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Assessment of intake from the diet

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Summary

Exposure assessment is one of the key parts of the risk assessment process. Only intake of toxicologically significant amounts can lead to adverse health effects even for a relatively toxic substance. In the case of chemicals in foods this is based on three major aspects: (i) how to determine quantitatively the presence of a chemical in individual foods and diets, including its fate during the processes within the food production chain; (ii) how to determine the consumption patterns of the individual foods containing the relevant chemicals; (iii) how to integrate both the likelihood of consumers eating large amounts of the given foods and of the relevant chemical being present in these foods at high levels. The techniques used for the evaluation of these three aspects have been critically reviewed in this paper to determine those areas where the current approaches provide a solid basis for assessments and those areas where improvements are needed or desirable. For those latter areas, options for improvements are being suggested, including, for example, the development of a pan-European food composition database, activities to understand better effects of processing on individual food chemicals, harmonisation of food consumption survey methods with the option of a regular pan-European survey, evaluation of probabilistic models and the development of models to assess exposure to food allergens. In all three areas, the limitations of the approaches currently used lead to uncertainties which can either cause an over- or under-estimation of real intakes and thus risks. Given these imprecisions, risk assessors tend to build in additional uncertainty factors to avoid health-relevant underestimates. This is partly done by using screening methods designed to look for "worst case" situations. Such worse case assumptions lead to intake estimates that are higher than reality. These screening methods are used to screen all those chemicals with a safe intake distribution. For chemicals with a potential risk, more information is needed to allow more refined screening or even the most accurate estimation. More information and more refined methods however, require more resources. The ultimate aims are: (1) to obtain appropriate estimations for the presence and quantity of a given chemical in a food

Abbreviations: ADD, (potential) average daily dose; ADI, acceptable daily intake; ARfD, acute reference dose; DAFNE, data food networking; DON, deoxynivalenol; EAN, European article number; EFCOSUM, European Food Consumption Survey Method; EPA, US Environmental Protection Agency; EPIC, European Prospective Investigation into Cancer and Nutrition; EU, European Union; EUROSTAT, Statistical Office of the Commission of the European Union; FBS, food balance sheets; FFQ, food frequency questionnaire; FIFRA, Federal Insecticide, Fungicide and Rodenticide Act; GAP, good agricultural practice; GEMS, (WHO) Global Environmental Monitoring Programme; GMP, good manufacturing practice; GVP, good veterinary practice; HAAs, heterocyclic aromatic amines; HACCP, Hazard Analysis and Critical Control Point; HBS, household budget surveys; INFOODS, International Food Data systems; JECFA, Joint FAO/WHO Expert Committee on Food Additives; JMPR, Joint FAO/WHO Meeting on Pesticide Residues; LADD, lifetime average daily dose; LOD, limits of detection; NHANNES III, Third National Health and Nutrition Examination Survey; MSDI, maximised survey-derived intake; OECD, Organisation for Economic Cooperation and Development; OTA, ochratoxin A; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine; PTWI, provisional tolerable weekly intake; SIDE, Software for Intake Distribution Estimation; SRMs, standard reference materials; TAMDI, theoretical added maximum daily intake; TEF, toxic equivalency factor; THERdbASE, Total Human Exposure Relational Database and Advanced Simulation Environment; TTC, threshold for toxicological concern.

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and in the diet in general; (2) to assess the consumption patterns for the foods containing these substances, including especially those parts of the population with high consumption and thus potentially high intakes; and (3) to develop and apply tools to predict reliably the likelihood of high end consumption with the presence of high levels of the relevant substances. It has thus been demonstrated that a tiered approach at all three steps can be helpful to optimise the use of the available resources: if relatively crude tools — designed to provide a "worst case" estimate — do not suggest a toxicologically significant exposure (or a relevant deficit of a particular nutrient) it may not be necessary to use more sophisticated tools. These will be needed if initially high intakes are indicated for at least parts of the population. Existing pragmatic approaches are a first crude step to model food chemical intake. It is recommended to extend, refine and validate this approach in the near future. This has to result in a cost-effective exposure assessment system to be used for existing and potential categories of chemicals. This system of knowledge (with information on sensitivities, accuracy, etc.) will guide future data collection.

Keywords: Exposure assessment; Risk assessment; Food consumption; Concentration of chemicals in food; Probabilistic modelling

Contents

1. Introduction

Risk assessments are performed in a four-step process: hazard identification; hazard characterisation; exposure assessment; and risk characterisation. This latter step integrates the information collected in the preceding three steps; that is, it interprets the qualitative and quantitative information on the toxicological properties of a chemical with the extent to which individuals (parts of the population, or the population at large) are exposed to it. After all, according to Paracelsus, it is the dose which makes the poison.

In the case of foods, exposure is intended. Not eating is obviously a higher health risk than eating, and as a rule, not eating puts someone at a far higher risk than most toxic substances known to occur in foods. Food does contain naturally, intentionally or unintentionally, a wide range of substances which are either desired — nutrients, additives and some other components such as dietary fibre, or some "phytochemicals" — neutral (which may mean in some cases that we simply do not know their properties) — or undesired, such as natural toxins, pesticide residues, mycotoxins, or excess amounts of otherwise desired components, including nutrients. For all these materials, excessively high but in some cases also insufficiently low amounts can create a risk. Thus, reliable estimates of the amounts ingested are required.

Exposure assessment, as part of risk assessment, is defined (WHO, 1997) 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. Several methods can be used to estimate the intake of a food chemical, and the choice will depend on what information is available and how accurate and detailed the estimate needs to be (Parmar et al., 1997). No single method can meet all the choice criteria that refer to cost, accuracy, time frame,

etc. Therefore, the methods have to be selected and combined on a case-by-case basis. For this a framework, characterized by a hierarchical and stepwise approach, is needed. Guiding principles and examples of such an approach are available in the literature (Parmar et al., 1997; Tennant, 1997; WHO, 1997; IOMC, 1999). The first step is most likely the definition of the purpose of the assessment and/or the selection of the chemical.

Owing to the variety of purposes, exposure assessments cannot be easily regimented into a set format or protocol. Assessments use a similar set of planning questions. According to Rees and Tennant (1993) there are four guiding principles when estimating chemical intakes namely:

1. The estimate should be appropriate for the purpose to which it is put.
2. The estimate should have an assessment of accuracy.
3. Any underlying assumptions used should be stated clearly.
4. Critical groups of the population should be taken into account when these groups are disproportionally affected by the chemical.

The US Environmental Protection Agency (EPA, 1992) distinguish three different approaches in quantitative exposure estimation of environmental chemicals, namely:

1. The exposure can be measured at the point of contact, measuring both concentration and time of contact and integrating them (point-of-contact measurement).
2. The exposure can be estimated by separately evaluating the exposure concentration and the time of contact, then combining this information (scenario evaluation).
3. The exposure can be estimated from dose, which in turn can be reconstructed through internal indicators (like biomarkers) after the exposure has taken place (reconstruction).

These approaches also apply to food chemicals. Duplicate diets are the point-of-contact measurements, food supply, acquisition and consumption in combination with the food composition information are scenario evaluations and biomarkers are reconstructions. Probabilistic modelling is an advanced combination method in scenario evaluation.

For an exposure estimate — or preferably — an exposure assessment based on solid data three pieces of information are needed, for example:

(a) which substances are present in which amounts in a given food and/or the diet in general, and what affects their levels and characteristics, especially their biological activity?
(b) how much of the foods containing these substances are consumed and what is the consumption of potentially relevant risk groups, including high users?
(c) what are the conditions and the probabilities of consuming occasionally or regularly high amounts of such foods which at the same time contain high levels of the substance(s) in question?

These topics have been summarised in the scheme presented in Fig. 1, which is also the basic design of the structure of this review as presented in the subsequent sections.

In many cases it is possible to prioritise chemicals for more detailed exposure assessment by using screening methods based on worst-case assumptions. For example, the highest reported concentration of a chemical may be multiplied by the highest reported consumption of a given food. Even more conservative models such as the budget method (Hansen, 1979) assume that large proportions of the diet (e.g. all processed food) may contain the chemical in question.

However, once it appears that with these assumptions safe intake levels could be exceeded, data and/or assumptions need to be refined using a stepwise or tiered approach up to the appropriate level of precision.

One may need to determine more precisely how much of the substance is present in the various foods and what the distribution of the levels might be — there will nearly always be significant variations even for macronutrients in closely related plant cultivars. One needs to understand how much of a food is typically and/or under extreme conditions consumed by the relevant groups of the population, be it high end-users in general or specific groups such as the elderly, children, pregnant women, or people with a specific health condition. At the end it must be determined how frequently, under which conditions, and for what periods of time high intakes of the relevant food(s) would be combined with amounts of the substances in question that might lead to undesired intake levels.

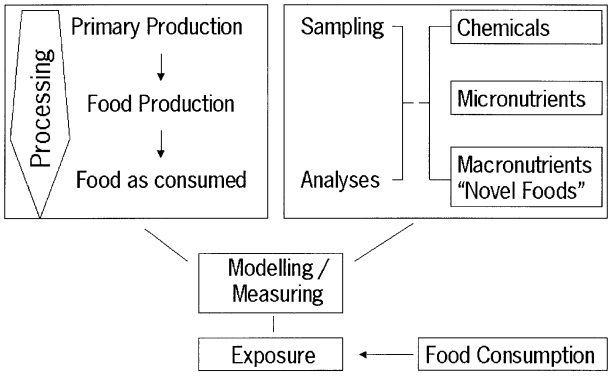

Fig. 1. Considerations for levels/qualities of chemicals in foods.

This chapter evaluates the methodologies currently used for the three steps of exposure assessment indicated under (a)–(c) above for their suitability both in general or for specific applications, for their application in a tiered approach of increasing precision, for their current strengths and weaknesses and for ways of improving them, for their practical applicability, and of course cost. It also examines interdependencies of these methodologies and other sources of potentially useful information, some of which may be well established in other fields, others quite new. It is recognised that the intake evaluation for chemicals in foods will depend largely on the nature of the substances. This is not only related to their origins — natural vs man-made, beneficial vs toxic, macro- vs micro-components — but importantly also to the background information available both on their presence and the consumption of foods containing chemicals. It is necessary to critically review the facts provided in food composition tables (used as convenient sources for information) and the reason for the differences reported between countries and/or within countries, consider the way foods are categorised and thus made comparable (or not) in food consumption surveys, and explore how one can try to refine assessments as more information becomes available — from early pre-market evaluations to post-launch data collection confirming or correcting the initial assumptions. This can include, at all stages, information on existing food or non-food sources of exposure; many substances in foods have multiple uses or origins — tocopherols are present as vitamin E or as antioxidants in foods but may also be present in personal-care or other non-food products. A pesticide usually leads to a much higher level of exposure among operators than among consumers of pesticide-treated foods. A qualitative or semi-quantitative comparison between a new or newly recognised source of exposure and existing uses may thus help to prioritise the need for more detailed evaluations: if a substance has been used historically in large amounts in other applications (or other regions) without problems it may be less of an issue than a chemical without any known background.

A particular challenge is the evaluation of food allergens and components causing other forms of intolerances, and how to determine the levels present and actual intakes vs the limited knowledge of amounts needed for induction or elicitation of a response.

To determine whether biomarkers provide a promising lead for the future, one needs to examine and categorize them according to their broad use, and determine realistic expectations when specific biomarkers for intake or effects might become available, and the cost of validating them compared to alternative approaches.

There is a wealth of information available in all three of the areas discussed, and it is hoped that the best suitable approaches can be extracted for various situations both from standard methods in use in the food world and beyond, and forthcoming models promising better, easier or cheaper solutions.

2. Presence and fate of the chemical: points to be considered in exposure assessment

2.1. Introduction

Food as consumed contains many different chemicals which are either desirable (e.g. micronutrients) or undesirable (e.g. pesticide residues or mycotoxins). For all these chemicals, levels in the diet that are either too high (e.g. mycotoxins) or too low (e.g. essential vitamins) may be detrimental to health. In the course of the risk assessment process, exposure estimates are required based on the consumption of the foods containing these substances and the level of the substances present in those foods. This section focuses on the chemical aspects of the intake/exposure assessment, that is, the determination of the amounts of relevant substances in foods at various stages of processing and factors affecting the levels and characteristics of these substances.

Intake estimates for a given chemical are based on a number of factors where errors, wrong assumptions or inaccurate measurements can lead to results differing significantly from the real exposure. One central aspect is the concentration of this chemical in food as consumed. Factors influencing this concentration are presented in Fig. 1.

First, food sampling procedures for subsequent analysis can critically determine how close the measured value is to the real value. Relevant aspects in this regard are the representation of sampling, the completeness of sampling in relation to the distribution of the chemical within the sample (variability within composite samples and local foci of substances), and the variation in concentrations between samples.

After representative samples are taken, the accuracy of the analytical methods used is important. Analytical methods used for screening purposes or for the evaluation of substances present at high levels tend to be less precise than methods used for accurate quantification, especially at low levels of detection. Data collected at different time points may be affected by improvements of methods but also by changes in actual compositions. Another aspect to be considered is lab-to-lab variation depending on the expertise of the analysts involved and differences in equipment and reagents. The measurement of the same chemical present in the same sample by different laboratories (or even repeat analyses in the same laboratory) may lead to different analytical results.

Aspects such as climate, ripeness, soil conditions, etc. are likely to influence the absence or presence of a chemical. This should be considered when food products

are sampled for analysis and methods are chosen. When samples are taken at different stages of the food production chain it becomes important to consider the possible effects of food processing, like washing, peeling or cooking, on the chemical of interest. The effect of further processing appears to be less when measuring chemical levels at a late stage of the food production chain after the chemical was first introduced. To some extent, the presence of the chemical may be diluted by the effects of homogenisation. There may, however, still be a significant influence of processing at the stage of household preparation.

In this section, the different strategies used for the monitoring of various chemicals in food are described. The focus is on sampling procedures, the precision of analytical methods, and effects of processing in relation to the outcome of exposure assessments. This section can only provide a general overview, but intends to indicate the most relevant issues for the most important groups of components and contaminants in foods.

2.2. Levels of chemicals in food

In many of the current methods of exposure assessment (e.g. point estimates, deterministic approach, budget method), the variation in chemical levels in food is not routinely taken into account. In general, only one concentration is selected, which may represent average (mean or median) or even less defined "typical" concentrations; only rarely defined upper percentiles are used. More accurate data to describe the distribution of values are frequently not available. It is, however, well known that levels of chemicals in food products can vary significantly, and this needs to be included in exposure assessment. It is therefore important to review the natural vs process-related variation of chemical concentrations in food items and to understand which factors influence them, to understand the implications for the intake or exposure assessments. These aspects will be addressed below.

2.2.1. Factors influencing the presence or absence of chemicals in food

2.2.1.1. Nutrients and non-nutrients. Nutrients form a natural part of food and are the basis for all human nutrition and the core constituents of all foodstuffs. In some cases, especially in processed foods, they may also be added to provide specific product qualities. Some (micro)nutrients are also used as additives (e.g. antioxidants or colorants), or enter the food as a component of an additive such as calcium e.g. present in the emulsifier calcium stearate. Increasingly, 'other' components of natural foods, such as various phytochemicals, become of interest due to their assumed beneficial effects. Their intake may increase both by an individual's selection of specific foods and by active enrichment in functional foods or the use of dietary supplements. This means that data need to be obtained on possibly wide ranges of compositions, that is, both on the levels needed to demonstrate the presumed benefits and on potentially excessive levels likely to cause adverse effects.

Levels of nutrients in basic and particularly common foods are listed in food composition tables. A recent study by Deharveng et al. (1999) has reviewed these levels and examined whether comparability could be determined across European countries, suggesting ways for improvement. These tables are mainly composed at national levels, and have been developed at different times and for different purposes, using different criteria for inclusion and exclusion of food categories and compositional parameters. Since the 1970s, much work has been done to compose and improve such tables; the International Food Data Systems (INFOODS) project carried out within the United Nations University's Food and Nutrition Programme (http://www.fao.org/infoods) provided guidelines on the organisation and content of food composition tables and databases, methods for analysing foods and compiling those tables, and procedures for the accurate international exchange of the data. A number of additional programmes have been conducted in recent years and are partly ongoing.

Various sources of error have been identified relating to food composition databases, including:

- missing values: some nutrients such as vitamin D do not appear in all composition tables. For many foods the degree of detail in, for example, fatty acid or amino acid composition differs significantly; not all relevant foods are included in the tables, and in many cases processed foods are omitted. Counting missing values as zero may lead to underestimation of intakes.
- effects of processing: as most processed foods are not included, extrapolation from the raw materials listed may lead to an overestimate, for instance in cooked products, unless correction factors are defined and used.
- variability of data: some tables provide ranges for at least some of the parameters, but in many cases only average (mean or median) values are given. Even with agricultural raw materials there is a huge compositional variation due to geographical origin, degree of ripeness, plant cultivar/animal strain, climatic or geological conditions, or post-harvest storage. These variations may be partly balanced by subsequent processing steps, but processing itself may add further variability (see above).
- differences in sampling and analytical methods: this is applicable for all chemical parameters for food chemical evaluation.

- differences in definition: partly due to historical reasons in food science, partly based on actual food preparation and selection habits in individual countries, the individual food items may be defined quite differently in different European countries, thus affecting comparability of data.
- developments over time: food composition tables prepared at different time points provide different values for the same food. Changes in the nutrient database can be caused by real changes in the composition of a product but also by artificial changes (EFCOSUM Group, 2001). Real changes in the composition may represent differences from reformulations by manufacturers, agricultural (breeding) or food processing changes. Artificial changes may reflect changes in the improved knowledge regarding the composition of a food, such as improvements in the analytical techniques, better sampling method, more analyses of a specific food or information on previously unknown nutrient values. Then it is important to correct the earlier food composition estimates so that they accurately reflect the composition of foods at the time they were consumed (Beemster et al., 2000).

In some cases these deviations can be extremely large, because of changes in consumer preference for the fat content in meat, due to agricultural or environmental changes affecting mineral contents of foods, or simply to changes in predominant food trade streams. It is often unclear for the user to what extent subsequent editions of national tables are using new or refined data or simply re-use historical values, possibly from a different region.

It is important to recognize that the nutritional parameters listed in these tables may also be used for extrapolation to other applications. One example is the fat content in foods that can give an indication of the possible levels of lipophilic compounds — contaminants or phytochemicals — or may affect their bioavailability due to changes in meal/diet composition. Another aspect is the need to recognise the occurrence of other components side-by-side in foods or diets to understand the relevance of interactions between micronutrients (e.g. calcium and iron) or between micronutrients and other food components. It would be desirable to extend these tables to also include data on other natural components not currently seen as nutrients (e.g. some phytochemicals) and a wide range of other chemicals present in foods.

In fortified food nutrients are added deliberately to improve their nutritional quality, especially their nutrient density and the nutrient density of the diets containing them. This fortification of foods is done to restore nutrients lost during processing or storage, to provide substitute foods with the same nutritional properties as the original products (e.g. margarines as alternatives to butter), and to provide consumers with a wider range of foods rich in nutrients which otherwise might be consumed in suboptimal quantities. The extent of fortification varies between countries depending on national rules. In Germany, where fortification has a long tradition, the proportion of fortified foods increased by about 20% over the last decade but seems to have stabilized in recent years (Sichert-Hellert et al., 1999). Overall, fortified foods make up only a small fraction of the total food supply and intake by most individuals (Wasserbacher and Elmadfa, 2001). However, especially in countries such as Austria, with a wide range of fortified products, the added nutrients provide a significant fraction of the total intake and requirements at least for subgroups of the population (Wasserbacher and Elmadfa, 2001). This was the original purpose of fortification both of staple foods and of individual food products preferred by an identified target group. In the United States, it was determined that fortified cereals might be a useful addition to the menus in child-care centres to meet nutritional needs (Briley et al., 1999).

2.2.1.2. Additives and process aids. Additives (e.g. antioxidants, sweeteners, coloring agents, emulsifiers, flavours and flavour enhancers) are almost exclusively used in processed foods to provide them with specific properties. Similarly, process aids are used in some food processes to help preparation, but do not have a technological effect in the finished product itself. Additives are generally indicated on the product label, whereas process aids are usually not labeled. This is an important aspect when looking for the presence and levels of such materials, particularly for substances that may be used both as an additive and a process aid.

Food additives may be added at various processing steps, but this tends to be done at the latest product stage before final marketing to ensure their optimal functionality in the product as sold. Residues of additives used at earlier production stages, for example of individual product ingredients, may be still present in the final formulation. However, if they do not have a further function at that stage, they are considered as process aids and are thus not indicated on the label. In the case of food additives, the amounts that may be added are usually regulated by maximum permitted levels defined in food legislation for each food category to ensure product safety and to avoid consumers being misled about the actual qualities of a food (Wagstaffe, 1996). In the case of food additives for which a low toxicity has been found and thus no "Acceptable Daily Intake" (ADI) was determined, and for example, for some flavours used at very low levels, the use under "Good Manufacturing Practice" (GMP) conditions may be permitted. GMP is usually also the criterion for the selection of process aids.

Starting from these permitted maximum levels, the manufacturer will select the additives actually needed and 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 GMP. These levels may range from the maximum permitted level to nothing at all. Most foods contain only a small number of all additives permitted for a given category, especially if alternative substances with the same function are available, or other alternatives, for example a suitable process or storage conditions, help to avoid additive use at all. When, as is the rule, several additives with the same function are permitted, they can be used either as alternatives or as simple mixtures. In some cases, such as in the case of the intense sweeteners aspartame and acesulfame K, they show synergistic action which not only provides an improved end result (in this case sweetness profile) but permits the reduction of the amounts needed for each individual component.

Particularly in highly processed foods, additives are used to standardize product parameters and stability to reach the required shelf-life in the trade and in the home, while maintaining the consumer-expected product properties. While some products with a long shelf-life are dependent on the use of additives, it should be recognized that some additives also decompose with time so that the levels present at the end of shelf-life may be comparably low. An example is antioxidants, which are designed to stabilise products by interacting with oxygen in the product or permeating through the packaging. In those cases, it is important to understand which decomposition products are likely to be formed so this can be considered in exposure and risk assessments. The degree of ripeness of the original agricultural commodity may also be a factor determining the use of additives. Thus it may necessitate the use of additives for correction purposes, for example the use of citric acid (or sugar) to balance the sweetness vs acidity profile of fruit juices or other fruit preparations, or of colours to standardize the colour of other types of food.

Data on the use patterns of additives are difficult to obtain. Although, as indicated, additives, like all other ingredients, must be included on the product label in descending order, it requires major effort to evaluate even the simple presence on this basis, which would provide at best only limited information on the amounts used. Individual flavour components are usually not specifically indicated beyond the statement that flavours are used. In most cases quantitative analytical controls are limited to efforts by control authorities to determine compliance with legal limits — levels below these limits are of limited interest and are usually not published. For process aids, the actual use is even more difficult to assess, not only due to the lack of labelling but also to the potentially large variability of levels left in a finished product, depending on the degree of prior processing and actual need at each process step. Difficulties in quantification also exist for additives and other components also used directly by the consumer, such as salt and many herbs and spices.

In the case of flavour materials it must also be recognized especially that the use of natural flavour components, due to their natural occurrence in many foods, is less controlled than artificial and nature identical flavours, and thus an evaluation of total intakes of flavour materials is problematic. In some cases, for instance smoke flavours, risk assessments are based on a limited number of marker components (especially the polycyclic aromatic hydrocarbons benzo[*a*]pyrene and benzo[*a*]anthracene) where the levels present are known to be significantly lower the more processed the smoke concentrate. Liquid smoke as used in most industrial processes today contains only a small fraction of these 'markers' compared to direct smoking (Lijinsky, 1991). The same can be expected in other cases, but may not be as well documented.

Based on production/import data the amount of an additive available for use can be estimated, but such data is only helpful in demonstrating average exposure levels or to check the plausibility of data obtained by other methods. Even though flexibility has increased, the manufacturers themselves are reluctant to share their proprietary information with ''outsiders'' for confidentiality and competitive reasons (Hall and Ford, 1999).

2.2.1.3. Agricultural chemicals (pesticides and veterinary drugs). Pesticides are used in agriculture for different applications: to control insect or fungal infestations or growth of weeds, either to handle immediate infestations or to anticipate long-lasting problems, thus leading potentially to different patterns of residues in line with their authorization for specific applications under conditions of good agricultural practice (GAP). During the authorisation process, their toxic pattern is evaluated to determine acceptable exposure for both farm operators and consumers. GAP deals with the applicable doses of the pesticide and the time interval between applying the pesticide and harvesting the crop. If these conditions are not met, harvested crops may contain unacceptable levels and types of residues (FAO/WHO, 1999). When the use of a certain pesticide in a certain agricultural crop is authorized in a region it is likely to find its residues at least in parts of the crops produced. Application according to GAP will, however, reduce the probability of finding unacceptable levels. Incorrect use of pesticides still occurs, although application of excessive amounts or application at the wrong times is usually not very cost effective.

There is a large variation in use patterns of pesticides, which influences the presence of residues in crops and

derived foods. This variation is related to climatic differences and year-to-year variations (Van Klaveren, 1999) as well as cost and of course to the authorisation, which may differ from country to country.

Veterinary drugs (e.g. hormones, antibiotics), like pesticides, may only be applied after authorisation for a specified application. Although the use of illegal growth promoters (e.g. clenbuterol) occurs, the absence or presence of these chemicals depends mainly on their correct use. Some veterinary drugs are used broadly for disease prevention, but most are applied only when needed. Their use is regulated by good veterinary practice (GVP) that includes a prescribed waiting period between application of the drug and time of slaughter. The longer this period, the more likely the veterinary drug will be metabolised or excreted by the animal, and the less likely residues will be found in animal products (e.g. milk, meat).

2.2.1.4. Toxins and environmental contaminants. A number of potentially toxic chemicals are found more or less regularly in foods. These include natural toxins that are inherently part of the foods or the plant producing it. Examples are solanine in the green parts of potatoes, phasine in green beans, or cyanogenic compounds in manioc. Their levels are partly controlled by selection of the products harvested and processed — such as in the case of solanine, where avoidance of the green parts of potatoes eliminates the potential risk. In other cases, for example green beans or manioc, appropriate processing destroys the toxic compounds. Still, inappropriate handling can occasionally lead to significant exposure and resulting toxic effects. In most conventional foods, there is significant knowledge about the toxicity of individual components and the way industrial or home processing does ensure safety. The identification of the possible presence and levels of toxic components in new types of foods, especially products newly introduced into Europe, may require attention even when a history of safe use is established in the region of origin: appropriate transfer of the information how to make a fruit or vegetable "safe" may be a relevant step for introduction into European markets.

Other substances that may be present, depending on specific conditions, include both natural components such as mycotoxins or geologically-derived levels of heavy metals and man-made chemicals from different sources, including environmental pollutants, contaminants derived from animal feed or plant fertilizers, and substances migrating from packaging materials into the food.

According to published estimates (Charmley et al., 1994; Miller, 1998), mycotoxins can be found in up to 25% of the world food supply, introduced either directly by molds growing on crop plants (e.g. fumonisins), on foods after harvesting (e.g. ochratoxin A), or indirectly via contaminated animal feed. A large number of different mycotoxins are known to occur in foods, 20 of which are serious crop contaminants. For example, aflatoxins are very common in peanuts, ochratoxin A (OTA) occurs worldwide in barley, maize, wheat, oats and rye grown in temperate climates as well as, for example, on coffee beans or dried herbs. Fumonisins are found in maize all over the world, and patulin is found in apples and apple products (Medlock, 1996).

Contamination with mycotoxins is strongly related to climate; cereals cultivated in hot and humid climates are more likely to contain mycotoxins, and outbreaks of infections occur more frequently during years with relatively high rainfall, high humidity and high temperatures around the time of harvest (Sweeney and Dobson, 1998). Quality control systems like the Hazard Analyses & Critical Control Points (HACCP) concept can help to minimise the risk that significant levels of mycotoxins develop and reach the finished food products. The same concepts are also useful for other toxic species and, in general, for the control of potential risks from excessive amounts of otherwise desired chemicals like micronutrients or phytochemicals.

Selection of resistant crop cultivars for planting and/or effective use of fungicides in critical climatic situations at the pre-harvest stage allows the farmer to reduce the risk of significant contamination. Harvesting can be scheduled for appropriate weather conditions to minimise risks of mold formation during storage. Protection against moisture, insects or other environmental factors during storage can serve the same purpose (Park et al., 1999).

Heavy metals, PCBs, dioxins and radionuclides are well-known environmental contaminants. For example, dioxin concentrations in milk were elevated around improperly operated waste incinerators, and PCB and dioxins levels are higher in fish caught in Lake Michigan or the river Rhine compared to the Atlantic Ocean (Anderson et al., 1998; Van Klaveren, 1999). Lead levels in many products decreased after its use in gasoline was restricted. The fallout of cesium was greatest around Chernobyl (after the reactor accident) and in large parts of Belarus, but elevated levels were also found for some time in many agricultural products in northern and partly in western Europe. Once the source of pollution is identified and further emission of the pollutant is minimized, levels of contamination in the food chain decrease with time. Most of these contaminants are due to environmental pollution; however, in some cases it must be recognized that also natural sources play a role, for instance for some heavy metals and, to a limited extent, radionuclides.

Contamination of products of animal origin (e.g. meat, organs, milk) with environmental contaminants is largely due to the pollution of animal feed — more frequently hay or grain than processed feeds — with these chemicals and/or the basic potential especially of lipophilic substances to be accumulated in the food chain.

Another example of contamination is that of the elevated dioxin levels found in milk in Germany, which were traced to inappropriately dried citrus pulp from Brazil used in cattle feed: the dried pulp was found to contain excessive levels of dioxin. This illustrates that ingredients of animal feed originating from all over the world make it difficult to directly correlate emission of pollutants and levels in feed. Another source of contamination can be misuse of components, including outright crime: the Belgian dioxin crisis in 1999 was caused by the use in animal feed of recycled fats which had been — intentionally or unintentionally — contaminated with discarded synthetic materials containing PCBs and dioxins. Many environmental contaminants are persistent chemicals, which means that they do not or hardly degrade over relevant time periods and will thus accumulate in both the environment and animals used for food production. This leads to a relationship between the age of animals and chemical levels in animal products.

2.2.1.5. Food allergens. A small but significant fraction of the population in Europe (1–2%) suffers from true food allergies; a larger group is affected by non-immunogenic forms of food intolerances from lactose intolerance to coeliac disease triggered by gluten in some cereal products. In particular, the true allergies are potentially life-threatening, while other forms of intolerances may lead to more or less severe inconvenience.

In both fields, a very wide range of materials — mainly natural foods and their components — are known to carry allergenic potential, but a limited range of substances is responsible for the vast majority of the problems (Bousquet et al., 1998).

In the case of foods known to contain allergens or substances causing intolerances, labelling is often sufficient, and more quantitative exposure assessments may be unnecessary, so long as the individuals affected are advised to avoid 'their' problem materials completely. Problems can arise in cases where the presence of the relevant allergen is not expected. Here again, the preferred approach is to understand any possible source in a processed food and either include them actively on the label, or eliminate them if alternatives exist. Particularly in the case of less common food allergens and/or allergens in foods not usually containing them, a system of data banks may help consumers avoid problem foods. Practical issues arise due to updating of the data banks in line with formulation or process changes, overlap in availability of different versions of the same food (with/without the allergen) on the shelf, especially with long-shelf-life products, and to a large extent legal protection needs of manufacturers leading to over-labelling.

Problems can arise in situations where cross-contamination or carry-over from unknown or unidentified sources may occur. Apart from best efforts to trace the origin of all components used in a product for the detection of possible contamination, analytical steps to provide added reassurance may be needed, especially if a product is to be declared as "free from" the allergen. In this case one is confronted with a situation where, theoretically, no threshold exists for some of the patients, at least in the case of some allergens such as peanuts. This means that highly sensitive — usually immunological — methods are required to determine the presence of the material either for spot-checks of production processes and/or for the exploration of the cause of a reaction once it has occurred to minimise the risk of recurrence.

Alternatively, mainly in the case of "other" intolerances, limits for the presence of the causative agent are set. This is the case, for example, for levels of gluten in cereals and foods containing it. Defining such limits and controlling adherence is particularly important for foods claiming to be "free from" the offending agent and thus most likely to be selected by the individuals affected.

In some cases, an additional evaluation of possible cross-reacting substances may be needed to understand the risk of such responses occurring and to help individuals to avoid products containing such materials.

2.2.2. Sampling considerations

2.2.2.1. Representative and target samples. There exist at least two different sampling strategies. The first strategy aims to obtain a representative picture of chemical levels present in food. This type of sampling is without a priori knowledge on what levels can be found. In the representative sampling strategy the sample numbers of different varieties or brands can be stratified according to production or consumption figures (varieties) or market share (brands). In general, food composition tables are based on information obtained from representative samples. The second sampling strategy, directed or targeted sampling, is aimed at sampling those products expected to contain higher levels in a cost-effective way (Codex Alimentarius, 1993, 1999). Law enforcement bodies and food control agencies, and also manufacturers, are taking this approach when it is suspected that a production batch might be outside the intended or the legal range. Similarly, HACCP systems are focusing sample collection at such "critical control points"; however, in this case, the routine sampling at these points is intended to be representative for the specific process step, but the steps are selected either as more likely to show deviations or as enabling rapid intervention in case of problems. In this latter situation the samples are meant to be overall representative.

Many measurement programmes for residues and contaminants are based on a mixture of both types of sampling. This is partly due to lack of statistical understanding, and partly to ambiguously defined aims of the

measurement programmes for which the samples are to be used. Many pesticide monitoring programmes in Europe organised by public institutions were initially set up for law enforcement reasons, thus looking mainly for illegally high levels (EC, 2000). Especially regarding public activities, there is, however, an increasing need to compare the results of pesticide monitoring between countries and to use these data for overall risk assessment purposes rather than for regulatory controls. Because of this, current directives on pesticide monitoring programmes include more specific rules on representative sample-taking.

Many monitoring programmes regarding toxins and contaminants are focused on suspected areas or seasons, years or periods when elevated residue levels might be more likely to occur. Nitrate measurements focus on leafy vegetables sampled in critical seasons, and PCB and dioxin analyses are mainly performed in fish caught in polluted areas such as rivers, the Baltic Sea or Great Lakes.

From a risk management perspective, focus on areas and/or periods of concern appears correct. For reasons of limited budgets and overall costs vs benefits obtained it is questionable whether sampling should move towards complete representative monitoring for the purpose of exposure assessment. However it must be recognised that measurements of contamination based on "suspect", that is, presumably above average, samples does not provide a realistic basis for exposure assessments; these data can exaggerate the actual level of contamination dramatically. The World Health Organization (WHO) published recently a document of a workshop on the methodology for exposure assessment of contaminants and toxins in food on the Internet (http://www.who.inst.fsf). This workshop also agreed that targeted data (e.g. non-random data usually collected in response to a specific problem) are not useful for the purpose of exposure assessment. However, such data may be used when no other data are available, so long as it is recognized that the use of such data will result in an overestimate of exposure.

2.2.2.2. Homogeneity of materials. Another important aspect of sampling products for the measurement of chemicals is the expected or known (in)homogeneity of the samples. In general, the number of samples to be analysed rises with increasing variation in expected levels. In this way, a reliable distribution of possible levels will be obtained. In general, variation in natural levels of nutrients, naturally present toxins, and other components such as phytochemicals, is low to moderate within a plant variant harvested when ripe in a given region, but may be very high between different plant variants from different regions and different degrees of ripeness. Also storage time and conditions can affect measured levels. In the case of additives, the effective levels tend to fluctuate in a relatively moderate range depending on the product type, but will in very many cases be zero for a given substance even if permitted. A large variation in levels of residues of agricultural chemicals, "external" toxins such as mycotoxins and environmental contaminants can be observed (MAFF, 1996; Pineiro et al., 1996; Deharveng et al., 1999), in all cases including the possibility of complete absence. Thus, the number of samples must be sufficient to ensure statistical validity when not only mean values but also the high-end percentiles of the distribution curves are to be reported (http://www.inst.fsf).

Mycotoxins are examples of substances with an extremely high heterogeneity of the distribution even within a lot. The toxins are formed by molds, and very small foci of mold infestation — sometimes affecting only a few units like peanuts or coffee beans — will determine the result of an analysis: if the sample taken happens to include such a focus, the analysis will be clearly positive, but may exaggerate the level of contamination for the lot; if the foci are missed the sample may appear falsely "clean". Taking a representative sample is the most critical stage of monitoring (Brera et al., 1998).

Concentration data are often presented under an aggregate format, that is one result corresponds to several initial samples. In order to estimate the mean concentration of a chemical, each result should be weighted as a function of the initial number of analyses. Moreover, even when a sufficient quantity of results is available, data are often not sufficiently homogeneous to build a full distribution curve. Therefore, several assumptions can be made in order to combine those types of data. For example in the field of food contaminants, the log-normality of the distribution is generally assumed and the log-transformation of the data can provide a geometric standard deviation. The resulting distribution can therefore be combined with intake data in a stochastic model.

Sampling procedures for pesticides or for most environmental contaminants in fruit and vegetables usually include sampling of composite samples (i.e. 10 apples, 2 kg of lettuce) to be homogenized for analysis (Codex Alimentarius, 1999). Until recently the focus was primarily on law enforcement, and from that perspective it is effective to take composite samples. However, recently the UK Pesticide Safety Directorate has asked that attention also be directed at the variability of residue levels within a composite sample (Harris, 2000). In a 10-unit composite sample (e.g. 10 carrots), all pesticides found may originate from only one or two units. In this example, the concentration on a single carrot may have been 10 times higher than the concentration of the composite sample. This finding has large consequences for exposure assessment to acutely toxic compounds at the international level. In the current process of authorizing new pesticides, there are different

procedures for pesticides either with or without acute toxic properties. When the pesticide is not acutely toxic, results of composite samples derived from experiments testing the effectiveness of a pesticide (field trials) are multiplied with an average consumption. When the pesticide is acutely toxic the same results of composite samples are used, but in addition a variability factor accounting for the above-illustrated variation within composite samples should be included in exposure assessment. This variability factor can be derived from a sampling design that samples individual fruits or vegetables. When such an experiment is not available, a high default variability factor is used (FAO/WHO, 1997; Walsh, 2000).

2.2.2.3. Sampling primary agricultural products or food as eaten. In exposure assessment, levels of chemicals in food as eaten is more meaningful than levels in primary agricultural products. However in many cases — especially for natural toxins, pesticide residues or environmental contaminants — the data available are derived from basic crops or staple foods. They usually do not take into account effects of processing which may either decrease levels e.g. by elimination of particularly highly contaminated parts (peeling) or discarded cooking water, or increase them e.g. by accumulation in dietary fat.

The same applies, for example, to information on nutrient levels as they appear in food composition tables: the data originate mainly from measurements in the edible parts of basic foods and only in some cases from analyses of more processed or composite foodstuffs. The more processed a food is the more likely are the nutrient values derived from more basic products by extrapolation. Obviously, the more data available from direct analyses on processed foods and composite products (which provide an increasing part of Western diets) the more useful will this data be. Inclusion of foods with added nutrients (for which the amount are usually exactly known) will also be of benefit. The EPIC study has identified this as an area where improvements are needed and will address it in the next steps of the programme (Deharveng et al., 1999). It will also be useful to provide in such tables more data on the effect on nutrient levels by storage or processing. Similarly, to clarify in those cases where ranges are provided if these do include effects of storage and processing or address only the natural variability within a food type, for instance due to ripeness, plant cultivar or animal breed.

For critical parameters, manufacturers may include analyses of chemical concentration in their data collection before market introduction, and expand their database after large-scale production has started by evaluating products sampled in the market place. When this sort of information can be made available, the real concentration at time of consumption can be estimated more accurately.

Sampling for pesticide monitoring is almost exclusively done in primary agricultural products or at early process steps of such staple foods, and it is not very likely that this practice will change. As indicated, sampling and analysis are mostly done for reasons of law enforcement, and both national and international legislation have laid down limits for pesticide residue levels in primary agricultural products, recognizing that these limits are in many cases not based on risk assessments but on levels seen as achievable by GAP. It must be noted that in many cases the limits set include parts of the plant which are either not edible or usually removed before marketing or consumption, like outer leaves or peel. It is well recognised that peeling, cooking, milling or any relevant food processing affect the pesticide concentration in food as eaten (Petersen et al., 1996; FAO/WHO, 1999).

Primary agricultural products are, although not as regularly as for pesticides, also sampled for analysis of many other chemicals such as veterinary drugs, environmental contaminants and mycotoxins. Sometimes food as eaten is measured as well, such as patulin in apple juice, deoxynivalenol (DON) in breakfast cereals, and aflatoxin M1 in milk. However, samples taken for most of the fumonisins, ochratoxins and DON are focused in the case of cereals either due to their use as animal feed to control possible accumulation in the food chain, or in the case of direct human consumption before these are processed in porridge, bakery products, etc. (Medlock, 1996; EC, 1999). It is recognized that even basic cleaning steps like dust removal can significantly reduce the levels of ochratoxin A in grain. In general, processing can have a very significant impact on the levels of mycotoxins in foods (Scott, 1994).

To make use of monitoring data for primary agricultural products in exposure assessment, all food items that might contain certain levels of a primary product should be considered. In other words, there is a need to translate food as eaten in terms of primary agricultural products. For example, how much cereal (with the possibility of contamination with mycotoxins) is present in an average pizza, and how much meat (with the possibility of containing antibiotics or other veterinary drugs) and how much green peppers or tomatoes (with the possibility of containing pesticide residues) are used in a pizza filling (Van Klaveren et al., 1999).

As a consequence of the introduction of quality care systems like Hazard Analysis & Critical Control Points (HACCP), the attention will shift from a simple "descriptive" approach to a more preventive concept, such as where in the food chain will a chemical most likely occur at critical levels and how can these levels be best influenced. For quite a few substances, including agrochemicals, natural toxins and environmental contaminants, this may also mean that future sampling and analytical control strategies will focus on primary

agricultural products rather than processed foods, and even include earlier production steps such as the composition of animal feed or sewage sludge used as fertilizer.

Given the different options for sampling and the differences in the resulting analytical data, it is important to select the sampling strategies based on their fitness-for-purpose in a given situation, also recognising the cost implications of sampling techniques and the subsequent analyses and balancing them against the additional information obtained for use in risk assessments.

2.2.3. Analytical considerations

2.2.3.1. Developments in analytical techniques. Developments in analytical chemistry have improved both specificity and sensitivity of methods for determining chemicals in foods. Improved sensitivity has consequently led to an increased incidence of reported positive findings of low levels of contaminants in foods. Although the significance of these results in isolation has frequently been difficult to assess, when determining intake it is of course better to work with measurable albeit low levels than handle the uncertainties associated with "less than" values.

However, it should be realized that in some cases more sensitive analytical methods do not provide additional advantages. For example, in the case of most micronutrients, analytical techniques showing their presence below the microgram range will be meaningless since at those levels they provide no benefits and no risks. The situation for most food additives is similar: they are approved for use because they are of low toxicity, and at very low levels they do not provide technological benefit. Thus, in such cases moderately sensitive analytical tools will be sufficient to provide the data needed for risk assessments.

Another development in analytical chemistry is the increased use of screening methods or bioassays as opposed to quantitative methods. Bioassays have been described for compounds such as endocrine disrupting agents, dioxins and compounds with cholinesterase inhibition. These assays are based on measuring an effect of a certain chemical on cells. In general, the effect is not related to one compound but to a group of compounds having the same biological effect (Hoogenboom et al., 1999). Furthermore, these tests are less quantitative but fast performing and considerably cheaper. For some chemicals there is already a tendency for these methods to be used more frequently compared to quantitative methods. This development will raise questions on how to use this type of information in exposure assessment.

Overall, one needs to strike the right balance between very sensitive analytical methods and more conventional approaches. If a particularly sensitive method takes a long time for completion and is relatively expensive, this will not only affect its use in real practice but also the usefulness of the results in some situations. This is especially true for perishable products, where it can be important to determine the presence of a contamination problem quickly in order to avoid the consumption of contaminated product(s) by the time the results are available. Rapid screening methods with appropriate sensitivity for acute control purposes are needed, and at least in some cases highly sensitive methods (which then may require more time) for regular data collection. Judgement is needed to determine which of these approaches is appropriate.

2.2.3.2. Concentrations below limit of detection. As indicated, in relation to exposure assessment of agricultural chemicals, mycotoxins and environmental contaminants, the limits of detection (LOD) should be discussed (EC, 1999); for instance, the level below which no residues can be detected using a certain analytical method. When amounts below LOD occur (especially when this concerns a large part of the samples), the exposure assessment should be clear about how to deal with such results. There are a few options:

- Non-detects are assumed to be 'real' zeros. This is always appropriate when the LOD is far below those concentrations likely to cause any adverse health effects.
- Non-detects are assumed to indicate that the sample contains half the LOD or the LOD. This may be appropriate when the chemical in question is relatively toxic and also low levels may contribute significantly to the total exposure. This assumption should be used only if the presence of a contaminant appears plausible.

When other information becomes available further refinements must be considered. An example is the approach taken by the EPA, which positions the percentage of non-detects that are real zeros depending on the percentage of the crop that has been treated with the pesticide (FAO/WHO, 1999; EPA, 2000). The percentage of a crop treated is, however, not always predictable and data regarding use patterns of pesticides are lacking in almost all countries, although data on the availability of a pesticide are usually available and can help to support estimates of use. More reliable information might, however, become available in the future. In the assessment of dietary intake of OTA by the population of different EU member states it was proposed to use half-LOD for non-detects. Although this seems the best approach for samples below LOD infected by the mold producing ochratoxin, certainly not all samples have been infected and are likely to contain ochratoxin. Also in such a case, a percentage of the samples, for example those not being infected, could therefore be assumed as real zeros. A similar example of

real zeros might be the use vs non-use of a given pesticide on the food crop.

This discussion on how to treat non-detects becomes really important in cumulative risk assessment, where simultaneous exposure to chemicals with the same mode of action is considered. This is known to be rare for most chemicals in foods (Cassin et al., 1998). However, a few examples of cumulative risk assessment have been performed so far for pesticides (EWG, 1998). Similarly, in the case of 'dioxin' it has been agreed to include 10 dibenzofurans (PCDFs), seven dibenzo-*p*-dioxins (PCDDs) and many non- and mono-ortho PCBs in a cumulative exposure assessment due to the proven similarities of action. The toxic potential of all these compounds is cumulated in a weighted fashion using the 'Toxic Equivalence Factor (TEF)' approach (Berg et al., 1998). In many analyses at least some of these compounds are non-detects, which are in current practice of dioxin exposure regarded as zero. When other assumptions are made (half-LOD or LOD) the outcome of exposure calculations will increase, which may or may not be biologically relevant depending on the analytical method used and the LOD of that method.

2.2.3.3. Laboratory-to-laboratory variation. It is well recognised that there can be much variation between laboratories, despite the availability of various validated methods of analysis, often laid down in regulations. For many mycotoxins, there have been check-sample programmes which have shown evidence of wide variation in results (Friesen and Garren, 1982). However, this has often been the consequence of the participation of inexperienced laboratories and those using only semi-quantitative methods. In recognition of the need to have analytical quality in trace analysis, various proficient testing schemes have been initiated such as through FAPAS (Key et al., 1997) and WHO GEMS (Weigert et al., 1997), which enable laboratories to examine and monitor their performance on "blind" samples containing known levels of mycotoxins. Performance is benchmarked against best practice, and confidential results are reported on the basis of z-scores which indicate whether a laboratory has performed satisfactorily (Key et al., 1997).

Although much progress has been made regarding quality assurance systems and the need for proficiency testing is well recognized, analytical differences between laboratories and even within a laboratory remain a problem. There are no general guidelines on how to include these uncertainties in exposure assessment using a deterministic approach. In the near future probabilistic modelling might be helpful to study the effect of these uncertainties on the outcome of exposure assessment. These variabilities need to be better understood in all fields of food chemistry when data are used in risk assessments, but it is also important to recognize where the effects are most relevant, as has been shown in the case of sampling for mycotoxins in agricultural crops.

2.2.4. Effects of processing

All chemicals mentioned above are more or less sensitive to processing effects. Particularly for those chemicals measured at the start of the food chain (in primary agricultural product), such as pesticides, some environmental contaminants and mycotoxins, effects of processing should be considered in exposure assessment. Neglecting this effect may often lead to highly exaggerated estimates of exposure but may at times also underestimate the levels found in foods as consumed.

For these chemicals, as well as other substances naturally or commonly present in agricultural crops, processing means considering the effect of removing inedible parts (peeling), washing, cooking or other forms of processing on the chemical level. This may also include the use of some additives such as food acids, which can help to destroy pH-sensitive components. Many pesticides or environmental contaminants used for example on citrus fruits or potatoes will disappear partly because of removal of the peel; some of these substances may be washed off partly or completely from foods that are not peeled. As indicated, food processing will usually result in a decrease in pesticide or contaminant levels (Petersen et al., 1996; FAO/WHO, 1999). However, sometimes the levels will increase, for example due to water removal (e.g. in tea leaves, in tomatoes used for tomato ketchup or during frying of potatoes), or due to accumulation of lipophilic materials in the fatty phase of a foods such as butter compared to milk. High concentrations in foods as sold may be significantly diluted when these foods are consumed, as in the case of tea. In making fruit juices, there is a decreasing effect on external contaminant levels due to removal of the peel for the juice production. Another factor in fruit juice and also in many other crops is dilution by homogenization: individual fruits with high contamination levels are mixed with less or non-contaminated fruit. Similarly, the above-mentioned foci of mycotoxins as in peanuts will be diluted to usually quite moderate levels when making peanut butter. It should also be noted that in many cases sorting of the raw material — apples for apple juice in the case of patulin, peanuts for peanut butter in the case of aflatoxins, or coffee beans before roasting in the case of OTA — will eliminate obviously contaminated units. This is occasionally done specifically to reduce contamination, but is in many cases needed for other quality parameters like taste. In general, substances that have their main effect on the outer parts of a product or are deposited on the outside of a crop from soil or air are more sensitive for such processing steps than those entering a product.

As is the case with pesticides, there is also a large body of data on veterinary drug residues in primary

foodstuffs. This arises, in the main, from the requirement placed on EU member states to test for veterinary residues in meat, fish and other commodities. All of the samples in these programs are analysed in the raw, uncooked, state. If such data are used for risk assessment purposes they may over-estimate human exposure. A number of studies (e.g. Rose et al., 1997, 1998) have shown that losses can occur on cooking as a function of chemical transformation and/or loss from the matrix via exuded, cooked-out, juices.

The reduction by processing of mycotoxin levels has been described, such as wet and dry milling procedures (Bennett and Richard, 1996). The stability of fumonisins in thermally processed corn products has also been studied. Roasting corn meal at high temperature removed fumonisins almost completely. Fumonisin levels in baked corn bread were 9–48% lower than in non-processed corn flour (Castelo et al., 1998). Losses of 60–70% of the initial amount of fumonisins occurred during the entire cycle of corn flakes processing, with less than 30% losses occurring during the intermediate extrusion step (De Girolamo et al., 2001). In the case of patulin in apples and apple juice, it has been shown that it is at least partly destroyed by fermentation, so that exposure is not seen as relevant from cider. However, washing and sorting remain the most critical steps in reducing patulin levels in apple juice (Acar et al., 1998).

Additives are also sensitive to processing, especially household processing. The effect varies between additive classes, the way an additive is used and the foods in which it is used. A preservative used for surface treatment of cheese loaves is likely to be removed by more than 90% when the coating is removed. Heat sensitive or oxidizable additives such as antioxidants may be destroyed to a large extent by cooking. Discarding cooking fat or water will reduce levels of additives that are either water or fat soluble. For many other additives, household processing will have little or no effect on the concentration at the moment of consumption. New techniques for food preservation, such as irradiation or high-pressure sterilisation, are likely to reduce or even eliminate the need for conventional preservatives. The use of packaging gases may also reduce the need for antioxidants.

Any form of processing can influence micronutrient levels. As a rule, cooking will hardly affect minerals or trace elements but can destroy part of the vitamins. It can, however, also increase their bioavailability (e.g. β-carotene). By washing or discarding the cooking water some of the water-soluble minerals or trace elements can be lost. Similar effects can be expected for other food components such as biologically active 'phytochemicals', depending on their chemical characteristics. In many cases the effects of typical processing steps on micronutrients are included in food composition tables.

When considering the effects of processing on the levels of a given chemical in foods, consideration should be given as to what happens with the amounts lost. It is easy when the material is simply eliminated by washing, sorting, or discarding cooking water or fat. However, if the substance is destroyed one should try to understand which, if any, decomposition products might be left in the food as consumed, and what their levels might be: intake estimates for such substances may lead to a new risk assessment for a new chemical entity in foods.

Also other forms of processing can lead to the formation of new chemical entities in foods. In some cases this is intended, for example the effects of cooking or frying on the taste of foods. But some of these changes may be adventitious and specific information on the components formed might not be available. This can indeed be relevant in the case of conventional processes applied to foods not so far treated that way. In the case of industrial processing, usually under tightly controlled conditions, some information on the type and levels of newly formed chemicals will be available, which is not necessarily the case in home cooking, especially when insufficiently or excessively heated ('burnt') food is consumed.

2.2.5. *Pre- and post-launch data collection*

Especially in the case of processed foods, the manufacturer collects extensive information on the relevant chemical parameters before a new product is introduced to the marketplace and continues this evaluation over extended periods of time also for the product as sold. In some cases, this work is co-ordinated for industry segments such as the fruit juice industry, which collects a very broad reference base for all critical components (AIJN, 2001). This information provides very accurate data on the levels of a chemical in real life, especially the process and/or raw material related variability. Owing to the usually large number of analyses collected over time, it provides a solid basis for the assessment of chemical levels present in a product or category. It is used to review initial assumptions by the manufacturer and can help to position the results of spot checks by control authorities.

The information collected depends on the specific relevance of the parameters for the quality, stability, and/or safety of a raw material or product, or their assessment as potentially controversial. It is thus not normally comprehensive but focused on the levels of the substances added (or naturally present), their expected variation in raw material receipts and finished formulations, and their fate during processing and storage over the product's shelf life. It may also include perspective on possible interactions between the substance and other components in the product and its package, or — occasionally — in the dietary context.

The data collected after launch especially refer to a large number of raw material or product batches. These data also include information on the changes in chemical

composition over the shelf life of a product. This may be important given that some label information relates to the amounts of components present at the end of the shelf life, whereas the levels may well be different when the product is made or at normal consumption age: most products are purchased and consumed well before the "best before" date. Data collected before and especially after market introduction provide a perspective on the way the product is stored by the trade and by the consumer (temperature, light, risk of microbial access, etc.) focusing especially on deviations from recommendations or historical experience. Thus, both typical and realistic worst-case scenarios can be predicted.

These compositional and stability data are in most cases proprietary for the manufacturer and rarely published or shared externally. They are used, however, in internal risk assessments. Given that the data are essential to predict and maintain product acceptance, all manufacturers have an interest to make these evaluations as reliable as possible — after all, the brand's success depends on them.

In consumer tests, test markets, and of course long-term marketing not only the basic composition of the products is evaluated, but especially any indication of spoiled or "off-standard" product, particularly if associated with real or perceived health issues. Any such report will trigger some level of follow-up to understand if any chemical changes — production errors or chemical degradation — may have been involved. This will lead to a (re)evaluation of the data collected and/or a consideration to extend the analytical scope. It may also involve tracing of raw materials to determine if at an earlier production step undesired substances may have been introduced. Typically, in such cases the left-over product is requested from the consumer or the trade for specific analysis.

2.3. Conclusions and research needs

In this section many factors have been discussed that influence the variation in chemical levels within food products and their evaluation in monitoring programmes or targeted assessments. The inherent variation is large for many natural components such as micronutrients or phytochemicals, for agricultural chemicals, mycotoxins and environmental contaminants.

Sampling strategies for data collection and monitoring vary from strictly random sampling to direct or targeted sampling. Different analytical methods can be used for the detection of the same chemical. Depending on the aim of the study, the analytical method can provide results very close to the true value and results can be very replicable, or limit itself for screening purposes to minimising the risk of false negatives without being necessarily accurate as to the quantification or achieving similarly low detection limits.

Although these factors influence significantly the outcome of exposure assessment, there is very limited information on how to include them in the process of exposure assessment. International organisations recommend the use of representative data for exposure assessment, but it is also known that most of the available data will have limitations regarding one or more of the factors mentioned above.

If exposure assessment has to rely on available data that apply to only a few groups of chemicals, guidelines are needed on how to include effects of sampling, differences in analytical methodology, incomplete information on processing effects, etc. These effects cannot be studied in current approaches (point estimates or deterministic approaches) of exposure assessment.

Areas where specific issues are identified include:

- Sampling: the effect of sampling methods on the results for the specific component must be recognised and agreement should be reached on which approaches are most relevant in a given case.
- Analyses: standardization and validation of analytical techniques remains a central point. In addition, it is important to recognise on a case-by-case basis the most suitable analytical method that may not necessarily be the most sensitive one. For the improvement of exposure assessment it is important to provide information on the accuracy of the method, the laboratory-to-laboratory variation, repeatability and the level of detection.
- "Non-detect" values: depending on the knowledge of the toxic properties of a chemical, a harmonised approach for the interpretation of "non-detect" values is needed, using these values as true zeros for low toxicity chemicals and giving them an appropriate numerical value for highly toxic substances. Statistical methods on how to treat non-detects that use information on variation of the positive levels might be helpful.
- Food composition tables: these tables are the basis for most evaluation of nutrient compositions of foods and for indirect evaluation of other chemicals possibly associated with nutrient levels. Harmonisation of these tables and possible extension to include other parameters (non-nutrients), foods with added nutrients, and in general processed foods is desirable.
- Other natural components: better knowledge of their presence in conventional foods and their addition to "functional" foods is desirable.
- Agrochemical residues: better data and understanding of the variability of pesticide concentrations within composite samples are essential if such composite samples are used in

exposure assessment. Effects of processing are only known for a fraction of agrochemicals. Sharing information on effects of processing at the international level and on general rules on assumptions when information on processing is lacking are recommended. A validated method to translate food as eaten into amounts of primary agricultural products is needed.

- Additives/process aids: monitoring systems and use of supplier data are needed to improve intake estimates based not only on maximum authorised levels or assumptions of excessively high use where no legal limits exist.
- Toxins/environmental contaminants: monitoring programmes on these compounds emphasize high risk products, areas or periods. Attention should be paid to data selection or assumptions regarding completeness and representation of the data used in exposure assessment.
- For all chemical classes, appropriate standards need to be developed to correct analytical results for recovery.
- Processing: on a case-by-case basis the effects of processing must be integrated into the assessments of levels of chemicals in foods. For agrochemicals, toxins and environmental contaminants the databases for effects of processing are far from complete.

In all these fields it is necessary to develop a good understanding of the intended and expected use of the data collected in order to select the most suitable methods for sampling and analysis choosing from screening tools with limited sensitivity and highly sophisticated systems, depending on the expected levels and fates of the substances to be evaluated. In data collection systems, it is necessary to also address the usefulness of average vs high-end percentile levels depending on the subsequent evaluation systems, such as point estimates vs probabilistic assessments. Obviously, if the most conservative assumption of the presence of a chemical and the resulting intake does not indicate any risk, this will usually be sufficient. However, any indication of potential problems at that level will necessitate a critical evaluation of the actual presence and level of a chemical.

3. Food consumption in exposure assessment

3.1. Introduction

Exposure assessment is the qualitative and/or quantitative evaluation of the likely intake of (in this case) chemical agents via food as well as exposure from other sources if relevant (WHO, 1997).

Information needed for quantitative exposure assessment is (partly) generated by monitoring programmes. For monitoring, appropriate methods are needed to provide data that are useful for subsequent evaluations. As illustrated in Fig. 2 for nutrients, monitoring ideally provides information on a wide range of variables, from food availability, distribution and consumption and nutrient utilisation to, ultimately, health status and mortality.

This section starts with a discussion of methods to measure food supply, acquisition and consumption, and an inventory of the existing European surveys used for risk assessment purposes is presented, followed by a discussion of the comparability of these surveys. Thereafter, general methodological issues are treated from a risk assessment perspective. The section is completed with a consideration of future challenges and conclusions.

3.2. Sources of dietary information

In principle, to assess food consumption four different types of data can be used: food supply data, data from household consumption surveys, data from dietary surveys among individuals and the collection of duplicate diets (Hulshof et al., 2002; Hulshof and Lowik, 1998). Each type of data correspond to a different stage in the food chain and is obtained by different methods. The duplicate diet method differs from the other methods in that the intake estimation does not depend on composition data from other data sources. The concentration is measured by chemical analysis of the duplicate diet. Biomarkers form a fifth type of exposure data, whereby these measures reflect both the consumption of food and the concentration of the chemical in these foods.

In Table 1 selected characteristics of the methods are presented and these will then be briefly discussed.

3.2.1. Food supply data

Disappearance data provide gross annual estimates of the national availability of food commodities. Food supply data are calculated in food balance sheets (FBSs), which are accounts, on a national level, of annual production of food, changes in stocks, imports and exports, and agricultural use and industrial use. The result is an estimate of the average value per head of the population, irrespective of, for instance, age or gender.

Food supply data refer to food availability, which gives only a crude (over-estimated) impression of potential average consumption. Food and nutrient losses prior to consumption, due to processing, spoilage, trimming and waste may not be adequately accounted for.

Despite their limitations, FBSs are useful in that they indicate the (in)adequate aspects of food supply and give crude indications of (un)desirable changes in terms

of potential (adverse) expected health impact. As a result of their long history, FBSs are especially used for assessing trends over time. To correct for the likely fraction of users in a population and/or as a very crude indicator of high consumption the per capita supply is often multiplied by a factor of 10 (see also section 4.2).

The current use of food supply data is the exposure assessment regarding contaminants and pesticides residues that are mainly evaluated in raw commodities. This approach is used by many European and non-European countries as a first step in the risk assessment procedure or may be useful for comparisons among countries.

International FBSs are prepared and published by the FAO, the Organisation for Economic Cooperation and Development (OECD) and the statistical office of the Commission of the European Union (EUROSTAT). The FAO has published FBSs since 1949, also covering the period 1934–48.

EUROSTAT publishes FBSs for the 15 member countries of the European Union. The OECD FBSs cover several European countries. Although FBSs are compiled in a similar way, they differ in coverage, food grouping and level of processing of commodities (e.g. FAO lists 300 food items classified into 17 food group categories; OECD 70 items in 13 categories) and in nutrient conversion.

In addition to the international FBSs, many countries publish national FBSs. National FBSs tend to be more up to date. Owing to different methodologies underlying their compilation and presentation, these data can differ from international FBSs.

3.2.2. Household surveys

Food available at the household level may be estimated by budget surveys and by consumption surveys. The first type of survey gives information on the purchases of food in terms of expenditure and is used for economic policy. In household consumption surveys, the amounts of foods and drinks brought into the household are also recorded. For the most part, only the expenditures of meals taken at home are noted. Some household surveys may even measure changes in food stocks, in addition to acquisition. In general, household surveys do not provide information on how food is handled within the household, or on actual consumption by its members. Data on the quantity of and/or expenditure on food may be collected by record

Table 1
Selected characteristics of the quantitative methods used in Europe to assess food consumption

	Level of measurement	"Normal" time frame of observation	Over- or under-reporting consumption	Between-subject variation	Within-subject variation	Uncertainty of outdoor consumption and composite dishes	Total food consumption
Balance sheets							
Country							
1 year	Over-reporting	No	No	No	Yes		
Budget surveys	Household	2 weeks	Over-reporting	No	No	Yes	Yes
Individual surveys							
- Food records	Individual	1–7 days	Under-reporting	Yes	Yes, >2 days	Yes	Yes
- 24-h recalls	Individual	1–2 days	Under-reporting	Yes	Yes, >2 days	Yes	Yes
- Food frequencies	Individual	1–12 months	Under-reporting	Yes	No	Yes	No
- Dietary histories	Individual	2–4 weeks	Under-reporting	Yes	No	Yes	Yes
Duplicate diets	Individual	1 day	Under-reporting	Yes	No	No	Yes
Biomarkers	Individual	1–30 days	Not	Yes	No	No	No (1 chemical)

	Check on portion size and recipe	Relies on memory respondent	Respondent burden	Food composition data needed	Specific for 1 chemical	Other sources included
Balance sheets	No	No	Absent	Yes	No	No
Budget surveys	No	No	Intermediate	Yes	No	No
Individual surveys						
- Food records	Yes	No	Intermediate	Yes	No	No (yes, for nutrients)
- 24-h recalls	Yes	Yes	Low	Yes	No	No (yes, for nutrients)
- Food frequencies	No	Yes	Low	Yes	No	No (yes, for nutrients)
- Dietary histories	Yes	Yes	Intermediate	Yes	No	No (yes, for nutrients)
Duplicate diets	Yes	No	High	No	No	No
Biomarkers	Not applicable	No	Low	No	Yes	Yes

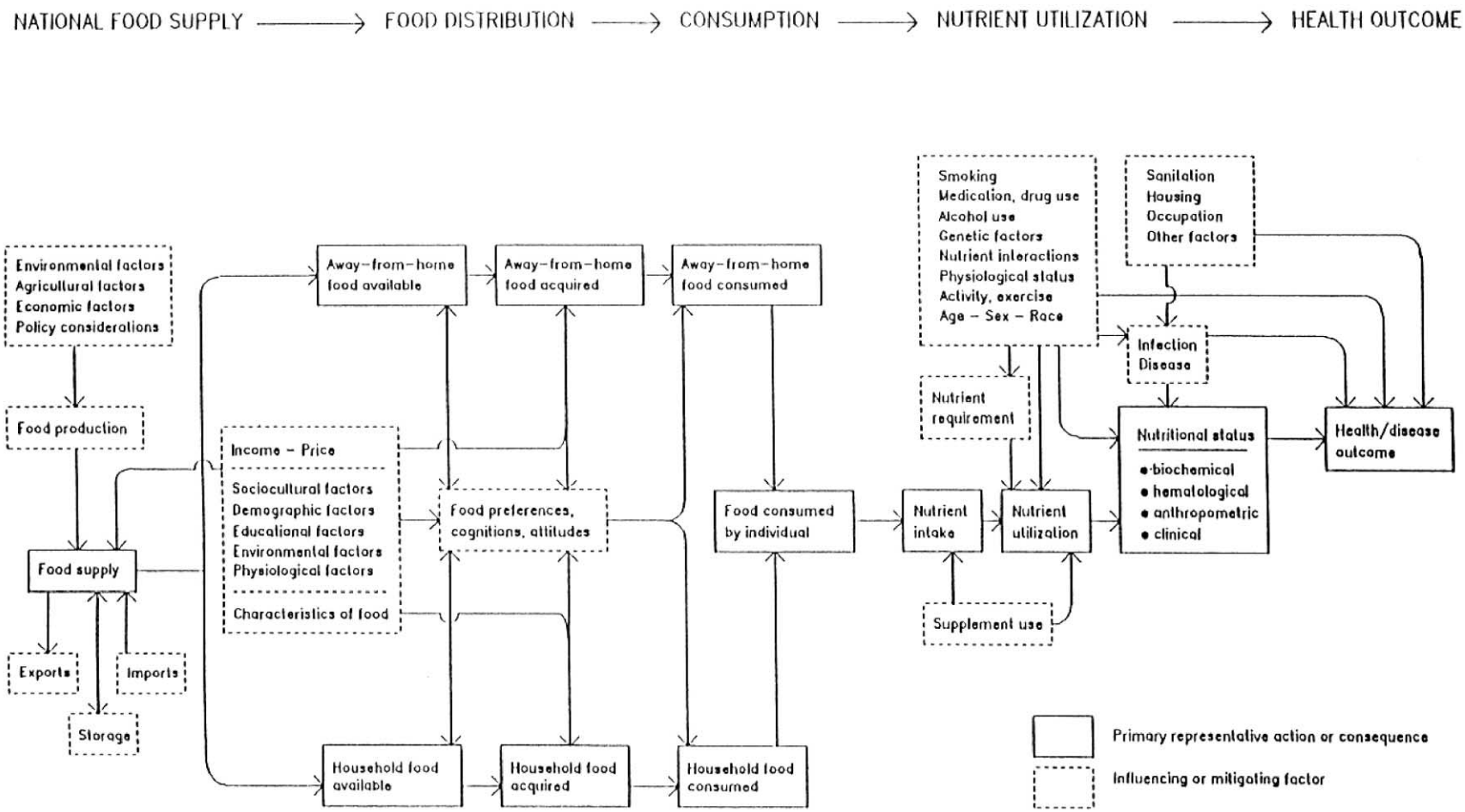

Fig. 2. A general conceptual model for food choice, food and nutrient intake and nutritional and health status. Source: Life Sciences Research Office, FASEB (1989).

keeping, by interviews or by both methods. Household accounts for non-food items can cover a period of 4 weeks, but for foodstuffs 2 weeks is more usual.

In most countries, household surveys started in the 1940s or 1950s. Only few countries have a continuous system, some repeat surveys every 3–4 years, others only every 5–10 years. In Europe, one of the best-known studies is the specialised and ongoing household food consumption survey of the UK. At present, a wide range of data on household surveys is available, as shown in the FAO Food and Nutrition Policy Papers and WHO publications. As the dietary data are based on a variety of methods, the surveys are not very suitable for comparisons among countries.

Differences exist in sampling procedures, food grouping, conversion to nutrients, and period, frequency and technique of data collection.

3.2.3. Individual dietary surveys

In contrast to FBSs and household surveys, data from individual surveys provide information on average food and nutrient intake and their distribution over various well-defined groups of individuals. These data more closely reflect actual consumption.

To collect dietary intake data at an individual level, several methods can be used. Briefly, the methods can be divided into two categories: record and recall methods. Record methods collect information on current intake over one or more days. Recall methods reflect past consumption, varying from intake over the previous day (24-hour recall) to usual food intake (dietary history or food frequency). For a more specific description the papers of Pao and Cypel (1996), Thompson and Byers (1994), Hulshof and Lowik (1998) and Hulshof et al. (2002) can be consulted.

3.2.3.1. Food records. Food records, dietary records or food diaries are kept for a specified time period, usually 1–7 days. If total daily intake of energy and/or nutrients is required, the food records should include all foods and beverages consumed at meals and in between, in quantified amounts.

In a precise weighed record the respondent notes the weights of all ingredients used in the preparation of the meals, as well as the inedible waste, the total cooked weight of meal items, the cooked weight of the individual portion and plate waste.

3.2.3.2. 24-hour recall method. In the 24-hour recall the subject is asked by a trained interviewer to recall and describe the kinds and amounts of all foods and beverages ingested during the immediate past, mostly a 24- or 48-hour period. Dietary recalls may be administered in person or by telephone interview. Food quantities are usually assessed by using household measures, food models, or photographs.

3.2.3.3. Food frequency method. A food frequency questionnaire (FFQ) consists of a structured list of individual foods or food groups. The aim of the FFQ is to assess the frequency with which these items are consumed during a specified time period (e.g. daily, weekly, monthly, yearly). Brief FFQs may focus on one or several specific chemicals. Comprehensive FFQs designed to estimate a large number of nutrients generally include between 50 and 150 food items.

FFQs may be qualitative, semi-quantitative or completely quantitative. Qualitative FFQs generally obtain only the usual number of times each food on the checklist is eaten during a specified period. Semi-quantitative methods allow estimation of a standard portion by the researcher or ask respondents to indicate how often, on average, they consume a specified common amount. A quantified FFQ allows the respondent to indicate any amount of food typically consumed.

The FFQ is often used to rank individuals by food or nutrient intakes and also by food group intakes into categories so that high and low intakes may be studied.

3.2.3.4. Dietary history method. With the aid of the dietary history method, a trained interviewer assesses an individual's total usual food intake and meal pattern. The respondent is asked to provide information about his/her pattern of eating over an extended period of time (often a 'typical' week) and also to recall the actual foods eaten during the preceding 24 hours. In addition, the interviewer completes a checklist of foods usually consumed. Finally as a cross-check, the respondent is often asked to complete a 3-day estimated record. The reference time frame is often the past month or several months, or may reflect seasonal differences if the time frame is the past year.

3.2.3.5. Current use. Probably all (industrialised) countries have carried out small-scale dietary surveys. These surveys provide valuable information, but due to samples of convenience and different food consumption methods their use in national nutrition policy and nutritional surveillance is often limited.

Several European countries have performed individual surveys on a national basis. For a detailed inventory see Hulshof et al. (2002) and EFCOSUM Group (2001). The surveys differ in coverage of population, methods used to collect dietary data, nutrition-related health indices, etc. In several countries dietary data were collected using a record method, but the number of record days varied from 1 to 7. A 7-day weighed record is thought to be the most accurate method of dietary assessment.

3.2.4. Complete diets

For estimating dietary exposure of the population, FAO/WHO recommends the use of total diet studies. In

total diet studies, representative samples of widely consumed foods are collected and analysed for the constituents of interest. The accuracy of population intakes estimated using total diet study results depends on the extent to which the foods analysed represent important dietary sources of the chemical.

The following approaches in total diet studies are distinguished:

(i) market basket;
(ii) individual food items; and
(iii) duplicate portion.

The market basket approach is based on the dietary intake of a defined population group. All food items, which are part of the average diet, are purchased, prepared according to standard household procedures and aggregated into a number of food groups. Each food group is analysed for a number of additives, contaminants and nutrients.

In the individual food items approach, a list of foods representing the products most commonly consumed is composed based on national food consumption surveys for several age–sex groups. All selected food items are prepared according to methods most commonly used and analysed. In the duplicate portion or duplicate diet approach, the individual daily diet as consumed is analysed (Van Dokkum and de Vos, 1990; Macdonald, 1991).

Although not statistically based, total diet studies yield data useful in assessing food chemical intake. Total diet study results are used mainly for identifying trends in concentrations of pesticide residues, contaminants and nutrients in the food supply and population intakes. However, total diet studies use only a certain number of foods to represent thousands of foods, and therefore it is not appropriate to make extrapolations for the amounts of a contaminant in the sampled foods to the amounts consumed by individuals. Nevertheless, concentration data on the foods sampled can be used as reference point in intake assessment (Douglas and Tennant, 1997). The duplicate portion method, although being a total diet study, presents some remarkable features. Initially, duplicate diet methods provide information on individual intakes. They are particularly useful for estimating exposure where no national consumption data are available or where an investigation of the exposure of a particular population subgroup is being carried out (WHO, 1999). In conjunction with weighed food intake records, the duplicate portion method is the nearest practicable approach to a precise measure of actual consumption by individuals (WHO, 1985). However, this approach requires a considerable commitment from the participants and during the trial there is a risk of a change in the pattern of food consumption.

There are a number of different ways to collect exposure data. Duplicate diet methodology was selected as the approach for measuring personal dietary exposures that would yield data comparable to other exposure pathways monitored in the US Environmental Protection Agency (US EPA) exposure assessment studies (Berry, 1997).

An emphasis was placed on methods that can be used in the general population and on methods that will examine personal exposures from multiple exposure pathways and are usually conducted in the household of study participants (Thomas et al., 1997).

Total diet studies have been carried out since the early 1960s in many countries. An example is the US FDA Total Diet Study, conducted on a yearly basis since 1961 (FDA, 2000). Initially, the purpose was to estimate average intakes or background exposures of the population to pesticide residues (Harries et al., 1969) and levels of radioactive contamination in foods from atmospheric nuclear testing (Pennington and Gunderson, 1987). The original purpose in the UK was also oriented at nutrients. At present, regular total diet studies are carried out in many countries such as the USA, Australia (ANZFA, 1998), New Zealand (Cressey et al., 2000; Vannoort et al., 2000), the UK Ministry of Agriculture Fisheries and Food (MAFF, 1996) and the Basque Country, Spain (Urieta et al., 1996; Jalón et al., 1997) among others, with the purpose of estimating exposure of the general population to a wide range of chemical contaminants, pesticide residues, food additives and nutrients.

Duplicate diet studies have also been conducted in many countries. Thomas et al. (1997) published a table summarising 29 studies, most of which have been directed towards dietary intake of toxic and heavy metals, arsenic or essential elements. Far fewer studies have been reported for organic chemical contaminants such as pesticides and PAHs. In the last few years duplicate diet studies have been conducted in the UK and The Netherlands to estimate exposure to nitrates (Vaessen and Schothorst, 1999; Ysart et al., 1999). In the Basque Country, Spain, a duplicate diet study is being carried out at present to estimate exposure of extreme fish consumers to PCBs, dioxins, mercury and arsenic as well as intake of selenium and omega-3 fatty acids. Also, the UK has two ongoing duplicate diet studies to estimate exposure to OTA of the UK population and of vegetarians to natural toxicants (FDA, 2000).

3.2.5. Biomarkers

Biomarker-based methodologies may be employed to determine human exposure to food chemicals. They involve usually two main stages. In the first of these human volunteer studies (or — for contaminants — total diet studies) are undertaken to establish whether a quantitative relationship can be established between the

dietary intake of the chemical in question and the amount of the corresponding biomarker detected in an appropriate body fluid or tissue. Information is also needed on biological factors, including other components of the diet (e.g. lipids in the case of lipophilic food components), affecting the presence and the level of the biomarker selected. The validation process for a biological marker includes the confirmation of its physiological relevance and reproducibility and a clear understanding of the extent and limitations of the analytical and sampling methods required.

In most cases the biomarker is either the food chemical itself or a metabolite. The chosen body fluid is frequently urine or blood, although other options exist including especially breast milk, but also hair, adipose tissue, buccal swaps, exhaled air and faeces.

Having established a quantitative relationship the method is then applied, in the second stage, to individuals in the target population by collecting and analysing appropriate samples. By way of a simple illustration: if the first stage reveals that a particular food chemical is totally excreted in the urine within 24 hours of ingestion, then analyses of 24-hour urine samples from volunteers within the target population will enable their intake of the food chemical on the previous day to be quantified. Evaluations of, for example, adipose tissue on the other hand would usually lead to a time-integrated evaluation of exposure. When looking at populations, biomarkers can also help to determine changes of exposure over time. Analyses of breast milk for dioxins or pesticides are examples for such applications.

Apart from their application in estimating exposure, the concept of biomarkers may also be used in other aspects of risk assessment. Thus, any biomarker that retains an element of variability in kinetics and/or dynamics (e.g. metabolism or covalent binding) will include aspects of hazard characterisation as well as exposure assessment. Pure biomarkers of exposure contain no variability due to inter-subject differences in absorption, metabolism or excretion (see also Edler et al., 2002; Eisenbrand et al., 2002).

Biomarkers have the potential to probe the sequence of steps in the etiology of many chronic diseases. A model has been described by the Committee on Biological Markers of the National Research Council, 1987, that categorises biomarkers in terms of those reflecting: internal dose, biologically effective dose, early biological effect, altered structure/function, clinical disease and susceptibility.

In principle, the chemical class to which a food chemical belongs is not the prime determinant in terms of assessing whether it is suitable for a biomarker approach. However, some class-specific observations can be made. Where very low levels of the food chemical are involved, as in the case of food contaminants, the development of a biomarker method may be more challenging due to the need for a highly sensitive analytical method. Additionally, the larger and more distinctive the chemical structure (e.g. OTA and the aflatoxins), then the less likely it is that the method will be subject to confounding influences associated with lack of specificity of the biomarker.

Biomarker methodology does not have universal applicability as a means of assessing human exposure to food chemicals.

One of the most important determining factors is inter-individual variability in the pharmacokinetic and metabolic behaviour of the food chemical (see Dybing et al., 2002). This is particularly the case when the putative biomarker normally has a positive value even in the absence of exposure. This is, for example, the situation for the sphinganine/sphingosine ratio which is currently being investigated as a possible biomarker for fumonisin exposure (Solfrizzo et al., 1997). Issues other than inter-individual variability may also limit the application of a biomarker approach for a particular food chemical. A key factor here will be whether the selected biomarker reflects, with high specificity, exposure to the presence of that particular food chemical only. A problem specific to potentially toxic, especially carcinogenic, food chemicals is that for ethical reasons it is not possible to conduct stage 1 by adding the chemical to the food that is to be consumed. In such circumstances it is necessary to conduct, say, a duplicate diet or diary record study (with appropriate analyses) and thereby measure the intake of the food chemical during stage 1. For other food chemicals it is feasible to add the chemical to the diet, provided the relevant ADI/PTWI is not exceeded. However, care needs to be taken to ensure that the pharmacokinetic behaviour of the extrinsically added chemical reflects accurately that of the chemical when it is naturally present in the food.

The overall effect of such factors is to restrict the percentage of food chemicals for which the exposure can be assessed by biomarker methodology. However, where a biomarker method is successfully developed and demonstrated to be a reliable and accurate measure of dietary exposure then it is likely to be applicable to many subsets of interest within the human population.

To enhance the chances that a method is successfully developed it is essential that the biomarker selected for investigation in stage 1 is chosen with care. In this context, existing pharmacokinetic and metabolic studies on humans, and also animal models, may prove to be valuable sources of information.

While biomarker methodology has been applied in the field of occupational exposure for many years, its application to intake assessment of food chemicals is of more recent origin. The following examples provide a non-exhaustive overview of applications of biomarkers to different food chemicals.

3.2.5.1. Mycotoxins. One of the first applications of biomarkers to human exposure to food chemicals is illustrated in the studies on the mycotoxin aflatoxin B1 in the late 1980s (Zhu et al., 1987; Gan et al., 1988). In these studies statistically significant correlations were observed between the dietary intake of aflatoxin B1 and urinary excretion of the metabolite aflatoxin M1. Subsequent investigations have tended to utilise aflatoxin B1 bound to serum/plasma albumin (Wild et al., 1992; Turner et al., 1998) and urinary aflatoxin B1–DNA adducts (Groopman et al., 1992), where a correlation coefficient of 0.80 with dietary exposure was obtained. Biomarkers have also been investigated as a means of assessing exposure to the fumonisin class of mycotoxins. Pharmacokinetic data and metabolism animal studies have indicated that direct measurement of fumonisins, or their metabolites, are unlikely to be feasible as biomarkers in blood or urine. Attention has therefore turned to an indirect biomarker, namely the ratio of two sphingoid precursors, sphinganine and sphingosine, in blood and/or urine. A number of studies (e.g. Turner et al., 1999) are now assessing whether this ratio will be of value as a biomarker of exposure to fumonisins in humans. The first such study has recently been published (van der Westhuizen et al., 1999), but no significant differences were observed for either plasma or urine. An alternative approach that is also currently being explored involves using fumonisins in hair as a biomarker (WHO, 1999; Sewram et al., 2000). The occurrence of OTA in human blood has been established for some 20 years (Hult et al., 1982), raising the possibility that its presence may provide a quantitative biomarker of exposure. However, it has proved difficult to assess the potential of such a method. Breitholtz et al. (1991) have proposed that a plasma clearance equation be used to relate OTA intake to plasma levels, using estimates for unknown toxicokinetic constants, such as the bioavailability of the mycotoxin. Comparison of intakes by this method with those derived from occurrence/consumption data has since been undertaken (EC, 1997). The level of agreement was rather variable and, for two of the five data sets, the plasma-derived intake estimate was lower by a factor of between five to 10. More recently, Gilbert et al. (2001) reported the results of a study in which both plasma and urinary levels were examined as a function of dietary intake, the latter being quantified by means of duplicate diet analysis. A statistically significant correlation coefficient ($r = 0.52$) has been demonstrated between dietary intake of the mycotoxin and its urinary excretion in humans and further work is currently in progress to further improve the correlation.

3.2.5.2. Other food contaminants. A biomarker method has been developed and applied for the food-contact material plasticiser di-(2-ethylhexyl)adipate (Loftus et al., 1994). The biomarker selected was the metabolite 2-ethylhexanoic acid, collected over a 24-hour period. The method was successfully applied in this study to some 112 individuals, but does not appear to have been used subsequently. A biomarker-based method is currently under development for a range of dialkylphthalates (Anderson et al., 2002). The method involves measurement of the monoester metabolite of each phthalate as excreted in 24-hour urine samples. Packer and Leach (1991) have developed a biomarker-based procedure for assessment of exposure to nitrate. Nitrate levels are quantified in 24-hour urine samples from which, after correcting for metabolic losses and also endogenous synthesis, dietary intake data are calculated. This method has subsequently been used in a large international study (Hill et al., 1996). Heterocyclic aromatic amines (HAAs) are formed during broiling/frying of meat. 2-Amino-1-methyl-6-phenylimidazo [4,5-*b*]pyridine (PhIP) is the most abundant in fried meat and has been detected in human urine, along with other HAAs, following consumption of such meat. However, rather large inter-individual variations were observed, possibly due to differences in activities of the metabolic enzymes, thereby limiting the use of urinary biomonitoring as a means of quantifying exposure (Reistad et al., 1997). More recently, PhIP has been detected in human hair, raising the possibility that its presence may be useful as a biomarker of exposure (Reistad et al., 1999). Smoking, however, may be a confounding influence (Peluso et al., 1993). The situation is also similar for polycyclic aromatic hydrocarbons. DNA adducts and the metabolite 1-hydroxypyrene-glucuronide have been consistently detected in human urine following consumption of charbroiled meat (Strickland and Groopman, 1995; Sithisarankul et al., 1997). However, there appears to be considerable inter-individual variation in the excretion patterns of the adducts and metabolites, suggesting that they may have only limited application as biomarkers of exposure.

3.2.5.3. Nutrients. Dietary intake of protein may be quantified by measurement of nitrogen in 24-hour urine samples (O'Donnell et al., 1991; Bingham et al., 1995; Ocke and Kaaks, 1997; Bingham and Day, 1997; Black et al., 2000) and serum urea and creatinine (O'Donnell et al., 1991). Correlation coefficients of weighed dietary intakes and urinary nitrogen are typically in the range 0.5–0.8 and 0.4–0.5 for serum urea and creatinine, respectively. Statistically significant correlations, ranging from 0.3 to 0.8 between dietary intake and plasma and/or urine levels have also been reported for zinc (O'Donnell et al., 1991), vitamin C (Bingham and Day, 1997; Ocke and Kaaks, 1997), sodium (O'Donnell et al., 1991; Bingham et al., 1995), potassium (O'Donnell et al., 1991; Bingham et al., 1995; Bingham and Day, 1997)

and vitamin A (Ascherio et al., 1992; Forman et al., 1993; Scott et al., 1996; Carroll et al., 1999). A similar situation exists for vitamin E (Schafer and Overvad, 1990; Ascherio et al., 1992) and for fatty acids (London et al., 1991; Tjonneland et al., 1993), where correlations have been demonstrated between dietary intakes and body depots of adipose tissue. However, notwithstanding these correlations, the current level of usage of biomarkers to assess intake of nutrients and micronutrients is very limited. Indeed, the main application of "biomarker" methods seems to have been the validation of other, less expensive, intake estimate procedures such as weighed diet records. This is a curious state of affairs bearing in mind that these "biomarker" methods have themselves not been validated in most cases. It therefore needs to be emphasised that all methods used for the quantification of food chemical intake must be validated in an appropriate manner. This holds true irrespective of whether the procedure involves biomarkers, duplicate diets or food records etc.

3.3. Selection of an appropriate method

It should be noted that there is no single ideal method for assessing food or chemical exposures. The choice depends on the objectives of the study, the foods of primary interest; the need for group vs individual data; the need for absolute intake vs relative intake estimations; characteristics of the population (e.g. age, sex, education/literacy, motivation, cultural diversity); the time frame of interest; the level of specificity needed for describing foods; and available resources. The most important criterion as to the appropriateness of a method is the purpose and/or research question to be addressed. Currently, most methods used are not developed explicitly from the perspective of risk assessment, and the available data are used for other purposes (than the original ones) as well. In these cases, the limitations of this should be noted. An example is the usage of earlier collected duplicate diets for the chemical analysis of other chemicals. In this potential application, biases due to food sampling and losses during storage should be considered.

In general, to characterise the average usual intake of a group, a 24-hour recall or 1-day food record method is appropriate, provided the sample is representative of the population under study, and all days of the week are equally represented. If the distribution of usual individual intakes within the groups is also needed, at least two (non-)consecutive days are required to permit estimation of within-person day-to-day variability.

Repeated 24-hour recalls or replicated estimated or weighed food records can also be used to determine actual or usual nutrient intake of an individual. The number and days needed for the measurements depend on the day-to-day variation and, in some cases, on the seasonal variation in food consumption. A minimum of 3–4 days of intake is generally required for characterising usual individual intake of energy and macronutrients. If seasonal variability is a concern, collection over several days of intake in each season of the year is recommended. For some other nutrients, for example cholesterol, vitamins A and C, 20 to more than 50 days of intake are required for accurate estimation of individual intakes; in such cases a FFQ focused on the selected nutrients for which relatively few food sources are important, might be a better choice.

The dietary history and the FFQ can be used to assess usual food consumption patterns over a relatively long time period. With certain modifications they can also be used to provide an estimate of usual intake of nutrients.

Sometimes a combination of two or more methods can provide greater accuracy by counterbalancing the shortcomings of one method with strengths of another. When the methods and data are independent regarding error (structure) the methods can be used to verify and validate results. For example, in the NFCSs conducted by the USDA a combination of a 24-hour recall and a 2-day food record was used. In the Third National Health and Nutrition Examination Survey (NHANES III) a FFQ focused on selected nutrients was used in addition to the 24-hour recall.

Wider aspects of validation of a biomarker method require comparison of intake estimates with those derived from other techniques such as duplicate diet, total diet and calculation-based methodologies. There are, however, two major difficulties with such comparisons.

First, different methodologies may well measure different aspects of intake. For instance, duplicate diet studies reflect exposure from all dietary sources while total diet methodologies generally exclude food consumed outside the home. In such cases the process of validation will inevitably involve rationalising differences between the various methods. If the required information is not available such interpretation of the differences will become increasingly subjective. The second problem is that the comparative data may be absent, incomplete and/or refer to a different target population.

For example, a comparison of nitrate intake data in the UK generated by various studies has been reported (Massey, 1997): the biomarker-derived intake was 157 mg/person/day compared with figures of 108 mg/person/day for a food frequency study and 54 mg/person/day for a total diet study investigation. The total diet study did not include nitrate intake associated with a number of factors including food consumed outside the home and the nitrate contribution from drinking water and beverages. The biomarker method would have included all of these additional sources, but there are some concerns that the method may be subject to a positive bias associated with the possible conversion of a small proportion of dietary protein to

nitrate (Mallett et al., 1988). While these differences in estimates for nitrate exposure are of interest, in terms of method-derived bias, it should be noted that all are below the ADI (219 mg/person/day, for a 60-kg individual).

In the case of nutrients, there seem to be few instances where the existing biomarker methods have been formally validated. Rather, biomarker methods have instead been used to validate calculation-based intake methodologies such as those involving weighed dietary records (Schafer and Overvad, 1990; London et al., 1991; O'Donnell et al., 1991; Ascherio et al., 1992; Forman et al., 1993; Tjonneland et al., 1993; Bingham et al., 1995; Scott et al., 1996; Bingham and Day, 1997; Ocke and Kaaks, 1997; Carroll et al., 1999; Black et al., 2000). There appear to be very few instances where these biomarker methods for nutrients/micronutrients have themselves been validated against other, more direct, techniques such as that of duplicate diets. The development of biomarkers in relation to intake assessment is an important topic that is also discussed in Eisenbrand et al. (2002).

A combination of methods is a cost-effective strategy in risk assessment. An example of this is has been reported by Brussaard et al. (1997). In that study, oriented at micronutrients (especially vitamin B6), a food frequency method was used to pre-select adults with a habitual low vitamin B6 intake. A 3-day dietary record was used to quantify the total food consumption from which relevant components could be extracted. Biomarkers of exposure were measured to quantify the exposure and validate the intake figures. Biomarkers of effect were used to estimate the biological relevance of the observed low intake levels. The statistical analysis combined the data to study, for example, the (dietary) determinants of a low vitamin B6 status (measured with a biomarker). To determine the proportion 'at risk' of inadequate intake, the food consumption of each subject must be measured over more than 1 day, or retrospective information on intake over a longer period may be used (e.g. dietary history method). The appropriate period depends on the purpose of making an estimate, the precision desired, the food component(s) of interest, the intra- and inter-individual variation components, and the period over which an intake has to be low or high before health risks are introduced.

The selection of a method also depends on whether the chemical is an existing one, a newly introduced one or a chemical that still has to be introduced. In the context of risk assessment, a much higher exposure level can also be considered as equivalent to an introduction of a ''new'' chemical. The best known and most frequently used methods to assess exposure are already described and relate mainly to monitoring of existing chemicals. Selected characteristics of this type of study are presented in Table 2.

Table 2
Characteristics of types of studies in relation to exposure assessment of chemicals

	Assessment oriented at	Relevance for risk assessment	Focus on	Avoidance of	Mainly used for
Supervised trials	- Residue of chemical	- Fate of the chemical	- Concentration	- Underestimation	- New chemicals
Pre-marketing studies	- Doseresponse	- Fundamental	- Concentration	- Under- and overestimation	- New chemicals
	- Scenario's of potential intake	- Robustness of assumptions	- Concentration/consumption	- Underestimation	- New chemicals
Post-launch monitoring	- Intake distribution	- Check on intake assumptions	- Consumption	- Underestimation	- New chemicals
Monitoring	- Screening of potential risk	- Cost-effective selection	- Concentration/consumption	- Underestimation	- Existing chemicals
	- Quantitative risk assessment	- Fundamental	- Concentration/consumption	- Under- and overestimation	- Existing chemicals

As a consequence of the introduction of functional and novel foods, it is expected that the use of pre-marketing studies and post-launch monitoring studies will be intensified. With regard to pre-marketing research, typically three types can be distinguished:

- Consumer use tests.
- Human intervention studies to test efficacy and safety.
- Test market evaluations.

The latter type of study overlaps with post-launch monitoring studies. The main intake information obtained before market introduction can be obtained from consumer use tests. Most pre-marketing information, especially the information related to consumer behaviour, has a commercial value. Therefore, the use of this information will be limited due to its confidential nature. When pre-marketing information is available it will contribute to the improvement of predictions of the intake distribution (and the corresponding effects). Without any information, simulation models with a robust character can, to a certain extent be used.

Data collection after market introduction of a product permits the confirmation of assessments in key areas, including:

- Real presence of relevant substances in regular production of a given food.
- Actual consumption/intake data for population at large and target populations.
- Changes in consumption patterns, for example products replaced by the newly introduced one.

Although no adverse effects are expected, a structure (for instance via the Internet) to collect data on subjective health comments and unexpected effects is relevant for post-launch monitoring. This information can be correlated with actual intake data so long as the possibility of spurious relationships is taken into account. Post-launch monitoring is a relatively new phenomenon for food products and it is commonly accepted that such data are not really needed for the majority of cases where a new product or component is introduced. Conceptual issues on post-launch monitoring are described in more detail by Van Dusseldorp et al. (2000).

As to exposure assessment, the major goal of post-launch monitoring is a check on the intake assumptions. These studies can be closely linked to marketing research, especially since information on individual brands is needed. As a consequence of this, the use of data from bar-code scanning of retail foods in exposure assessment is one of the future possibilities and needs. A validation study (comparison of household purchasing data obtained with scanners with individual consumption data obtained through 2-day records) performed in The Netherlands (Van Erp-Baart et al., 2002) indicated promising results.

Based on the afore-mentioned considerations, two approaches have to be distinguished in the selection of a method. The first is the use of existing data collected for other purposes. In that case, special attention should be given to the discrepancy between the data and the (new) purposes. Validation should concentrate on the potential biases introduced by these discrepancies. In the second approach, new data are going to be collected, and in that case validation should be concentrated on the most important uncertainties in data collection given the purposes of the study.

3.4. European comparability

The available national dietary surveys provide valuable information for use in national policy and are central in nutritional surveillance, and when repeated in a proper way, trends over time can be studied. However, for a detailed evaluation of dietary intake in Europe there is a need for increasing comparability of sampling designs, dietary methods and selected population descriptors. In contrast to national surveys, European surveys can be used for comparisons of dietary intake data across countries, provided that the methods used to collect dietary intake data and food composition tables across the countries are comparable. Several European studies on dietary intake have been conducted, such as CALEUR (van de Vijver et al., 1999), DAFNE (Trichopolou and Lagiou, 1997), EPIC (Riboli and Kaaks, 1997), SENECA (De Groot et al., 1991) and TRANSFAIR (Hulshof et al., 1999). These studies differ in quality of providing comparative dietary intake information across countries.

To improve the possibilities for international comparison of household surveys data in Europe, since 1993 an ongoing project of the European Union (DAFNE, DAta Food NEtworking) is harmonising the international level dietary exposure data from household budget surveys. DAFNE focuses on the creation of a pan-European food data bank based on national household budget surveys by the development of the most appropriate way of using food and related data from these surveys. Methods were designed to calculate, for instance, the overall average availability per person per day of comparable food items or groups among DAFNE countries, as well as average availability by degree of urbanisation and educational level of household head. DAFNE has been successful in harmonising at the international level dietary exposure from household budget surveys. The overall aim of DAFNE initiative is the formation of a European Food Data Bank based on household budget surveys (HBS). The tasks of DAFNE include: to study current methods of

HBS data collection and processing in the different countries, and to select parameters from the national HBS that would be of use to the DAFNE project such as general, nutritional and socio-economic information (Trichopolou and Lagiou, 1997).

EPIC developed methods to collect comparable individual dietary intake data in specific populations. The rationale of the EPIC project is setting up a large European prospective cohort study combining epidemiological and laboratory methods in order to expand the presently limited knowledge of the role of nutrition and related factors in cancer epidemiology. The EPIC project was designed with the aim of minimising the variance ratio of within-subject variations due to random measurement errors over the between-subject variations in true dietary intake levels by both reducing the numerator and increasing the denominator. This can be achieved by developing better dietary assessment methods and conducting studies in populations with very heterogeneous dietary habits. Therefore, on the one hand country-specific dietary assessment methods capable of measuring habitual food intake at the individual level in as much detail as possible were developed and validated and, alternatively, a highly standardised dietary assessment method was designed for calibration of dietary measurements between EPIC centres (Riboli and Kaaks, 1997).

The establishment of the Health Monitoring Program in Europe should make it possible to measure health status, trends and determinants throughout the Community; facilitate the planning, monitoring and evaluation of Community programmes and actions; and provide member states with the appropriate health information to make comparisons and support their national health policies. As part of this program, since the end of 1999 the project European Food Consumption Survey Method (EFCOSUM) aims to define a (minimum) set of dietary components, which are relevant determinants of health. Moreover, the study aims to define a method for the monitoring of food consumption in nationally representative samples of all age–sex categories in Europe in order to provide internationally comparable data. This method will be used alone, or as a calibration method for ongoing studies. The project will make use of progress in relevant projects carried out until now such as DAFNE and EPIC, and ensure the possibility for data fusion with other health monitoring studies. Fourteen EU member states as well as eight other European countries are participating in EFCOSUM. The final report was published in 2001 (EFCOSUM Group, 2001) Several more or less ad hoc EU initiatives have been carried out to use the existing food consumption data banks for risk assessment purposes. Those carried out within the framework of European Scientific Co-operation (SCOOP) are the most visible and direct. General examples are ''Improvement of knowledge of food consumption with a view to protection of public health by means of collaboration between database managers'', ''Development of methodologies for the assessment of the dietary intake of food additives'' and ''Examination of scientific aspects of the addition of nutrients to foodstuffs''. Chemical-specific examples are ''Assessment of dietary intake of ochratoxin A by the population of EU member states'', ''Assessment of dietary intake of nitrates by the population in the European Union, as a consequence of the consumption of vegetables'' and ''Dietary exposure to cadmium''.

3.4.1. Comparability of data

For intercultural comparisons of mean dietary intake levels, the 24-hour recall method is considered ideal since it has generally a very high participation rate and is an essentially open-ended method which allows a detailed reporting of amounts of very heterogeneous types of food or dishes. The EPIC-study selected the 24-hour recall method as reference method to validate food frequency questionnaires in each country. Moreover, they used this method as a reference measurement in a between-country calibration study to correct for some systematic over- or underestimation of the average dietary intake in some of the countries (Kaaks and Riboli, 1997). In EFCOSUM, the 24-hour recall method is chosen as the best alternative for Europe.

With regard to the coding of food, the so-called PROCOME food codification system was examined in the DAFNE project. The revised PROCOME version represents a fourth level of classification, taking into account the specific requirements of HBS, and adds a fifth level for national needs. Besides the PROCOME food codification system, two other important general European food coding systems exist (LANGUAL and EUROCODE).

In multi-center studies, the level of detail on the recorded food data varies from one country to another. Furthermore, food groups appear to overlap among countries. As the data do not share the same degree of detail, aggregation of the food items to the lowest level of information is necessary. Therefore, food aggregation tables were developed in the DAFNE project, which provide comparable categories of food items among participating countries (Trichopolou and Lagiou, 1997). EPIC developed a computerised 24-hour diet recall interview program (EPIC-SOFT), which was adapted for each participating country, to provide comparable food consumption data between several European countries. Common rules were pre-entered into the system to describe, quantify and check automatically approximately 1500–2200 foods and 150–350 recipes of the different EPIC-SOFT versions. In addition, the dietary data collected with national versions of EPIC-SOFT were pre-coded and classified according to a common classification system (Slimani et al., 1999).

In comparing values across countries Löwik et al. (1998) observed some differences. For instance, the mean total fat intake among adults ranged from 79 g/day (Greece) to 119 g/day (Belgium). On the other hand, the data also indicated a large variation within the separate countries. For example, among adults the lowest mean value for fat intake in the EU (in Greece) was 79 g/day. The corresponding standard deviation was 40 g/day, whereas the P95 and the maximum value was 148 and 259 g/day, respectively. The data, therefore, indicate that the variation in comparable indices, like a P95, across countries is less than the variation within a particular country. These differences are due to the method of data collection, the population groups concerned, sample size and time frame. Despite the differences, the major implication of the relatively large within-country variation is that an estimation of a high intake level does not depend much on a complete coverage of member states of the EU. This implies that no great effort should be made to include extra surveys with a small sample to get a more complete picture.

To a certain extent this reasoning is in line with developments within the Global Environment Monitoring System/Food Contamination Monitoring and Assessment Programme (GEMS/Food) regarding regional diets. This development results in 13 regional diets for predicting dietary intake of pesticide residues according to internationally accepted methodologies (WHO, 1997, 1998).

At present there are no existing European Monitoring Programmes or projects oriented at a systematic monitoring of biomarkers and/or total diets. At an international level, WHO organised a Workshop on Total Diet Studies in Kansas City, MO, USA (WHO, 1999) and more recently (July 2001) GEMS/Food-Euro convened a Workshop in Berlin on Total Diet Studies in Europe. However, several nutritional studies have incorporated biomarkers. Most frequently the chemical analyses were carried out in a central laboratory, since standardisation procedures such as proficiency testing do not yet exist for biomarkers. An example being the SENECA study (Haller et al., 1991). The choice for a central laboratory was also made in the TRANSFAIR study, which consisted in part of a total diet study. This study was focused on fatty acids, especially *trans*-fatty acids (van Poppel et al., 1998).

3.5. General methodological and validation issues

3.5.1. Uncertainties

Realistic assessment and prioritisation of risks depend on accurate estimation of exposure and toxicity. Although more resources have been devoted to toxicity, a paucity of knowledge concerning important exposure mechanisms remains a major source of uncertainty in many risk assessments (Wagener et al., 1995).

Any estimate of exposure is confronted with uncertainties. A summary of potential errors relevant for exposure estimates in risk assessment is presented in Table 3.

Measurement errors can be considered as:

$$Xi = Ti + b + Ei$$

where the observed measure (Xi) differs from the true value Ti by a systematic error or bias (b) which occurs, on average, in the measurements of all measured subjects, and the non-systematic error (Ei) that varies unpredictably from subject to subject. X, T and E are variables with distributions (Armstrong and Bofetta, 1999). Errors will be introduced, for instance, by the conversion of food data to nutrient data by using food composition tables. In these tables mostly one concentration figure is given for a product/nutrient combination. In reality, food composition varies widely. If, over time, a subject is consuming a food product that does not contain the standard concentration, a systematic bias is introduced. All the identified errors apply to a certain degree to the individual surveys and as a result to comparisons of the results of different surveys. As a matter of course, the impact of the various measurement errors on the results will differ. Furthermore, when population groups are compared, the measurement error can either be differential or non-differential. Differential means that the bias differs between the groups and/or the precision of the observed measurements differ between the groups (Armstrong and Bofetta, 1999). However, hardly any quantitative and comparable data are available. Therefore, there is an urgent need for research oriented at a quantification of the potential impact of measurement errors on the estimates in a comparable way. Based on this research,

Table 3
Critical uncertainties in food consumption surveys

Temporal (in case of habitual) lifetime intake
Under- and over-reporting (of specific food groups)
Representativeness of the population sample
Other sources of exposure (for instance supplements)
Coding system is not specific/detailed enough
Missing data
- food consumption (for instance tap water)
- food composition (for instance nutrient value for a food product)
Standard (average) figures for
- food composition
- recipes
- portion sizes
- household food preparation
Composition data before moment of consumption
- (indirect) observations in food chain
- household food preparation
Chemical analytical method
- different from standards like RDA/ADI
- for different food products in same table

the most important errors can be selected for future work regarding quality control systems.

Uncertainties associated with intake estimates will be affected by all of the potential biases and should be evaluated and presented in all food chemical intake assessments. Uncertainty can be characterized qualitatively, namely, which criteria were used to select or reject specific data, or quantitatively, for example ranges of intake. Uncertainty in estimated daily intake assessment may result from missing or incomplete data, measurement error, sampling error, use of surrogate data, gaps in scientific theory used to make predictions, and how well the theory or model represents the situation being assessed. Analysis of uncertainty provides decision-makers with information concerning potential variability in intake estimates and the effects of data gaps on intake estimates.

Collecting food consumption data in surveys as well as in duplicate diet samples for exposure assessment can alter the diet of study participants, resulting in a bias in intake estimate. Intake may be altered if people change their food consumption in one or more of the following ways:

- Consume more or less food than usual (consuming less is most likely).
- Consume different foods than usual.
- Consume foods from different sources than usual.
- Prepare or consume foods in a different location than usual.
- Use different cooking or other preparation and consumption practices.

These changes in dietary habits can be attributed in part to fatigue or loss of interest by the participant that can affect the collection of samples. Researchers face the sometimes conflicting goals of using methods that are simple and which minimize burden on study participants on the one hand, and in obtaining accurate exposure data over a duration adequate for the data's intended use on the other.

An exposure estimate may also be biased if the participant fails to provide a sample of all the food consumed during the collection period. Also, the weighing and measuring of food portions may also create consumption and collection bias.

Assessing the bias of the intake measurement that results from changes in dietary intake or during collection of samples is desirable. However, measuring this bias will be difficult and costly for individuals, while for groups of individuals it will be important to determine whether the dietary parameter used to assess bias is an adequate surrogate for the contaminant of interest.

One of the particular advantages of the biomarker approach is that all of the foods and beverages consumed are automatically, and by definition, covered by the methodology. In this context it is immaterial whether food/beverages are consumed at home, work, takeaway outlets or places of entertainment. Any exposure to a food chemical that occurs from all these sources will be included in a biomarker measurement. An additional aspect is that the act of participation in the study is most unlikely to alter the dietary habits of the individuals concerned. Factors such as choice of food/beverage, portion size, alcohol consumption and site of consumption should largely be unaffected by participation in a biomarker study. From these perspectives biomarker-based methods are probably freer from bias than other procedures used for exposure assessment.

3.5.2. Under-reporting

Except for biomarkers, all dietary methods are vulnerable to over- and under-reporting. In clinical studies it is common practice to supply extra energy in the trial than the amount assessed with, for instance, a dietary accord.

Stockley (1985) published a review on validation of duplicate diet collections. Duplicate diet collections underestimate true intake. Studies in which weighed records are kept for several weeks, with a period of collecting duplicates of the diet, can indicate the extent to which food intake changes during the collection period. Any changes are relative to estimates using another dietary method rather than being absolute, since the keeping of a diary may in itself affect customary consumption.

Energy intake is one dietary parameter often used to measure bias for food collection. Energy intake (from the food diary) and estimated energy expenditures are compared to the analysed caloric content of collected foods. Laboratory measurements of the caloric content of collected foods are, in most cases, lower than energy intake estimates from both the food diary and energy expenditure calculation. Kim et al. (1984) reported a mean decrease in energy intake of 13% for 29 subjects collecting foods for 1 week during four different seasons. Other research has reported similar decreases in energy intake during food collection studies. There are several possible reasons for the results: participants could have consumed less food than usual during the food collection period; collected smaller portions than those they actually consumed; or failed to provide samples of all the foods they consumed. Energy intake estimates cannot distinguish between these potential biases but errors in the validity of the duplicate diet method may be of as much or more importance than measurement errors.

Many dietary surveys reported energy intakes consistently lower than would be expected from the estimated basal metabolic expenditure and physical activity. This problem of under-reporting of energy

intake is widespread. Under-reporting has been shown to be present across a range of energy intakes and has been observed with all methods of measuring energy intake (Lissner et al., 1989; Livingstone et al., 1990).). Obese or weight-conscious subjects in particular are found to be over-represented among under-reporters (Jebb and Prentice, 1995). Furthermore, under-reporting varies for different components of the diet. Components reported to be prone to under-reporting are for example, alcohol and fat (Feunekes et al., 1999; Goris et al., 2000). For micronutrients, under-reporting will lead to an overestimation of the proportion of the population not meeting a certain recommendation or target intake. Generally, under-reporting is associated with a lower consumption of most foods, which can be due to a larger proportion of non-consumers, less frequent consumption and smaller portions. Under-reporting will influence the usefulness of dietary data in risk assessment, whereby the degree of distortion will depend on the purposes of the assessment and the chemical of interest.

3.5.3. Analytical considerations

To assess the intake of a chemical, information on its concentration in foods is needed. The strengths and weaknesses of the analytical concepts for foods are discussed in detail in section 2. Food consumption data have to be combined with chemical concentration data in order to predict the intake of the chemical. In Fig. 3 different ways of incorporating the chemical concentration are presented and they have to be implemented (as scenarios) at the different levels of aggregation. Computer software should be used for nutrient calculations, which are tedious and prone to error if done manually. Quality control procedures for data entry should be carefully adhered to. Recipes and other methods of food preparation should be adequately accounted for in the calculations.

An important consideration for nutrients and essential for pesticides and additives is the fate of the chemical before the moment of consumption. The difference between nutrients on the one hand and pesticides and additives on the other is that food composition tables are ''output'' (concentration at the end of the food chain or at moment of consumption) oriented and the information on additives and especially pesticides is more ''input'' (concentration at the start of the food chain) oriented.

The nature of a duplicate diet study poses several challenges in addition to those associated with the complex food matrix itself, which place greater demands on food analytical procedures. Duplicate-diet collections involve many different food types normally composited into a single sample for analysis because of the cost of analysing individual food types. These composites are very diverse and contain different amounts of fat and other substances that interfere with analysis. Compositing foods into groups compatible with analytical methods may not be practical or cost efficient. Contaminant levels in the composite diet samples may be very low because contaminated food items will be diluted with non-contaminated food items, necessitating use of sensitive analytical methods. The methods must also be efficient enough to deal with the large number of collected samples so that analytical costs do not limit the study. Sample analysis cost is usually the single most expensive part of an exposure study, sometimes amounting for two-thirds of the total study cost (Berry, 1997).

In contrast to foodstuffs analysis, there are no certified reference materials for example, for fumonisins in urine, OTA in blood, etc., that can be employed to support biomarker studies. The situation with respect to participation in suitable proficiency testing schemes is exactly the same. Examples of the analytical aspects of a biomarker method being collaboratively tested by a number of laboratories are also very rare. Hence, those working with biomarker methods will be reliant on other procedures to validate the analytical aspects of their work such as recovery checks, reagent/field blanks, repeat analysis and the use of in-house reference materials. The application of different analytical methodologies to quantify, and thereby confirm, the concentration of the biomarker is also a helpful contribution to method validation. This is particularly important when trace amounts of closely related metabolites are involved (Groopman et al., 1992; Wild et al., 1992).

Owing to the dosimetric nature of biomarker studies sometimes bias is detected, and corrected for, in stage 1 for the very reason that a satisfactory dosimetric relation cannot be established. For example, Groopman et al. (1992) noted that there was a poor correlation between dietary intake of aflatoxin B1 and urinary metabolites as measured by immunoassay. More detailed analysis revealed that while the aflatoxin P1 metabolite contributed greatly to the immunoassay response it showed no correlation with dietary exposure to aflatoxin B1. This led to the selection of an individual urinary metabolite, namely aflatoxin-N7-guanine, as the biomarker of choice.

3.5.4. Temporal aspects

The length of time over which dietary samples are to be collected will depend on the intended use of data. If the study is designed to provide a measure of the exposure distribution in a population at one point in time, then collecting samples from each participant over one short time period (1–3 days, for example) may be adequate. Alternatively, if a study is designed to provide data for risk assessment purposes, then it may be necessary to collect samples for several consecutive days at multiple intervals of months, seasons, and even years.

In biomarker-based studies the period of time for which the biomarker reflects exposure will be dependent on two major factors, namely the pharmacokinetics/metabolism of the food chemical and the body fluid location of the biomarker (for review see WHO, 2000). Hair, depending on proximity to the follicle, will reflect intake from a few weeks up to a year or more.

Faeces, when used to assess exposure to unabsorbed food chemicals, will be applicable for short-term exposure assessments of 1–3 days. The exposure period associated with blood will largely depend on the pharmacokinetics and metabolic details of the particular food chemical. OTA for example is bound to albumin in the bloodstream following its absorption from the gastrointestinal tract, albumin having a half-life of some 15 days. The amount of OTA in blood, and in urine, therefore reflects exposure over the previous 1–2 months. Similar time periods will occur for aflatoxin B1 bound to albumin (Wild et al., 1992). Biomarkers located in urine are typically associated with shorter exposure periods, of a day or so. This includes the biomarkers for nitrate and the intense sweeteners, where the parent food chemical is rapidly excreted intact and measured. Urinary metabolites and DNA adducts may also be employed as biomarkers of short-term exposure, as is the case with adipates and aflatoxin B1, respectively. The exposure duration associated with biomarkers in adipose tissue will depend on a number of factors, including particularly the lipophilicity of the food chemical concerned. Typically, however, adipose

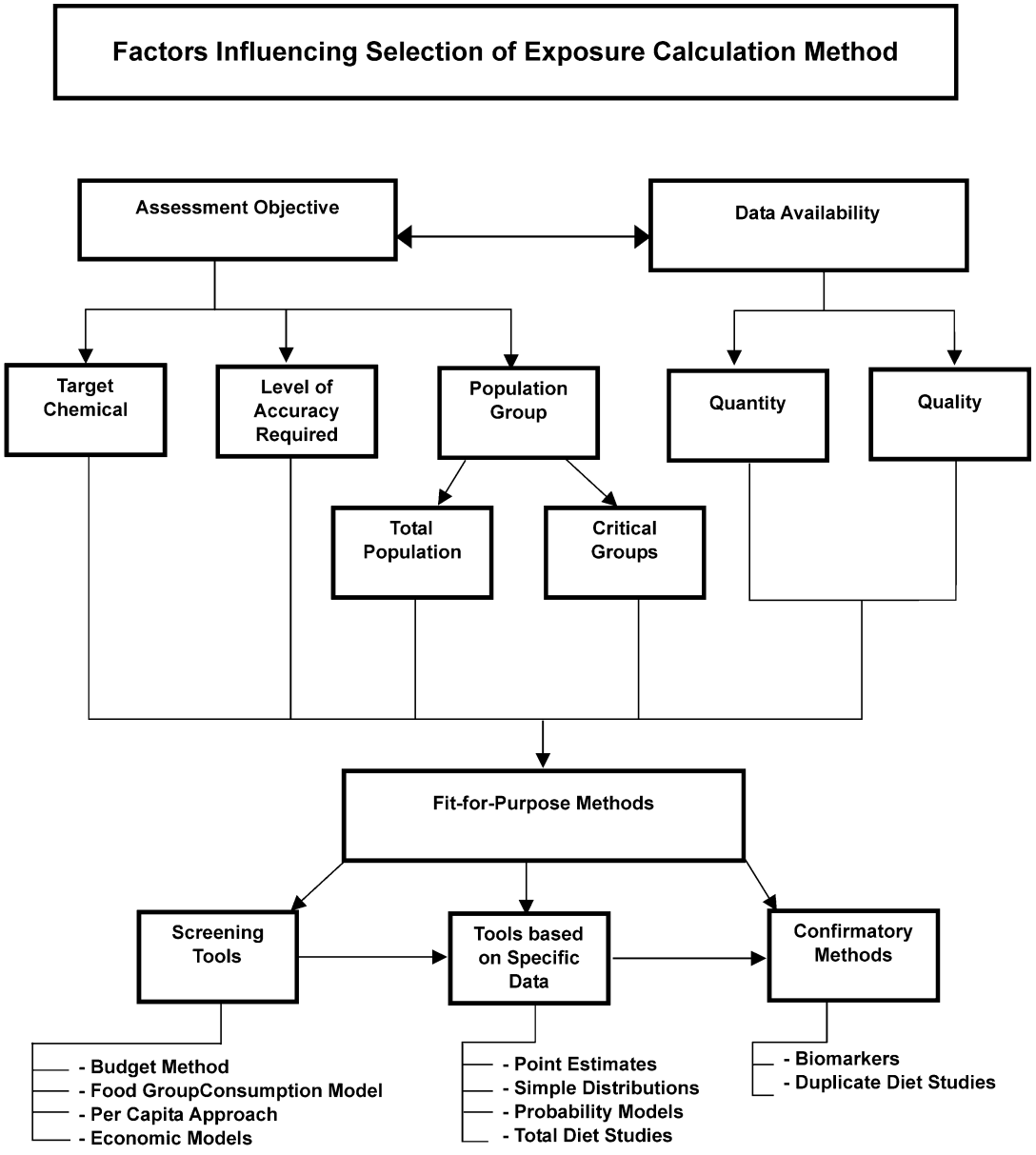

Fig. 3. Schematic presentation for exposure assessment from the perspective of a top down approach in risk assessment management.

tissue-based biomarkers will reflect exposure over several months.

Regarding assessment of intake of food chemicals, there is no consensus as to the time frame to be used for exposure assessment. For the time being, three broad categories can be distinguished (Löwik et al., 1999):

- acute intake corresponding with the intake on a single day;
- habitual intake, corresponding with the usual intake of individuals during a particular stage of life; this means that intake values are corrected for within-subject variation;
- a category within habitual intake is frequent high intake. Binge drinking of alcoholic beverages is an example of this behaviour;
- lifetime intake, corresponding with integration of habitual intake values.

Short-term data provide a snapshot of exposure during that time and an inference must be made about what the meaning is for a longer-term exposure. This must be done with caution, and the degree the short-term data represent the longer period should be demonstrated (EPA, 1992). Within the framework of EFCOSUM, Hoffmann et al. (2002) discussed the issue of "How to get the distribution of usual dietary intake?". In their paper, the methods of NRC (1986), Nusser et al. (1996), Wallace et al. (1994) and Slob (1996) were compared. The application of the method of Nusser et al. (1996) was considered the best alternative.

3.5.5. Users only

An issue with a dependence on the time frame is the concept of "users only". This concept probably originates from the legislation regarding setting permitted use levels. From this perspective, it makes sense to concentrate the attention on "users only" and perhaps even on users of particular food products or product groups. However, from the perspective of comparative risk assessment it may be argued that the total population or subgroups such as children should be taken as a point of departure. As a result of this, the intake among users is studied from the perspective of intake of the population, in which quantification of the risk as a prevalence value will have the same basis for the various chemicals. In comparisons within and between surveys the usage of "users only" can distort the results substantially (Lowik et al., 1996, 1999).

As to the concept of "users only", there are potentially different aggregation levels, namely brand, product, product group, chemical and food. As ADIs are formulated for chemicals from all sources, the starting point should be the chemical rather than a lower level of aggregation. Lower levels of aggregation can, of course be used as proxies for the total intake of a chemical. The concept of "users only" means that the calculations of characteristics of the distribution, such as mean and percentile values, are based on the users of a particular chemical, with the percentile value depending not only on intake level but also on the proportion of users, which in turn depends on the design of the survey. The proportion of users will be lower and intake levels will be higher at a shorter time frame (Lowik et al., 1996). This means that calculations based on "users only" result in different percentile values for different chemicals as to the proportion of the population that exceeds or does not exceed a particular value. For instance, P95 will be closer to the maximum value when the proportion of users is relatively small. Let us suppose that 10% of the population are users of a particular chemical; then the P95 among the users corresponds with about P99 in the total population.

The reasoning regarding "users only" applies to quantitative risk assessment and comparison purposes. In the case of quantification of (potential) effects (benefits as well as risks), particularly in relation to permitted use decisions, it makes sense to take the "users only" as a starting point. Some (novel) foods intend to have positive health effects in a specific target group. This implies that consideration should be given to a balance of benefits and risks for different (user) groups. Thus the usage of "users only" depends on the purposes of the quantification that have to be addressed.

3.5.6. Other sources

In estimating dietary intake of chemicals consideration should be given to sources other than food consumption. Examples are cosmetics, exposure to pesticides among farm workers or workers in greenhouses, and the use of dietary supplements. Very often a relevant contribution to the total exposure applies to a subgroup of the population. The contribution of a non-food source to total exposure can be substantial among the groups affected by the particular route of exposure. For instance, the intake from dietary supplements can be much higher than through food consumption, at least for limited periods of time, and exposure to agrochemicals is usually much higher in production or application than via residues on foods. On the other hand, in the initial round of data collection it can become clear that such sources are either not relevant overall due to the type of use and/or the level present, or that only small and readily identified groups of people are exposed, such as factory workers.

In the case of micronutrients, but also potentially other biologically relevant substances, intakes from restoration, substitution or fortification of food needs to be considered. For micronutrients included in food compositional tables it can be assumed that this will be the case, although the time lag inherent in the updating of the existing tables might introduce uncertainties.

Furthermore, the intake of bioactive substances from herbal extracts are of increasing importance.

Based on the increasing trend of micronutrient fortification and use of dietary supplements, higher intake levels may occur in the near future. Alternatively, it should be noted that as to potential health effects, one is still dealing with low doses. Low-dose extrapolation is among the most contentious scientific issues in quantitative risk assessment (Moolgavkar et al., 1999).

Bias will also be introduced in biomarker studies if exposure from non-food sources is significant. Obvious confounding sources include cosmetics, smoking, personal hygiene commodities, occupation, environment and lifestyle. Bias will also be introduced if the selected biomarker is not unique to the food chemical in question. This would be the case if the biomarker were either naturally formed endogenously, or via metabolism of other components of the diet. The inclusion of other sources in exposure assessment has to be considered on a case-by-case basis. Additional methodology is required to make this possible.

3.5.7. Food coding systems

In dietary assessment food products have to be identified and thereafter categorised in line with the purposes of the study. For this, national and international systems exist. According to Poortvliet et al. (1992), general food coding systems for all purposes tend to serve their users poorly. With regard to exposure assessment of a broad range of chemicals, unconventional categorisation systems might be needed. For instance, food consumption factors in relation to substances migrating from packaging material use the starting point of four categories corresponding with different solubility of chemicals. These categories are fat, water, acid and alcohol (FCA, 1997). For acidity, no coding system applicable to existing food consumption surveys has been created and validated. Hence, many uncertainties are introduced when the existing categorisation (mostly designed for nutrients) is used for a new application. Four options can be used to improve future estimates.

1. Add extra information to the existing surveys and combine the data with validated calculation procedures. The back conversion of food products as consumed into primary agricultural products to estimate the intake of pesticides is an example of this.
2. Collect data on a lower aggregation level and with more details. For example, define food products as brands in combination with information on the label regarding additives. The more intense use of bar-code scanners will be a great stimulant for this development. Studies on the feasibility of creating food consumption data on the basis of purchase data based on bar-codes carried out in The Netherlands are promising (Van Erp-Baart et al., 2002).
3. Use more than one categorisation system in the data collection. For example, classify the products according to food composition tables for nutritional purposes and classify the same products according to the CIAA and Codex system designed for additives regarding the permission of additives.
4. Create validated stochastic models based on the existing food consumption surveys with the aim to assess the exposure to new (categories of) chemicals.

The most efficient strategy for improvement is probably a combination of these options, whereby the combination will differ for categories of chemicals. To improve the comparability of European surveys it is recommended to use common European or international (e.g. Codex Alimentarius) food classifications as the starting point.

3.5.8. Sample size

In most surveys, point estimates are presented. Such an estimate has a confidence interval. The confidence interval depends on the existing variation in the chemical intake and on the sample size. The sample size of the population needed in exposure assessment depends on the parameter (for example the mean) to be estimated and the desired precision of the estimation. Other considerations may also apply in the choice of the sample size. For instance, in The Netherlands the sample size was determined by the goal to allow the total sample to be broken down on at least three characteristics of the subjects. Age and gender were among these three.

Several percentile values can be calculated to characterise the distribution. The acceptability of the use of percentile values (in relation to the reliability of estimates) strongly depends on the sample size. For a simple random sample, the sample size (n) satisfies the rule $n(1-\mathrm{P}) \geqslant 8$ for high ($>$P75) percentile values. For a complex sample, for instance skewed to high intake levels, the minimum-sample-size requirements are higher.

The definition of high-level consumers varies, but is normally either the 90th, 95th or 97.5th percentile of the distribution of individual intake values. A high percentile, rather than the maximum value, is usually chosen because maximum intakes are unlikely to be maintained over long periods of time and are hence not representative of high-level intakes in relation to chronic exposure (Benfort and Tennant, 1997). Therefore, percentile estimates are the preferred approach. Chambolle (1999) considered the 95th percentile level a good compromise between a high level of protection and precision in the estimates of the intakes. These considerations imply that

the choice of the percentile value and the needed precision level has a large impact on the sample size.

Two aspects are still to be mentioned in relation to sample size, namely subgroup representation and within-subject variation. When particular subgroups are of interest, the representation of these groups will determine the total sample size in a random sampling procedure. With regard to within-subject variation, it should be recognised that for dietary intake variables, the within-subject variation is mostly as large or larger than between-subject variation (Nelson et al., 1989; Löwik et al., 1994). For estimates on habitual intake this implies that both the within-subject and the between-subject variation has to be captured in a cost-effective way. According to Beaton et al. (1979) this can be done by using the following formula:

$K = RvC_1/C_2$ with

K = number of repeated interviews
R = ratio of within- to between-subject variation
C_1 = cost of an extra subject
C_2 = cost of an extra dietary interview

3.5.9. Age-gender groups

The existing surveys differ in the age–gender groups included in the survey. Furthermore, even when comparable age ranges are included, the data presentation varies among surveys as to the age–gender groups. The last aspect can be standardized relatively easily, whereas the age groups classification should be based on relevant differences in risk. For nutrients the classification is mostly related to the requirements and thereby the recommended daily allowances. The age–gender groups in these allowances are not always the same.

To allow smaller surveys to present the data according to standardized age–gender groups it is necessary to keep the number of groups as small as possible. Therefore, it is recommended to start with the total sample and thereafter use the categorization of the European Commission (see Table 4). As this categorization is based on nutritional considerations, toxicologists have to check case-by-case whether the categorization is in accordance with differences regarding toxicological hazards.

Table 4
Age–gender classification groups by the European Commission

European Commission		
Children	Men	Women
1–3 years		
4–6 years		
7–10 years		
	11–14 years	11–14 years
	15–17 years	15–17 years
	18+ years	18+ years
		Pregnant, lactating

3.5.10. Population groups of special interest

In risk assessment, groups of special interest originate from two categories, namely factors linked to physiological or pathological conditions and factors linked to the amount and composition of the consumption. The procedure most often used in the identification of special groups is to determine the distribution of consumption in the general population followed by a priori identification of groups potentially at risk such as infants, children, diabetics, and vegetarians (Verger et al., 1999).

Infants and children, because of their higher food consumption rates per kg body weight, are generally expected to have a higher relative risk due to the higher exposure level and are therefore a susceptible subset of the population. Other subsets of concern are women of childbearing age. This exposure scenario is particularly important for chemicals with demonstrated potential for developmental toxicity through in utero exposure. In the EU Monte Carlo project, duplicate diets of infants aged between 9 and 12 months will be collected in The Netherlands and in the Basque Country (FFP, 2000). Duplicate diet methods are particularly appropriate for exposure assessments for "extreme consumers" and "susceptible subsets".

For assessment of chronic intake and intake per episode, various questions must be addressed. Data on intake per episode are needed to assess potential risks associated with acute exposures (e.g. reproduction toxicity effects). In that case we are dealing with effects considered to be irreversible since even a single critical day of exposure within the response part of the dose–response relation could produce a permanent change in the offspring (Renwick and Walker, 1993). For a carcinogen, information on chronic intake is needed as an estimate of lifetime average daily dose (Driver et al., 1996). For chronic exposure, individuals with a high lifetime intake per kg body weight are of special interest. Often young children are mentioned as a group of special interest because of their relatively high intake per kg body weight. However, a decrease of the consumption per kg body weight is a normal biological phenomenon (Larsen and Pascal, 1998). From a perspective of lifetime intake, it is not the children as a (total) group who are of interest but children who have, and sustain during adulthood, a high intake level per kg body weight. This holds, of course, only when there are no (direct) adverse effects of the high intake per kg body weight during childhood. Identification of groups of special interest as to high lifetime intake per kg body weight should be oriented at a prediction of this sustained high intake. One predictor is physical activity, and this may even be the single best one. Therefore, research aimed at identifying and characterizing subjects with high lifetime levels as a result of physical activity is recommended for questions related to chronic intake per kg body weight.

Examining risk groups regarding potential effects of episodic high intake (for example 1 day) requires a different reasoning. In this case, the starting point should be the metabolic (including diseases) or physiological state of the body, since this forms the basis of a higher vulnerability to a particular effect. In this respect, children may be of special interest because of their higher intake level per kg body weight due to growth processes. Reproductive toxicity effects potentially apply to women (before and during pregnancy) and men (formation of sperm) in their reproductive phase of life. These considerations imply that risk group identification regarding acute intake should start from the potential adverse effects rather than from groups with a potentially high intake.

It is anticipated that future developments in gene/nutrient and gene/contaminant interactions will serve to identify subsections of the population which are potentially at risk and for whom accurate dietary exposure data are required. Biomarker-based methods should be highly applicable to extreme consumers. Such methods should be directly applicable irrespective of the nature of the dietary pattern. For example, biomarker methods are likely to be equally applicable to extreme consumers of fish, meat, vegetables or carbonated soft drinks, etc. It is difficult to see the need for substantial modification of study plans designed for "normal" consumers in order to accommodate extreme consumers. However, for those who for genetic and/or medical reasons are susceptible, then depending on the nature of the susceptibility, it will be necessary to revalidate the method for each group examined. The applicability of biomarker methods therefore depends on the ability to undertake both stage 1 and stage 2 studies for each of the different susceptible subsets that is to be examined. The majority of susceptible groups likely to be of interest should be amenable to the biomarker approach. These includes the elderly, pregnant women, nursing mothers and those with a chronic medical condition such as diabetes or osteoporosis. Biomarkers methods are unlikely to be feasible for infants due to the impracticality of performing either the stage 1 or the stage 2 components of the study. In addition to these considerations there may be instances where participation in a biomarker study would not be acceptable to certain subsections of the target population due to ethnic/religious reasons, for example Muslim women not wishing to provide blood samples.

3.5.11. Industry data on consumption patterns

The survey methods described so far try to obtain data on the overall food consumption patterns of populations based on reports by individuals. They are usually not suitable to address aspects of individual food items, especially branded products, and are often of limited use in regard to categories of processed foods. Several approaches by industry are useful to provide added perspective, although it has to be recognised that neither methods used nor results of such surveys by individual companies are normally published due to the competitive sensitivity of such information. On the other hand, it should be recognised that the market success of manufacturers depends on their ability to understand the expectations and behaviour of "their" consumers.

Methods used include, for example, include the evaluation of data from market research companies. They keep (and sell) very detailed records on market shares and on purchase behaviour for categories or individual brands with excellent information on the composition, age distribution, related consumption/purchase habits, and overall socio-economics of the households participating in their panels. Panel sizes can be very large, depending on the questions asked, and the composition of the panels is relatively stable: it is thus possible to observe changes of food purchase patterns over several years.

This information can be particularly useful when looking at food categories or brands predominantly purchased in the retail trade and consumed at home. As indicated, these data are collected on a per-household basis and thus provide in this regard only limited information for the consumption by individuals. However, especially when dealing with individual brands or well-defined categories, it can be supplemented by specific manufacturer data on in-household consumption to provide perspective on the distribution of consumption of the amounts purchased among household members.

Manufacturers do conduct a wide range of consumer tests to understand the consumption patterns for their own products and those of their competitors in regard to eating occasions, amounts consumed by relevant quantiles of users, fractions of users in the population, other products replaced by the specific brand, and foods consumed in connection with their products. Data are often available also on the success of product positioning towards specific subgroups of populations, evaluating for example for a product marketed towards adolescents which fraction is indeed consumed by that target group and which other groups are relevant consumers. Most of these data are collected before market introduction, but they are often extended after some time of marketing to confirm predictions.

This type of information is sometimes considered very critically, and it is indeed necessary to understand the quality of the data when used in risk assessment. However, when this kind of information (trade surveys or manufacturers' research) is available in the right quality, it can provide often a more specific and accurate basis for an assessment than the generic survey data can offer. In any case, this type of information is frequently used in the internal intake and risk assessments conducted by manufacturers for their products.

3.6. Future challenges and needs

3.6.1. Challenges and needs from trends

Methods that are used in exposure assessment are in a continuing state of development and refinement. For the application of risk assessment it is a new and developing field with rapid evolving methodology. Furthermore, actual exposure assessments are very often confronted with limited and distorted information sources. Priorities are constantly changing and new compounds are being added to reflect current priorities. Flexibility in the programmes should be encouraged in order to ensure a timely response to changes in the priority of risks and chemicals.

Substances migrating from packaging material are an example where extra information is needed regarding exposure assessment. The food consumption factors used for this are very crude and a validated refinement is needed.

Research in the field of molecular genetics and nutrient–gene interactions might be promising. Monitoring systems may also provide more information on variations within the human genome. This will enable us to focus progressively on the risks of individuals and subgroups introduced by a chemical. The developments in genomics, proteomics and metabolomics may lead to biomarkers of exposure and of effect. Screening for predefined exposure and effects might be the first application as to risk assessment.

As it might be expected that in the coming years bioactive components, additives and contaminants will increasingly become a topic of interest, future food consumption databases should also allow the assessment of these non-nutrients. Therefore, there will be a need for more descriptive specificity such as brand names, and more information on the food composition. The use of computer technology and advanced statistical methods may facilitate wider applications of survey data and cost-effective data fusion.

Prevailing trends are higher consumption of composite dishes (like a pizza) and/or more away-from-home consumption. Both trends will introduce a higher degree of uncertainty regarding the amount and composition of the ingredients that are used. Although biomarkers could solve this problem, other methods should be developed as well. The intake of bioactive substances, e.g. nutritional supplements and herbal extracts, is increasing. The inclusion of these sources in exposure assessment has to be considered on a case-by-case basis. For this, additional methodology is needed.

Functional foods and novel foods will be introduced into European markets and this will create a need to monitor the exposure to and health effects of these products. Future monitoring programs should allow product specific analyses and conclusions. Post-launch monitoring and pre-market simulation studies might be a specific component of these programs.

3.6.2. Challenges and needs regarding methods

Useful information for dietary exposure evaluation currently exists. Further research is needed to integrate this information into a practical model for estimating potential dietary exposures to priority compounds. The resulting model will aid EU monitoring programmes by providing information about the expected importance of diet as a component of total exposure. The model will also identify the food items or categories with the highest potential for exposure, i.e. foods consumed often and/or foods containing high levels of a chemical residue. Through the use of modelling, the results of field studies can be extended to other populations or other geographical locations in which limited data are available. The ultimate aim of dietary modelling is to predict exposures with reasonable accuracy and to focus on the extremes of the population distribution that are most exposed to a specific chemical.

Under-reporting is identified as one of the major biases in exposure assessments based on dietary surveys. Quantification of the potential distortion of the assessment as well as improved data and correction procedures are needed.

There is an increasing awareness of the potential use of biomarkers for assessing exposure to food chemicals. A number of methods for specific individual food chemicals are currently being developed and it seems certain that this trend will continue. However, very few such methods have been fully developed and validated, particularly in the case of food additives and contaminants. Even fewer are the instances where such methods are currently being employed, at either member state or European level, to assess exposure. A workshop to address these issues might well be of value.

High priority must be given to making an inventory of the databases from programs carried out in EU countries that provide both food consumption or contamination information potentially useful for dietary exposure assessments in the EU. Duplicate diet studies can be used to validate the appropriate models constructed.

To improve valid comparisons between diet and health at the international level a better harmonisation of data collection, methodology and standardisation of data analysis will be needed.

Duplicate diet sampling procedures must be further refined, standardised and validated to establish a protocol that is recognised and accepted as an agreed-upon technical procedure for dietary exposure measurements.

Currently, no suitable food materials have been sufficiently characterised for use as field and laboratory control samples. Food materials representative of relevant composite food sample are necessary to evaluate the possible contamination aspects of food sample collection, handling and preparation. Standard reference materials (SRMs) are also needed for foods. Currently, only few SRMs are available, for example some metals in food samples.

Methods, databanks, as well as statistical tools that improve the comparability of the exposure assessment in European countries are becoming more important. The use of bar-codes (EAN; European Article Number) is a promising tool to identify food products in a cost-effective standardised and comparable way. This should result in better harmonised surveys in the EU.

3.7. Conclusions

3.7.1. Biomarkers

Biomarker-based methodologies have a number of advantages over other exposure assessment techniques. There are good grounds for believing that biomarker methods, where validated, provide a highly accurate estimate of the amount of a food chemical that has been consumed. There are, however, a number of disadvantages associated with biomarker-based methods. They are expensive to undertake. Results are not generated quickly and it may take 3–5 years from the commencement of stage 1 to the completion of stage 2. In addition, the methodology cannot be applied to all food chemicals.

One application of biomarkers in risk assessment is in the validation of other methods such as the duplicate diet, total diet and calculation-based weighed dietary record and food frequency questionnaire approaches. A number of the concerns with each of these methods are generic and are not specific to any one food chemical. The answers to generic issues could be very usefully addressed by examining the exposure estimates for a selected food chemical as quantified, in the same study, by a biomarker, a duplicate diet, a total diet, a weighed dietary record and a food frequency questionnaire.

Biomarker methods, where available, are highly suitable for investigating individual intakes. In particular, the exposure of those in subsections of the population which may be at increased risk as a consequence of either extreme dietary consumption patterns or inherent susceptibility. Full validation of biomarker methods is a challenging area, and one that merits greater attention.

3.7.2. Time frame

The concept of "users only" should be used at the pre-marketing stage of a chemical and/or (novel) food. In the decision-making process of permitting a chemical it is correct to use the implicit worst-case scenario of (potential) users only. For quantitative risk assessment the concept of users only should be avoided. In order to allow comparisons of different chemicals, the starting point should be the total population. The concept of "users only" is, however, useful when more specific assessments are needed regarding (potential) intake levels and their effects.

As to the time frame, three concepts have to be distinguished, namely:

- acute, corresponding with 1 day;
- habitual for a life stage, corresponding with an adjustment for within-subject variation;
- lifetime, corresponding with an integration of the habitual intakes during the different life-stages.

As to the acute time frame, it is suggested that also repeated acute exposures are considered, with repeated being the frequency that an acute exposure occurs. An example of this last concept is binge drinking in relation to alcohol. The four temporal concepts cover the different types of hazards.

Regarding the hazard, a threshold may exist and this should be combined with the (repeated) acute exposure concept.

Most interactions between chemicals as well as with the food matrix occurs in the short term (same day), which should be taken into account in the development of instruments for exposure assessment.

3.7.3. Methods

The increasing need for individual brand information in (post-launch) monitoring as a consequence of the existence of brand-specific concentration levels and the need for more flexible systems to categorise food products makes the use of existing scanner data (based on European Article Numbering: EAN) in exposure assessment a challenging option for the near future.

The duplicate diet approach is necessary when direct comparisons to other exposure pathways measured for an individual are required for the assessment of that individual's total exposure. It is the most accurate approach for measuring the real exposure of an individual. However, the duplicate diet approach is not easily interpreted beyond the monitoring period and may not be the most cost-effective approach for a long-term assessment of a large population.

In order to standardise the data presentation, starting points have to be formulated:

- age–gender group (proposal: start with total sample/population and thereafter use the age–gender groups distinguished by the European Commission);
- express the intake per kg body weight;
- use the 33 Euro Food Groups as the default for food group classification;
- to avoid misinterpretation for existing data the following parameters are recommended: mean, standard, error of the mean, or confidence intervals and proportion of users of one day. For data based on 2 days or more and on sufficiently large sample size, parameters of interest are: mean, median, quartiles, P5 and P95 (EFCOSUM Group, 2001).

Employment of literature values is an integral part of calculation-based methods, such as weighed food diary records, which limits the accuracy of the estimate of an individual's intake data.

European food consumption data show that the variation within countries is as large or larger than among countries. This observation provides a basis for (selected) regional (aggregated) diets. Furthermore, it is better to focus future work more on the (methodological) problems and other relevant issues, like probabilistic modelling, than on the aim to obtain as complete as possible a picture of food consumption in Europe.

There is a clear need for (statistical) models that identify the most critical (as to potential impact on the result) measurement errors in the perspective of risk assessment. Based on this knowledge, quality control procedures can be developed and implemented in future surveys.

The instruments and methods currently used in exposure assessment are not always designed in the perspective of risk assessment. Therefore, special attention should be given to validation from the background of exposure assessment in that the proof of fitness of data and methods in relation to the purposes becomes more evidence-based.

A pan-European survey for the purposes of exposure assessment in risk assessment is needed. This survey should take into account the practice of risk assessment by incorporating various approaches and methods from the perspective of a step-wise hierarchical approach. The protocol developed in EFCOSUM is a good starting point for a pan-European survey.

4. Methodologies to integrate food consumption and chemical concentration for the purpose of modelling exposure to food chemicals

4.1. Introduction

The links between food consumption and food chemical occurrence and concentration are rarely direct. With the exception of duplicate diet studies, exposure assessments do not have consumption, occurrence and concentration data related to the same individuals 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. The modelled estimates can then be compared to toxicological endpoints and the relevance for human health established. In its broadest sense, the model to represent dietary exposure can be considered as $Consumption \times Residue/Concentration = Dietary\ Exposure$. There are, however, a number of different models for combining or integrating the consumption data with the residue/concentration data and a number of factors which influence the choice of model for any given exposure assessment. The following sections of this paper will consider the various ways of combining data sets of food consumption and chemical concentration for the purpose of estimating exposure to dietary components and the relative advantages and disadvantages of each.

4.2. Methodologies for integrating food consumption and chemical concentration

When separate data sets are available for food consumption, as measured in food consumption surveys, and chemical concentration, one of three approaches is usually applied to combine or integrate the data to provide an estimate of exposure: (i) point estimates; (ii) simple distributions; and (iii) probabilistic analyses. The method chosen will usually depend on a number of factors, including the purpose of the assessment (target chemical, population group, degree of accuracy required) and the availability of data. The position of these approaches in the overall scheme of assessment methodologies is considered in section 4.9, research needs.

Each of these approaches may vary in their potential to over- or under-estimate exposure depending on the surveys used to provide the data and the parameters used to represent the variables. For example, estimates based on food balance sheet data will over-estimate average consumption (see section 3.2.1.). However, it is important to note that individual dietary surveys will be associated with some degree of under-reporting, and this may potentially lead to some degree of under-estimation of exposure (see section 3.5.2.).

Point estimate or deterministic modelling involves using a single 'best guess' estimate of each variable within a model to determine the model's outcome(s) (Vose, 2000). In the context of exposure assessments, the term 'point estimates' refers to a method whereby a fixed value for food consumption (such as the average or high level consumption value) is multiplied by a fixed value for the residue/concentration (often the average residue level or upper tolerance or permitted level according to legislation) and the intakes from all sources are then summed. Examples of point estimates of dietary exposure include the theoretical maximum daily intake (TMDI) for food additives (FAO/WHO, 1985) and the theoretical added maximum daily intake (TAMDI) for flavouring substances (Cadby, 1996). The 'per capita×10' approach can also be considered under the heading of a point estimate since this method provides a single estimate of exposure by dividing the amount of the chemical entering the food supply by an assumed 10% consumers within the population. Point estimates are commonly used as a first step in exposure assessments based on food consumption surveys

because they are relatively simple and inexpensive to carry out. Inherent in the point estimate models are the assumptions that all individuals consume the specified food(s) at the same level, that the food component (additive, pesticide, nutrient) is always present in the food(s) and that it is always present at an average/high concentration. This approach therefore does not provide an insight into the range of possible exposures that may occur within a population or the main factors influencing the results of the assessment. When high-level values are used to represent either the food consumption or chemical concentration values, summing the intakes from multiple sources may lead to high and often implausible overestimates of intake. As Petersen (2000) noted, it may obscure the ability of regulators, industry and consumers alike to determine which scenarios present a risk that is likely to occur and therefore needs to be addressed. Point estimates are generally considered to be most appropriate for screening purposes (Parmar et al., 1997). If they demonstrate that the intake is very low in relation to the accepted safe level for the chemical or below a general threshold of toxicological concern for food chemicals in general, even when assuming high concentrations in the food and high consumption in this food, they may be sufficient to decide that no further exposure assessments are required (Kroes et al., 2000). In order to refine estimates of exposure, more sophisticated methods of integrating the food consumption and chemical concentration are needed and/or more detailed data from industry, monitoring programmes, etc.

In the context of exposure assessments, 'simple distributions' is a term used to describe a method that employs distributions of food intake but uses a fixed value for the residue/concentration variables. This usually involves using computerised databases of food consumption surveys. The results are more informative than those of the point estimates because they take account of the variability that exists in food consumption patterns. None the less, they usually retain several conservative assumptions (e.g. all soft drinks that an individual consumes contain a particular sweetener at the maximum permitted level; 100% of a crop has been treated with a particular pesticide, etc.) and therefore usually can only be considered to give an upper bound estimate of exposure. Examples of this approach are Tier 1 of the EPA Office of Pesticide Programs tiered approach to acute dietary exposure assessment (EPA, 1996; Petersen, 2000) and the Step 2 approach described in the SCOOP Task 4.1 report of the European Commission (EC, 1997). For macro- and micronutrients, one value is used to represent the content of each nutrient in each food. However, in principle, the variety in concentration is taken into account in the sampling design (before chemical analysis). The aim is to create a representative figure. The reasoning is that nutrients normally only have an effect in the chronic situation, whereby the average concentration over (a long) time is at stake and not the variety at a particular moment. This approach is biased when subjects choose products with systematically higher or lower concentrations.

In contrast to the point estimate approach, probabilistic analysis involves describing variables in terms of distributions to characterise their variability and/or uncertainty. It then takes account of all the possible values that each variable could take and weights each possible model outcome by the probability of its occurrence. Probabilistic analysis can be used in food chemical risk assessments to generate distributions of risk from food chemical exposure, for example the probability of occurrence of specified health effects. It can also be used to generate distributions of exposure that may ultimately be used in probabilistic risk analyses. In this section, the term probabilistic analysis or probabilistic assessment is used to refer to probabilistic exposure assessments only. Probabilistic analysis of dietary exposure to chemicals utilises distributions for both the food consumption data and the residue/concentration data in the model and simulates dietary exposure by drawing random values from each input distribution in a manner consistent with the mathematical model which describes the exposure process. From a practical point of view, once the model and input data have been selected, combined, and entered into an appropriate software system, the required number of simulations and iterations are set and the model is analysed to determine the range and probabilities of all possible outcomes (Palisade Corporation, 1997). Efforts can also be made to quantify the uncertainty associated with exposure estimates. For example, techniques such as bootstrapping can be used to get a measure of the uncertainty associated with parameters of a distribution due to sample size (Cullen and Frey, 1999). The more limited the data set, the wider the confidence intervals will be. Also, where there is doubt about the model structure, including a comprehensive range of plausible models can help to quantify the model uncertainty. The process of setting up and running the models requires appropriate modelling software and a high level of computer processing power. There are a variety of risk analysis software products on the market, mainly for PCs, which include software for modelling and distribution fitting. Probabilistic analysis is also beginning to benefit from advances in parallel processing technology. Parallel processing makes use of all available hardware in a server or on a network to dramatically speed up simulations.

Although probabilistic techniques, such as Monte Carlo analysis, have been used in physics, chemistry and many other disciplines for over 50 years, they were rarely used in human health risk or exposure assessment prior to 1989 (Finley and Paustenbach, 1994). Since then, however, a number of exposure assessments

employing probabilistic approaches have been carried out for environmental contaminants and microbiological hazards (Paustenbach et al., 1991; McKone and Bogen, 1992; Copeland et al., 1994; Finley and Paustenbach, 1994; Cassin et al., 1998; Hoover, 1999). Although limited, examples of probabilistic approaches to exposure assessments of chemicals from food do exist and include assessment of acute exposure to pesticide residues from fruits and vegetables (Hamey and Harris, 1999; Hamey, 2000), radionuclide ingestion following radioactive fallout deposition (Whicker et al., 1990) and exposure to intentionally-added flavouring substances (Lambe et al., 2001). These studies show how probabilistic analysis can be employed in food chemical exposure assessments to utilise available information on variability in the proportion of foods containing the chemical and variability in the concentration of the chemical, in addition to variability in consumption patterns of those foods. For example, Hamey (2000) was able to replace a point estimate of carbaryl concentration with a distribution obtained from a residue monitoring study. Lambe et al. (2001) used probabilistic analysis to incorporate information on the probability of a brand containing a flavouring (according to a national food ingredient database), the probability of a flavouring containing a specific flavouring substance (data from industry), and a distribution of flavouring substance concentration (data from industry). These studies, therefore, make better use of available data and provide more meaningful estimates of exposure. For low molecular weight chemicals, micronutrients and macronutrients, estimates of exposure will be based on an integration of chemical concentration data and food consumption data. In the case of novel foods, the assessment may require an estimate of the intake of the food itself or an estimate of the intake of the novel food as a component of other foods.

4.3. Deterministic vs probabilistic modelling of dietary exposure

The advantages and disadvantages of deterministic and probabilistic approaches for exposure assessment have been described in detail and are summarised in table format by Finley and Paustenbach (1994) (see Table 5). These authors not only highlight the merit of the point estimate approach as a screening tool but also the advantage of the probabilistic approach over the point estimate approach in terms of the increased amount of information that it imparts to the risk manager. The EPA (1997) has also described benefits from probabilistic analysis for risk and exposure assessors (Table 6). Two primary advantages of probabilistic analysis for exposure assessments are that (i) it permits the exposure assessor to consider the whole distribution of exposure, from minimum to maximum, with all modes and percentiles, and (ii) it includes a comprehensive analysis of the sensitivities of the resulting

Table 5
Advantages and disadvantages of using the point estimate or the probabilistic approach in health risk assessments (Finley and Paustenbach, 1994)

Advantages	Disadvantages
Point estimates:	
Simple, accessible	Repeated use of conservative point estimates tends to significantly over-estimate actual exposure
Readily accepted by regulators	Provides limited information for risk managers and public
Can provide a 'bounding estimate'	No associated measure of confidence
	Sensitivity or uncertainty analyses usually not very meaningful
Probabilistic assessment:	
Provides more meaningful information to risk managers and public	More complicated and therefore more time-consuming
Avoids disputes over best point estimates	More complicated to conduct quality assurance of the calculations
Risk estimates are associated with a quantitative measure of uncertainty	Current regulatory guidelines do not encourage its use
Eliminates creeping conservatism	Can fail to account for interdependent variables
Allows for quantitative evaluation of conservatism in point estimate (RME) approach	
Sensitivity analysis more meaningful	

Table 6
Benefits of probabilistic modelling as described by EPA (1997)

An appreciation of the overall degree of variability and uncertainty and the confidence that can be placed in the analysis and its findings
An understanding of the key sources of variability and key sources of uncertainty and their impacts on the analysis.
An understanding of the critical assumptions and their importance to the analysis and findings.
An understanding of the unimportant assumptions and why they are unimportant.
An understanding of the extent to which plausible alternative assumptions or models could affect any conclusions.
An understanding of key scientific controversies related to the assessment and a sense of what difference they might make regarding the conclusions.

exposures with respect to uncertainties in parameters. The results of sensitivity analyses permit risk managers to consider the relative merits of different strategies for reducing exposure in cases where levels of exposure are deemed unacceptably high. Also, because the probabilistic analysis provides information on the full distribution of exposures, the exposure assessor can determine how different scenarios will affect different sections of the distribution. For example, different scenarios of modelling nutrient supplementation or fortification can be applied to evaluate the impact at the lower tail of the distribution (possible inadequate nutrient intake) and the upper tail of the distribution (possible nutrient toxicity). Thus, probabilistic analysis may facilitate certain types of risk-benefit analyses. For food chemicals with acute toxicity, such as pesticide residues, probabilistic analysis may be particularly useful because point estimates of intake will often yield estimations that are unrealistically high. The point estimates offer no indication to the exposure assessor or risk manager of how likely the intakes are to occur in the population as a whole. Knowing that an intake is possible and is likely to occur in 1 in 1000 individuals may lead to a significantly different risk management strategy to knowing that it is possible but is only likely to occur in 1 in 10,000,000 individuals. Probabilistic modelling can help to focus resources for future data collection and identify strategies for remediation where necessary. This type of modelling is, however, more resource intensive than deterministic modelling.

The usefulness of both probabilistic models and deterministic models is dependent on the availability and quality of the input data. Extensive potential exists for the use of probabilistic approaches to many different types of food chemicals, but this potential can only be realised if there is sufficient knowledge of the pathways of exposure, effects on concentration at various stages of the food chain, food consumption patterns and other pertinent exposure factors, to create reliable models and provide reliable input distributions. While probabilistic modelling confers many advantages, Burmaster and Anderson (1994) point out that the old computer maxim of 'garbage in, garbage out' (GIGO) also applies to this technique and that GIGO must not become 'garbage in, gospel out'. The reliability of the results of a probabilistic analysis is dependent on the validity of the model, the software used and the quality of the model inputs. The quality of the model inputs will reflect both the quality of the data on which the input will be based and the selection of the distribution to represent the data in the model. Guidelines have been proposed for the selection of input distributions for a number of exposure variables (Finley et al., 1994; Lipton et al., 1995; Voit and Schwacke, 2000) but to date little information exists regarding the selection of input distributions for food consumption or concentrations of foodborne chemicals such as food additives or pesticide residues, or for nutrients or novel foods. The report of Driver et al. (1996) begins to tackle this issue, but much work remains to be done. An additional obstacle to the acceptance of probabilistic techniques in risk assessment, including exposure assessment, is the degree of subjectivity that may be associated with model design (Bier, 1999).

Before undertaking a probabilistic analysis, the exposure assessor should be equipped with a good knowledge and understanding of how to deal with uncertainty in quantitative exposure assessment and an awareness of the standard of practice necessary for conducting such assessments (Burmaster and Anderson, 1994). This necessitates skills in model development and selection of appropriate input distributions. Failure to recognise dependency or correlation between distributions is often the downfall of risk analysis models (Vose, 2000) and therefore information about interdependencies of variables is also required. Petersen (2000) provides a review of the theory and practice behind probabilistic modelling. Modelling software is also a requirement. There are a variety of risk analysis software products currently on the market (such as www.risk-modelling.com). These modelling programs can be used for modelling exposure to food chemicals but have a wider application, many of them being originally designed with economic risk analysis in mind. More specifically for exposure assessment, a number of software products have been designed in the US. DEEM™ was designed by Novigen Sciences for the purposes of estimating the intake of toxicants, nutrients, pesticides, food additives and natural constituents. The program has modules for estimating acute and chronic exposure and permits deterministic and stochastic assessments. It contains data from the USDA food consumption surveys and the USDA Pesticide Data Program. LifeLine™ was designed by the Hampshire Research Institute for the purpose of producing publicly available software to perform aggregate and cumulative exposure and risk assessment. The initial version focuses on residential, dietary and tap water exposure to pesticides. THERdbASE (Total Human Exposure Relational Database and Advanced Simulation Environment) was developed by The Harry Reid Centre for Environmental Studies and the EPA's Office of Research and Development. The aim of this product is to facilitate better total human exposure estimates to environmental pollutants (e.g. multiple agents, present in multiple media, entering through multiple pathways). Furthermore, development of modelling software within the EU is now under way as part of an EU-funded project entitled 'Development, validation and application of stochastic modelling of human exposure to food chemicals and nutrients'. This project is described in brief in the Research Needs section (section 4.9) of this paper.

4.4. Acute vs chronic intake

Differentiating the approaches to modelling dietary exposure on the basis of point estimates, simple distributions or probabilistic analyses considers solely whether single values or distributions have been chosen to represent the inputs in the model. Also fundamental to the process, however, is consideration of the parameters and model structure necessary to describe the exposure situation to be modelled. An exposure assessor must consider carefully the validity of existing models for answering a particular assessment question, the need for new models and/or the impact on the results of using different models. A key component of the usefulness of a model is the relevance of the exposure estimates for comparison with the toxicological endpoint. The exposure assessment may be required to reflect exposure over a prolonged period of time or to reflect peak exposures. Consequently, this will affect the relevance of different models for determining the exposure.

When considering an acute toxicological endpoint (e.g. for pesticide residues), it is not appropriate to use a risk assessment methodology that treats short-term exposures over the safety standards as insignificant (WHO, 1997). Because the acute reference dose (ARfD) should not be exceeded during the acute effect period, usually a single meal or day, the food consumption data should ideally be based on a single eating occasion or consumption over a single day (Rees and Day, 2000). Therefore, modelling acute intakes should employ databases of food consumption that are formatted to present information for each food, for each meal, for each day, for each subject in the survey. Obviously, as a prerequisite, the survey methodology must have originally been designed to record this level of detail for each eating occasion. High-level acute dietary exposure can be estimated by multiplying the upper percentiles of consumption during a meal or day by a conservative value for the concentration (i.e. the 'worst-case' point estimate approach). As noted in the previous section, this approach is of value for screening out exposures that are of little concern. However, the approach does not provide any information about the likelihood of occurrence of high concentration levels in/on a food coupled with high-level consumption of that food. Often quite large amounts of residue data exist and point estimates make no use of these data (Hamey, 2000). Therefore, for assessment of acute exposure to food chemicals that have a high degree of variability in concentration in individual food items, a probabilistic approach to dietary exposure assessment is fast becoming the method of choice.

Within the probabilistic approach for estimating acute exposure, a number of different methods can be used to integrate the food consumption and chemical concentration data. The methods may differ, for example, with regard to whether individual eating events over the course of a day are assigned individual probabilities of presence or absence of the chemical or the total daily intake is assigned a single probability. Hamey (2000) employed three different models for estimating acute exposure to pesticide residues. One of these models is described later in 'Examples of models for estimating exposure to food chemicals' (see section 4.6).

When chronic rather than acute toxicological endpoints form the basis for safety statements, then longer-term (habitual or lifetime) estimates of exposure are required. Obviously, it is not feasible to measure food consumption over prolonged periods or lifetimes of individuals. Therefore, it is important to consider the uncertainty that may be introduced into an exposure assessment by the use of short-term survey data. Many studies have demonstrated the marked effect which the duration of a food consumption survey may have on estimates of nutrient intake as a result of the high degree of within person variability that exists in food intake in both individuals and groups (Liu et al., 1978; Beaton et al., 1979; St Jeor et al., 1983; Freudenheim et al., 1987; Basiotis et al., 1987; Nelson et al., 1989; Sempos et al., 1991). These effects of short survey duration include low precision in estimates of usual intake (Beaton et al., 1979; St Jeor et al., 1983; Basiotis et al., 1987), overestimation of the prevalence of low and high intakes (Beaton et al., 1982; Sempos et al., 1991) and misclassification of nutrient intakes of individuals (Freudenheim et al., 1987; Nelson et al., 1989). The variation in nutrient intakes arises as a consequence of the high level of intra-individual variation which exists day to day in the foods consumed (Beaton et al., 1979), and therefore this issue will also have implications for the assessment of exposure to other food chemicals as well.

A number of methods have been proposed for extrapolating from short-term to long-term intake based on repeated short-term measures (NRC, 1986; Wallace et al., 1994; Nusser et al., 1996; Slob, 1996). Hoffman et al. (2002) reviewed these methods as part of the EFCOSUM project. These authors explain that by transforming data to normality it is possible to estimate percentiles of usual intake from the mean and variance of the individual's mean daily intake. Hoffman et al. (2002) considered each of the methods that have been proposed for transforming, adjusting and back transforming the data. The method of Nusser et al. (1996) was considered by Hoffman et al. (2002) to be the best approach. This approach has been incorporated into a software package, Software for Intake Distribution Estimation (SIDE), which is produced by Iowa State University Statistical Laboratory. Price et al. (1996) proposed an alternative strategy for modelling exposure which characterises long-term exposures as a series of individual exposure events (microexposure event approach). Under this approach, each event is modelled

separately and then summed to yield estimates of long-term dose rates. Price et al. (1996) considered the advantages of this approach to be (i) the ability to incorporate information on time-dependent changes in the values of exposure parameters (e.g. body weight, chemical concentrations of contaminants), (ii) the ability to investigate the effect of short-term variations in parameter values on the distribution of long-term dose rates in exposed populations, and (iii) the ability to characterise inter-individual variability in average dose rates for different averaging times. This approach has been incorporated into a modelling software package, LifeLine™ (Price et al., 1999). Because habitual and lifetime exposures cannot be measured, it is not possible to validate any of these approaches. It may, however, be useful to compare the results of the different approaches and to assess the uncertainty associated with using one method relative to another.

4.5. Other factors influencing model structure

The potential for exaggerated and implausible estimates of intake increases substantially when estimates of exposure from multiple sources for a compound (aggregate exposure) are required. An example of an aggregate exposure is the combined exposure of a pesticide via ingestion from foods and tap water and inhalation from domestic or industrial use. Assessments of aggregate exposure should consider the probability that exposures from more than one source may occur on a single day. An aggregate exposure assessment will require a model to be structured such that the intakes from the various sources are temporally, spatially and demographically specific; that is, they are calculated for the same individual at the same time, in the same place and under the same demographic conditions (Petersen, 2000). Unless such internal consistency is maintained within a model, nonsensical results may be obtained. Even when looking solely at dietary intake from foods, it is very important to consider any correlations or dependencies that may exist between the intakes of certain foods. Within an ILSI project that examined aggregate exposure assessment (ILSI, 1998), each of the participating consultant groups proposed models with the capability to show the intermittent exposures from residential applications, the variation of exposures with age, the day-to-day variations in dietary intakes, and other features. Again, taking account of time trends in both food consumption and chemical concentration is vital for ensuring that models are valid. When modelling food consumption for exposure to a chemical with a chronic effect, the sustainability of high intakes should be considered; for example, how likely is an individual to remain a high consumer (i.e. at the 95th percentile) for a sustained period of time?

Where chemicals have the same mode of action, a cumulative exposure assessment may be necessary and the model chosen must take this into account. This may involve using a toxicity equivalents approach, whereby exposure to a series of chemicals is normalised in terms of one standard chemical. Price et al. (2000) used such an approach, referred to as their relative toxicity potency (RTP) model, for demonstrating how to evaluate the cumulative risks from concurrent daily exposures to multiple pesticides operating by a common mechanism.

4.6. Examples of models for estimating exposure to food chemicals

A number of models have been proposed for estimating exposure to chemicals. As mentioned in a previous section, the choice of model may vary depending on whether acute or long-term estimates of exposure are required. The choice of model may also vary if cumulative or aggregate estimates of exposure are required. The following paragraphs provide examples of models that have been proposed/used to estimate exposure to food chemicals. These models are intended solely as examples to give readers a more practical insight into modelling. They do not reflect the full spectrum of models that may be available.

4.6.1. Example 1

Carbaryl is a carbamate insecticide used on fruits which was found to occur in composite samples taken from batches of apples, nectarines, peaches and pears in the UK. When intake of carbaryl in toddlers was modelled using point estimates, for example 97.5th percentile of apple/nectarine/peach/pear intake×maximum detected residue level, the results indicated the potential for toddlers to exceed the ARfD from unpeeled apples. The point estimate for carbaryl exposure, however, gave no indication of the probability of such intakes occurring. Therefore, three probabilistic models were constructed to provide more realistic and informative estimates of intake (Hamey, 2000). This author provided detailed descriptions of the three models used. As an example, the steps for model 1 (the 'individual fruit model') are presented below:

Step 1: The model first selected, from a continuous distribution, the amount of apple consumed.

Step 2: The consumption of other fruit, in addition to apples was selected from a discrete distribution that reflected the frequencies of the combinations in the survey.

Step 3: For each type of fruit, the presence of residues was then sampled from discrete distributions that reflected the frequencies of batches with detectable residues.

Step 4: For those iterations where residues were simulated to be present, one of the observed residue profiles was then selected.

Step 5: For each fruit type, the number of whole and part fruit that were required to make up the total amount consumed was calculated using the mean of the samples from the batch for which the residue profile had been selected.

Step 6: For each whole or part item consumed, a residue level was selected from the batch profile.

Step 7: The total intakes were summed and then divided by a body weight sampled from the survey to give an intake per unit body weight per day.

4.6.2. Example 2

In the EU, two methods have been proposed for assessing the intake of flavouring substances: (i) the TAMDI and (ii) the per capita×10 approach, also known as the maximised survey-derived intake (MSDI). Each of these methods has been described by Cadby (1996). The TAMDI assumes a daily intake of 160.4 g/day of flavorable food and 324 ml/day of flavorable drinks. It also assumes the flavorings will be present at the upper usage level specified by the Council of Europe. The per capita×10 method is based on production statistics of flavoring substances, with corrections for an assumed 60% response rate from industry to the survey and 10% consumers within the population. Differences in estimates of exposure between these two methods are dramatic for many flavoring substances. While the conservative nature of the TAMDI is generally acknowledged, doubt has been expressed about whether the per capita×10 method is sufficiently conservative. Therefore, a study was carried out which used probabilistic modelling, based on data from the flavor industry, to investigate the probability of occurrence of intakes of intentionally added flavoring substances in excess of the TAMDI and the per capita×10 estimates (Lambe et al., 2001). The model took into account the following factors:

1. Foods are consumed at different levels by different individuals.
2. Not all brand foods within a food group will contain a flavouring.
3. Not all flavourings sold for use in a food group will contain each flavouring substance.
4. Flavouring substances may be present at a wide range of concentrations in the flavourings in which they are present.

In terms of the concentrations of flavouring substances in food groups, the range was so large that the data had first to be log transformed to give meaningful intervals to describe the distribution in terms of a histogram. The model was analysed using one simulation of 10,000 iterations in the software package @Risk.

In @Risk, the final model had the following structure:

Cell	Variable	Input distribution/Function
A1	Intake of Food A	@RiskHistogram {min,max} $\{p_{int1}, p_{int2}, p_{intn}\}$
A2	% of brands of Food A containing a flavor	@Risk Discrete {1,0} $\{p_{present fb}, p_{absent fb}\}$
A3	Chance of encountering flavoring substance in Food A	@Risk Discrete {1,0} $\{p_{present fsf}, p_{absent fsf}\}$
A4	Presence of flavoring substance in Food A	Excel logical function If A2 = 1, A3, 0
A5	Natural log of concentration of flavoring substance within Food A	@RiskHistogram {min,max} $\{p_{int1}, p_{int2}, p_{int18}\}$
A6	Exponential of concentration	Excel function Exponential of A5
A7	Actual concentration of flavoring substance in Food A	Excel logical function If A4 = 1, A6, 0
A8	Intake of flavoring substance from Food A Steps in cells A1 to A8 repeated for Foods B, C, D, etc.	A1×A7
A100	Total intake of flavoring substance (μg/kg body weight/day)	(A8 + A16 + A24 + A32...)/60

Where:

p_{intn} = probability of a value falling within interval *n*
$p_{present fb}$ = probability of a flavour (*f*) being present in a brand food (*b*)
$p_{absent fb}$ = probability of a flavour (*f*) being absent in a brand food (*b*)
$p_{present fsf}$ = probability of a flavouring substance (*fs*) being present in a flavour (*f*)
$p_{absent fsf}$ = probability of a flavouring substance (*fs*) being absent in a flavour (*f*)

4.6.3. Example 3

In 1992, the EPA described the potential ADD_{pot} of a chemical as

$$ADD_{pot} = [C \times IR \times ED]/[BW \times AT]$$

where C = concentration of the chemical, IR = intake rate, ED = exposure duration, BW = body weight and AT = averaging time; EPA, 1992). For lifetime average daily dose (LADD), the averaging time (AT) is replaced

by lifetime (LT). Price et al. (1996), however, considered ADD_{pot} to have two significant limitations as a model of variation in long-term dose rates in exposed populations. They argue that information on the inter-individual variability for many of the equation's parameters is difficult to obtain from existing data and the equation cannot easily address time-dependent changes in the parameters. The authors propose an alternative strategy for modelling exposure, which characterises long-term exposures as a series of individual exposure events (microexposure event approach). Under this approach, each event is modelled separately and then summed to yield estimates of long-term dose rates. Under the microexposure event model, the equation for ADD_{pot} is replaced with

$$\text{Dose rate} = \frac{1}{\text{Averaging time}} \sum_{j=1}^{\text{Duration}} \frac{1}{\text{Body weight}_j} \sum_{i=1}^{\text{Events}_j} \text{Environmental Concentration}_{ij} * \text{Intake}_{ij}$$

where Environmental $\text{Concentration}_{ij}$ is the concentration of the contaminant in the environmental media to which the individual is exposed during the ith exposure event in the jth year of his or her life; Intake_{ij} is the amount of the contaminated media entering the individual during the ith exposure event in the jth year or his or her life; Events_j is the number of exposure events that occur during the jth year of the individual's life; Body weight$j$ is the average weight of the individual during the jth year of the individual's life; Duration is the number of years between the first and last exposure events; Averaging Time is defined by the toxicity endpoint being evaluated. The model is designed to consider intake of chemicals by inhalation and dermal routes as well ingestion. It is described in full by Price et al. (1996).

4.7. Data availability for modelling food chemical exposure

Modelling of dietary exposure to any food component is dependent on the availability of data to represent the parameters in the model. According to Kaplan and Burmaster (1999), the main sources of uncertainty in risk analysis are the lack of complete data and how the available data are interpreted for use in the analysis. When modelling food chemical intake, the availability and appropriateness of the data must be examined and explicitly documented in terms of its relevance for the assessment objective or endpoint. The endpoint for variables such as food consumption and chemical concentration should be considered in terms of temporal relevance, spatial relevance, relevance in terms of food groups and relevance in terms of population groups. For example, can existing food consumption data be utilised directly or modelled in such a way as to reflect chronic intake, acute intake or intake over a specified period of time (i.e. infancy, childhood, adulthood, etc.)? Do data exist to reflect chemical concentrations relevant to the time period for which the exposure assessment is necessary (e.g. contaminants may decline over time, use of certain pesticides or food additives may cease)? Can food consumption data be expressed in terms of the foods for which residue data are available, such as primary agricultural products?

It is important to bear in mind that modelling should not be used to extend data beyond their limits. As part of an ILSI project exploring aggregate exposure assessment, the participants reached a general consensus that, when a database is marginal, it is preferable to collect more data rather than relying on estimates, surrogates or defaults (ILSI, 1998).

4.8. A pragmatic approach for modelling intake of food chemicals

It is accepted that for intake assessments a stepwise approach in regard to accuracy of the results should be used (WHO, 1997). In many cases a very rough estimate of intake will allow the determination as to whether any further work using more sophisticated models to provide results with higher certainty might be needed. If this initial screening indicates either that there is no practical likelihood that the intake exceeds the relevant safe levels, such as the ADI, or if the intake is clearly below an agreed threshold of toxicological concern (Kroes et al., 2000) it may be decided that no further refinement of the assessment is needed. This is especially the case when — as very frequently is the case — the initial assumptions both for food consumption and for the presence of the substance in question are judged to lead to a considerable over-estimation of intakes, and other sources of exposure are unlikely.

In any case, the method(s) used should be selected based on their "fitness-for-purpose"; that is, the suitability for the specific evaluation needed and the data available. This applies initially to the selection of the best suitable analytical approach to determine the concentration of a given chemical in a food or in the complete diet (see section 2) and to the choice of methods to assess food consumption (see section 3). If inexpensive screening methods demonstrate either a minimal presence of the substance(s) under consideration in foods and/or a very low consumption of those foods relevant for the assessment, no further information may be needed. Only if either analyses or consumption surveys suggest a potentially relevant exposure, does the question of the appropriate integration method arise.

The considerations leading to suitable (sequences of) evaluations are summarised in Fig. 4.

4.8.1. Screening tools

For the initial screening phase used for primary assessments and priority setting for further evaluations, very crude indicators of high consumption were developed for specific categories of chemicals for which an intake assessment was required. Those models were constructed using extremely high and thus usually unrealistic, and over-estimating assumptions about food consumption combined with maximum assumption for the levels of the chemical in question in specific food categories or the diet in general. As indicated, the resulting exposure estimate is usually compared with the ADI prior to the authorisation of the chemical for foods or a given food category or to similar "safe" levels in the case of other substances which are not regulated. With resulting exposures that are extremely low, a comparison with the "**Threshold of Toxicological Concern**" (TTC) mentioned above may be appropriate; that is, an amount which after ingestion would not lead to toxic effects for the overwhelming majority of chemicals.

In the field of food additives, the so-called "**Budget Method**" initially developed in Denmark (Hansen, 1979; Ireland and Moller, 2000) assumes the maximum physiologically possible intake of foods with the starting points being 100 ml per kg body weight for liquids and 100 kcal/kg body weight for energy. Based on an energy density of 2 kcal per gram of food, daily consumption corresponds with 50 g per kg body weight per day. Alternatively, in a food group consumption model high consumption of individual food groups is assumed for chemicals contained therein. In the case of veterinary drugs the daily consumption of a large amount of food from animal origin is assumed (JECFA, 1989). For food-packaging materials, the EU Scientific Committee for Foods considers the migration of a chemical from the package to 1 litre of olive oil as the parameter for initial estimates (EEC, 1990).

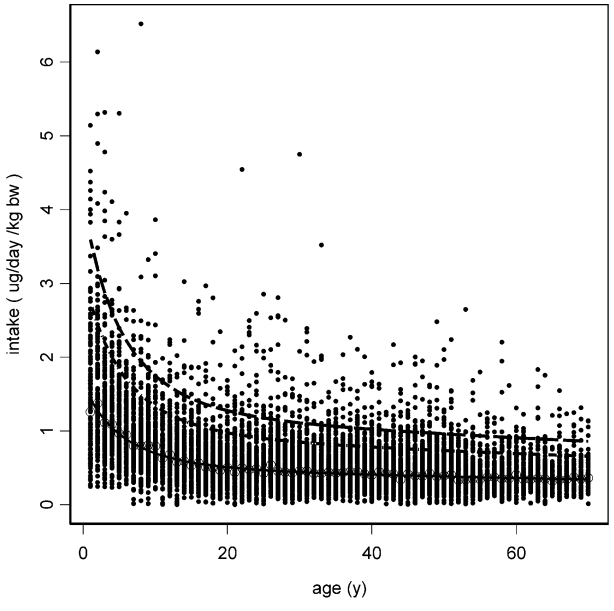

Fig. 4. Daily intake of DON as a function of age. Each dot denotes one daily intake of a single individual (6247 individuals, two daily intakes each). The open circles denote the age class geometric means, the lower curve the fitted regression function. The dashed curves represent the 95th and 99th percentiles, indicating the long-term variation between individuals.

All these methods are used as a first screening for authorised chemicals at an international level. The result of such a screening is generally valid for the general population including most subgroups of age and sex, but its relevance for specific subgroups of consumers such as infants, children or diabetics may need to be confirmed on a case-by-case basis.

Another simple way of screening is the so-called "**per capita approach**". This concept considers the total amount of the chemical under evaluation available on the market (production plus imports minus exports) and divides it equally across the whole population, or a subpopulation if it can be clearly identified. Additional assumptions can be made about the percentage of consumers of the food containing the substance. For example, in the field of flavouring substances, 10% of the population is considered to be consumers. This method is considered useful to observe trends over time but is also recognised to not represent adequately the exposure to chemicals that are not broadly distributed over various food categories, for instance a substance contained in a very specific exotic food consumed by a very low percentage of the population, such as 3-MCPD in soy sauce and similar products. The method can provide a reasonable estimate for amounts available only if the market for the relevant raw material is reasonably well assessed; it can normally not account for imports/exports of foods containing this substance, which may on rare occasions also affect the net availability.

More refined methodologies use data on the availability of foods. These data are normally collected for economical purposes at national or supranational level by government institutions but can be provided to some extent also by relevant industry associations.

Two types of data are most commonly used. One is the FAO food balance sheet (http://www.apps.fao.org/lim500/wrap.pl), which represents the availability of food commodities at the national level. These kinds of data are generally recognised to over-estimate the mean intake by more than 15% but can be used at an international level to allow comparison between countries

The second type of data are represented by household purchase data, which can be divided by the number of people in the household to represent a mean individual consumption by this group or the population at large. It must be recognised, though, that this kind of survey can largely under-estimate the consumption for certain members of the household.

The use of mathematical modelling can potentially improve the usefulness of data from economical surveys by simulating the distribution of individual consumption within a country or within a household. Such modelling exercises related to (groups of) products/brands can be more accurately positioned for individual household members based on specific information on the distribution of consumption within households. Conversion factors to transform data to individual household members have been developed by WHO (1991), and are occasionally generated by food manufacturers for their consumer understanding. However, such refined data will usually not be used at the screening stage.

4.8.2. Exposure assessments based on specific data

A second series of evaluation models uses actual data on food consumption and on the levels of the chemical present, either based on analytical results, on known amounts added, or on the legal authorization, such as for food additives in specified product categories; that is, assumed use in the whole food supply. Depending on the quality and amount of data, and the precision of results needed, methods fit for the specific purpose will be selected.

The "**point estimate**" approach combines a single data point (estimate) of actual food consumption with a single estimate for residue/chemical concentration for the relevant foods considered. Within the point estimate approach, there are a number of choices regarding both the consumption and the chemical level values, that is, median or high level. The choice of values will be influenced by factors such as the number of foods in the assessment, and the availability of residue and consumption data. If high-level values are used to represent consumption and residues for multiple foods, then the point estimate approach will over-estimate exposure; it can potentially lead to a very high over-estimation. A refinement to the point estimate concept can be made, for example, by inclusion of processing factors or migration rates from packages. Usually, such point estimates provide a more realistic estimate of the level of possible exposure than the screening methods mentioned above. However, this method does not provide an indication of the likelihood of the exposure occurring.

In the context of exposure assessments, '**simple distributions**' is a term used to describe a method that employs distributions of food intake but uses a fixed value for the residue/concentration variables. This usually involves using computerised databases of food consumption surveys. The results are more informative than those of the point estimates because they take account of the variability that exists in food consumption patterns. None the less, they usually retain several conservative assumptions (e.g. all soft drinks that an individual consumes contain a particular sweetener at the maximum permitted level, 100% of a crop has been treated with a particular pesticide, etc.) and therefore usually can only be considered to give an upper bound estimate of exposure.

Probabilistic analysis involves describing variables in terms of distributions to characterise their variabilities and/or uncertainties. It then takes account of all the possible values that each variable could take and weights each possible outcome by the probability of its occurrence. With good data and valid models, this type of modelling should help to provide more realistic estimates of exposure.

Although at present there is a lack of validated probabilistic models for food chemical exposure, the Monte Carlo project (www.iefs.org/montecarlo) is currently evaluating the fitness for purpose of probabilistic models for food additives, pesticide residues and micronutrients in comparison with consumption at brand level, duplicate diets and biomarkers, respectively. While probabilistic modelling may help to provide more meaningful estimates of exposure, the method is still data-dependent and should not be seen as a means to compensate for poor quality or inappropriate data. A distinct advantage of this approach is its capacity to provide sensitivity analysis which allows the assessor to analyse the sensitivities of the calculated exposure with respect to uncertainties in parameters and to consider the relative merits of different strategies for reducing exposure in cases where levels of exposure are deemed to be unacceptably high.

4.8.3. Confirmatory methods

This includes studies which are either direct measurements of exposure or can be used to confirm the relevance or applicability of results derived from the abovementioned studies. This includes the measurement of **biomarkers of exposure**, where they exist and are validated. It needs to be recognised, though, that this approach will take account of exposure from all sources, including non-food sources. One should thus be careful to understand to what extent such other sources exist and are likely to be relevant, especially if one attempts to compare the results of such measurements to exposure estimates developed with any of the above models for food sources only.

Another tool that can be utilised are **duplicate diet studies**. It needs to be recognised, though, that in practice these studies are usually limited in the number of participants and samples evaluated, Thus, their results are more useful for looking at mean exposure than at high-end exposure since conclusions from a few extreme intake situations are not likely to be statistically supportable.

All these models have their place in intake assessments. They have to be chosen based on their expected fitness-for-purpose, namely the availability of data and the accuracy of results expected. They will usually be

applied in a tiered approach, whereby if a simple method provides a potentially problematic result a more sophisticated method can be used to provide added perspective and/or accuracy.

4.9. Research needs

Two of the reasons that have been cited for the limited use of probabilistic techniques in exposure assessment are the lack of consensus on the proper distributions to use for key exposure variables (Finley et al., 1994) and the resource implications in terms of computing power for analysing complex models (Burmaster and Anderson, 1994). The improvement in processing power of computers in recent years has significantly reduced the time required to run simulations. None the less, complex models requiring numerous simulations and iterations can still take days to run if using a stand-alone PC and modelling software written in an interpretive language. Hamey (2000) encountered memory resource problems when using increasingly complex models of exposure to pesticide residues from fruit.

A further problem is the lack of validation of models used. Models should obviously represent as closely as possible the reality that is being modelled. Ideally, all models should be validated, although it is acknowledged that this process can be difficult and costly (Kaplan and Burmaster, 1999). The conclusions of the ILSI Expert Group on Aggregate Exposure Assessment (ILSI, 1998) suggest that a number of steps are needed for model validation:

- Validation of the software program to ensure that it is computing as intended, that there are no hidden errors that inadvertently bias the output. It was suggested that the best way to accomplish this is to make the full program (including source code) publicly available for peer review. For example, both DEEM™ and LifeLine™ have been presented to the FIFRA Scientific Advisory Panel.
- Making the model accessible and encouraging other practitioners to use it and provide feedback. This should provide a type of peer review that may lead to further improvement and development of the model, as well as acceptance of the model within the risk assessment community.
- Comparing the results of different modelling approaches using the same data sets. If different approaches lead to similar conclusions, confidence is increased in both the models and the results. It must be borne in mind, however, that different modelling approaches may lead to similar but inaccurate results and therefore such comparisons can only form one component of the validation process.
- Comparison of model outputs with actual exposure measurements. This constitutes a central feature of any validation process. In addition to comparison of the overall model output with exposure measurement, it may be possible to validate certain subparts of the model.

To begin to tackle some of these issues as they relate to assessing exposure to food chemicals, the EU Commission has funded a 3-year shared-cost project under the Fifth Framework Programme. The project, entitled 'Development, validation and application of stochastic modelling of human exposure to food chemicals and nutrients', includes work-packages to develop modelling software using high-performance parallel computing, to assess the best means of inputting food consumption and chemical concentration data in models and to validate the developed models against true intakes of food additives, pesticide residues and nutrients (http://www.iefs.org/montecarlo). The new software will be validated against existing probabilistic modelling software (i.e. @Risk). The results of modelling the intake of a variety of food chemicals using a variety of approaches will be compared. Exposure measurements of pesticide residues, nutrients and food additives will be made using duplicate diets, biomarkers and brand level consumption and concentration databases, respectively. In the final phase of the project, modelled intakes will be validated in the context of the measured exposures.

From a risk assessment perspective, one of the most important considerations is that a model should not underestimate exposure. Many of the deterministic models do not accurately estimate exposure but can be useful for ruling out the need for further assessment. Therefore, validation studies should consider not only the predictive accuracy of the model but its overall usefulness as a tool for assessing exposure. One approach that has been proposed for dealing with unvalidated models is to address all plausible models and determine the implications of each for the decision. Advances in computer technology that increase the speed of simulations and reduce the time to run multiple models should help in this regard.

Advances in modelling dietary exposure should also keep in mind the need for assessments of aggregate exposure (multi-route, multi-pathway) and cumulative exposure (both in terms of multiple chemicals with the same mode of action and accumulation in the body over time). One of the expert panels contributing to the ILSI report on aggregate exposure set out the following expectations for any approach to aggregate risk assessment (ILSI, 1998):

- the approach should be responsive to the toxicology in terms of preserving exposure contributions from different routes for any toxicologically relevant time period;

- it should use all the information available to describe the conditions and activities of the potentially exposed;
- it should have the capacity to accomplish the assessment of exposure from multiple chemicals (cumulative exposure) so that an approach for aggregation does not have to be abandoned or contorted to accommodate cumulative exposure;
- it should be flexible enough to accept new algorithms and data in the future. This process will be evolutionary in nature. No one perfect exposure system can be developed at a given moment in time;
- it should provide universality so that the approaches are applicable to risk assessments for many different types of applications.

Research in the area of modelling dietary exposure should keep these principles in mind.

An additional area of research related to modelling of dietary exposure is the linking of exposure models with toxicokinetic models to estimate internal dose. Some work has been done in this area (e.g. Slob and Krajnc, 1994), but strong links between toxicologists and exposure assessors is desirable for future work to advance this aspect of exposure modelling further.

Given that the use of probabilistic modelling is likely to be extended right across the spectrum of food-related health issues, our capacity to develop appropriate models will be constantly challenged. Modelling exposure to allergens and the probability of adverse effects arising as a consequence of these exposures may be among such challenges. It will therefore be necessary to consider how to include variables such as individual susceptibility into probabilistic models.

5. Discussion

As depicted above, exposure assessment in food is focused on three main areas: levels and fate of the chemical in food; food consumption; and integration of these elements to determine exposure by deterministic or probabilistic methods.

The description of these three main areas has shown that a wide range of methods and concepts for integration is available. Most of them have been used with good success at least for some applications. The remaining weaknesses have been indicated in the individual sections. Unless one is aware of these weaknesses there is a risk of combining data derived from less than perfect evaluation methods, which can potentiate errors and/or built-in conservatisms.

However, the awareness of such limitations can help to refine the results or should at least be considered in their interpretation. In all three main areas mentioned above, important improvements can be made, either within the existing methods, or in applying more suitable methods. In general, the more refined methods will be more time consuming and consequently be more expensive.

Depending on the situation, less precise but rapid methods may be more appropriate. The fact that a highly sensitive but expensive analytical method exists, does not mandate its application if a less sensitive method is capable of providing results appropriate for the assessment. Lower levels of the substance analysed may not contribute significantly to the total exposure or may not be toxicologically relevant, using for example the concept of a threshold for toxicological concern (Kroes et al., 2000). However, more sophisticated techniques may well be helpful in aiding preventive risk management such as in the context of the precautionary principle or the application of a threshold for toxicological concern.

When determining the amounts of a given chemical in foods we are confronted with three main areas of uncertainty:

1. Sampling — how can one ensure that the samples taken for analysis are representative for the supply to be covered? One issue is the inhomogeneity of a contaminant across a given food, another issue is the question of appropriate sampling patterns even if homogeneity is assumed. Given that analytical procedures are often expensive and/or time-consuming, one has to find an approach that minimises the need for frequent analyses by optimal sampling. Sampling becomes increasingly reliable as a food is processed and thus homogenised. However, not all foods are processed and one may also need to develop meaningful sampling methods for primary products and intermediates to minimise overall levels of contamination by excluding highly contaminated batches unless it can be convincingly argued that inherently homogenisation resulting from processing does eliminate inherently any risk of excessive levels of a given food chemical.
2. Analytical sensitivity — the methods used should be selected as "fit for purpose" should be assured. One needs to balance on a case-by-case basis the problem of false negatives from insufficiently sensitive methods not detecting potentially problematic amounts, vs the possibility of finding positives with extremely sensitive methods which provide biologically irrelevant results.
3. Fate of a chemical in the processing chain — how reliably can one extrapolate from data generated on agricultural crops to data for the finished products? What is the fate of the chemical when foods are industrially produced; prepared professionally in catering establishment, or prepared at home?

In some cases, especially when substances (i.e. additives or micronutrients) are intentionally added to a processed food, the manufacturer can reasonably predict the amounts to be expected in the marketed product. Based on post-launch observations, this information can be refined to establish the variability between batches and over the shelf-life of the product under real-life conditions. For other food chemicals such as contaminants, for example, such information needs to be obtained by appropriate analytical programmes investigating the different processed food items.

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.

For this purpose, a large number of food classification systems have been developed by different groups and for different applications (Ireland and Moller, 2000). 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. The fact that an IUNS/FAO Task Force has been formed to review and focus the work on food classification and description to their international use (Ireland and Moller, 2000) is encouraging for the future. It does however emphasize that comparisons of existing data should be carefully considered.

Regarding most nutrients and some non-nutrients, one is relying largely on food composition tables. This is also true for some other factors, like lipophilic contaminants, which may be derived from the fat content of a food. It has, however, been shown (Deharveng et al., 1999) that it is difficult to compare data between food composition tables developed by different countries due to differences in food use or in the way the nutrient value is defined or determined. Even between tables from the same country differences might be found because they are either developed at different times or for different purposes.

Similar questions on the suitability of approaches available apply to intake and consumption surveys. As the actual responsibility to minimise any risk is with the manufacturer of a given product, intake assessments for this brand only is based on actual knowledge of the specific consumer groups, and will provide an indication whether intended or expected levels of a chemical in this particular brand are likely to cause or contribute to excessive intakes. Thus, here again, uncertainties can arise: focusing on one brand will in many instances where a substance is not uniquely or predominantly restricted to one brand, not yield a reliable figure since characteristics such as distribution in the food supply, consumer preference, target population and the like should also be considered. This requires more comprehensive intake assessments to determine whether a risk might become evident when considering intakes from all sources.

It has been shown, particularly in the case of food consumption surveys, that the information collected for one purpose — assessment of food category intakes — is used for a range of other applications, for example intake assessments for chemical contaminants or minor food components becoming of interest after the data are collected. In such cases the weaknesses identified in the review of the available methods should be judged on a case-by-case basis to permit a reliable assessment.

It is important to anticipate the potential uses of data when they are being generated. This includes the planning for statistical evaluation in advance, including possibly beyond the initial purpose of a study. The right perspective is particularly important when looking at high quantiles of a population for which the statistical basis may not have been planned initially. It is thus desirable to develop an intensified exchange between those familiar with data in the field of exposure assessment early in the preparation of the individual data sets. This is especially the case when, for example, probabilistic models can optimise the use of extensive data sets, provided they are of appropriate quality.

Assessments will usually be directed to the total population in that they should cover all individuals. In specific cases, however, they may be defined as subsets of the population, for example as percentiles or by their susceptibilities.

When attempting to integrate assessments based on consumption and on the levels of a chemical in foods, one will usually start with crude screening tools and subsequently try to refine the assessment as required. When a crude screening tool such as a worst-case approach like the budget method results in an intake above an accepted level, more refined deterministic methods such as point estimates and simple distributions may provide more accurate estimates but may still overestimate the actual intake. In contrast, probabilistic approaches are typically more resource-intensive than deterministic approaches but they permit the characterisation of the variability and uncertainty that may exist in such exposure estimates and thus facilitate more meaningful and realistic assessments. Thus the application of tools, rules and instruments to screen and assess exposure levels should apply on a case-by-case basis a tiered approach to reduce efforts and costs. One needs to remain critical of the assumptions made, for example in which foods a substance is likely to be found and how much is likely to be consumed over time. It has been postulated that for at least a number of substances expected in foods at low levels a threshold of toxicological concern can be established: substances ingested at lower amounts than that threshold will not cause any appreciable risk for the consumer (Kroes et al., 2000). Conservative intake estimates suggesting such very low intakes may thus also help to prioritise the need for other — often more expensive — steps in the risk

assessment process. It should also be noted, however, that in certain cases regulatory limits are set for low-level residues, which are not primarily based on the ADI concept, but take into account considerations like good agricultural practice.

In the case of a food additive approved for use across a range of food categories (as foreseen for example in the General Standard on Food Additives by Codex Alimentarius) an initial assumption may indeed be that it is used across all these foods at the highest level permitted and that these foods are consumed in large amounts. If, under those conditions, there is no indication that safe levels would be exceeded, no further exposure assessments may be needed. However, if such extreme assumptions lead to figures surpassing safe levels, the apparent over-estimation may be refined by relating it to the amounts available on the market, which may be much lower, and the availability of alternative substances with the same technical properties. In addition, one should include the basic understanding of the substance's technological properties – it is unlikely that for example, a food acid would be used in non-acidic foods, at least not in large amounts, or that significant amounts of yellow β-carotene would be added to a food which the consumer expects to be green or white. Finally, processing of a food may also lead to the reduction or disappearance of a substance. These issues, though, may well differ from country to country. It is evident that in the end specific data need to be obtained to provide the basis for solid assessments.

Another point of consideration may be the consumption pattern for a given chemical. Is it likely to be consumed incidentally at substantial levels (which in that case may be better related to acute toxicity data) or is it consumed chronically thereby related to (sub)chronic toxicity data? In this latter case, it should be recognised that children, for example, have a higher intake of a given food per kg body weight as compared to their adult life: the total intake over a lifetime may therefore be the decisive parameter. Finally, although difficult to include in assessments, it should be recognized that a food preferred by children (or dedicated to children like infant formula) may not to be consumed by the same individuals when they are adults, since individuals tend to change their preferred diets several times in a lifetime.

As a rule, food manufacturers know their consumers quite well and include their knowledge of actual consumption patterns in their pre-market evaluation as a possible source of information on consumer behaviour. It has to be recognised, though, that such proprietary information is usually not shared with outside parties.

A question in the context of risk assessment for chemicals in foods relates to possible interactions between individual components. This may relate to additive or — less frequently — antagonistic or synergistic effects. Such effects can only be expected when it concerns chemicals acting via similar mechanisms of action, and even if that is the case they are only occurring at levels surpassing the no-observed-effect level (NOEL). Such interactions are rare in the case of food additives (Groten et al., 2000) and pesticides (Ito et al., 1996) which are usually present at low levels. For micronutrients and non-nutrients (''phytochemicals'') as well as some natural toxins which may be present at biologically active levels, such interactions may be more likely and affect especially their bioavailability. For example, the bioavailability of iron is affected by the presence of vitamin C or calcium (Deehr et al., 2000). Similarly, the utilisation of fat-soluble vitamins is determined by the presence of fat containing such substances in the diet. Any risks related to such interactions depend again on the co-ingestion of biologically significant amounts within relevant time periods. This requires a good understanding of their presence in the relevant foods and the actual consumption of these foods.

Food allergens, that is, substances triggering true immunological responses rather than other forms of ''intolerance'', are possibly a specific case in intake assessments for two reasons:

1. Today no reliable data seem to be available regarding the type of exposure (amounts and duration) required to induce a food allergy and regarding the potential of ''cross-induction''. It has been suggested that at least in some cases Type 1 allergies to non-food components (latex, pollen, etc.) are the basis for allergic reactions to food components. It is therefore desirable to understand better the exposure conditions for the relevant agents leading to the development of food allergies.
2. Once a food allergy is established, it is argued that in extreme cases the proverbial ''one molecule'' could trigger a response, even an anaphylactic shock with potentially fatal consequences. This means that any source of exposure, far below any reasonable threshold for analytical detectability, might be of concern. Even if one assumes that practical thresholds do exist, they seem to be in some cases at extremely low levels. Thus, traceability rather than analysis of raw materials and processes may be the critical tool to anticipate and exclude possible sources for such potent allergens. This includes the application of GMP and HACCP concepts to determine where a risk for trace contamination may exist and may need to be controlled.

The development of specific models regarding the chance of exposure to such allergens, the possibilities of cross contamination and further research whether thresholds do exist for allergens, will shed more light on these questions in the future.

In many cases, the exposure assessments discussed here are conducted before a product is introduced to the market or before all relevant data are available. It is thus necessary to anticipate revision steps, which allow the inclusion of any new information. As indicated before, pre- and especially post-launch surveillance are important tools to evaluate under real-life conditions both the actual chemical qualities of the food and the consumption patterns: the chemical qualities of products that consumers are actually exposed to may be different from what has been assumed for a modelling exercise. Similarly, actual consumption may well be different from initial assumption. In the initial assessments one tries to take a conservative approach. Actual experience may help to reduce the uncertainties and thus may influence uncertainty factors or required margins of safety.

One may also find that assumptions have not been sufficiently conservative. In these cases, post- launch monitoring data can be helpful in confirming the validity of initial assessments both regarding the chemical qualities and the amounts consumed by target groups.

Based on the data discussed, it is obvious that intake assessment methods as currently applied differ in accuracy and may either under- or over-estimate consumption depending on the assumptions made and possible under-reporting. There is a need, however, for more refined estimations in those cases where the current methods do provide insufficient accuracy and/or sensitivity or lead to excessively conservative assessments. Future needs and challenges on chemical levels and fate, food consumption, and their integration are presented in section 6.1, also suggesting priorities for the work needed.

6. Conclusions

As indicated, the screening methods currently used most commonly for intake assessments are useful to develop a general indication of potential high exposures and thus for prioritisation, but are imprecise in more specific situations. Based on the data presented in the three main sections, the following identifies areas where either improved methods or conscious selection of the available methods may help to improve and refine the exposure evaluations and suggests activities that can help to improve this part of the risk assessment process in future. Especially when specific assessments rather than general estimates of intake are needed, is it important to recognise that due to the multifactorial nature of the assessments, errors in the individual assumptions or results tend to potentiate each other. A general suggestion regarding method validation is to utilize as far as possible work on highly sophisticated models and to validate in the same context also less complex (''cheap and easy'') methods to understand their potential and limitations.

6.1. Priority research needs for food composition

Priorities are set because of the recognition that data for different chemicals and nutrients have been collected in the different countries. The data are, however, in many cases not easily available for risk assessment, especially at the international level. And even when available, they are often not directly comparable.

1. *Pan-European food composition database:* it is desirable to develop a standardised pan-European database for chemicals in foods including not only nutrients but also low molecular weight chemicals such as additives, contaminants/residues, and relevant non-nutrient plant components. Such a database should include information on sampling and analytical methods used. The database should preferably contain individual data points or at least information on ranges of levels found (mean/standard deviation) and the number of analyses from which this mean is derived. Key is the harmonization of methods, whereas integration of results across Europe should be approached with care considering the significant differences in actual food composition.

2. *Processing*: understanding the processes applied between farm and fork; that is, throughout the production chain down to the consumer's kitchen, and their effect on the levels and qualities of food chemicals including substances originally present, added or formed during processing. Such a project should also provide a background on how this information has been obtained to position its usability in the process of exposure assessment.

In the context of a harmonised database, information should also be collected (and included as feasible) on natural variability of foods, for instance due to differences between cultivars, effects of ripeness, geographical origin, including geological factors affecting, for example, heavy metal content, harvest and storage conditions, The latter aspects will also be relevant for the information on process effects. To be able to evaluate changes over time, the selection of appropriate analytical methods should be regularly re-evaluated for their technical appropriateness as well as for changes in production methods in agriculture and food industry, in consumer preference, and for example, regulatory and economical factors, and it should be determined how to maintain information on historical compositional data. Some work in this context is currently under way in the context of the EU EPIC programme. The optimisation of analytical methods and of sampling procedures is not normally under the control of experts involved in exposure/risk assessment, but needs to be consciously monitored to ensure applicability of data over time.

6.2. Priority research needs for food consumption

Data on the per capita mean consumption of food are available for most countries either through food balance sheets or household survey methods. At the international level, per capita mean consumption of food is provided by the GEMS/Food Regional Diets, which are used by JECFA and JMPR as the basis for exposure assessments (WHO, 1998).

In some countries, food consumption data based on data collected for individuals are available, and even when such information has been obtained, it does not always include information on sex, age, body weight or other relevant factors, such as smoking.

Such individual food consumption surveys should be carried out in a way that serves as many data users as possible with the resources available. For example, food codes should allow food consumption to be expressed in terms of processed food categories for food additive exposure assessment and in terms of raw agricultural commodities for assessment of pesticides and environmental contaminants. The data collected should be maintained as individual records to facilitate future use in probabilistic models. Optimisation of methodology should include:

1. *Harmonisation of food consumption survey methods*: this includes the need to precisely determine exposure to priority compounds, including the determination of reasonable extremes and to understand the degree of possible under-reporting and options for correction. It should ideally involve considerations to include foods on a brand name basis, for instance via the use of barcodes, and attempt to account for the consumption of ready-to-eat dishes and away-from-home consumption, which make up an increasing part of European diets.
2. *Evaluation of occasional peak consumption vs mean long-term consumption*: this will also help to consider possible effects of acutely toxic substances in food.
3. *Population variability*: More information is needed on the variability of populations to allow better focus on the susceptibilities of individuals and specific subgroups. This applies also to genetic variability. Research in molecular genetics and nutrient–gene/gene–nutrient interactions will provide this insight and will also lead to the development of biomarkers of exposure and effects.
4. *New food types*: the development of novel and functional foods creates a need to assess exposure for possible health effects.
5. *Pan-European food consumption survey*: it is desirable to organise a broad survey using such harmonised methods and parameters to ensure the availability of sufficient and comparable data also for risk assessments.

When preparing such new research, it should also be considered how pre-market simulations, and post-launch data collection can be optimally used, considering the cost and resource implications, and how information available from manufacturers can be optimally integrated in intake assessments. In general, food consumption surveys need to be linkable to the proposed food composition database for optimal evaluation, regarding the inclusion of minor food constituents beyond the macro- and micronutrients most commonly evaluated, and a common categorisation of foodstuffs. The results of such surveys should be validated for example, by duplicate diet studies using unified and standardised protocols.

6.3. Integrating food consumption and chemical concentration for the purpose of modelling exposure to food chemicals

As indicated in section 4.8, the quality of the intake assessments not only depends on the quality of the data collected, but especially also on the integration tools used for initial screening, more precise estimations, or accurate calculations. Using such considerations will help to optimise the use of a tiered approach and selection of "fit-for-purpose" methods and thus the optimal use of resources. In this context it is important to recognise that methods to assess peak intake and methods to assess chronic intake are likely to be different and will produce different results for subsequent use in risk characterisation. For food chemicals that have a high variability in concentration in individual food items, assessment of acute exposure can be most accurately done by probabilistic approaches. Overall, probabilistic methods are seen as the potentially most accurate (where a high degree of accuracy is indeed needed). However, these methods for estimation of exposure require further refinement including a quantitative measure of uncertainty.

Specific needs for improvement of existing approaches are required in the following areas:

1. Evaluation of probabilistic models, including validation of the software program, comparing results of different modelling approaches using the same data sets and comparison of model outputs with actual exposure measurements, based on but probably going beyond the EU Monte Carlo project.
2. Development of aggregate (multi-route/multi-pathway) exposure and cumulative exposure (exposure to multiple chemicals with the same mode of action/accumulation of one chemical over time) assessment methodology.
3. Development of models for exposure to allergens and methods to predict the probability of adverse effects arising from such exposures (e.g. including variables such as individual susceptibility in probabilistic modelling).
4. Development of more validated screening tools at low cost with more realistic assumptions.

For optimal use in the context of the risk characterisation process, appropriate methods are needed to link exposure models that evaluate the amount of a chemical entering the digestive tract with toxicokinetic models to estimate internal exposure.

6.4. Intake assessments as part of risk assessments

All these proposed areas of improvement must be seen in the context of a tiered system supporting the risk assessment process. Resources should be used most efficiently within each step of the risk assessment process, and similarly, it should be decided where in this process of hazard identification, hazard characterisation and intake assessment added effort will have the highest impact. Thus, if a crude evaluation tool confirms that no significant intake is to be expected, or — after relating the estimate to results of hazard identification and characterisation — the expected exposure is not likely to be problematic considering the toxic properties of the substance in question, more sophisticated and thus usually more time-consuming and expensive methods are not usually required. However, if these screening tools indicate an undesirable level of exposure but additional facts or common sense suggests that in reality the exposure will be acceptably low, it is necessary and justified to apply the more sophisticated methods. It should be noted that these needs exist also in the case of nutritional or health benefits of foods as they are being discussed, for example, in the EU FUFOSE and PASSCLAIM projects, and in the context of genetically modified foods covered such as in the ENTRANSFOOD project of the EU.

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