residue limits.

2.1.2. Use of legislated maximum levels or usage levels

When evaluating the presence and levels of chemicals in food it is valuable to distinguish between substances intentionally added, like additives and flavourings, from others, such as pesticide residues and contaminants. In the case of chemical substances intentionally added to food at various processing steps, the amounts that may be added are usually regulated by Maximum Permitted Levels (MPLs) or Maximum Residue Levels (MRLs). They are defined in food legislation for each food category to ensure product safety and to avoid consumers being misled. MPLs or MRLs can be used for a preliminary assessment of exposure in order to identify those substances for which acceptable or tolerable intake limits may be exceeded in a worst-case scenario.

Information about the presence of intentionally added substances might be indicated on the product label, and is compulsory in the case of food additives. Occurrence levels can also be obtained from the producers. These levels range from the maximum permitted level to nothing at all. Manufacturers use the chemicals, e.g. an antioxidant, at the lowest effective levels in a given formulation, unnecessarily high addition is usually avoided for cost reasons and prohibited by the requirement to work according to ''Good Manufacturing Practice'' (GMP). Usage levels provided by the industry are often the only available information in pre-marketing situations.

2.1.3. Monitoring and surveillance data

Two types of monitoring and surveillance data for assessing the concentration of a defined chemical in a food are frequently used: results of a random nature from stratified sampling plans or targeted sampling. The first tries to obtain a representative picture of chemical levels present in food whereas the second is aimed at sampling those products expected to contain higher levels in a cost effective way (Kroes et al., 2002). Targeted data are often collected for enforcement purposes in response to specific problems. They should be used with caution in dietary exposure assessment, as they may not be representative of all food available for sale (WHO, 2009). However, clearly representative data are often not available and unspecified or targeted data have to be used as an alternative resulting in more conservative estimates of exposure. A major limitation of using monitoring data is that often not all commodities entering the food chain are monitored. This information might therefore not be sufficient to estimate exposure from all possible dietary sources. In addition, sampling design, analysis and reporting procedures are critical for obtaining consistent and comparable data on chemical concentrations in food. In particular, food sampling procedures preceding analysis can critically influence how representative the measured value for the individual sample is to the true value in the overall distribution.

After representative samples are taken, the accuracy, specificity and sensitivity of the analytical methods used are also important. Generally, analytical methods used for screening purposes (e.g. for enforcement of Maximum Residue Levels or Maximum Levels) tend to be less precise and are not suitable to detect residues at low levels. This is to a large extent due to the fact that the objective of analytical methods used for screening purposes is to separate the compliant from the non compliant results. For accurate dietary exposure assessments, the limits of detection (LOD) and quantification (LOQ) should be as low as technically possible. Different recommendations exist for the handling of non detected or non quantified values when assessing exposure (EFSA, 2010a; WHO, 2009; Kroes et al., 2002). For example, when calculating the "upper bound", foods that do not contain detectable residues are assumed to contain a level of the residue at the respective limit (WHO, 2009). Other factors influencing the final result are the accuracy of the method, laboratory-to-laboratory variation, repeatability and recovery (Kroes et al., 2002).

2.1.4. Estimation from modelling

In order to reduce the amount of tests to be undertaken, occurrence levels can also be estimated through mathematical modelling. In particular, this procedure is used to estimate the migration of substances from food contact materials. The European Plastic Directive 2002/72/EC states that the verification of compliance with the specific migration limits may be ensured by the determination of the quantity of a substance in the finished material or article provided that a relationship between that quantity and the value of the specific migration of the substance has been established either by an adequate experimentation or by the application of generally recognised diffusion models based on scientific evidence.

2.1.5. Data from Total Diet Studies

A Total Diet Study (TDS) consists of selecting, collecting and analysing commonly consumed food purchased at retail level, processing the food as for consumption, pooling the prepared food items into representative food groups, homogenising the pooled samples, and analysing them for harmful and

beneficial chemical substances. TDSs are designed to cover the average diet or the most commonly consumed foods, based on data from dietary surveys, in a country or by a specific population group.

In principle, a TDS should provide the most accurate measure of the average amount of a chemical actually ingested through food by the population or population subgroups living in a country. The data from a TDS also differ from data obtained from other monitoring or surveillance programs in that concentrations of chemicals are measured in foods after they have been prepared for normal consumption. In 2011, EFSA, FAO and WHO jointly published a guidance document providing best practices on methods and protocols for a future collaborative and harmonised TDS worldwide with particular focus on Europe (EFSA/FAO/WHO, 2011). However, the accuracy of a TDS survey depends on the sampling design and, in particular, on the sample size. The TDS method might not be suitable for the assessment of acute dietary exposures when a high degree of compositing of samples is used since high contamination of less consumed foods might be masked by the dilution effect (WHO, 2009).

2.2. Food consumption data

2.2.1. Approaches for food consumption data collection

Food consumption data reflects what either individuals or groups consume in terms of solid foods, beverages, including drinking water, and supplements. Food consumption can be estimated through food consumption surveys at an individual or household level or approximated through food production statistics. The latter two provide gross annual estimates of the type and amount of food available for human consumption within a household or country, respectively, and can be used to derive a gross estimate of average food consumption per capita without indicating the distribution of consumption in the population. Such data at international level can be obtained through EUROSTAT[5], FAOSTAT[6] and OECD.stat[7]. In particular, the Global Environment Monitoring System - Food Contamination Monitoring and Assessment Program (GEMS/Food), coordinated by the WHO, used FAO Food Balance Sheet data to develop regional dietary patterns of raw and semi-processed food commodities specifically aimed at assessing the potential exposure of populations to chemicals in food. The household budget survey (HBS) is a national survey which focuses on households' expenditure on goods and services. It is carried out by each Member State and is used to compile weightings for important macroeconomic indicators, such as consumer price indices (which are measures of inflation) and national accounts. In contrast to food balance sheets, household surveys can supply information on the distribution of food consumption at household level, but not separately for the individuals belonging to the household. Foods consumed out of the home are not considered in HBS.

Individual dietary surveys are the only surveys that provide information on the distribution of food consumption in well-defined groups of individuals and are therefore preferred for the assessment of dietary exposure within the risk assessment process. Data from individual dietary surveys are also understood to more closely reflect actual consumption (Kroes *et al.*, 2002; WHO, 2009).

2.2.2. Food consumption data collection at EFSA

Reliable food consumption information has been collected by EFSA over the last five years at an increasing level of detail. In 2007, EFSA created a first food consumption database for the purpose of pesticide exposure assessment called the Pesticide Residues Intake Model (PRIMo) (EFSA, 2007a, b). It is based on summary statistics of food consumption information expressed as raw agricultural commodity consumption for children and adults provided by Member States. A total of 22 national diets for long-term and 19 diets for acute exposure assessment have been compiled in the PRIMo database. In addition to the national diets, five international diets are also considered. Consumption

[5] http://epp.eurostat.ec.europa.eu/portal/page?_pageid=1090,30070682,1090_33076576&_dad=portal&_schema=PORTAL
[6] http://faostat.fao.org/default.aspx
[7] http://stats.oecd.org/wbos/Index.aspx?usercontext=sourceoecd

figures refer to the food commodities listed in the EC Directive 396/2005, regulating pesticides residues in food. Information is not available for all 263 commodities, missing data typically refer to rarely eaten commodities (e.g. exotic fruits) or for commodities eaten in very small amount (e.g. spices).

In 2008, following recommendations issued by the EFSA Scientific Committee (2005a), EFSA created the "Concise European Food Consumption Database" (EFSA, 2008a). It contains information from individual dietary surveys from 19 EU Member States for a limited number of broad food categories (15 main food categories with some split into sub-categories giving a total of 28 categories and sub-categories). It was intended to be used for preliminary exposure assessments and was followed in early 2011 by the EFSA Comprehensive European Food Consumption Database to be used for detailed exposure calculations. The Comprehensive Database has been built from existing national information on food consumption at a detailed level. Competent organisations in the European Union's Member States provided EFSA with data from their most recent national dietary survey in the country, at the level of consumption by each individual. The Comprehensive Database currently includes food consumption data concerning infants, toddlers, children, adolescents, adults, elderly and very elderly from a total of 32 different dietary surveys carried out in 22 different Member States (EFSA, 2011a).

The use of these data for direct country-to-country comparisons is not advisable because the database comprises data collected using different methodologies. The collection of accurate and detailed food consumption data derived from a harmonised methodology across Europe is therefore still a primary long term objective for EFSA and has been recognised as a top priority for collaboration with the EU Member States. A guidance document was published for future food consumption data collections across the EU (EFSA, 2009). An activity is underway to build the harmonised pan-European Food Consumption Database through the EU Menu project.

2.3. Food description and classification

The links between food consumption information on the one hand and chemical concentration data on the other are rarely direct. Both food consumption surveys and the use of analytical or compositional data rely on the understanding of food definitions and the comparability of the results obtained. Many national and international food description and classification systems are available. Most of them are designed to be fit-for-purpose focusing on e.g. food consumption, food composition, legislation or trade. National food classification systems are often based on national criteria and the food groups can be very specific. However, the systems are not necessarily compatible and the user needs to get a clear understanding of the way the systems are designed and how they are used for specific applications.

EFSA recently evaluated the appropriateness of several food classification systems in providing accurate dietary exposure assessment results for chemical compounds in food. Existing systems were not considered suitable for all exposure assessments within EFSA's remit and it was therefore decided to draft a food classification system (referred to as FoodEx) that could better address the current needs. This system is currently used for the classification of both food consumption and contaminant concentration data on a trial basis. Further refinements are being introduced to address the needs of most units in EFSA with the aim of introducing an agreed system by the end of 2011.

For estimating dietary exposure, data on levels of chemicals in food as consumed are more accurate than levels in primary agricultural products. However in many cases - especially for natural toxins, pesticide residues or environmental contaminants - occurrence data are often only available for basic crops or staple foods (Kroes et al., 2002). In particular, sampling for pesticide monitoring is almost exclusively done using primary agricultural products or at early process steps of such staple foods since Maximum Residue Levels (MRLs) set for pesticides most often refer to Raw Agricultural Commodities (RACs). Such commodities include parts of the plant that are either not edible or usually removed before marketing or consumption, like outer leaves or peel, and it is necessary to use consumption data expressed accordingly (sometimes in terms of RAC and sometimes in terms of food product ready for consumption).

EFSA is currently working on the development of a database of standardised factors in order to convert the food consumption information from the Comprehensive Database to the Raw Agricultural Commodities (RAC) level.

2.4. Methods for estimating dietary exposure

A number of different methods exist to combine or integrate consumption estimates with chemical concentration data, ranging from quick worst-case estimations to refined methods aimed at assessing actual exposure. The selection of the method usually depends on a number of factors, including the purpose of the assessment (target chemical substance, population group, degree of accuracy required, etc.) and, above all, the availability of information.

In general, it is considered neither cost-effective nor necessary to collect detailed food consumption and concentration data for every hazardous substance (Lawrie and Rees, 1996). A stepwise or tiered approach in which the initial steps rely on conservative screening methods is commonly used to minimise estimation costs and focus resources on the most important issues for which there is a potential health concern. The stepwise approach to dietary exposure assessment is such that as the accuracy of dietary exposure assessments increases, the cost of collecting adequate data and human resources needed to undertake the assessments also increases (WHO, 1997a; WHO 2009). If at a lower tier estimate, the exposure to a given pesticide residue, food additive, veterinary drug residue or contaminant exceeds its health based guidance value (e.g. Acceptable Daily Intake (ADI) or Tolerable Daily Intake (TDI)), a more refined method of dietary exposure assessment should be applied. Exposure is therefore first assessed by using screening methods following a simplistic approach based on conservative assumptions, often considering proxies for high percentile consumers. Such conservative estimates and assumptions are not suitable for estimating actual exposure since they are designed to cover the worst-case scenario.

The described approach has been adopted by EFSA for its risk assessments. In particular, the EFSA opinion on exposure assessment (EFSA, 2005a) clearly affirms that exposure assessment has to be conservative and that a stepwise approach should be used.

2.4.1. Refined methods for exposure calculation

When screening methods cannot rule out a safety concern, more refined methods should be applied. With access to food consumption survey information, actual mean and high percentile consumption can be used as inputs into an exposure model. Such calculations can be further refined by splitting the population into age groups and by using the actual body weight of the individual subjects to estimate the mean and high percentile consumption per kg body weight. A further refinement is possible when food consumption is available at individual level. In such cases, chemical concentrations and food consumption can be directly matched for each subject and the respective food or food category and a distribution of total exposure estimates produced, where any percentile of interest can be calculated. The average contribution of each food or food category to the total exposure can also be estimated. EFSA started to use the individual food consumption data and body weight information from the Concise Database for the assessment of exposure to contaminants in 2010. Data from the Comprehensive Database are currently used and this is now EFSA's preferred model for refined exposure assessments. For chronic exposure calculations the mean chemical concentration is used as the input in the model whereas for acute exposure calculations there might sometimes be a case for also using high percentile chemical concentrations. Dietary exposure estimates are in the majority of cases produced by considering the consumption of all foods and all subjects involved in the dietary surveys, but estimates for "consumers only" are also calculated under specific circumstances.

Characterising the full distribution of dietary exposure is the most resource-intensive assessment, as data are required that characterise the full range of food consumption practices as well as the full range of chemical concentrations in the foods as consumed. Therefore, such methods are usually reserved for later steps. When such methods are employed, appropriate statistical models are used to evaluate the data and to describe the range of consumer exposures and the associated probabilities of consumers

having each level of exposure. These exposure assessments are generally referred to as probabilistic exposure estimates (WHO, 2009). With probabilistic models it is also possible to fill some of the gaps in the input variables and consequently include aspects like brand loyalty, seasonality and age-related behavioural patterns.

Due to the methodological differences in the collection of the food consumption data mentioned above, dietary data collected within different dietary surveys cannot be merged together with the aim to assess the exposure at European level. Refined exposure estimates are therefore always calculated, for the different age groups, at Member State level. In order to be protective of public health for the whole of Europe, multi-national calculations should provide exposure estimates that are equal to or greater than the highest exposure observed at national level. If the estimated multi-national dietary exposure to a chemical does not exceed its respective health-based guidance value then the level of exposure should be acceptable at national level, because the level of overestimation for international dietary exposure assessments for any region would tend to be greater than that for national estimates (WHO, 2009). This applies to both acute and chronic exposure assessments. Where nutrient deficiency is addressed both the multi-national intake estimate and the lowest intake observed at national level should be compared to nutrient reference values and the percentage of subjects at or below the Lower Threshold Intake (LTI) and at, below or above the Average Requirement (AR) (or AI-Adequate Intake) should be calculated, ideally given with a distribution of values.

2.4.2. Alternative methods for the assessment of exposure

As explained above, dietary exposure should be assessed by combining data on the concentration of a chemical in a food with its consumption. Unfortunately, exposure assessments are not always performed on the basis of consumption and concentration data related to the same food as consumed by the individual within a population. Therefore, assessments of exposure to dietary components will usually require some degree of modelling to attempt to create a representation of the real-life exposure situation. Exceptionally, within a dietary survey and within a well-defined population subgroup such as vegetarian or children, the duplicate portion technique can be used (Wilhelm at el., 2002). In these type of studies a duplicate portion of all food and drink consumed by the subject throughout the day is retained and chemically analysed. However, this approach requires a considerable commitment from the participants and risks to influence the food consumption pattern during the trial. Due to its costs, duplicate diet studies are usually limited in the number of participants and samples evaluated and their results are, consequently, more useful for looking at mean exposure than at high-end exposure (Kroes et al., 2002).

An important exception is migration from food packaging. Rather than collect a duplicate food sample, the packaging materials used for foods eaten in the home can be retained for analysis. This analysis can reveal information on the chemical composition of the packaging and potential migration levels into food. Since the packaging material can be linked directly to the foods consumed, and since concentrations in the food can then be estimated, collecting and analysing the packaging in this way has the character of a Duplicate Diet Survey. The used packaging can be collected rather easily, compared to duplicate food samples at least, and surveys of the general population or of targeted sub-groups numbering some hundreds of individuals is logistically and economically feasible. Such studies have been done in a number of Member States.

There is an increasing interest for the potential use of biomarkers for assessing exposure to food chemicals. It needs to be recognised that this approach takes account of exposure from all sources, including non-dietary sources. It is thus important to understand to what extent such other sources exist and are likely o be relevant, especially if attempting to compare the results of such measurements to dietary exposure estimates assessed by means of conservative models (Kroes et al., 2002; WHO, 2009). A number of methods for specific individual food chemicals are currently being developed and it seems that this trend will continue. However, very few methods have been fully developed and validated. Even fewer are the instances where such methods are currently being employed, at either Member State or European level, to assess exposure. Nevertheless, there is currently an on-going

initiative on harmonisation of human biomonitoring collections across Europe called the Consortium to Perform Human Biomonitoring on a European Scale (COPHES, 2011).

2.4.3. High consumers and special population groups

The methodologies to assess exposure to chemical substances through the diet must always take into consideration non-average individuals, and in particular those who consume relatively large quantities of foods containing higher concentrations of substances that may lead to a health risk (European Commission, 1998; WHO, 2009). The definition of high consumers is crucial to the outcome of the risk assessment because, in practice, it provides a measure of the proportion of the population that could exceed health-based guidance values and indicates if risk management measures should be considered.

Different percentiles (95^{th}, 97.5^{th}, 99^{th} and even 99.9^{th}) can be used to identify high consumers. The percentile selected to represent a high consumer depends on the purpose of the dietary exposure assessment (acute or chronic estimates) and the type of food consumption data available, but also social and ethical criteria have been used. It is important to bear in mind that the reliability of high percentiles is related to the number of subjects used to calculate them. Percentiles calculated on a limited number of subjects should be treated with caution, as the results may not be statistically robust. A clear indication concerning the minimum number of observations necessary to estimate a given percentile cannot be found in the literature. Different options are presented and discussed in the guidance on the "Use of the Comprehensive Database in exposure assessment" (EFSA, 2011a), none of them being a widely accepted standard.

With respect to the different population groups for which special consideration is needed, infants and young children are considered the most exposed. This is due to the fact that infants and young children present the highest food consumption levels per kilogram body weight (Lowik, 1996; WHO, 2009). In most cases, exposure assessed in this population group is consequently higher than that estimated for all other age groups and it guides the risk assessment process.

In relation to vulnerability, infants, young children, pregnant and lactating women are also considered important population groups within most areas related to food safety studies (WHO, 2009). Data on the consumption patterns of the elderly, especially of those older than 75 years, are of particular interest when biological agents are considered, whereas, in most of the cases, they are not a priority when chemical substances are under consideration. Their vulnerability relates to a diminished efficiency of the immune system with increasing age that makes them more at risk of infection and more severely affected by communicable diseases.

In order to identify consumption patterns that might be associated with a higher risk of exposure, subjects with special dietary habits due to their personal choice (e.g. vegetarians) or special dietary requirements due to health problems (e.g. diabetics and celiacs) can also be considered. Information should also be collected in order to assess exposure in subjects belonging to different ethnic groups and different socio-economic strata since these two aspects might be correlated with particular consumption patterns.

The lack of consumption data for the above mentioned population groups is an important drawback when assessing dietary exposure. The importance of acquiring reliable and representative consumption information for these population groups, at a European level, has been emphasised in the guidance of EFSA on the "General principles for the collection of national food consumption data in the view of a pan-European dietary survey" (EFSA, 2009).

2.4.4. Exposure estimates and evaluation of uncertainty

The method applied in any dietary exposure assessment should be clearly stated and reproducible. Information about the model and data sources used, assumptions, limitations and uncertainties should also be documented. In the report of a FAO/WHO consultation held in Geneva (WHO, 1997a), it is

recommended to distinguish between the contribution of variability (heterogeneity) and true uncertainty (lack of knowledge) in exposure assessment. In 2006, the Scientific Committee published a guidance document on a tiered approach for describing uncertainties, qualitatively or quantitatively, within the context of dietary exposure assessments (EFSA, 2006a). Initially all relevant uncertainties may be analysed qualitatively using a tabular approach and, in many cases, this may be sufficient. If needed, those uncertainties that appear to be critical to the outcome may then be analysed deterministically or probabilistically (EFSA, 2006a). This approach has been used by different EFSA Panels (e.g. CONTAM and PPR). Uncertainty and variability is also discussed in a guidance document of the Scientific Committee focused on transparency in the scientific outputs produced by EFSA (2009c). It is stated that, although it may be impossible to identify all the uncertainties and to distinguish them from the real variability, each scientific output should describe the types of uncertainties encountered and considered during the different risk assessment steps, and indicate their relative importance and influence on the assessment outcome.

3. Dietary exposure assessment carried out at EFSA

EFSA's remit covers food and feed safety, nutrition, animal health and welfare, plant protection and plant health. In particular, some of the EFSA scientific Panels and units perform risk assessment for the following chemical substances:

- food additives and nutrient sources added to food (ANS Panel)
- food contact materials, enzymes, flavourings and processing aids (CEF Panel)
- pesticides and their residues (PPR Panel and the Pesticides Unit)
- additives used in animal feeding (FEEDAP Panel)
- natural toxins, environmental, industrial and process contaminants and residues of unauthorised substances not covered by another Panel (CONTAM Panel)
- foods or food constituents, e.g. nutrients or other substances, novel foods, food allergens and infant formulae (NDA Panel)
- newly expressed proteins (or altered endogenous compounds) in genetically modified food and feed (GMO Panel)

In all these fields the assessment of dietary exposure to potential hazardous substances, or the estimation of dietary intake for substances with potential beneficial effects, is performed by EFSA Panels and units within the risk assessment process. Different assumptions made to compensate for the lack of food consumption and/or occurrence data are made across the different Panels. The different exposure models are presented in the following sub-sections.

Table 1 shows an overview of the different sources of consumption and chemical concentration data fitted to the different exposure models that are used by the different EFSA Panels.

Table 2: Overview of the different input parameters to fit the different exposure models which are used by the different EFSA Panels

Panel/Unit	Harmful or beneficial chemical substances	Exposure method	Food consumption source	Chemical concentration source	Reference (example)
ANS	Additives (chronic)	Budget method (Tier 1)	Theoretical data based on a physiological upper limit to the amount of food and drink	Maximum permitted levels	EC, 1998
		SCOOP model (Tier 2)	Summary statistics from the Concise Database and EXPOCHI project	Maximum permitted levels	EC, 1998
		SCOOP model (Tier 3)		Actual use levels	EC, 1998
	Nutrient sources (chronic)	Poundage method	Summary statistics from the literature	Highest supply use	EFSA, 2009c
CEF	Flavours (chronic)	MSDI	None (poundage data)		
		mTAMDI	Model diet	Normal use levels	EFSA, 2010a
		APET	Model diet based on standard portions	Normal occurrence levels (added and as natural constituent)	
	Food contact materials (chronic)	Model diet	Theoretical diet (1 kg of food in contact with 6 dm^2)	Maximum permitted migration level or data from targeted analytical projects	EFSA, 2006b; EFSA, 2009b
	Enzymes (chronic)	Budget method	Theoretical data based on a physiological upper limit to the amount of food and drink	Highest use level	EFSA, 2009a
CONTAM	Contaminants (chronic and acute)	Individual based model	Food consumption data from national dietary surveys at individual level	Summary statistics from national monitoring and surveillance data	EFSA, 2009d; EFSA, 2009e; EFSA, 2010c
FEEDAP	Additives (chronic)	Model diet	Theoretical diet	Summary statistics from national monitoring and surveillance data	EFSA, 2008e
GMO	Newly expressed proteins (or altered endogenous compounds) in GM food and feed (chronic and acute)	Defined by the applicant	Summary statistics from the literature (e.g. GEMS/food, FAO food balance sheet)	Provided by the applicant	EFSA, 2010d

Panel/Unit	Harmful or beneficial chemical substances	Exposure method	Food consumption source	Chemical concentration source	Reference (example)
NDA	Novel foods and ingredients (chronic)	Defined by the applicant	Summary statistics from the literature (usually, but not exclusively based on national dietary surveys)	Provided by the applicant	EFSA, 2010d
Pesticides	Pesticides (chronic) (Tier 1)	TMDI	Summary statistics from national dietary surveys (PRIMo)	Maximum Residue Levels	EFSA, 2007a; EFSA, 2007b; EFSA, 2008d
	Pesticides (chronic) (Tier 2)	IEDI		Summary statistics from supervised trials or national monitoring and surveillance data	
	Pesticides (acute)	IESTI		Summary statistics from supervised trials or national monitoring and surveillance data	

3.1. The Panel on Food Additives and Nutrient Sources added to food (ANS)

3.1.1. Food additives

To estimate the exposure to food additives, the principles of the stepwise/tiered approach, as described in the report of the Scientific Co-operation (SCOOP) Task 4.2, are applied (European Commission, 1998). In each of the three tiers used by the ANS Panel, additives are assumed to be present in all food products in which they are authorised. Tier 1 is based on theoretical food consumption data and maximum usage levels for additives as permitted by relevant Community legislation. The second and third tiers refer to assessment at the level of individual Member States, combining national data on food consumption with the maximum permitted usage levels for the additive (Tier 2) and with its actual usage patterns (Tier 3).

The Budget method (Tier 1) uses theoretical food consumption data and maximum permitted use levels (MPLs) for additives as permitted by relevant Community legislation. The Budget method is based on the physiological upper limit to the amount of food and drink that can be consumed each day, and thus of food additives. For beverages this is assumed to be 100 mL and for solids 25 g per kg b.w. and day. A further assumption is that only a certain proportion of the diet is likely to contain food additives. The default proportion of beverages and solid food that could contain the additive is typically assumed to be 25%, but varies depending on the additive in question and the population under consideration. Full details of the budget method are described in the above-mentioned SCOOP report.

The second and third tiers refer to dietary exposure assessments at the level of individual Member State by means of food consumption summary statistics (average for all population and for the 95th percentile consumers only) from the EFSA Concise Database and, in order to take advantage of more refined food categories, the last national dietary survey of the United Kingdom (Henderson et al., 2002), for the adult population, and from the EXPOCHI project (Huybrechts et al., 2010), for children. These data are combined with the relevant MPLs for the food additive (Tier 2) or with its actual usage levels provided by industry (Tier 3). The model used to estimate high percentile exposure, at Tier 2 and 3, assumes that a subject can be a high consumer of only one food category and an average consumer of all the others. The considered body weight is generally the mean weight declared by the food consumption survey used in the model, for example, see latest opinions on food colours (EFSA 2010i).

Considering the new applications of food additives, the procedure is simpler as no MPL are defined and only the third tier can be performed.

In addition, the ANS WG on Exposure Assessment is currently developing a new methodology for estimating the dietary exposure to food additives. This will include the use of the EFSA Comprehensive Database and will be based on the Commission Regulation amending Annex II of the Regulation (EC) N°1333/20088. This annex (Commission regulation (EU) No 1129/2011), published in November 2011, list the authorised food additives and their conditions of use in food categories defined following an updated food categorisation system.

3.1.2. Nutrients sources added to food

The estimates for intake of nutrients are calculated by the ANS Panel by summing the highest nutrient use level reported by the petitioner (per day) with the average dietary intake and the "high" dietary intake (based on either the 95th or 97.5th percentile), both these values are taken from scientific literature. Estimates are calculated for adults and children. For example, this model was used for estimating exposure for potassium molybdate added for nutritional purposes to food supplements

[8] Regulation (EC) No 1333/2008 of the European Parliament and of the council of 16 December 2008 on food additives.

(EFSA, 2009c). There is a large uncertainty associated with mean dietary exposure derived from poundage data as they do not adequately describe highly exposed consumers (WHO, 2009).

3.2. Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)

3.2.1. Flavourings

Most of the safety evaluations carried out by EFSA on flavourings until now have not used actual food consumption data. Dietary exposure estimates were solely based on either poundage data (production volumes of the chemical) reported by industry by means of the Maximised Survey-Derived Daily Intake (MSDI) method or on the combination of standard portion sizes with rough use levels reported by industry through the modified Theoretical Added Maximum Daily Intake (mTAMDI) method.

In 2010 EFSA adopted a guidance document that specifies which data industry should submit to EFSA for the safety evaluation of new flavourings (EFSA 2010) and the CEF Panel developed a new approach for dietary exposure assessment for new flavouring submissions. The new approach is in line with the methods that have been used for flavourings until now, but it takes into account some of their limitations. In the guidance document the following four different exposure assessment methods for flavourings are recommended to be covered:

- chronic dietary exposure to flavouring substances from the consumption of flavoured foods and beverages in adults and children;
- dietary exposure to flavouring substances that may be used in foods specifically designed for infants and young children;
- total dietary exposure from added flavourings and from naturally occurring flavourings in adults and children; and
- acute dietary exposure.

Chronic dietary exposure should be assessed in adults and children consuming foods and beverages containing the substance of interest. The highest of these values among adults and children, expressed per kg bodyweight, should be used as the basis for the safety evaluation of the substance. The new method, called the “Added Portions Exposure Technique” (APET), is an adaptation of the Theoretical Added Maximum Daily Intake (TAMDI) method and is planned to be used by the CEF Panel by September 2011. This new method makes use of standard portions established for each food category of the CODEX General Standard for Food Additives (GSFA). More variability in potential dietary exposure can be captured with this technique than with the TAMDI. Thus, the dietary exposure estimated with the APET will be lower when a flavouring substance is intended to be used in food categories consumed in smaller portions. The occurrence data used to estimate the exposure through the APET method are provided by the applicants for each of the food categories defined in the guidance document on the basis of:

1. normal occurrence level from added flavourings;
2. normal occurrence level of the flavouring substance as natural constituent and/or developed during the processing and/or as carry over resulting from their use in animal feed;
3. normal combined occurrence levels from all sources (as added flavouring or from other sources).

The APET is calculated for each of the above-mentioned scenarios by summing the highest potential dietary exposure within each of the two groups (“beverages” and “solid foods”). Such an estimate, based on daily consumption of one single standard portion of beverage and one single standard portion of solid food, is likely to provide a conservative assessment of long-term average dietary exposure for

consumers of flavoured products. The APET is expressed in mg/kg bw per day. For an adult, a body weight of 60 kg is used and the portions are those established by the JECFA when developing the SPET (Single Portion Exposure Technique) method (FAO/WHO, 2008).

The diets of infants and young children tend to be less varied than those of older children and adults; an ad hoc method has therefore been developed for estimating the exposure in these age groups. A specific exposure assessment is required. It is based on a model diet of a 12-month old child fed with milk and a variety of processed baby foods containing the flavouring substance of interest.

Data on acute toxicity and acute dietary exposure are not needed on a regular basis in the case of flavourings. However, if the estimated level of dietary exposure may raise any concern about acute adverse effects of a flavouring substance, the Panel may need to consider safety aspects in terms of acute exposure. Then, the assessment is based on the maximum concentration of flavouring substances in foods and beverages and on an estimate of the largest quantities (high percentiles) of foods or beverages that can be consumed by a subject within one day. The acute consumption is assessed by considering as large portions three times the size of the standard portions used for chronic exposure, for either a solid food or a beverage.

The above mentioned guideline also requires the estimation of the cumulative dietary exposure to flavouring substances structurally and metabolically related to the substance under study in order to ensure that the concomitant dietary exposure to all flavouring substances belonging to the same group does not exceed the capacity of the body to metabolise them. To this aim, an assessment of cumulative dietary exposure within one day is needed. EU poundage data (total annual volumes of production at EU level) must be used by the applicant to identify the most important flavouring substances structurally and metabolically related to the flavouring under evaluation. Normal occurrence levels for these substances, used as added flavouring substances, must be used to calculate the APET in adults only. The APET of five "high poundage substances" will be added up and used as an estimate of potential cumulative dietary exposure within one day, expressed in mg/kg bw per day in adults.

3.2.2. Food contact materials

In contrast to food additives and flavourings, substances comprising food contact materials are principally not intended to be present in food, but some chemical migration is unavoidable. Existing guidelines (SCF, 2001) inform applicants for new substances that come in contact with food that, in order to permit estimation of the likely maximum daily intake of the substance, information on concentrations in food should be provided. Alternatively, the guidelines also allow for information on migration into food simulants under standard conditions of migration testing, or concentrations derived by applying the worst case scenarios, can instead be provided. In practice, virtually no applicant provides this kind of information. In general, there are no data available on the actual concentration of these substances in food or beverages or on the consumption of food or beverages in contact with materials containing the substance. Therefore, for authorisation purposes, no assessment of the dietary exposure is made by combining concentration data in actual foods or beverages with consumption data. Instead, the exposure is estimated routinely on the basis of a model diet assuming that a person weighing 60 kg may consume daily 1 kg of food including beverages that is in contact with 600 cm^2 (surface of a 10 cm cube) of food contact materials which release the substance at the highest concentration measured using food simulants or calculated using worst-case scenarios or by migration modelling (EFSA 2009a). For fatty foods, which are important for the migration of organic (mainly lipophillic) substances, it is assumed that a person may consume daily an amount of food or beverages containing up to 200 g of pure fat.

In its recently published document, "Criteria to be used for safety evaluation of a mechanical recycling process to produce recycled PET intended to be used for manufacture of materials and articles in contact with food" (EFSA, 2011e), the CEF panel has described three typical exposure scenarios for evaluation of the safety of this recycled plastic. These scenarios are for adults, children and infants and they allow for the high and regular consumption of the affected foods. Applicants for the safety

evaluation of recycling processes for PET can also formulate and submit their own exposure scenarios if these describe better the particular applications of PET in contact with food and beverages that are planned.

Data on the actual concentration of a substance migrating from food contact material into foods are mainly generated from targeted analytical projects on substances raising a safety concern. This occurred for example in the safety evaluation of ITX (EFSA, 2005b), bisphenol A (EFSA, 2006b) and 4-methylbenzophenone (EFSA, 2009b) In general, for materials other than plastics (such as printing ink constituents, adhesives, coatings, silicones, colorants, paper & board), the evaluation of dietary exposure of consumers can be based on actual migration data of the substance itself. Read-across from substances with similar technological function can also be used. When no such data are available, migration modelling can be used. Recognised models use the molecular weight of the substance as molecular descriptor and its concentration in food contact materials as key parameters.

3.2.3. Enzymes

A guidance document was published by EFSA in 2009 (EFSA, 2009a) specifying the type of information that industry should provide to enable EFSA to carry out the safety assessments on food enzymes. In this document it is stated that a conservative technique such as the above mentioned "budget method" should be used to assess potential dietary exposure in a standard adult of 60 kg body weight consuming large amounts of the categories of food and beverages for which use levels have been proposed, assuming that they always contain the food enzyme at its proposed upper use level.

It is also stated that, if needed, the technique should be adapted to consider the potentially higher consumption per kg body weight of these foods and beverages in children and that all assumptions and data used for the dietary exposure assessment should be clearly described and justified. Moreover, in case the use of the food enzyme is proposed for products specifically designed for infants (0-12 months) or young children (12-36 months), as defined in the Commission Directive 2006/141/EC, ad hoc conservative exposure estimates must be produced taking specifically into account these population groups.

3.3. Panel on Contaminants in the Food Chain (CONTAM)

The methodology to assess exposure used by the CONTAM Panel evolved, thanks to the support of the EFSA Dietary and Chemical Monitoring (DCM) Unit, in the last years. From 2004 to 2006, ad hoc food consumption data were submitted by Member States together with data on chemical concentration. These very heterogeneous data were used in a conservative way, e.g. the amount of fish consumed in Norway was used for the whole EU to assess exposure to organotin (EFSA, 2004b). When national data were not submitted or not adequate, the WHO GEMS/Food data were used. This was the case in the aflatoxins opinion (EFSA 2007c). From 2006, the CONTAM Panel used the EFSA "Concise European Food Consumption Database" (Concise Database) (EFSA, 2008a) having started with the summary statistics of 3 and 4 countries in order to assess exposure to ochratoxin A (EFSA 2006c) and PFOS/PFOA (EFSA 2008b), respectively. The Concise Database was further extended and from 2008 contained summary statistics on food consumption data for adults from 19 countries. The model used to estimate high consumers changed with the increasing availability of food consumption data across the years. First, a method recommended by the European Commission (1998), and reported in the guidance document for the "Use of the Concise Database in exposure assessment" (EFSA, 2008a), was used. It consists of adding the two highest food group contributors at the 97.5th percentile and the other food group contributors at the mean level of consumption. The considered body weight is 60 kg for adults and 15 kg for children. Since 2009, following a recommendation from the Dietary and Chemical monitoring unit (DCM) and starting with the opinion on uranium (EFSA, 2009e), individual food consumption data from the 19 national databases from the EFSA Concise Database were directly used to estimate mean and high percentile exposure levels instead of the previously described model. Individual body weights were used as well. As data were used at the individual level, there was no need to identify the two most contributing food-groups at the aggregated level. Until 2010, the dietary exposure for children was extrapolated from the one of adults assuming a

similar consumption and a lower body weight. For infants, the dietary exposure was generally extrapolated from the DONALD study (Kersting et al., 1998). A default value for total drinking water (2 litres for an adult weighing 60 kg) was also used to assess exposure to uranium (EFSA, 2009e).

Since the end of 2010, the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) has been available and it is used in all exposure estimates presented in the CONTAM opinions (e.g. EFSA, 2010g, EFSA 2010h). Individual food consumption data from adults (21 surveys) and children below the age of 10 years (16 surveys) are combined with mean occurrence values in order to provide mean and high percentile exposure estimates. Typically, chronic exposure estimates are for mean and high percentile consumers of the total population. High percentile consumers are expressed as the 95th percentile.

Average and 95th percentile of exposure are also assessed among adult vegetarians, when this is considered relevant, despite the very few subjects (417 in total from 9 countries) in the Comprehensive Database that declared themselves as vegetarians. These estimates have been, for example, included in the CONTAM opinion on the risks for public health related to the presence of zearalenone in food (EFSA, 2011c). Previously, the CONTAM Panel assessed the exposure among vegetarians by means of French data only, which was the case for cadmium (EFSA, 2009f). Consumption data from the Concise Database for women of childbearing age (defined as those from 20 to 40 years of age) has also been used as a surrogate for pregnant women, as shown in the opinion on lead (EFSA, 2010c).

When the toxicological evaluation indicates a need for an acute dietary exposure assessment the consumption data are taken into account independently at the level of individual and day. These data are combined with the mean and the 95th percentile levels of the chemical contaminant and percentiles to express high consumers as the 95th percentile of all days and/or consuming days only. As suggested in the EFSA guideline on the "Use of the Comprehensive Database for exposure assessments" (EFSA, 2011a), all dietary surveys included in the Comprehensive Database are considered when assessing acute exposure whereas those with one day per subject are excluded when calculating chronic consumption statistics. Acute consumption statistics were provided in the CONTAM statement on the consumption of shellfish meat (EFSA, 2010).

Regarding occurrence data, a concern repeated many times in the assessments of contaminants is the management of results below the Limit of Detection (LOD) or Limit of Quantification (LOQ). The Panel, in general, used the WHO recommendations and estimated both the lower and the upper bound of the contamination (WHO, 2009). Recommendations, based on a minimum number of available samples and to different proportions of censoring percentages, to handle left-censored distributions of chemical contaminant data in the context of exposure assessment have been proposed by EFSA (EFSA, 2010e). However, the proposed procedure has not yet been implemented.

3.4. Panel on Additives and Products or Substances used in Animal Feed (FEEDAP)

In the technical guidance document for establishing safety of additives for the consumer (EFSA, 2008e), the FEEDAP Panel specifies the model diet for humans to be used when conducting studies concerning consumer safety. In particular, the applicant dossier should contain all relevant data to allow the assessor to calculate the potential exposure of the consumer that would result from the use of the additive and to enable comparisons with the exposure to the same active substance from other sources, where relevant. Estimates of the daily theoretical dietary exposure must be based on concentration data of total relevant residues and a model diet based on a worst-case scenario. The model diet consists of the daily consumption of 300 g of muscle (from mammals, birds and/or fish), 100 g of liver (from mammals and/or birds), 50 or 90 g of fat (from mammals or birds, respectively), 50 or 10 g of kidney (from mammals or birds, respectively), 1,500 g of milk and 100 g of eggs.

The above described model diet has to be used for the safety evaluation of all additives for which residue data is required. For additives intended for multi-species use, the daily theoretical exposure

resulting from the consumption of tissues should be independently calculated for all target species for which data are available. If bees are identified as the target species, 20 g of honey shall be considered.

The Technical Guidance also specifies that, for certain additives (e.g., some nutritional and sensory additives or for additives intended for minor species), it may be appropriate to subsequently refine the human exposure assessment using more realistic consumption figures, but still keeping a conservative approach. Where possible this should be based on Community data (e.g., the EFSA Comprehensive European Food Consumption Database).

Ad hoc dietary exposure assessments are also performed by the FEEDAP Panel in which different methodologies and assumptions are used based on the dietary data available and the objective of the assessment. For example, in the opinion concerning the "Consequences for the consumer of the use of vitamin A in animal nutrition" (EFSA, 2008f), the FEEDAP Panel made a calculation on the vitamin A intake for adults based on the food consumption survey within the EPIC project (27 study centres, ten European countries, consumption of relevant food groups) (Slimani et al., 2002; Linseisen et al., 2002; Hjartåker et al., 2002; Welch et al., 2002). On the other hand, data from Italy (Turrini et al., 2001), Germany (Mensink and Beitz, 2004) and Ireland (Harrington et al., 2001) were used to estimate the intake of preformed vitamin A from liver only.

In the view of updating the existing guidance document a new model diet is currently under preparation based on the data from the Comprehensive Database. The new model was already used in the opinion on Selplex (not published yet).

3.5. Panel on Dietetic Products, Nutrition and Allergies (NDA)

A dietary exposure assessment is required by the NDA Panel in order to evaluate novel foods. Applicants are requested to calculate an anticipated dietary intake by using food consumption data from literature (typically, national dietary surveys) and the maximum usage levels of the novel food or of the novel food ingredient under evaluation. Although encouraged, the use of food consumption data from different EU countries in estimating dietary intake is not a mandatory requirement. For example, in the Scientific Opinion concerning the safety of "Sardine peptide product" (EFSA, 2010b), the applicant estimated the sardine peptide intake using food consumption data from the UK NDNS (National Diet and Nutrition Survey) program (Henderson et al., 2002). Food consumption data from the Netherlands have served applicants in a few other novel food applications.

In the context of its work on the reference values for nutrient and energy intakes, the NDA Panel is also reviewing nutrient intake data from several national dietary surveys in EU countries. Currently, for its opinions on dietary reference values for energy and macronutrients, the NDA Panel used published nutrient intake data from surveys in different EU Member States (e.g. EFSA, 2010f). However, in the future, such information may also be obtained from the Comprehensive Database, enabling a better comparison between countries with respect to nutrient intake.

3.6. Plant protection products and their residues

Routinely, for pesticide residues the long-term (chronic) exposure and, if the pesticide has acute toxic properties, also a short-term (acute) exposure assessment is performed. Depending on the objective of the dietary exposure assessment (pre-regulatory or post regulatory), different data on the level of pesticide residues in food and food consumption data are used by the Pesticides Unit. According to the WHO guidelines for the pre-regulatory exposure assessments a tiered approach is applied. In the first tier a screening method is used to identify those residue levels that are of no safety concern using a simplified approach. If no consumer risk is identified with the screening methodology, it is not necessary to use more sophisticated calculation tools. For chemicals for which a potential risk cannot be excluded in the first tier calculations, more information is needed to allow more accurate estimations in a second tier calculation. However, in EFSA's routine risk assessment work in the framework of MRL setting, in most cases the more refined tier two calculations are performed.

3.6.1. Pre-regulatory exposure assessment to pesticides

At Tier 1 the calculation of the chronic exposure to pesticides is carried out by merging the proposed MRL(s) with the food consumption data contained in the EFSA Pesticide Residues Intake Model (PRIMo) (see chapter 2.2.2) by means of the Theoretical Maximum Daily Intake (TMDI) method, an internationally agreed methodology (WHO, 1997a, Hamilton & Crossley, 2004). Thus, the overall exposure is calculated by summing up the individual mean intakes (for the total population) for each food commodity. The calculated intake, normalised for the body weight, is then compared with the Acceptable Daily Intake (ADI) of the pesticide. The TMDI is supposed to grossly overestimate the exposure. In order to increase the reliability and accuracy of the method, the exposure is calculated with the supervised trials median residue (STMR) level instead of the MRL to calculate the International Estimated Daily Intake (IEDI) (WHO, 1997a). The STMR is the median residue concentration in the edible part of the crop, which is derived from supervised field trials performed according to the intended Good Agricultural Practice. At EU level normally eight trials have to be provided for the major crops, whereas for minor crops the number of trials may be less. The EFSA PRIMo also provides the possibility to calculate the IEDIs by replacing the MRLs with the appropriate STMR values, if available. It is noted that the STMR has to be calculated for the edible part of the crop by taking into account the residue definitions, which include all metabolites and degradation products of toxicological concern. In addition, other relevant factors for refinement (e.g. processing or conversion factors) are incorporated in the assessment of exposure.

In order to calculate acute exposure arising from pesticide residues, the International Estimated Short Term Intake (IESTI) method is used (FAO, 2009). Also this calculation can be performed by using the data contained in the EFSA PRIMo. This method requires data on the consumption of large portions (usually the 97.5th percentile from the single-day consumption data among consumers) together with typical unit weights of the edible part of the commodities and the body weights of the population associated with the food consumption data. The baseline assumption is that a consumer may eat a large portion (high level consumer at the top end of the distribution curve among consumers only) of a food that may contain residue levels higher than the composite sample, which was derived from supervised field trials. The acute assessment is conducted for each commodity separately as it is considered unlikely that a consumer will eat two or more different commodities with a large portion size within a short period of time and that those commodities have the highest level of the same pesticide. If available, processing factors can be taken into account in the model for assessing acute exposure.

3.6.2. Post-regulatory exposure assessment to pesticides

As no agreed international methodology for estimating the actual chronic and acute exposure to pesticide residues measured in monitoring activities is available, EFSA decided to adapt the risk assessment methodology developed for the pre-regulatory risk assessment. A modified version of the EFSA PRIMo is therefore also used to estimate the actual dietary exposure in the framework of the EFSA Annual Report on Pesticide Residues.

The mean residue value (instead of the STMR) observed in the monitoring program is combined with the consumption data for the total population to assess long-term exposure for a given pesticide/commodity combination. Similarly, for actual acute exposure the highest residue level observed for a specific commodity is used as input value together with the 97.5th percentile of the consumption among consumers only in the exposure assessment. Both acute and chronic exposure estimates are refined at the Tier 2 using processing factors in case the calculated intake at Tier 1 exceeds the Acute Reference Dose (ARfD) or ADI.

In recent years there has been growing interest internationally in the application of probabilistic techniques for the estimation of exposure to chemicals in food. The PPR Panel is of the opinion that probabilistic methodology is a potentially useful tool for conducting refined consumer exposure assessments. In particular, in its opinion on cumulative risk assessment (EFSA, 2008d), the PPR Panel stated that refined cumulative exposure assessments cannot be done without probabilistic methods and

recommended that guidance for performing probabilistic exposure assessments should be developed. For these reasons the PPR Panel was asked by EFSA to provide guidance on how probabilistic methodologies can be used for estimating dietary exposure, as additional tools to deterministic methods. The PPR Panel is currently finalising a guidance document on the use of probabilistic methodology for modelling dietary exposure to pesticide residues. This guidance document is planned to be published in 2012.

3.7. Panel on Genetically Modified Organisms (GMO)

Exposure assessment was carried out in the evaluation of GMO pre-market approval applications within the framework of Regulation (EC) 1829/2003. A recent document (EFSA, 2011d) provides guidance for the risk assessment of food and feed products derived from genetically modified (GM) plants.

An estimate of the expected intake is an essential element in the risk assessment of GM plants and derived food and feed. The applicant should determine the concentrations of the newly expressed proteins, other new constituents and endogenous constituents with levels altered as a result of the genetic modification (e.g. due to changes in metabolic pathways) in those parts of the GM plant intended for food or feed use. Expected intake of these constituents should be estimated taking into account the influences of processing, storage and expected treatment of the food and feed in question, e.g. potential accumulation or reduction. In cases where the genetic modification has resulted in an altered level of an endogenous constituent, or if a new constituent occurs naturally in other food and feed products, the anticipated change in total intake of this constituent should be assessed considering realistic as well as worst case scenarios.

The applicant should estimate the anticipated average and maximum intake levels of the food and feed based on representative consumption data for products derived from the respective conventional plants. No methods are specifically prescribed by the EFSA GMO Panel for the assessment of exposure, probabilistic methods may be used to determine ranges of plausible values. The applicant should identify particular groups of the population with an expected high exposure and should consider them within the risk assessment. Any assumption made on the exposure assessment should be described. Recent developments in methodologies and appropriate consumption data should be used. Data on import and production quantities may provide additional information for the intake assessment. The applicant should provide information on known or anticipated human intake considering all possible routes of exposure.

In practice, applicants provide very different exposure calculations depending on the type of food products. Some intake estimate was based on actual consumption data from European populations (for example the UK national nutritional dietary survey, EFSA Comprehensive Food Consumption Database, databases from the Health Council of the Netherlands) or actual consumption data from US population (for example the US Dietary Exposure Evaluation Model – Food Commodity Intake Database). Some intake estimate was based on for example WHO Global Environmental Monitoring System – food contamination monitoring and assessment programme (GEMS/food) Consumption Cluster Diets) that includes the European population and FAO food balance sheet. The food balance sheets are based on the total amounts of food produced, imported, exported and utilised for various purposes, not on dietary surveys, and are generally considered to overestimate average consumption.

Estimated dietary intake of newly expressed protein is estimated by multiplying the daily consumption of each commodity by individual protein concentration and other relevant constituent concentration. The intake calculations make the conservative assumption that 100% of the GM crop or grains would be used for processing human food.

With regard to the exposure assessment particular attention should be paid to GM plants and derived food and feed with modified nutritional properties. This category of GM plants and derived food and feed may require post-market monitoring to confirm the conclusion of the exposure assessment. It is

worth noting that up to now most GMO plants that have been evaluated by the EFSA GMO Panel are not expected to influence human intake pattern or habit. However, plants like GM soybean with altered fatty acid composition are calling for exposure assessment for specific plant constituents.

4. Discussion

4.1. Dietary exposure carried out at EFSA

Different procedures are currently used in the dietary exposure assessment of the different classes of chemical substances at EFSA. Three different approaches can be distinguished. A tiered approach (stepwise approach) is used by the ANS Panel and Pesticides Unit when evaluating additives and pesticides. Conservative screening methods without a tiered approach are applied by other Panels when evaluating pre-regulatory chemicals (CEF and FEEDAP Panels, ANS Panel when evaluating nutrient sources). Only the CONTAM Panel, supported by the DCM Unit, is currently using a more refined exposure model based on individual food consumption data.

Some of these methodological differences are not fully justified by the specific requirements of the class of substances under evaluation. Among the Panels using only screening methods it might be opportune to question why a stepwise approach has not been consistently implemented as suggested in the EFSA opinion on exposure assessment (EFSA, 2005a) to harmonise as much as possible the approaches in EFSA.

The different screening methods used within EFSA are not fully harmonised. The methods based on model diets are the most commonly used for screening among the Panels (ANS, CEF and FEEDAP Panels). The screening method used to estimate exposure to pesticides is currently the only method based on summary food consumption data from different countries.

Different methods for conducting dietary exposure assessments may need to be selected based on the length of exposure times required to elicit the toxic effects. Two timeframes including chronic (long term) and acute (over a whole day or even a single meal) exposure have been considered by the different EFSA Panels and units. All Panels cover chronic assessments. Some chronic exposure estimates (CEF and FEEDAP Panels) are based on worst-case scenarios with modelling of high consumers. The Pesticides Unit does not specifically consider high consumers within their chronic exposure estimates and use only the mean or median consumption values for the total population for each of the 27 diets included in the EFSA PRIMo. The ANS Panel assumes that a subject can be a high consumer of only one food category and average of all the others. This assumption is not in line with the recommendations on how to use the summary statistics of the Concise and the Comprehensive Databases (EFSA, 2011a). The latter states that a subject can be a high consumer of up to eight different food categories of the FoodEx system. CONTAM derives the 95th percentile for chronic exposure from individual data. All Panels and units base their calculations on the total population.

In EFSA, only the Pesticides Unit evaluates on a regular basis acute exposure to pesticides based on the 97.5th percentile among consumers only. Acute estimates are conducted for each commodity separately. Occasionally for contaminants, when the toxicological evaluation indicates a need, the CONTAM Panel assesses the acute exposure based on the 95th percentile of all days and/or consuming days only. In the applicant guideline document for flavourings it is required to estimate acute exposure based on the three standard portion sizes established by the JECFA (FAO/WHO, 2008). Assessment of acute exposure is not requested in the case of food additives.

Historically, the safety of food additives and residues of pesticides and the risk posed by chemical contaminants have been evaluated on the basis of single-chemical and single-exposure pathway scenarios. Risk assessors examined each chemical exposure scenario separately. Although different chemicals may act by the same mechanism and produce the same effect, consideration has seldom been given to the fact that exposure to multiple chemicals could occur and that the toxicological effects might be additive or synergistic. Currently in EFSA, cumulative exposure assessments of

structurally and metabolically similar substances are only being discussed for contaminants, pesticides and flavourings.

For substances requiring further refinement beyond screening methods or conservative estimates of exposure, a probabilistic analysis to capture variability in exposure can be conducted. In EFSA, probabilistic distributional analysis is not performed on a routine basis. Only the CONTAM and PPR Panels have started to perform ad-hoc probabilistic exposure assessments.

In food safety, one of the main interests is the reliable estimation of the percentage of the population exceeding a substance's Acceptable or Tolerable Daily Intake (ADI/TDI). Estimates of usual intake - average intakes modelled over long periods - are therefore needed for use in chronic exposure and risk assessments. Different statistical methodologies are currently available for the estimation of usual intake from short-term dietary data (Dodd KW et al., 2006), none of them being a widely recognised standard. No EFSA Panel is currently using a technique for the estimation of usual exposure. However, the DCM Unit is currently carrying out an Article 36 project "European Tool for Usual Intake" (ETUI), aimed at evaluating and testing existing models in accurately predicting usual intake. This project is expected to deliver its results by the end of December 2011.

4.2. Data on concentrations of chemicals

In EFSA, two different sources of chemical occurrence data are used. CONTAM, DCM and Pesticides unit, within the framework of the Annual Report on Pesticide Residues, are basing their exposure estimates on data collected mainly through monitoring programs at Member State level. Monitoring programs provide results on occurrence data that are collected across varying ranges of commodities, most often analysed as purchased. However, commonly these data are based on targeted sampling and do not cover the whole range of food commodities. Calculations of exposure to chemicals based on data from targeted monitoring programs have the potential to be either underestimated, if not all relevant commodities are sampled, or overestimated, if particular problem areas with high contamination are sampled. Testing the product as purchased does not reflect the impact of further storage, transportation or final preparation of the food. Ideally, these exposure estimates should be complemented with results from Total Diet Studies in which the whole range of consumed food items is analysed as prepared for consumption. On the other hand, results from TDSs are not appropriate to estimate acute dietary exposure, or when contamination occurs rarely, locally, inhomogeneously or limited in time. Although the TDS approach would provide the least uncertainty, it is the most resource intensive. EFSA sporadically received data from TDS surveys in the past.

On the other hand, other EFSA Panels base their exposure estimates on usage levels, MPLs, MRLs or experimental data from supervised trials of a certain chemical, which is not necessarily reflecting the real occurrence in the food as consumed. Exposure estimates based on usage levels or MPLs are likely to be overestimated and less accurate than those based on monitoring programs, but they provide a good basis for screening methods and related worst-case scenarios. In case of intentionally added substances, usage levels provided by the industry are often the only available information in pre-marketing situations. Whereas the use of occurrence data from supervised field trials is the only option to estimate the potential exposure to pesticide residues within the framework of authorisations of new products. In case conservative exposure estimates raise health concerns, a refinement based on more accurate data is needed. Intended usage levels and experimental data from supervised trials are currently the only information available at EFSA in the case of added substances in a pre-marketing situation.

No harmonised approach is applied to manage the non quantified concentration data from the monitoring programs. For the post-marketing exposure assessment, Pesticides unit calculates exposure based on the upper bound scenario but, if no residues are expected due to information on use patterns, the lower bound approach is used. Dietary exposure estimates from CONTAM are based on the lower and upper bound scenario. Both approaches are in accordance with recommendations provided by the WHO (2009).

4.3. Food consumption data

Two different food consumption sources are used in EFSA. Until now Pesticides unit, CONTAM and DCM have used food consumption data collected from national dietary surveys. Only CONTAM and DCM are using individual-based food consumption data whereas Pesticides unit, through the PRIMO model, uses summary statistics from national dietary surveys from different population groups (e.g. adults, children, vegetarians). The remaining Panels base their exposure estimates on standard portion sizes and model diets. Most of them are currently starting to update the method used based on the food consumption data contained in the Comprehensive Database. Ideally in the future, all screening methods using model diets across EFSA should be based on and, if possible, validated by means of information extracted from the Comprehensive Database.

Consideration of food consumption patterns for highly exposed or highly vulnerable subpopulations (e.g. infants, young children, pregnant women, vegetarians) is important. All dietary exposure estimates in EFSA consider adults and children with the exception of the FEEDAP Panel. Most of the exposure estimates for infants carried out in EFSA are based on German data published by Kersting et al. (1998). Food consumption data for infants are still scarce in the Comprehensive Database whereas more recent and representative data for children (3-10 years) and toddlers (1-3 years) are now available from different Member States (EFSA, 2011a). Exceptionally, special target populations like vegetarians (CONTAM Panel, Pesticides unit) are considered. Data on special target population groups is limited and exposure calculations for such groups are not performed on a regular basis in EFSA.

Ideally, food consumption data used at the international level should take into account the differences in food consumption patterns in different regions. To the extent possible consumption data should include information on the demographic characteristics of the population (at least age and gender), body weight, the geographic region, day of the week and the season in which the data are collected (WHO, 2009). All this information is available in the Comprehensive Database.

Given that the design of consumption studies can have a critical impact on the results of any dietary exposure assessment, harmonisation of study design is a priority in EFSA.

CONCLUSIONS AND RECOMMENDATIONS

In conclusion, it has been noted that:

- three different approaches can be distinguished in EFSA's exposure assessment procedures: a tiered approach, conservative screening methods without a tiered approach and a more refined exposure model based on individual input data;

- two different sources of chemical occurrence data are used: on the one hand actual analytical data collected mainly through monitoring programs at Member State level and on the other hand indicative data on usage levels, legislative levels like MPLs and MRLs, or experimental data from supervised trials;

- two different food consumption sources are used in EFSA: food consumption data, collected from different national dietary surveys, and model diets, used in screening methods. Some Panels have started to modify the model diets by using data from the Comprehensive Database instead of consumption data from the literature;

- all dietary exposure estimates in EFSA consider adults and the majority of the Panels and units also consider children, while data on special target population groups, especially infants, are scarce and exposure calculations for such groups are not performed on a regular basis in EFSA; and

- cumulative exposure assessments of substances structurally and metabolically similar are only being discussed Panelfor contaminants, pesticides and flavourings and that probabilistic distributional analysis is not performed yet on a routine basis.

With the availability of more refined and accurate food consumption data in EFSA the following recommendations are suggested:

- to use the summary statistics of the Comprehensive Database for Tier 2 calculations when evaluating exposure to food additives; and
- to crosscheck and/or validate all standard portions and model diets used in EFSA's exposure calculations with the information available in the Comprehensive Database.

To improve the validity of the chemical concentration data used in calculating exposure the following recommendations are suggested:

- to propose, in collaboration with Member States, statistically based sampling frames for the monitoring programs;
- to promote the use of the Standard Sample Description (SSD) format across Member States for submissions of chemical concentrations data; and
- to complement chemical concentration data from monitoring programs with results from Total Diet Studies.

To better standardise dietary exposure methodologies used across EFSA as appropriate the following recommendations are suggested:

- to harmonise further the screening methods across the Panels:
    - by classifying them into either fit-for-purpose as is or needing further development;
    - to crosscheck the extent of conservatism of the Tier 1 calculations;
    - to reach international agreement, first of all within the European Union, in cases changes are proposed;
- to always consider, if relevant, the children population, and particularly toddlers that often consume the highest amount of food in relation to their body weight, when calculating exposure;
- to develop methods for identifying other groups that might be at risk under particular circumstances related to age, life style, ethnicity food choice, etc.;
- to harmonise across Panels the modelling of high consumers for calculating chronic and acute exposure using individual data and summary statistics;
    - common protection goals for the consumers should be agreed at EFSA in consultation with risk managers;
    - conditions concerning the use of exposure estimates for high consumers among consumers only should be defined;
- to identify for which further areas (other than pesticides and contaminants) acute exposure assessments could be needed;
- to consider probabilistic dietary exposure assessments on a more routine basis in case refinements are needed;
- to explore cumulative exposure assessment for all metabolically or structurally related chemical substances; and
- to test statistical methodologies for the estimation of usual intake from short-term dietary data.

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