Guidance for Exposure Assessment of Substances Migrating from Food Packaging Materials

Report of an ILSI Europe Expert Group
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Table of abbreviations

Only abbreviations used more than twice are given here. The others are explained in the text.

bw	Body weight
DG SANCO	Directorate General for Health and Consumer Protection (of the EU)
EFSA	European Food Safety Authority
EU	European Union
FCM	Food contact material[1]
FCS	Food contact substance
FSA	Food Standards Agency (UK)
LoD	Limit of detection
LoQ	Limit of quantification
NIAS	Non-intentionally added substance(s)
SML	Specific migration limit
TCC	Threshold of toxicological concern
TDI	Tolerable daily intake
US EPA	United States Environmental Protection Agency
US FDA	United States Food and Drug Administration
WHO	World Health Organization

A glossary of terms related to exposure assessment is available from the International Programme on Chemical Safety (IPCS 2004) and can be accessed at: http://www.who.int/ipcs/methods/harmonization/areas/ipcsterminologyparts1and2.pdf

[1] The scope of this report is restricted to substances migrating from packaging materials in contact with foodstuffs. However, the term FCM is used throughout the document for easier readability.

Foreword

This guidance document summarises the state-of-the-art in assessing exposure to substances migrating from food packaging materials and gives principles and practical guidance on how exposure assessments should be conducted and reported. It is written for users with some background in exposure assessment.

The document was drafted by an Expert Group commissioned by the Packaging Materials Task Force of ILSI Europe. It builds on the earlier ILSI Europe Report of a Workshop on Exposure from Food Contact Materials held in October 2001 (ILSI Europe 2002) and reviews the implementation of the conclusions of the 2002 report.

This guidance document is intended to give the user an overview of the available approaches and provide direction as to the most appropriate approach to use for a particular situation. The options might range from the EU approach of assuming consumption of 1 kg food packaged in 6 dm^2 packaging material per person per day, through more refined deterministic approaches to sophisticated probabilistic approaches.

The scope of this report is restricted to chemical migration from packaging materials for foodstuffs. Although the term food contact materials (FCMs) covers a wider group of materials, including food-processing equipment, home cookware, crockery and utensils, these are not considered here. The majority of exposure assessments made to date have been for plastics and coated metal, thus many of the examples and references used relate to these two materials. However, this guidance is not restricted to these materials but applies equally to paper and board, rubber, inks etc.

1 Introduction

1.1 Overview

The risk that a chemical will cause adverse effects on human health is determined by two things: toxicity and exposure. Therefore, exposure assessment is a key part of risk assessment and is defined by Codex Alimentarius (CAC 2003) as “the qualitative and/or quantitative evaluation of the likely intake of biological, chemical and physical agents via food as well as exposures from other sources if relevant”. Thus an exposure assessment will often comprise a quantitative exposure estimate, together with a qualitative evaluation of the supporting evidence. It is frequently not possible or practical to measure exposure directly, so quantitative estimates are usually based on predictive models.

EU legislation on FCMs requires that materials should not release substances into food in quantities that may pose a risk to human health (Article 3, Framework Regulation (EC) No 1935/2004). This applies to all “intentionally added substances”, including authorised substances, as well as those packaging materials where no positive lists of authorised substances exist and no limits are set. This also applies to impurities and reaction or degradation products of substances often referred to as “non-intentionally added substances” (NIAS). No levels of migration or exposure are set for which compliance with this requirement can be demonstrated. In these cases, it is the responsibility of the producer of the food packaging and/or the food packer to conduct a risk assessment and define a level below which migration does not pose a threat to human health and, hence, demonstrate compliance with the Framework Regulation. For intentionally added substances the use in certain areas, such as

plastic materials is regulated but it should be noted that the same substance can be intentionally used in other areas where no legal provision/limit exists, e.g. coatings. No differentiation should be made between these two areas as this document is aimed at performing an exposure assessment regardless of the legal context.

Risk assessment is defined as a process comprised of the following four elements:

- Hazard identification
- Hazard characterisation
- Exposure assessment
- Risk characterisation.

Hazard identification and characterisation aim at identifying whether a chemical substance causes an adverse effect on human health and at elucidating the severity (dose-response) and biological mechanism underlying any adverse effect. As long as humans are not exposed, e.g. via food, air or other sources, to a hazardous substance no real risk exists. Risk characterisation combines the information on a health hazard (e.g. toxicity of the substance) and the exposure to the substance. Information on the toxicity of substances can be acquired from scientific publications, structural alert analysis or toxicological testing. The exposure assessment is not well defined at the European level as no common protocol or methodology exists. Different sectors apply different approaches, as can be seen in the recently published European Food Safety Authority's "Opinion of the Scientific Committee on a request from EFSA related to Exposure Assessments" (EFSA 2005).

In the context of authorisation of FCM substances in plastic materials within the EU, generally a deterministic model is used to estimate exposure. This assumes that 1 kg of food is consumed each day and that this food is packaged in the same material with 6 dm^2 of packaging surface area with a uniform level of migration for the substance of interest. This aims to be an overestimate of exposure and allows for general authorisation of substances.

To assess the exposure to food contact migrants several parameters have to be investigated:

- Which substances are used in the application in question, e.g. a food contact material?
- Is an exposure assessment necessary only for one application or does it concern the application of a substance in different materials?
- With which foodstuff is the material intended for contact?
- How much of the packaged food is consumed?
- What is the availability, relevance and suitability of different food consumption surveys for use in assessing exposure?

For a given application, the migration into food can be measured, estimated using food simulants or calculated by diffusion modelling. The relationship between migration into simulants (liquids that are intended to mimic different types of foodstuff) and actual foods needs to be better understood. Different methods for measurement and calculation by modelling migration are possible. The applicability of the different methods is explained.

The scientific tools for assessing exposure to migrants from food packaging are evolving. Thus, this document should not be treated as a rigid set of rules but as a starting point where it can be used to demonstrate that all of the points raised have been considered in deriving the resulting exposure estimate. Following the guidance given in Section 3 and relevant supporting data in Section 2 will ensure that the

approach(es) taken has (have) considered and accounted for all of the pertinent factors that could influence any resulting estimate for exposure.

For any exposure assessment, it is necessary to combine a knowledge of how much of different foodstuffs are consumed with how much of the substance(s) of interest is (are) in each of the foodstuffs consumed. Clearly, this cannot be undertaken completely in every situation because the data required do not always exist. Therefore, in the absence of data, it is necessary to make estimates of both consumption and migrant concentration data, which are then used to derive an estimate for exposure.

1.2 Tiered approaches for assessing exposure

A range of approaches exist for assessing exposure, ranging from simple deterministic approaches using fixed values and default assumptions to refined deterministic approaches or probabilistic modelling. It is important to bear in mind that in many instances the more sophisticated approaches may not be necessary to demonstrate that there is not a health concern with a given migrant(s). Instead, a tiered approach is recommended, in which the exposure assessment is refined as far as it is necessary to support a conclusion on the risk to human health.

In the absence of health-based guidance values (e.g. a TDI, for which an extensive knowledge of the toxicological behaviour of a substance is required), other reference values could be used to decide whether further exposure refinement is necessary. Currently, EFSA applies a migration-dependent approach for the toxicological information to be provided on the migrant. The general principle stipulates that the greater the exposure through migration, the more toxicological information will be required. The threshold values for high, medium and low migration are 60, 5 and 0.05 mg/kg food, respectively. Assuming that a person consumes 1 kg food per day leads then to the respective exposure values. More detailed information can be found in the Note for Guidance (EFSA 2006b), available at:
http://www.efsa.europa.eu/EFSA/Scientific_Document/afc_noteforguidancefcm_en1.pdf

The tiered approach comprises various approaches. These start with deterministic approaches, which range from the current EU approach through that of the FDA as well as incorporating *per capita* approaches based e.g. on total production statistics and total population sizes. Others utilise statistics, being refined deterministic or probabilistic approaches. Whilst the tiered approach is recommended, starting from the simplest to the more complex, it should be borne in mind that the entry point can be at any stage provided there are adequate data available. Each level represents an increasing degree of sophistication and refinement in assessing exposure but they also need increased knowledge of the input data required and of their accuracy. Thus, if at the coarsest level a satisfactory estimate can be made, then there is no need to pursue more sophisticated approaches.

Box 1A. Tiered approach to exposure assessment

- The assessment of exposure to food chemicals should begin with the simplest of data and use conservative approaches
- By definition, this will over-estimate the actual exposure
- If there is cause for concern, the input data and treatments should be further refined in order to obtain a more realistic exposure assessment
- Higher tier assessments tend to require more complex modelling and more detailed data and/or assumptions than lower tiers
- Whatever approach(es) and data are used, they should be clearly described and be transparent to a third party.

1.3 Objectives and scope

For the area of packaging, this guidance document gives an overview of the approaches for exposure assessment that are or should be available. It gives guidance on: which approach is applicable in which situation; the data needed for the different models; how the suitability of different sets of data should be assessed; what data gaps may exist and how these gaps can be filled or handled; the advantages and disadvantages of the different approaches; how to implement each approach (or approaches) in an efficient manner; and the outputs and documentation that are required. The end result is a proposal to enable assessment of the exposure to migrants from any food packaging material scenario and to facilitate the assessment of a margin of safety for the resulting exposure estimate. It should be borne in mind that the margin of safety derives not only from the exposure but also from the toxicological information. Furthermore, data gaps will be identified and where possible recommendations to obtain or overcome these deficiencies going forward will be given.

There are a number of uses for this guidance document and these depend upon the question being asked and by whom. It is envisaged that the following groups could utilise this guidance document in order to arrive at an assessment of exposure to any migrant from packaging of foodstuffs:

- Industry
- Control authorities and risk managers
- Risk assessment bodies (EFSA, national authorities)
- Non-Governmental Organisations.

This guidance document could be used to many questions, such as:

- How can compliance with Article 3 of the Framework Regulation (EC) No 1935/2004 be demonstrated, particularly for non-listed substances?
- If an unexpected non-regulated substance is detected, how can the exposure to it be assessed in order that risk assessment/risk management can be applied?
- What is the most likely exposure to a migrant “x”?
- In the event of a substance exceeding a migration limit, can estimates of exposure be used to assist the risk manager in checking if there is or is not a risk to human health?
- How does the assessment of exposure protect the high-level consumer and how can it be demonstrated?
- Is there additional exposure to brand- or packaging-loyal consumers and by how much is it increased compared to a non-loyal consumer?

Annex I contains a list of further questions that were raised during the preparation of this report, along with proposed answers.

1.4 The structure of this document

Section 2 contains details of the data required in order to undertake an exposure assessment:

- §2.1 Considers the different types of surveys available for obtaining information on the foodstuffs consumed and their suitability for our purposes.
- §2.2 Addresses the information required in order to allocate foodstuffs to different types of packaging as well as considering where the substances of interest may be used. Not all plastics use the same additive or monomer. Coatings may use the same monomer as in a plastic material. In addition, there are both known and unknown NIAS substances.
- §2.3 Describes sources of concentration data, covering analytical determinations in foodstuffs and food simulants. Migration modelling is also discussed. The treatment of non-detects and level of quantification can be important in some instances and these are reviewed along with approaches that can be used to obtain concentration data for use in exposure assessments.

Section 3 discusses the various approaches that can be used to take these data and perform an exposure assessment:

- §3.1.1 Gives an introduction of exposure to migrants from FCMs.
- §3.1.2 Discusses refining exposure estimates.
- §3.2.1 Contains a general consideration of approaches for assessing exposure.
- §3.2.2 Describes exposure distributions.
- §3.3.1 Introduces the different approaches for assessing exposure.
- §3.3.2 Reviews the different deterministic approaches that can be used, including an introduction (§3.3.2.1), the EU approach (§3.3.2.2), the FDA approach (§3.3.2.3), and *per capita* approaches (§3.3.2.4).
- §3.3.3 Describes refined deterministic approaches that can be used, with §3.3.3.1 giving an introduction, §3.3.3.2 describing a matrix approach, §3.3.3.3 giving steps for refining a deterministic approach and §3.3.3.4 describing potential further refinements for a deterministic approach.
- §3.3.4 Considers probabilistic modelling, with §3.3.4.1 giving an introduction, §3.3.4.2 describing the principles of probabilistic modelling and §3.3.4.3 describing the types of output that can be obtained by probabilistic modelling.
- §3.3.5 Compares deterministic and probabilistic modelling.
- §3.4 Considers the elements necessary for good practice.
- §3.5 Addresses special considerations for any exposure assessment, with §3.5.1 giving an introduction and §3.5.2 considering who and what should be included in any exposure assessment. §3.5.2.1 addresses high consumers and sub-populations, §3.5.2.2 population characteristics, §3.5.2.3 the percentile of the population that should be used, §3.5.2.4 packaging loyalty, and §3.5.2.5 body weights.
- §3.6 Addresses exposure assessments for multiple countries.
- §3.7 Considers contributions from multiple sources of the same migrant.

Section 4 summarises the minimum level of documentation considered necessary in order to support any assessment of exposure.

Annex I contains a question and answer section, with §A.I.I addressing general questions, §A.I.II hazard assessments, §A.I.III migrant concentration data, §A.I.IV packaging usage data and §A.I.V food consumption data.

Annex II is an expanded description of probabilistic modelling, with §A.II.I discussing uncertainty and variability, §A.II.II describing quantifying variability, §A.II.III describing quantifying uncertainty, §A.II.IV deals with dependencies between input data and §A.II.V discusses propagating variability and uncertainty.

Annex III considers validation of probabilistic models. It is important that any model used for an exposure assessment is fully validated.

1.5 Conducting an assessment of exposure

The following list is not intended to be definitive but it serves to introduce the concepts expanded on in subsequent sections and outlines how they link together.

Consumption

1. Obtain estimates of consumption for the foods and population groups relevant to the assessment. For a first tier assessment, simple default assumptions may be sufficient (§3.3.2).
2. If further assessment is necessary, develop refined estimates of consumption by the following steps:
    a. Firstly collect and compare all sources of consumption data (§2.1) that are considered relevant.
    b. Review suitability of consumption data and its relationship to its packaging (§2.1 and §2.2). Is a packaging description included in the description of the food item consumed or purchased etc?
    c. If only food consumption data are available, then it is necessary to obtain information about its packaging by a different route (§2.2.1).
    d. Identify the packaging containing the substance(s) of interest (§2.2.2).
    e. Identify and list foodstuffs that could possibly be packaged in any of that packaging.
    f. Allocate market shares for consumption of foodstuffs in the packaging of interest. It could be assumed that all or only some of the food items consumed were packaged in the material of interest.
    g. Calculate estimates of exposure for each relevant type of packaged foodstuff and sum them to give an estimate of total exposure.

Concentration and occurrence

3. Obtain estimates of concentrations of the substance(s) of interest in relevant foodstuffs. For a first tier assessment, measurements in standard food simulants may be sufficient (§2.3.3).
4. If further assessment is necessary, develop refined estimates of concentrations by the following steps:
    a. Allocate concentration data to any foodstuff in the packaging of interest (§2.3). This may be simulant (§2.3.3) or foodstuff data (§2.3.1) or a combination of both. Modelling may also be used (§2.3.4).

b. With lack of concentration data it may be necessary to be conservative and apply concentration values at the top end of a range, e.g. the SML (§2.3.5).
c. Decide how to treat LoD and LoQ values. There are various treatments available (§2.3.6).

Exposure assessment

5. Decide if a value can be set below which the exposure can be declared as safe or not of concern to human health (see §1.2 and §3.1.2).
6. Use a screening conservative approach first, as outlined in §3.2.1. Is this value exceeded? If not, there is no need for further assessment.
7. If it is exceeded then use a stepwise-tiered approach to estimate exposure as outlined in §3.3. This involves deterministic (§3.3.2), refined deterministic (§3.3.3) as well as probabilistic approaches (§3.3.4).
8. Whichever method is used, link the foodstuffs consumed with their packaging and their concentration data to estimate exposure for each type of packaged foodstuff, and sum these to give an estimate of total exposure. Include other sources of exposure if relevant (§3.7).
9. Compare each stepwise estimate of exposure against an appropriate endpoint, allowing for uncertainties. If the endpoint indicates that there is no problem, paying due regard to any impact of packaging loyalty, socio-economic or ethnic groups, regional variation (§3.6) and vulnerable groups (§3.5.2), then there is no need for a more refined approach.

2 Data required for exposure assessments

There are three key elements:

1. The amounts of foodstuffs consumed in the daily diet – this should ideally cover consumption of foods by individuals in different countries, socio-economic groups, ages and any other groupings likely to influence their level of consumption and subsequent exposure on a body weight (bw) basis. The high level of consumption and not the total distribution of consumption may be of interest, depending on the objective of the exposure assessment.
2. The presence or absence of the chemical in question in each and every foodstuff consumed – information on the type of FCM that each food item or food ingredient was packaged in along with information on the chemical composition of the material. If data on chemical concentration in food products are available, then there is no need for information on packaging materials, unless the source of the contaminant is required.
3. The concentration of the chemical in each and every foodstuffs consumed – either measured as such or by extrapolation using the information from item 2.

Of these, data on food consumption are by far the most abundant and readily available. Thus, the limiting factors are:

a. Ascertaining the use of a particular food packaging material for a specific foodstuff
b. Ascertaining the concentration of a migrant at the point of consumption.

Information on the likely accuracy (validity) of these data, any important uncertainties and/or assumptions made, and the impact of these on the exposure estimates made should be clearly described.

2.1 Food consumption data and their use in assessing exposure to food contact materials

2.1.1 Introduction

All European countries undertake surveys of food consumption, primarily for nutritional purposes. There is no standard method for the collection of food intake data, with different countries using different methods, balancing their needs and resources in national dietary surveys. These differences in approach are often cited as a weakness. However, it remains the case that food intake data are widely available and probably all the main survey methods can play their role in exposure assessment. Some consider the different methods as direct (at the individual level) or indirect (at food purchase or market surveys or production level).

The availability of data for foodstuff consumption is generally not the limiting factor in assessing exposure to packaging migrants. Data for the packaging of the foodstuff and its migrant concentration are much more difficult to obtain. The structure of surveys will not change quickly due to the need for many Member States to have historical records in order that they can monitor trends in food consumption from a nutritional viewpoint.

2.1.2 Direct methods for obtaining food consumption data

Direct methods rely on obtaining consumption information from individuals in the population. Rather than re-iterate the many reviews that describe these methods in detail, Table 1 summarises their key points and their strengths and weaknesses.

2.1.3 Indirect methods for obtaining food consumption data

Indirect routes for obtaining consumption data include:

- Household budget data, which are routinely collected for economic purposes. The food expenditure when linked to prevailing prices can give estimates of food intake per family
- Food disappearance data collated annually by the FAO, which estimate "disappearance" of foods based on figures for production, export, import and animal use of primary agricultural produce
- These indirect methods provide excellent longitudinal approaches to nutrition surveillance but are not well suited to cross-sectional application to food chemical exposure assessment. The major issue with indirect methods is that the consumption by more than one person is obtained and, ideally, for purposes of exposure assessment the consumption of individuals is required. For example, a household budget survey, whilst listing the purchases for a household, does not give the consumption of the individuals in the household and the consumption habits of children and adults may (almost certainly will) be different.

In many cases, consumption data obtained by indirect methods will be the only data available for any exposure assessment.

Type	Brief description	Strengths	Weaknesses
Prospective			
Food diary **A**	Subjects record details of all eating occasions and quantify using a variety of techniques, from weighing of some standard foods to the use of food photograph atlases	Provides detailed information on the types of food consumed and is slightly less labour intensive than the weighed food intake method.	Although less invasive than the weighed intake, it still requires considerable interview time on the part of the subjects
Weighed food intake **B**	Subjects are given a balance and weigh all meals and ingredients of meals	An apparently accurate quantification of intake	This is a very invasive method that can cause alterations in food choice and its use is rapidly declining
Retrospective			
Diet history **C**	Subjects are helped to reconstruct the diet of a typical recent week	Because it is seven times longer than the 24-hour recall it leads to a better measure of intake	Recalling large quantities of information may encounter memory problems and also allow bias to enter. Brand level data is not collected
24-hour recall **D**	Subjects are asked to simply recall all the food consumed over the previous 24 hours	Inexpensive and low resource requirements, which allows large numbers to be included in the study	Produces large standard deviations leading to an overestimate of high intakes and an underestimate of low intakes. Brand level data cannot be collected
Food frequency questionnaire **E**	Subjects are given a prepared list of food groups and options for frequency of consumption and serving size	This is the least resource-demanding method and can capture a large sample. The food frequency questionnaire can be targeted or general	A prepared list of food groups will often lack sufficient detail in food chemical exposure assessment, e.g. “fish” will conceal detail on white versus oily fish versus shellfish. Brand level data cannot be collected

Table 1. Overview of the main methods of direct food consumption survey methods and their strengths and weaknesses

2.1.4 Coding of foodstuffs consumed

Although food consumption databases are widely available, not all European countries have data at the level of the individual consumer. Moreover, the data might not be detailed enough to make the proposed changes in the food consumption database. Thus, there are significant challenges to food consumption database managers.

One such challenge is the need for re-coding of foods listed in the database into the five classifications (aqueous, fatty, alcoholic, acidic and dry) used in the legislation (Directive 85/572/EEC; CEC 1985). The choice of simulant depends on the type of contact the food has with the packaging. This Directive gives examples of broad food categories, e.g. “Cheese” with sub-categories of cheese as A – whole with rind, B – processed, and C – all other cheese. This latter category can be classified as aqueous, acidic or fatty with a reduction factor of three. It also specifies that “if it can be demonstrated by means of an appropriate test that there is no fatty contact with the plastic, the test with simulant D may be dispensed with”. This does not lead to easy migration-relevant classification of foods listed in national food consumption surveys because their national descriptions and classifications of food groups are different.

The current EU food classification system results in extra uncertainty in an exposure assessment for migrants from food packaging. Although the uncertainty is probably quite small, compared to other uncertainties, such as packaging usage, efforts should be made to develop a more detailed protocol for classifying foods or use the physico-chemical properties of the foods (e.g. Franz 2005, Foodmigrosure 2006). Other challenges for the use of food consumption databases are to link the food consumed with the packaging type used, as different packaging types may be used for the same food or, in cases where brand level information has been recorded in the food consumption database, the packaging type may vary depending on the unit weight of the product. However, packaging data can still be used with food consumption data, although these challenges may cause some extra uncertainty in the exposure estimate.

Whilst individual consumption data may be gathered, database managers may opt to combine groups by aggregating data, as is the case for some food additive surveys. Again, one has to use what is available and explain its shortcomings.

Efforts are underway to standardise the methodology for food consumption surveys in the EU. Examples are the European Food Consumption Validation project (EFCOVAL; http://www.efcoval.eu) and the European Food Information Resource Network (EuroFIR; http://www.eurofir.net).

Whilst certain food intake surveys have limited value for assessment of packaging migrant exposure, it is only possible to work with the survey data currently available. However, in many instances, the primary data from food intake surveys are simply not available and the risk assessor is obliged to work with mean intake data. Two cautionary notes need to be made here. Exposure data should be confined to only those who eat foods containing the chemical in question. If the total population data are used, a significant number of zeroes from non-consumers will be included, effectively leading to an underestimate of the exposure to the “consumers only” group. This issue is linked with the issue of categorisation of foods, as shown in Table 2. When a food category is at its broadest (spreadable fats, all milk, or all fish and fish products) the difference in the estimate of intake for the “total population”

and “consumers only” becomes negligible. This is true at the mean and at the 95th percentile. The reason is that the percentage of consumers is high so that eliminating the small number of non-consumers has little effect. However, as the categorisation becomes less aggregated, the differences between the estimated intake for the total population and for consumers only becomes distinctly different with the consumer-only value being much higher. A second issue to consider is the multiple between the mean total population intake and the 97th percentile of intake in the same population (consumers and non-consumers included). Thus, where data are available for the total population, extrapolating to the higher intake will require some knowledge of the percentage of consumers of the food. Taking the data in Table 2 alone, a linear relationship can be seen between the multiple of the mean intake required to match the 95th percentile. Thus, when there is a high percentage of consumers, the 95th percentile intake will be two to three times that of the mean intake. However, when the percentage of consumers is low, the multiple may be as high as six to eight, as shown in Fig. 1.

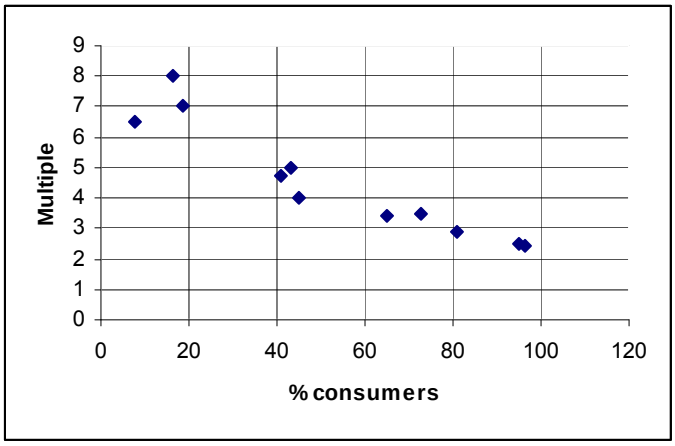

Figure 1. Relation between % consumers and the multiple of the mean population intake at the 95th percentile of intake, based on the data in Table 2

Food	Total population				Consumers only		
	Mean (g/d)	SD	95th %tile	% Consumers	Mean (g/d)	SD	95th %tile
Fats							
Low-fat polyunsaturated margarine	2.9	8.3	20.6	19.8	14.9	13.0	42.6
Polyunsaturated margarine	6.1	11.3	28.6	40.6	15.1	13.3	41.4
Margarine	16.0	15.7	46.1	81.2	19.8	15.2	49.0
All spreadable fats	21.8	16.4	54.1	95.9	22.8	16.1	55.0
Milk							
Skimmed milk	11.3	56.6	70.6	7.9	142	148	433.1
Low-fat milk	87.7	140	360	45.2	194	151	485
Full-fat milk	150	187	504	73.2	205.4	192	566
All milk	243	183	588	97.2	250.2	181	597
Fish							
Salmon	5.1	14.9	42.9	16.8	30.3	23.6	78.4
Fatty fish	9.5	18.7	46.9	33.9	28.1	22.6	72.3
All fish and fish products	23.0	26.6	75.1	66.1	34.8	25.7	85.7

Table 2. Comparison of food categories (broad to narrow) and the impact of considering consumers only versus consumers and non-consumers

2.1.5 Other factors to consider with food consumption data

Amongst the potential parameters that could impact any exposure assessment are:

- Under- and over-reporting of consumption, for example under–reporting of alcohol and over-reporting of fruit. The intake of alcohol and fat are prone to underreporting in a food consumption survey, whereas food balance sheets report the availability of food to the population and overestimate the average *per capita* intake
- Correction for within-subject variation
- Correction for consumption over a lifetime. Food consumption surveys reflect the intake of a short period of time (for instance 2 days), which does not match with the time frame of most (i.e. chronic, not acute) risks associated with migrants.

However, these parameters may have limited relevance to the final outcome as packaging use data and concentration data may have a greater uncertainty/be unknown and most probably will have a greater impact.

As refinements of the available data for total food consumption, it may be better to consider individually the types of foods: dry, aqueous, acidic, alcoholic and fatty. It is recommended to create general steps (estimation models) that can be used for categories of foods, chemicals (for instance NIAS), population groups (adults, children), surveys etc. These steps are conservative for the whole category and any exposure assessment can be used without or with (pre-defined) specific data. A good and transparent classification of the case is then sufficient, which although a “crude” option may lead to a satisfactory result. This is part of refining a deterministic approach (§3.3.3.). For certain cases, it may be required to go back to the initial raw data with the individual eating events.

Box 2A. Food consumption data and their use in assessing exposure to food contact materials

- In any assessment, the food consumption surveys should be given with whatever limitations they may have. Example: if only indirect data such as household consumption is available then the actual consumption by individuals within the household cannot be known accurately
- The preference of the surveys is given in Table 1, with **A** being first choice and **E** the last choice, but quality of data or other factors may significantly influence this choice
- The proposed approach is to use food consumption surveys, wherever possible, in preference to basket surveys etc
- Wherever possible, food consumption of individual consumers is preferred to those that aggregate individual consumers
- The relevance of surveys of individual consumers compared to other sources of food consumption should always be taken into account
- Some methods of collection of food intake data may cease to be of value when the procedure for assessing exposure becomes more refined as the procedures may demand more complex data than are available from the food intake database.

2.2 Data on the types and extent of packaging used for food and substances present therein

(Packaging usage data and potential for presence of migrants in the packaging)

2.2.1 Packaging used for foodstuffs

2.2.1.1 Introduction

For the purpose of assessing exposure to migrants from food packaging, the initial focus has to be on the primary packaging. This would be, for example, the plastic film for a packet of crisps, whereas the cardboard case containing multiple packets of crisps is secondary packaging.

The primary focus of food surveys to date is, understandably, from a nutritional point of view, on what was eaten rather than on its packaging. In the case of raw foodstuffs with a thick outer covering, such as bananas, the packaging is most likely irrelevant but with raw fish or meat or processed foods, knowledge of the packaging is needed in order to determine potential exposure to a (or any) given migrant. In a few surveys, an indication of the packaging may be given, for example in the National Diet and Nutrition Survey (UK) or surveys sometimes describe the packaging of some items (e.g. canned fruit). In a recent survey (e.g. Duffy et al. 2006a), the packaging of the foodstuffs consumed has been recorded. However, this is not the norm.

Thus, the question is how can the required data be obtained or estimated? Complete and accurate knowledge of the packaging for each food item consumed is unavailable, even though it is desirable it is an unrealistic goal. Even if a consumer describes the item consumed as being in plastic or paper or metal, this does not necessarily identify the grade of paper or plastic or if the metal is coated or uncoated. This is further compounded by the growth in mixed packages and multi-layer materials, particularly multi-layers of different materials. Another factor to be considered is that ingredients of convenience foods are often packaged before being used for the preparation of the food (or intermediates in the food preparation) and the finished food (or intermediate) is also packaged for retail purposes, most probably in a different form of packaging to most of its ingredients. Foodstuffs may have multiple packaging, all with different surface area-to-volume ratios, between production and consumption. Yet another complication is that the consumer may re-package a foodstuff at home after partial consumption of the original food, and the packaging is most probably totally different. For example, cheese may be purchased and the portion not consumed may be packaged in cling film. With today's knowledge, it is very difficult to allow for these last two scenarios.

Yet another complication is that for a definitive packaging description (such as a bottle) the nature of the closure is unknown and, furthermore, unless the bottle is described as glass, PET, PVC etc., uncertainty still remains despite a valid description from a consumer's viewpoint.

2.2.1.2 Allocating packaging to foodstuffs consumed

It will most likely be necessary to make assumptions and estimates as to what foodstuffs are packaged in what materials. For example, it is highly unlikely that bread would be packaged in glass. This approach may be adequate for some exposure assessments. Another example is taken from food item descriptions, "beer canned" or "beer not canned" or "beer bottled".

It is possible to obtain market share information for different types of packaging for different foodstuffs. In the USA, industry submits its usage of different food contact

materials. The US FDA derives from these data material use factors (MUFs), which allow essentially a *per capita* estimate of exposure. Consumption factors describe the fraction of the daily diet expected to be in contact with specific packaging materials. To account for the variable nature of food, the US FDA has calculated food-type distribution factors for each packaging material to reflect the fraction of all food contacting each material that is aqueous, acidic, alcoholic or fatty. A description of how these data are used in order to estimate exposure is given in §3.3.2.3.

In the EU comparable packaging use factors do not exist, although industry is starting to compile such data. Therefore, it is necessary to utilise whatever data are available, bearing in mind that it should be from reliable sources. The quality and representativeness of the data has to be considered in order to argue the validity of any estimate of exposure based upon it. This was considered in the ILSI publication "Food consumption and packaging use factors" (ILSI Europe 1997).

2.2.1.3 Available packaging data

There are some sources of data available, of variable quality and usefulness, for the packaging for different foodstuffs. These include:

- The Dutch Food and Consumer Product Safety Authority (VWA) prepared a database on the domestic use of food packaging materials in the Netherlands. (http://www.vwa.nl/cdlpub/servlet/CDLServlet?p_file_id=10411). The report (Bouma et al. 2003) also includes surface area–to-weight ratios, which has importance when simulant concentration data are used
- Maurice Palmer Associates developed for DG-SANCO a database from the results of a number of studies on the use of food packaging materials, mainly focused on the UK and Italy. Information on food type, package size, packaging material and contact coating was collected as part of this study (This report from 1995 is not publicly available; parts are published in Palmer 1993)
- The Dutch Grootverbuik Product Informatie database was established in 1995 by a number of wholesalers who provide food to the catering, hospital and restaurant industries (http://www.gpi.nl). This database contains packaging descriptions for over 12 000 articles and is continuously being updated. It is for foods sold at wholesale level and not retail level and therefore, it lacks information on foods bought and consumed by the public
- The Dutch EAN DAS is a not-for-profit data pool for fast moving consumer goods (FMCG) established in 2000 and collects information on packaging formats used for products. They have packaging information on over 63 000 FMCG, of which approximately 35% are food products (http://www.eandas.nl). The quality of packaging information recorded in this database ranges from crude (e.g. box) to more specific (e.g. polypropylene bag)
- Commercial food and consumer databases such as the Mintel Global New Products Database (http://www.gnpd.com) or the Innova Food and Beverage database (http://www.innova-food.com) monitor worldwide consumer packaged goods markets and cover the food, beverage and non-food sectors. The level of packaging information in these databases ranges from crude to more specific
- The German Association for Packaging Market Research (GVM) also collates data on the packaging types used for foods. This data is collected at retail level and not at food consumption level (http://www.gvm-wiesbaden.de)
- The Food Standards Agency–Pira International studied packaging materials used for dietary staples (project A04006; FSA 2003). This report uses data from

Mintel Food and Drink reports and gives a possible stepwise approach to allocate packaging to different staple foodstuffs

- A novel food-packaging database, the Irish Food Packaging Database, was created as part of the Irish National Children's Food Survey in 2003–2004 (Duffy 2006, Duffy et al. 2006a,b). This database collected information on the type of packaging used for foods consumed in the survey along with information on their contact layer. This is the first database to link a food consumption survey with a packaging database and will be used to derive packaging consumption data for this sample population. This database is not publicly available
- Newcastle University has undertaken a survey of the dietary habits of children of varying ages including detailed statistics on the surface area-to-volume ratios. The different types of packaging of the foodstuffs consumed were identified with assistance from industry (FSA 2006). This report is available from the FSA Information Centre (infocentre@foodstandards.gsi.gov.uk).

Overall, these databases and reports are useful resources of general packaging information and give an overview of the types of packaging used for foods available on the market. With the exception of the last two, they provide no information on the likely consumption of foods packaged in these materials. However, they are a good first reference to gain information in order to refine the exposure assessment.

2.2.1.4 Summary on how to determine the packaging used for foodstuffs consumed

To summarise, in whichever way the data are used, there will be a degree of uncertainty in the estimate of the market share of a particular package for a given foodstuff. When compounded with the lack of absolute information on the packaging of the foodstuff consumed and the potential impact of packaging loyalty rather than brand loyalty, the degree of uncertainty of the packaging of each and every item consumed increases (see §3.5.2.4 and Annex I for further details).

Box 2B. Packaging used for foodstuffs

- The more refined any exposure assessment, the greater the need to go into the details of the food consumption survey(s) used and allocate packaging for the food items consumed, either at a coarse or detailed level
- The straightforward approach is to remove from any exposure estimate those foodstuffs that are unlikely to be packaged in certain forms of packaging.
- Depending upon the food consumption survey and detailed descriptions it may be possible to identify those items consumed in or not in a specific form of packaging
- The next step is to allocate packaging types to those foodstuffs where their packaging is unknown, from whatever sources, for the food descriptions (groupings) given. This will involve using any description of packaging in the food item, market shares for different types of packaging, and extensive use of the reference documents cited above
- In the absence of definitive answers, expert knowledge is needed.

2.2.2 Substances that packaging may contain and release into food

The Community legislation for FCMs considers two major groups of possible substances present in food contact materials that may migrate into foodstuffs, namely:

1. Intentionally used (added) substances used in the manufacturing process, either as raw materials or as a consequence of converting the raw materials into a FCM
2. Non-intentionally used substances (NIAS) present in the final finished article or raw materials or intermediates as reaction or degradation product or impurity of the intentionally used substance. These may be known or unknown, and their treatment, as far as an exposure assessment and consequent risk management is concerned, may differ.

It should be noted that whilst only a few FCMs are regulated by specific measures at European level, for example plastics or regenerated cellulose, the principles in this document for assessing exposure to migrants apply to *all* FCMs.

2.2.2.1 Substances intentionally added (used) in the manufacture of the food contact material

Substances intentionally used in all steps of the manufacturing process chain (including production of raw materials, intermediates, conversion, including laminating and printing) should be (but may not be) known by those involved in the various steps. However, it is not easy to find an overview of all possible applications of a substance in FCMs. Substances used in FCMs are regulated by EU legislation (Framework Regulation (EC) No 1935/2004). This does not mean that positive lists exist for all substances and all materials. In the EU legislation, positive lists exist for regenerated cellulose (with the exception of synthetic casings) and for monomers used in plastics. In EU and national legislation, lists of authorised additives used in plastic exist. However, these do not cover all types of additives and production aids and do not prevent the use of unlisted substances. For other types of materials and articles, lists of authorised substances exist in some national legislations or recommendations, such as those in France, the Netherlands, Germany, Italy, Spain and Belgium. Also, inventory lists exist in the resolutions of the Council of Europe. Not all substances and materials are covered in these lists. In addition only with expert knowledge is it possible to know which substances are used in which type of material. The nature of the substance may restrict its application, for example a monomer may only be used in one type of plastic or coating, unlike an additive, which may be used in many types of plastic. Polyethylene will always contain ethylene.

2.2.2.2 Non-intentionally added substances

Non-intentionally added substances (NIAS) essentially belong to one of two categories, namely:

1. Impurities in the intentionally added substances or formulations
2. Reaction products, which encompasses degradation products formed during the manufacture of the raw material, intermediates based on the raw materials, the process of manufacturing (converting) the FCM, or use of the food packaging material

To identify these substances, the process for synthesis of the starting material has to be known, as do the further processing steps up to the finished food contact article. Impurities should be known or have been subjected to toxicological screening as part of the submission of a dossier to EFSA for the evaluation of the use of the substance. Reaction and degradation products are formed in the process of manufacturing the

final material and article. In the manufacture of polymers, the majority of reaction products are high molecular weight products and generally do not migrate. However, substances, including reaction products, with a molecular weight above 1000 Da are not considered toxicologically relevant as they cannot be absorbed in the gastro-intestinal tract.

2.2.2.3 Variability in composition

It is important to note that FCMs, such as paper, plastic (polypropylene, polystyrene) or coated metal are typically manufactured by more than one company and may have different substances in the composition. Furthermore, concentration data may vary from batch-to-batch or from packaging type to packaging type.

2.2.2.4 Guidance for obtaining information on a substance in a food contact material

In order to be able to assess exposure to a substance, it is necessary to collate the following information, using whatever sources are available.

Box 2C. Determining the occurrence of a substance

- Which packaging materials use the substance?
- What is the possible concentration level of the substance in the packaging (not in the foodstuff!)?
- What are the likely conditions of use of the different packaging materials containing the same substance (e.g. filling/storage temperature and time)?

Accurate information on the presence of substances in FCMs will help to better refine the exposure estimate. It is also important to make the source(s) of the information transparent when documenting the exposure assessment.

Box 2D. Information required in order to assess exposure to any substance originating from packaging of foodstuffs

- Information on the presence or absence of the substance in the packaging material from the material producer or supplier
- Lists of authorised substances in EU national legislation, for example NL Warenwet (The Netherlands commodity law), DE recommendation, FR decrets, BE arêté royale, Council of Europe resolution, etc
- Literature
- Analytical investigation on the presence of this substance in the finished article
- Review of other food contact market applications, to ensure that other applications with migration to food are not overlooked (cumulative exposure route).

2.3 Migrant concentration data

Exposure estimates are obtained by taking information about the quantity of the specific foodstuffs consumed and combining it with concentration data for the substance of interest (migrant) in those foodstuffs. Migration is the process of mass transfer from the FCM into the food or food simulant. The concentration of migrant

found in the food depends on the composition of the food, the composition of the packaging material, the intimacy, time and temperature of the contact between the two.

2.3.1 Data requirements

Migration into a given food item or food category can be established in three broad ways:

Box 2E. Routes for obtaining migrant concentration data

- Directly by chemical analysis of the packaged food
- Indirectly by using simplified model foods ("food simulants") that are intended to mimic the food, using contact conditions of time and temperature that are intended to model the real application
- Using mathematical modelling of the mass transfer of the migrant from the FCM.

2.3.2 Migrant concentrations in foodstuffs

In an ideal case, migration concentration values should be known for:

- All the different combinations of food types and packaging materials that contain and may release the substance of interest
- Concentration values for all the different EU countries, reflecting differences in food composition (e.g. regional recipes) and preparation methods (e.g. cooking, processing). In the absence of data, information from other similar countries may be used
- All the different storage times between packing and consumption and for all the different in-pack food processing technologies and packaging technologies used
- Foods prepared ready for consumption in the case of unstable or volatile substances
- Concentration data for foods that do not come from the affected packaging materials in the case where FCMs are not the only source of oral exposure, for example migrants from food processing equipment
- The concentration at the time of consumption, which will be a distribution depending on when the item was purchased, its shelf-life and when consumed.

The availability of data on packaging usage or on concentrations in these uses may necessitate the adoption of approximations, assumptions and conventions. These should be declared. In the absence of data for a particular country or countries, then information from other similar countries may be used. Another example is the statistical distribution of storage intervals and storage temperatures, which may affect the extent of migration after packing and leading up to consumption. This is normally unknown and even if this information were known, the migration concentration data for all the time/temperature permutations may still be unknown. So it may be necessary to take migration concentration data at the end of the shelf-life of the packaged product, or to use concentration data obtained at a snapshot of the product lifetime. In either case the impact of the decision should be described.

It could be argued that high consumers of a particular item, particularly, if the packaging has a lag time, whilst eating more frequently are more likely to eat the item before the end of its shelf-life. Thus, the concentration data could be lower than that of an infrequent consumer. Any interdependencies must be taken into account.

Whilst it is not possible to define a minimum number of data points required for good concentration datasets, generally, the more data points the better. This also enables a distribution to be fitted for use in either probabilistic or refined deterministic exposure assessments. For the latter, the distribution may be used to derive a fixed point representing a percentile of the concentration distribution. The smaller the number of samples the greater the uncertainty but in order to assess the impact on any estimate of exposure, it is necessary to know the uncertainties and their effects in other parts of the exposure assessment.

One advantage of determining migration into foodstuffs is that all sources of exposure for that foodstuff and that migrant have been totalled. In other words, migrants from food being repackaged in FCMs with the same potential migrant have been accounted for.

2.3.3 Migrant concentrations in food simulants

The quantitative determination of migrants in foodstuffs can be expensive and time-consuming. In many cases, it may even be impossible due to a lack of analytical methods. As a consequence, food regulatory bodies such as the European Commission or the US FDA allow the use of food simulants as an alternative. These simulants are intended to mimic the five main types of foods (dry, aqueous, acidic, alcoholic and fatty) and they are used with standardised test conditions of time and temperature. These food simulants are used to give an indication of migration levels that may be expected into foodstuffs (for exposure estimates). They are also used in standardised, reproducible tests in checking for compliance with any legal limits on migration.

Food simulants coupled with the test conditions (time/temperature) under which they are used, are intended in most cases to be more severe (elicit higher migration levels) than the foods they mimic. In many cases, this is true and in particular for fatty food (simulant D) where there can be very large differences between the fat simulant test result and that of the fatty food it simulates. In these cases, the fat test result is therefore moderated by the use of reduction factors that aim at bringing the migration results for foods and simulant D more closely in line with one another. In some cases, however, for particular combinations of food/substance/material/time/temperature, the food simulant may in fact underestimate migration levels into foods. This can be the case for aqueous food simulants and lipophilic migrants when they are intended for simulation of otherwise aqueous foods but having a certain lipophilic character for solubilising organic substances, such as cloudy juices or milk. However, for exposure assessments the correlation between simulants and real foods is useful but not always available.

If food simulant data are used in lieu of concentration data for foods then the relationships between the simulant and the foodstuffs should be known wherever possible.

2.3.4 Migration modelling into food simulants and food

Diffusion within – and migration from – FCMs are predictable processes that can be described by mathematical equations. Mass transfer from a plastic material, for instance, into food simulants, obeys Fick´s laws of diffusion in most cases. Physico-mathematical diffusion models have been established, verified and validated for migration from many plastics into food simulants and are accepted in the USA and in the EU.

Because of the complex, heterogeneous and variable nature of foodstuffs, compared to four defined liquids that simulate a range of foodstuffs (food simulants), no general tools for modelling migration into foods are yet available. The EU project "Foodmigrosure" had the objective to develop a migration model for estimation of mass transfer from food packaging plastics into foodstuffs, by extension of the existing model for (less complex) food simulants (Franz 2005, Foodmigrosure 2006). In this project considerable efforts were made to provide quantitative data to link food-simulant migration with that into foods. The exact migration relationships, however, appear to be not yet fully understood. Nevertheless, these models probably represent the only practical way that the complete combination of relevant parameters, including variable food composition, in-pack processing and storage times (t) and temperatures (T) can be taken into account when compiling concentration datasets large enough to describe migrant concentrations in the foodstuffs as eaten by European consumers. Any experimental data used for modelling migration must conform to the guidelines established by a task force on migration modelling organised by the Institute of Health and Consumer Protection (IHCP) of the European Commission Joint Research Centre in Ispra, Italy.

2.3.5 Approaches for obtaining concentration levels to be used in exposure assessments

Concentration data are available via different routes and it may be necessary to combine one or more in order to undertake an exposure estimate. In line with a tiered approach, the simplest, most easily obtained and conservative concentration data should be used first. This can come from straightforward "worst-case" calculations, such as calculating the concentration that would be achieved in the food if total migration from the FCM were to occur. Since both simulants and modelling are intended to overestimate migration into foods, then logically in a tiered approach they should be used next. Finally, actual concentration data measured in food surveys should give the most accurate estimates of exposure but these data are often not available or are incomplete.

The following approach for a progressively refined exposure assessment should be followed until a usable conclusion can be derived. As stated above, it may be necessary to combine one or more elements of this scheme to give a complete set of input data.

In the absence of any other data and as a first step, assume migration is at the highest level possible. That is, based on compositional information, assume that the total quantity of substance in the material will migrate. If no issue arises, then no further refinements of concentration data are needed. The next step would be to assume migration is at the specific migration limit (SML).

The steps set out in Box 2F should be followed if the above approach requires further refinement. However, at all steps the relevance of the concentration data to the materials being evaluated and how realistic the values are should be reviewed. This is very important when the relevance of the simulant data to that expected in the actual foodstuffs is considered.

Box 2F. Approaches for obtaining concentration levels to be used in exposure assessments

1. Calculate total migration from the FCM, using formulation levels of the FCS or levels found using total extraction, taking account of actual or conventional surface area-to-volume ratios
2. Calculate total migration from the first layer of the FCM contact surface that is relevant for migration. For polyolefins this is conventionally assumed for the first 0.25 mm^2 whereas for other polymers and multi-layer structures this may differ significantly and needs to be rationalised
3. Measure and/or model migration into the worst-case simulant using the worst-case *t*/*T* conditions
4. Measure and/or model migration into all types of food simulants using the worst-case *t*/*T* conditions
5. Measure and/or model migration into all types of food simulants using all relevant *t*/*T* conditions
6. Measure and/or model migration levels in retail foods tested at the end of their shelf-life
7. Measure and/or model migration levels in retail foods tested at the time of purchase and correct for any additional storage by the consumer prior to consumption
8. Measure and/or model migration levels in retail foods tested according to the normal distribution of storage time and temperature between packing and consumption.

2.3.6 Treatment of limits of detection and limits of quantification

It is necessary to consider the impact on any exposure assessment of the values used for non-detects as well as the limit of quantification (LoQ), particularly for some of the more sophisticated approaches. In many instances, the concentrations of migrants in foods or food simulants are below either the limit of detection (LoD) or the LoQ of the analytical method. Thus, it is necessary to consider how these results should be treated, particularly if the foodstuffs concerned are high consumption ones such as beverages. Clearly, all of the concentrations cannot all be at the LoD or LoQ. Conversely all of the concentrations cannot all be at zero and they must therefore lie at a range of values between zero and the LoD. There are different ways of approaching this situation. If a substance is absent from a particular form of packaging, then it is reasonable for its concentration to be allocated a zero value in the food. However, if it could be present in the packaging then it is necessary to allocate a numerical value for its concentration in food. In probabilistic modelling approaches, it is possible to vary the concentration data using whatever distribution seems appropriate. For the less refined approaches, simpler approaches are possible, such as assuming a uniform distribution or half the LoD for values below the LoD. Both give the same value. The same approach can be applied when values are between the LoD and LoQ, namely:

$$\text{Concentration} = [(\text{LoQ} - \text{LoD})/2] + \text{LoD}$$

Whilst there can be long debates about the “best way” to treat levels below LoD and between LoD and LoQ, the above pragmatic approach is recommended for the purpose of assessing exposure as outlined in this guidance document.

[2] See EFSA Note for Guidance (EFSA 2006b)

Migration levels below analytically established LoDs may be accessible by migration modelling where applicable and they may be conservative enough for any particular case (Franz 2005).

Box 2G. Treatment of limits of detection (LoD) and limits of quantification (LoQ)

- When there is good evidence that a substance(s) is (are) not used in the packaging, allocate the concentration = [0]
- When the substance(s) could be present but the concentration measured is below LoD, allocate concentration = [LoD/2]. Alternatively, if migration modelling is applicable and returns a value in the range 0–LoD then use this value. As a second alternative, probabilistic distributions can be used to model the probability of a substance being present at levels between absolute zero and the LoD
- When a substance is detected above the LoD but below the LoQ, allocate concentration = [(LoQ – LoD)/2 + LoD].

2.3.7 Documenting how the concentration data were obtained

It is necessary to explain the sources of data used and how they were used as well as any assumptions used.

Box 2H. Guidance for documenting the concentration assessment

1. State how representative the foods tested are for the whole of Europe (i.e. is the foodstuff processed the same and in the same packaging in different regions of Europe, e.g. do Greek and UK foodstuffs have similar concentration data?)
2. State any assumptions made that one food-packaging group is the same/similar to another
3. State the level of uncertainty in the simulant migration concentration data used
4. State the level of uncertainty in the migration modelling results used
5. State how LoDs/LoQs are treated
6. Declare any assumptions, approximations and conventions used in order to obtain concentration data.

3 Exposure assessment

3.1 Introduction

3.1.1 Overview

Duffy (2006) summarised the current situation regarding assessing exposure to migrants from FCMs as follows: “Assessing the intake of a food chemical can be a complex procedure. A problem is that people normally eat a wide range of different foods, which may each contain a range of concentrations of the chemical of interest”. Traditionally, most risk assessments have been conducted using “worst case” estimates of potential exposure. This conservative approach produces estimates of exposure that are physiologically not likely to occur and in many cases 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 (Petersen 2000). A refinement in the exposure estimate would lower or clarify the uncertainty, so that a more accurate risk estimate could be obtained. In some cases, this may have implications for legislation, so that less restrictive limits could be set for chemical contaminants in food (ILSI Europe 2002). It may also be that, in certain cases, the conventional approach may underestimate true exposure and so more restrictive limits may be needed in such cases.

Assessing exposure to migrants from packaging could arguably be considered to be more challenging than most, if not all, other forms of chemical contamination of food. This is because for the majority of foodstuffs the foodstuff consumed is the important factor and is generally better defined or has less uncertainty than what the food was packaged in.

3.1.2 Refining exposure assessments

The refinement of the exposure assessment should follow a tiered approach and proceed from the level of least exactitude (i.e. most conservative) to the level of most exactitude, only if the less exact levels do not rule out the possibility of concern (Lambe 2002). This hierarchical approach is recommended by many authors (Gibney and Lambe 1996, US EPA 1997, WHO 1997a, van Drooge and van Haelst 2001, Lambe 2002, Renwick et al. 2003, Barlow 2005). However, this top-down approach does not generate (nor has the intention to generate) accurate estimates of the exposure. The goal is to decide whether the exposure to a particular chemical is “safe” or that the exposure to a chemical needs further research. A potential way of deciding if the exposure to a migrant is “safe” or not of concern to human health was discussed in §1.2. Refined exposure assessment models are intended to serve as tools for decision-making, such as for rule making or regulatory compliance purposes where screening analyses are inadequate (Frey and Patil 2002).

There are no set refinement procedures for the exposure assessment of food packaging migrants and therefore multiple methodologies have been employed in the past (Dionisi and Oldring 2002, EFSA 2004, Holmes et al. 2005, Thomson and Grounds 2005, EFSA 2006a). In a project conducted on behalf of the UK Food Standards Agency (FSA) a wide variety of information sources were used to assess the feasibility of providing a structured, tiered approach to estimating potential exposure to chemicals that may migrate from food contact materials. The approach used progressively refined assumptions, calculations and, finally, actual migration, usage and food consumption data where available (Castle 2003). Although this study was

successful in producing refined estimates of exposure there were no set guidelines developed on how to refine future exposure assessments. In general, it is recommended that in order to refine estimates of exposure, more sophisticated methods of integrating the food consumption and chemical concentration data are needed and/or more detailed data from industry, monitoring programmes etc. (Kroes et al. 2002). In one review, it was recommended that to develop a refined dietary exposure evaluation process for food packaging migrants and to prevent unnecessary toxicity testing (and the accompanying commitment in related resources and animal testing), there is a need to link to and make greater use of food consumption data (ILSI Europe 2002).

The reason refined exposure assessments for numerous food chemicals have been developed is because, generally, there is insufficient information available to carry out actual intakes and, instead, potential intakes must be estimated (Parmar et al. 1997). For example, in the case of pesticides, the international estimated daily intake (IEDI) is used as a refinement of the theoretical maximum daily intake (TMDI) (WHO 1997b).

3.2 General considerations for assessing exposure

3.2.1 Introduction

The basic approach to estimating exposure to a dietary contaminant, assuming that all of the necessary data are available, whether deterministic or probabilistic, is as follows:

1. Exposure for a single food item = weight of food item × concentration of migrant
2. Exposure to meal = sum of exposure of all items consumed during that meal
3. Exposure for person over period = sum of exposure to all meals
4. Exposure of population = repeat calculations 1–3 for every person in the population.

In order to perform part 1 of the calculation correctly, it is necessary to identify what concentration is relevant for each food item. Therefore, it is necessary to identify which foods are packaged in the material of interest, and to separate foods for which different concentrations of migrant are expected. This should be done by considering what factors are expected to influence migrant concentration and using these to define categories of foods for which different concentrations are expected. Typical factors to consider are outlined in Box 3A.

Box 3A. Factors to consider when undertaking an exposure assessment

1. Generally, migrant concentrations are assumed to be zero in foods not packaged in the material of interest (exceptions to this might occur if the migrant could be present from packaging used in an earlier stage of the food chain, or if it can be derived from sources other than packaging)
2. The usual default categories are those associated with the standard food simulants A–D: aqueous, acidic, alcoholic and oily or fatty foods
3. Category D (fatty/oily food) is often divided into five sub-categories (D/1, D/2, D/3, D/4, D/5) to allow for the effects of different levels of fat content in the actual foodstuffs
4. The detailed nature of the packaging is important, specifically the ratio of packaging area to food weight, and the proportion of packaging area containing the material of interest. For example, when assessing migration into drinks from metal coatings, it would be necessary first to identify which drinks are in contact with metal coatings, then separate canned drinks from those in glass bottles with metal closures (which have a smaller contact area), and finally subdivide the bottles and cans according to their volumes (which affect the area-to-weight ratio)
5. If measured concentrations are available from real foods, then these should be examined to see whether they appear similar, in which case those foods can be treated as a single category, or whether they should be divided into different categories
6. After the food categories have been defined, each food item must be assigned to the relevant category in order to perform step 1 of the exposure calculation.

Defining the food categories and assigning the food items can be a very laborious process, especially if the number of categories and food items is large. Also, it requires extensive information on the ways in which the packaging is used and how these will influence migrant concentration. Therefore, it is beneficial to adopt a tiered approach. This would start with a conservative assessment, using a few broad food categories (e.g. just the simulant categories A–D), and making worst-case assumptions for each category (e.g. using the measured simulant concentrations and conservative assumptions for area-to-weight ratios). If this conservative assessment resulted in an exposure estimate well below the relevant limit, it might be concluded without further assessment that the exposure is acceptable. Otherwise, it will be necessary to refine the assessment by increasing the number of categories and making more realistic assumptions to estimate more closely the actual exposure. The degree to which this is possible will depend on the quality of data available.

3.2.2 Exposure distributions

The variation or distribution of exposure within the population could be presented as a histogram, showing the number or proportion of individuals at each level of exposure but it is more common to show the results as a cumulative distribution, as shown in Fig. 2. This form of presentation is useful because exposure can be read off (on the horizontal axis) for any desired percentile of the population (on the vertical axis). However, it should be borne in mind that the above calculation for exposure requires very detailed information about what was consumed, by whom and how much of the migrant was in the foodstuffs consumed, and would only apply in an ideal world. Such complete data sets simply do not exist today and it is questionable whether they will

ever exist. Furthermore, such detailed knowledge might not be needed as it represents only a “snapshot” and is retrospective and thus not representative of the future consumption habits of an individual.

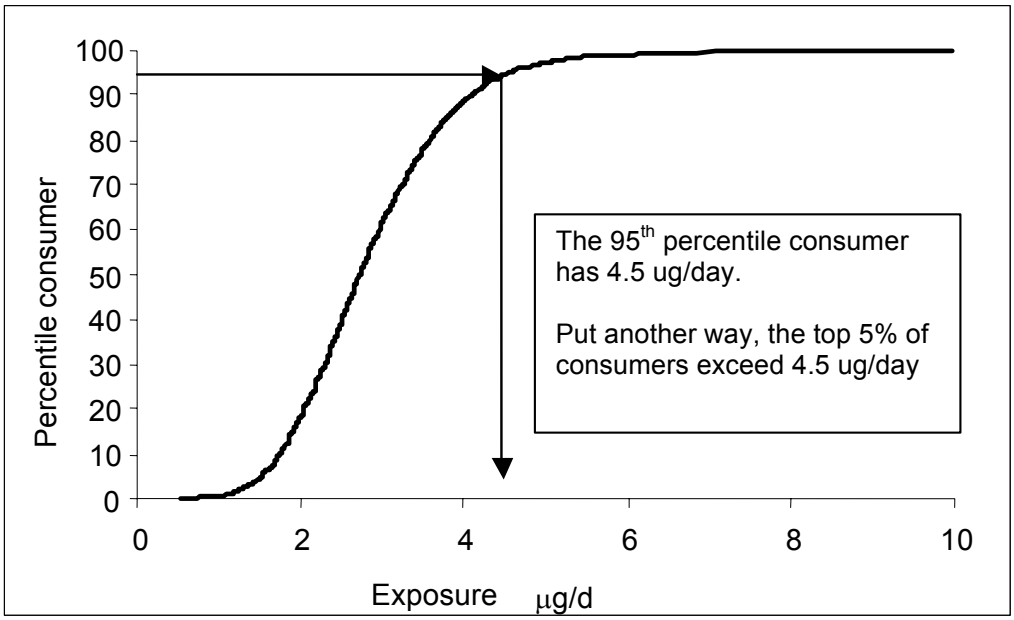

Figure 2. Illustration of a cumulative exposure distribution, showing the variation of exposure in a population. *Arrows* show how the graph can be used to read off exposure for any desired percentile of the population (in this case, the 95th percentile)

In order to perform the calculation correctly, it is necessary to identify what concentration is representative for each food item. Therefore, it is necessary to identify in which packaging material the migrant is/could be present and which foods are packaged in the material of interest, and to separate foods for which different concentrations of migrant are expected. This should be done by considering what factors are expected to influence migrant concentration and using these to define categories of foods for which different concentrations are expected.

This is the ideal situation and if all of the data required were available, then there would be no need to estimate exposure. In reality, only the more sophisticated techniques for estimating exposure, such as probabilistic and some deterministic methods, are capable of addressing exposure estimates at this level of detail.

3.3 Approaches for assessing exposure

3.3.1 Introduction

There is a need for simple approaches to estimate dietary intake of food chemicals in several situations:

1. Prioritise food chemicals for further investigation
2. Monitor trends and changes in dietary intakes
3. Provide estimates when detailed information is not available
4. Facilitate negotiations on acceptable levels between countries
5. Make a risk assessment when the food chemical is found in a limited number of foods (Rees and Tennant 1994).

One of three approaches is usually used to provide an estimate of exposure, namely deterministic estimates, refined deterministic estimates and probabilistic estimates. Some of the many different sub-group approaches to assessing exposure can be summarised as:

1. Deterministic
   a. EU
   b. FDA
   c. Per capita
2. Refined deterministic
3. Probabilistic.

These are the approaches recommended for migrants from FCMs. To refine the exposure assessment, the process can progress from a deterministic estimate using simple conservative assumptions to a refined deterministic estimate using more detailed or realistic data and then to a probabilistic exposure estimate, if consideration of the preceding estimates dictates the need to do so. However, as one descends, the complexity increases. It should be realised that whilst there may appear to be many different approaches, they are essentially based upon one of two basic concepts, i.e. deterministic or probabilistic. The first three approaches could be considered as being straightforward deterministic approaches where fixed values are allocated for both consumption and concentration. Refined deterministic or probabilistic approaches use distributions rather than fixed-point values (or any combination of both) for any exposure estimate calculations.

Box 3B. Recommended steps in assessing dietary exposure to any type of chemical

1. Define the objective and scope of the assessment including the units for exposure (e.g. µg/person/day or mg/kg bw/day)
2. Define the rule(s) for stopping the exposure assessment and not having to move to the next more refined tier (e.g. §1.2)
3. Use the most conservative approach to estimate exposure, e.g. deterministic with "worst case" assumptions
4. If this does not give cause for a safety concern (i.e. meets the rule in step 2) then stop at this stage!
5. If a more refined exposure assessment is required, review what data exist (concentration data, foods involved, application patterns, etc.) and their uncertainty and suitability for use in any estimate of exposure
6. Decide on an approach to refining the deterministic model based on the available data, bearing in mind that any uncertainties have to be considered
7. Compare the results of step 6 against the rule in step 2
8. If the results are acceptable (i.e. value < in step 2) no further evaluation is required. Go to step 11!
9. If the results are close to (e.g. 90%) or above the value in step 2, then further refinement is required. Steps 5–8 may need to be repeated several times depending on the information available and the approaches used, but each iteration should be evaluated against the rule in step 2
10. In general, when using a tiered approach and if a deterministic approach shows no cause for concern do not use a probabilistic method. The exception would be when the objective and scope is to more fully describe or to characterise the variability and/or uncertainty
11. The scope and objectives of the evaluation may require that several alternative values are developed to pass on to a risk manager, in which case it may be necessary to repeat steps 5–8
12. The final assessment should include appropriate documentation as outlined in Section 4. This should include a detailed discussion on the uncertainty and how that uncertainty was evaluated to provide the risk manager with the information to make an appropriate decision[3].

3.3.2 Deterministic approaches

3.3.2.1 Introduction

Deterministic estimates of exposure typically involve using fixed values (point estimates) for food consumption (intake) and fixed concentration data for those foodstuffs consumed. The concentration data may be measured in relevant food simulants, foodstuffs or modelled with other standard assumptions for parameters such as intake and body weight being used. The common examples are the EU and the US FDA approaches. Both use single point values and involve using a single estimate, e.g. best guess or worst case, for each variable within a model to determine the model's outcome(s). In the context of exposure assessments, the term "point estimate" 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 chemical concentration (often the average level or upper permitted level according to legislation) (Kroes et al. 2002, Lambe 2002). Point estimates are considered to be appropriate for screening purposes (Parmar et al. 1997) and they can represent methods that are both

[3] Guidance on methods for characterising uncertainties in exposure assessment has recently been published by EFSA (2006c).

conservative and more refined depending on the type of data used in the exposure assessment. A limitation of this approach is that it is difficult or impossible to express any associated uncertainty. The use of point estimates for either or both concentration and consumption data can be applied to total diets, model diets or duplicate diets (Oldring 2006).

The selection of which point estimates to use is the decision of the person undertaking the exposure estimate, in consultation with experts and risk managers. It depends, for example, on expert knowledge of the range of possible values, combined with a risk management decision on how conservative (precautionary or health protective) the assessment should be. For example, do you use high-level consumption (e.g. 100 or 97.5th percentile) with the highest level of concentration data or more reasonable consumption or concentration data? Clearly, if the use of the highest possible consumption combined with the highest possible concentration does not give cause for concern, then there is no issue and no need for a more refined estimate. However, if a conservative estimate exceeds the acceptable level for exposure, then a refined assessment is likely to be needed. This might either be a refined deterministic assessment using more realistic assumptions, or a probabilistic assessment.

3.3.2.2 EU approach

The default assumption is that a person eats, every day over their lifetime, 1 kg food, which is packed in 6 dm^2 of a single type of plastics material. It is further assumed that migration is always at the maximum level that is legal. This generally conservative approach is used by EFSA in the risk assessment process for the evaluation of substances for regulatory purpose.

3.3.2.3 US FDA approach

The US FDA estimates probable exposure to food contact substances (FCS) by combining migrant levels in food, often from migration studies, with information on the uses of food-contact articles that may contain the FCS (i.e. on the fraction of a person's diet likely to contact food-contact articles containing the FCS). Both the concentration in the daily diet (i.e. dietary concentration) and the estimated daily intake (EDI) from the FCS and the cumulative EDI (CEDI) from all regulated uses and effective food contact notifications are used by the US FDA in the safety evaluation of a FCS. The approach is designed to deal with the majority of FCSs intended for single use. In this calculation, a number of factors are combined to estimate potential exposure. Consumption factors describe the fraction of the daily diet expected to be in contact with specific packaging materials. To account for the variable nature of food contacting each food contact article, the US FDA has calculated "food-type distribution factors" for each packaging material to reflect the fraction of all food contacting each material that is aqueous, acidic, alcoholic, fatty and dry. This information is then combined with migrant levels in food (or extraction into food simulants) and a total food intake of 3 kg per person per day (total solids and liquids) to calculate exposure to migrant(s) from an FCM. The US FDA uses data on the types of food, packaging surface, the number of food packaging units in each food packaging category, the distribution of container size and the ratio of the weight of all food packaged to the weight of the package to develop these factors. All of these data were obtained from market data analysis (US FDA 2002).

3.3.2.4 Per capita approach

Per capita estimates of food chemical intake can be made for virtually every European country. They permit comparison between different European countries. There are in essence two basic approaches:

1. Multiply the average food consumption of the whole population by anticipated or actual levels of the migrant
2. Divide the total available food chemical by the number of individuals in the population.

An advantage of the *per capita* approach is that it is cost-effective and relatively straightforward. *Per capita* estimates can be used as a starting point for a more refined estimate, but as they average exposure over both consumers and non-consumers, they make no allowance for the high level consumer. Some (Rees and Tennant 1994) claim that a factor of three can be applied to the *per capita* estimate to give the exposure for the 97.5th percentile consumer, or a factor of two for the 90th percentile consumer. However, whilst this may be valid for single foodstuffs, it is less likely to hold when the migrant could be in a number of different foodstuffs (Rees, private communication). Others consider that the high consumer of a single foodstuff consumes three times the *per capita* consumption, whilst for the whole diet a factor of two is more appropriate. The accuracy of the simplistic assumptions of estimating exposure for the high consumer is uncertain.

Wherever possible *per capita* data should not be averaged, but a range retained in any subsequent calculations. The better the manufacturing data and demographic data the "better" and more reliable the *per capita* estimate. Some would argue that the *per capita* approach is a particular subset of the deterministic approach.

3.3.3 Refined deterministic approaches

3.3.3.1 Introduction

In the case of food additives, two deterministic approaches have been identified in the European Commission's Scientific Cooperation Programme (SCOOP). The first of these, the Step 1 approach, uses food consumption data at the population level (mean daily intake or some higher percentile) and uses food groups rather than individual foods (European Commission 1998). Where legally permitted to be present in a food or food group, a probability of 100% presence is assumed and the concentration is taken to be the maximum legal level. This is a highly conservative approach and if this leads to an estimate below the acceptable daily intake (ADI), then no further analysis is needed. The Step 1 approach for food additives is also, more-or-less, the default assumption in EU regulations on plastic FCMs, in which a substance is legally permitted in all materials and may migrate up to the specific migration limit into all foods.

The Step 2 approach also utilises food consumption but unlike the Step 1 approach, which uses population data, the Step 2 approach computes a value for each individual to obtain a distribution[4] for the intakes of all individuals, and then takes a particular percentile (most often the 97.5th) of the distribution for decision-making (European Commission 1998). In the Step 2 approach, for each eating occasion of a food in which the additive may legally be present, the assumption is that it is present and at the maximum permitted levels. However, in the case of exposure to food packaging migrants an alternative deterministic approach is needed because, whereas there are legal definitions of which foods particular additives may be used in, this is not the case for packaging materials. Thus, an alternative deterministic approach is used for such compounds.

[4] Note: The calculations for Step 2 are deterministic but the output is a distribution, which may be regarded as probabilistic.

3.3.3.2 Matrix approach for refining a deterministic approach

Rees and Tennant (1994) summarised the possible scenarios for chemical contaminants in food as shown in Table 3. If the combined worst-case does not give cause for concern then there is no need to refine any exposure estimate. Whilst this is strictly not applicable to migrants, the same philosophy applies. For example, assume that for a given migrant, migration is at the SML and that all the foodstuffs that *could* be packaged in that material *are* packaged in that material. This can be considered as a useful screening technique because if the exposure estimate does not give cause for concern, then there is no need for further refinement. This approach is useful if there are limited data or a sudden "unexpected" issue occurs where no data exist. These estimates by definition are imprecise. This matrix approach can result in four values for the risk manager to consider and also gives an idea of the potential range (spread) of the different estimates resulting from different assumptions.

		Food consumption	
		Typical (*per capita* or average)	Worst case (above average or high level)
Occurrence of chemical in foodstuffs	Typical (mean or most common value)	Likely The exposure calculated is likely in the majority of consumers, particularly if averaged over a year	Possible Fewer consumers are likely to have exposure of this level, but may require consideration if the dietary pattern is habitual
	Worst case (maximum value or high percentile)	Possible Fewer consumers are likely to have exposure at this level but may require consideration if there is a good chance of selecting high chemical levels on a regular basis	Unlikely Whilst this may be possible, there should be an estimate of whether it is probable on a regular basis and what the toxicological implications may be

Table 3. Matrix of intake estimates using the "scenario" approach (Rees and Tennant 1994)

3.3.3.3 Steps in refining a deterministic approach

Generally, deterministic estimates are conservative, they use over-estimates for consumption and concentrations and produce an over-estimate of exposure. This is efficient because it allows a simple calculation to be used for routine screening purposes. In cases where deterministic exposure estimates exceed the level of concern, probabilistic methods can be used to obtain a more realistic assessment of the actual range of exposures.

In refining a deterministic model one approach is to start with a simple refinement of existing or readily generated data on:

- Types of packaging containing the substance of interest
- Types of food that use that packaging
- Modelled or measured concentrations for migration of the substance into those foods
- Consumption of those foods by the relevant population
- Body weights of the relevant population.

Box 3C. Steps for refining a deterministic approach

1. Use the available data to make conservative deterministic estimates of consumption and concentration for each affected food type
2. Where data are not available or uncertain, use conservative assumptions (e.g. use large food groupings such as fish, vegetables, etc.; assume 100% of each group is packaged in the material of interest; use simulant concentrations; set non-detects equal to the LoD). In this first refined assessment, it is recommended that extreme percentiles be used (e.g. 99% or higher) for consumption and concentration to ensure that the result is clearly conservative (i.e. unlikely to be exceeded by any individual)
3. These values are then used to develop a conservative estimate of exposure
4. If this conservative exposure estimate is below the relevant level of concern then *no further assessment is required*, otherwise continue refining the assessment
5. Review each of the inputs and assumptions used in the assessment
6. Identify places where the assessment can be refined in ways that are still clearly conservative, i.e. producing results that are closer to, but not below, the highest actual exposure. The most likely opportunities for this will be increased detail in the treatment of food groups, removing from the analysis sub-groups of foods or even individual foods for which it is certain that they will never contain the substance of interest. At this stage, continue using conservative percentiles for concentration and consumption
7. As in the prior estimation process, use the revised estimates and assumptions to recalculate the deterministic estimate of exposure, which will still be conservative.
8. If it is below the relevant level of concern then *no further assessment is required*, otherwise continue refining the assessment
9. Review each of the inputs and assumptions used in the assessment. Identify places where the assessment can be further refined while still remaining deterministic.

3.3.3.4 Further refinements of a deterministic approach

In some instances, the first approach to refining a deterministic one may still give values that are above the rule or give cause for concern. Approaches for further refinements include those shown in Box 3D.

Box 3D. Further refinements for a deterministic approach

1. Repeat the assessment with a series of alternative values for concentrations and consumption (e.g. 99^{th}, 95^{th}, 90^{th} percentiles)
2. Introduce (conservative) factors to account for differences between foods in their composition (e.g. fat content) or packaging (e.g. area-to-volume ratios, or market shares)
3. Find or generate additional data, e.g. measured concentrations for key food groups or packaging types, information on market shares, etc.

This process may result in several estimates of exposure with varying degrees of conservatism. These should be clearly communicated to the risk manager/decision maker so that they can consider what level of conservatism is appropriate. This will also require a clear discussion of the uncertainties involved in the estimation and the rationale for all decisions made in the process.

If this assessment provides sufficient confidence that exposure is below the relevant level of concern then no further assessment is required. However, if questions remain, and refinements to the deterministic approach are not possible a probabilistic assessment should be considered.

3.3.4 Probabilistic approach

3.3.4.1 Introduction

An exposure assessment, performed using probabilistic methods, is similar in concept and approach to the deterministic estimate method, with the main difference being the methods used to incorporate the variability and uncertainty in risk. Each uncertain variable can be represented by a distribution function instead of a single value. Probabilistic techniques seem to be superior to the conventional deterministic/point estimate approach. However, deterministic techniques have been the traditional and widely accepted method of assessing the level of consumer exposure used by both regulators and industry. The justification for this is understandable: the large uncertainty attached to all aspects of exposure and the potential health risk for the whole population means that worst case scenarios and conservative estimates were thought to be the best way to protect consumers (Ferrier et al. 2002). The use of probabilistic modelling should be the second or third option when assessing exposure from contaminants in food (Kroes et al. 2002).

It should be noted that probabilistic modelling does not require that all of the input parameters are distributions. Indeed, in many instances probabilistic modelling can and is run with a combination of variable and fixed value input parameters.

The methods described in preceding sections are deterministic in that they normally use point estimates (fixed values) for food consumption and migrant concentration to produce point estimates of exposure. However, in reality, consumption, concentration and exposure are not fixed values but are variable and uncertain, e.g. consumption varies from one person to the next, and concentration data are affected by measurement uncertainty.

3.3.4.2 Principles of probabilistic modelling

Probabilistic methods (sometimes called stochastic) use distributions to take account of this variability and uncertainty. A variety of modelling techniques can be used to characterise variability and uncertainty. Monte Carlo analysis is perhaps the most widely used probabilistic method (Cullen and Frey 1999, Scientific Steering Committee 2003, Interdepartmental Group on Health Risks from Chemicals 2004, EFSA 2006c).

Probabilistic modelling is not readily available to all as it requires the use of complex mathematical models and generally a greater detail of input data. Probabilistic modelling has only recently been used to assess exposure to migrants from FCMs (Castle 2003, Castle et al. 2005, Duffy 2006, Holmes et al. 2005, Oldring et al. 2006). A more detailed description of Monte Carlo modelling is given in Annex II.

The basic principle is that distributions are used to represent inputs for exposure assessments that are variable and/or uncertain. The exposure calculation is then repeated many times, each time taking a number at random from each distribution. Each repetition or iteration of the calculation generates one estimate of exposure and these estimates are then combined to provide a distribution for exposure. This output distribution represents the variability and uncertainty of the estimated exposure. The number of iterations required to give a stable output distribution is often large (e.g. 1000–10 000 or more) but can be completed quickly with modern computers.

Inputs for exposure assessment are usually both variable and uncertain and this can be represented by additional distributions. For example, it may be known that variation of concentrations follows a log normal distribution, which can be defined by its mean and standard deviation. However, if the number of measured concentrations is small then the mean and standard deviation will be uncertain. This uncertainty can be represented by two further distributions, one for the mean and one for the standard deviation.

Distributions for variability and uncertainty can be sampled together (1D Monte Carlo) or separately (2D Monte Carlo). 1D Monte Carlo generates a single distribution for output, of the type shown in Fig. 3 (Annex II) with a single estimate for each percentile. 2D Monte Carlo, by separating variability from uncertainty, provides confidence intervals for each percentile. This provides an indication of the reliability of the exposure estimates, and how it is affected by the uncertainty of the inputs. Differences in the interpretation of 1D and 2D Monte Carlo outputs are discussed in Annex II.

3.3.4.3 Types of output available from probabilistic modelling

The primary output of a probabilistic exposure assessment will be a distribution of exposure for the population, together with confidence intervals if 2D Monte Carlo was used (see Annex II for further details). From these distributions, particular statistics of interest can be reported:

1. The estimated exposure for a specified percentile of the population, with or without confidence bounds
2. The proportion of the population exceeding a specified level of exposure, with or without confidence bounds
3. The probability of a randomly chosen individual exceeding a specified level of exposure.

Probabilistic assessment can also generate secondary outputs that may be helpful to risk assessors and decision-makers:

1. To estimate the percentage contribution of different types of food to overall exposure, together with confidence intervals if uncertainty has been handled separately. This may help to identify foods that could be targeted for risk reduction, e.g. by changing the packaging of a food or advising consumers to eat less of it. (Note: a deterministic approach can help identify contributions but would lack the ability to develop confidence intervals)
2. To identify which inputs contribute most to variation in exposure by using correlation coefficients, sensitivity analysis or scatter plots between different input variables and the output. This may help to identify variables that risk managers could manipulate to reduce exposure, e.g. by modifying a production process to reduce variability in migration
3. To identify which inputs contribute most to uncertainty by using the correlation coefficients or scatter plots between inputs representing uncertainty and the uncertainty of the output. This can be useful if the assessor or decision-maker

wants to decrease uncertainty, as it enables them to focus data collection on the inputs that contribute most to uncertainty.

Examples of these three types of secondary output are presented by Holmes et al. (2005).

3.3.5 Comparison of deterministic and probabilistic approaches for assessing exposure

In Table 4, advantages and disadvantages of deterministic and probabilistic approaches for assessing exposure are compared.

If used inappropriately (e.g. making wrong assumptions, using unrepresentative data), probabilistic methods will give misleading results. Because of the complex procedures that lie behind probabilistic methods, casual inspection of the output may not detect any fundamental flaws. So, good practice, including complete documentation, is essential. Guiding principles for Monte Carlo analysis have been published by several authors (e.g. US EPA 1997). Key elements for probabilistic exposure assessment are similar to those for other approaches and were outlined in Box 3C.

DETERMINISTIC (not refined)	PROBABILISTIC
Advantages	**Advantages**
▪ Guidelines exist for the risk assessment process ▪ Less need for extensive databases to support the input variables ▪ Standard default assumptions can be made ▪ Relatively easy to carry out ▪ Single risk estimate output is easy to understand and interpret ▪ Industry and regulators are familiar with this approach	▪ All available knowledge and data are used and the probability of a value occurring can be investigated ▪ Exposure estimates are presented as a distribution, with each value having a probability attached to it ▪ Probability of potential exposure can be accurately shown, accompanied by extensive information for decision making ▪ Variability and uncertainty can be quantified ▪ The relative importance of different sources of variability can be quantified, which may help to identify risk management options ▪ The relative importance of different sources of uncertainty can be quantified, which may help to target further data collection
Disadvantages	**Disadvantages**
▪ Not all the available (and potentially valuable) data for each variable are used ▪ Knowledge and data on patterns of use and exposure potential are not used ▪ Variability and uncertainty are not reflected ▪ Deterministic assessments are frequently intended to be conservative ▪ It is rarely known how conservative a deterministic assessment actually is ▪ Combining conservative assumptions for multiple input parameters will lead to extreme over-estimates of exposure (hidden compounding conservatism)	▪ Relatively complex to perform with more labour, expertise and resources needed ▪ Most extreme exposure estimated can be seen from the distribution, allowing consideration, quantification and undue focus on very infrequent or unlikely events ▪ Acceptance problems are confounded by the unfamiliar process, the lack of precedents and guidelines, and risk management decisions having to be based on probabilities and large amounts of information

Table 4. Advantages and disadvantages of the deterministic (point estimate) and probabilistic approach (adapted from Lunchick 2001)

3.4 Key elements of good practice

Whatever approach is to be used for an exposure assessment it is important that it follows good practices as outlined below. This applies to deterministic, refined deterministic and probabilistic approaches.

Box 3E. Key elements of good practice

1. Clearly define the objective and desired output of the assessment
2. Ensure the necessary expertise is available, including expertise on statistics if probabilistic modelling is used as well as expertise on dietary patterns, packaging use and migration
3. Specify an appropriate exposure model to derive the desired output from the available input data. This should include explicit definition of any extrapolation that is required between the available data and the measure that would ideally be required (e.g. concentrations in food simulants to concentrations in real foods)
4. If using probabilistic methods:
   a. Specify appropriate distributions to represent the quantified sources of variability and/or uncertainty. Pay particular attention to the tails of distributions
   b. Systematically consider the possibility of dependencies between all inputs and account appropriately for significant dependencies in the assessment
   c. Propagate uncertainty and/or variability in an appropriate way to obtain the desired output
5. Document and justify all methods and data inputs, and the extent to which they have been validated or evaluated (see Annex II)
6. Present and explain the results as clearly and transparently as possible
7. Systematically list all known sources of variability and uncertainty that were not quantified, since it is never possible to quantify them all, and discuss their potential impact on the assessment outcome [5]. This is essential for all assessments, whether deterministic or probabilistic, in order to communicate to decision-makers how different the real exposure might be from the estimated exposure.

3.5 Special considerations in exposure assessment

3.5.1 Introduction

In order to estimate exposure, it is necessary to identify what concentration is relevant for each type of food consumed. Therefore, it is necessary to identify which foods are packaged in the material of interest and to separate foods for which different concentrations of migrant are expected. This should be done by considering what factors are expected to influence migrant concentration and using these to define categories of foods for which different concentrations are expected.

[5] Some practical approaches for this are described by EFSA (2006c).

After the food categories have been defined, each food item must be assigned to a relevant category in order to perform the exposure calculation but this depends upon the food survey being used and its level of detail.

Defining the food categories and assigning the food items can be a laborious process, especially if the number of categories and food items are large. Also, it requires extensive information on the ways in which the packaging is used and how these will influence migrant concentration. Therefore, it will be beneficial to adopt a tiered approach. This would start with a conservative estimate, using a few broad food categories (e.g. just the simulant categories A–D), and making worst-case assumptions for each category (e.g. using the measured simulant concentrations and conservative assumptions for area-to-weight ratios). If this conservative estimate resulted in an exposure estimate well below the relevant limit or value of concern, then it might be concluded without further assessment that the exposure is acceptable. Otherwise, it will be necessary to refine the assessment by increasing the number of categories and making more realistic assumptions to estimate more closely the true exposure. The degree to which this is possible will depend on the quality of data available (see Box 3A).

Box 3F. Special factors that should be taken into consideration when assessing exposure for food packaging materials

- The usual default categories are those associated with the standard food simulants A–D/X: aqueous, acidic, alcoholic and oily or fatty foods and, if relevant, dry foodstuffs
- The detailed nature of the packaging is important, specifically the ratio of packaging area to food weight, and the proportion of packaging area containing the material of interest. For example, when assessing migration into drinks from metal coatings, it would be necessary first to identify which drinks are in contact with metal coatings, then separate canned drinks from those in glass bottles with metal closures (which have a smaller contact area), and finally subdivide the bottles and cans according to their volumes (which affect the area-to-weight ratio)
- If measured concentrations are available from real foods, then these should be examined to see whether they appear similar, in which case those foods can be treated as a single category, or whether they should be divided into different categories
- In many cases the required data are not available, therefore it is necessary to use whatever data are available and utilise the most appropriate protocols unless it is deemed necessary to further refine the approach to obtain a more realistic estimate. In most cases the simple high-level approach will normally suffice.

3.5.2 Who and what should be considered in any exposure assessment?

There are a number of common issues that must be addressed in any assessment of exposure, namely:

- High consumers and vulnerable sub-populations
- Population characteristics
- Which percentile of the population should be used for the exposure estimate
- Consumer loyalty

- Body weight
- Any uncertainties affecting the inputs and outputs of the assessment
- Conversion from short term to long term or usual exposure.

Approaches to these issues may vary, depending on the type of chemical involved and are discussed below in the context of food packaging materials.

3.5.2.1 High consumers and sub-populations

When estimating intakes of chemicals by the population, certain population characteristics, such as consumer habits, may lead to sub-groups within a population having higher exposure, being at the upper end of the exposure distribution. When completing an exposure estimate it is usually the upper end of the exposure distribution that is of interest to the regulators of migrants from FCMs, unlike nutritionists who may be equally interested in the low consumers of minor nutrients and the high consumers of foodstuffs that may adversely affect human health (e.g. alcohol, fats, sugar). This is to ensure that not only the average consumer is protected adequately but also those at the upper end of exposure. When completing an exposure estimate it is important to understand who these high consumers are and what characteristics are contributing to their high exposure. Individuals may be high consumers of a migrant for a number of reasons:

- Population characteristics
- High consumer of packaged foods
- High level of packaging loyalty
- Habitual consumption of a particular foodstuff(s), e.g. alcohol.

Individuals with particular lifestyles may have lower or higher intakes of packaged foods. There has been a large increase in the convenience meals market in the past number of years, as well as in the single-portion consumer market. The packaging used for these single portions has a larger surface area-to-food ratio than that for a family-sized package. Furthermore, packaging for convenience meals is often designed so that the food can be heated or cooked in the packaging. These factors may lead to consumers having a higher exposure to a chemical migrant, e.g. due to higher migration values. At the other extreme, there may be individuals whose main diet consists of home grown/home-produced foods that are not packaged. These individuals may represent the lower tail of the exposure distribution. These patterns of behaviour may be taken into account by using consumption surveys that distinguish these food types or by estimating their contribution from other information (e.g. marketing data).

3.5.2.2 Population characteristics

Applicability of a tolerable daily intake (TDI) for all ages and some populations as well as the significance of occasional excursions above a TDI are outside the scope of this report. If the migrant of interest is present more often or at higher levels in foods consumed by infants, there will be a higher intake of the migrant per day. This was demonstrated in studies that estimated the intake of epoxidised soybean oil in infants (Fantoni and Simoneau 2003). When completing exposure estimates sub-groups can be selected from a population sample if the appropriate data for demographics are included in the exposure model (e.g. age, weight, or gender). However, by selecting these sub-populations from the sample population a smaller sample size is generated, which leads to an increase in the uncertainty of the results of the exposure estimate, especially in the tails (i.e. the uncertainty around the 95^{th} and 97.5^{th} percentile).

3.5.2.3 What percentile should be used?

The definition of high-level consumers varies but is normally either the 90th, 95th, 97.5th or 99th percentile of the distribution of individual intake values (Rees and Tennant 1994). In other situations, attempts are made to ensure that the majority, if not all, of the population are included in any exposure estimate, e.g. the US EPA (2000) uses the 99.9th percentile for pesticides. If the 90th percentile value is used in the safety assessment, then one person in ten will exceed this value; if the 95th percentile is used then one person in 20 will exceed this level, and so on. It is worth noting that different agencies use different figures to represent extreme consumers and this may lead to differences in the interpretation of results. For example, whereas in many cases the EU uses the mean of the 95th percentile, the US FDA uses the mean of the 90th percentile (Benford 2001). At the present time, there is no agreed percentile value for assessing exposure to food packaging migrants.

This is a risk management decision but it should be guided in part by the nature and severity of the chemical hazard. For example, if a chemical causes mild and temporary stomach irritation the level of protection afforded could be less than that for a chemical that had profound and irreversibly damaging effects. Ideally, it should be possible to estimate the exposure to a migrant from a FCM for any percentile of the population. In practice, only the more sophisticated techniques, such as refined deterministic or probabilistic modelling are capable of deriving these results. In practical terms, more data are needed to provide reliable estimates of the higher percentiles. For example, at the 97.5th percentile level a survey of 1000 people will by definition only have data for 25 people in the upper 2.5th percentile. The uncertainty in the estimates increases as the percentile figure is increased.

To proceed through a tiered assessment it is necessary to have a value below which it is not necessary to continue but it must be consistent with the scope and objective of the analysis, including specified regulatory requirements. One such approach was outlined in §1.2. When such information is not available it is recommended that the value be derived to include the entire distribution of actual exposures or provide several alternative estimates of exposure that can be reported to the risk managers involved with the analysis.

3.5.2.4 Consumer loyalty

Consumer loyalty covers both brand and packaging loyalty. Little publicly available data exist on brand loyalty and this is only relevant when the brand has only one type of packaging and/or one supplier of that packaging. No data exist on packaging loyalty. Packaging loyalty is different to brand loyalty. For example, a brand loyal consumer may always drink a particular brand of cola irrespective of its packaging type (can, glass, PET) whereas a packaging loyal consumer will always drink a can of cola irrespective of its brand name. The exposure for a packaging (or brand) loyal consumer must always be considered compared to that of one who is not. By accounting for loyalty it is ensured that non-average consumers, particularly those with a high intake of a particular chemical, are protected. Some of the simpler approaches (e.g. EU) to assessing exposure assume loyalty by default, not explicitly.

Assessing the effects of loyalty is suited to probabilistic modelling. As no data exist on the packaging loyalty of consumers it is recommended that an exposure model be run twice, once including and once excluding packaging loyalty. In the first instance, packaging loyalty can be ignored. In this instance, the probability of a consumer choosing a particular packaging type is based on the market share of that packaging type for that product. In the second instance, it is assumed that total packaging loyalty exists, so that if a consumer chooses a particular packaging type once, they will always

choose that type of packaging. From previous work completed on brand loyalty, it has been shown that loyalty stretches the tails of an exposure estimate (Leclercq et al. 2003, Holmes et al. 2005).

3.5.2.5 Body weight

Body weights are usually recorded in food consumption surveys. These data can be used in exposure estimates to take account of variation in body weight between individuals, replacing the default single body weight used in deterministic estimates (e.g. 60 kg for adults). Usually, there is a positive correlation or dependency between body weight and total consumption – larger people tend to eat more. Infants and children consume a higher amount of food per unit body weight compared with adults. Therefore, when the intake of a migrant is compared on a per kilogram body weight basis infants and children often have higher exposure. Infants also have less heterogeneous diets and have a higher frequency of consumption of particular foods. It is important to ensure significant dependencies are captured by the exposure estimate to avoid misleading results.

3.6 Assessing exposure for multiple countries

When an issue involves more than one country or needs to be considered at an European level, it may be desirable to characterise exposure for multiple countries. The EU assumption of 1 kg food per person per day being consumed all in the same packaging is a pan-European exposure assessment. The question may arise if a particular issue arises for a foodstuff that is consumed in much larger quantities in a particular country. Examples could be fish in Scandinavia and vegetables in olive oil in Italy.

Ideally, a separate exposure assessment should be carried out for each country, using data on consumption, packaging use and concentrations that are specific to that country. In practice, however, such data are available for only one or a few countries. Deterministic or probabilistic approaches can be used.

Instead, therefore, it may be necessary to develop a picture of exposure for multiple countries by extrapolation from the data that are available. Clearly, this will involve more uncertainty than if data were available for each country. Therefore, either the uncertainty should be quantified, or the extrapolation should use conservative assumptions or both of these approaches should be used to provide a sound basis for decision-making. There are a number of options available, some of which are given in Box 3G.

Box 3G. Options for a pan-European approach

1. Carry out a worst-case exposure assessment based on estimates for consumption, packaging use and concentrations that are conservative for all the countries concerned
2. Identify which country is expected to have the highest exposures and conduct probabilistic or deterministic assessment for that country, if data are available
3. Conduct probabilistic or deterministic modelling for countries where data are available, but use a higher than normal percentile exposure for decision-making purpose as a surrogate for higher exposures in other countries. However, it is likely to be difficult to agree on how high a percentile is needed
4. Use data from one country to produce a probabilistic or deterministic assessment for another, but using extrapolation factors or different assumptions to take account of national differences. For example, packaging use in one country might be double that in another; or people in one country might typically consume 50% more of a particular food type. These factors and assumptions could be based on available data (e.g. household basket surveys) or expert judgement, and would need to be carefully evaluated and justified.

A tiered approach could be envisaged, starting with option 1 above and then proceeding to one of the more complex options if necessary. It may not be necessary to repeat this for every country, if a subset of countries can be selected that adequately represent the wider group (e.g. it might be sufficient to choose one northern and one southern country in Europe, to represent regional variation in diet).

Results for multiple countries would, most simply, be presented as a set, so that comparisons could be made between them. For example, estimates for the 97.5th percentile consumer in each country could be shown together in a single table. If it was desired to estimate statistics for an aggregated population covering several countries (or the EU as a whole), then it would be important to take account of the different sizes of the populations in each country.

3.7 Exposure from multiple sources of food contact materials

When completing exposure modelling of the intake of a migrant, assumptions often have to be made about the presence or absence of that migrant in the food. These assumptions are made due to the lack of experimental data on migrant concentrations in all foodstuffs. In order to make an assumption concerning the presence or absence of a migrant in the food, information is needed on what materials have actually been in contact with the food.

Foods may be in contact with a number of packaging materials during their preparation, processing or presentation. For a single food product, for example cheese, there are a number of stages during production, distribution and retailing at which it could be in contact with different packaging materials. It may also be re-packaged after purchase by the consumer before storing in a domestic refrigerator. A composite food that has a number of ingredients may also have migrants from a number of packaging materials, as different materials could have been used for the ingredients and then the composite food.

Many foods on the market have packaging formats that have more than one type of material in contact with the food. This is important information when modelling the probability that a migrant is present in the food and at what concentration, as the migrant may be present in one or both of the contact layers. Also, if packaging is made from a number of layers of materials, then there may be migration from these other layers and not just the food contact layer. Therefore, when assigning a migrant concentration to a food during the exposure modelling process, the potential concentration from all the layers and not just the plastic layer must be considered.

It is difficult to obtain a complete history of packaging materials used for all food items. If packaging information is recorded at any of these stages, then it can be used to improve the quality of the exposure assessment and to reduce uncertainty in the assessment. The concept of multiple sources of packaging migrants is important to keep in mind if analytical data demonstrate a high level of a migrant in a food as this migrant may be from a number of packaging sources (or other FCMs) and not just the packaging used at retail level.

Box 3H. Exposure from multiple sources of food contact materials

Contribution to exposure other than from the FCM must always be addressed in any exposure estimate.

4 Minimum requirements for data documentation

However good an exposure estimate, the underlying assumptions have to be understood and accepted by the target audience. Without explanation and without transparent, clear and concise supporting documentation, it is unlikely that an estimate would be acceptable. Thus, the question is what are the minimum requirements for documentation? Whilst this can only be answered in detail on a case-by-case basis, some general rules apply.

For cases where exposure to a known substance – either intentionally added or as a NIAS – is to be estimated, the following documentation is recommended as a minimum requirement:

1. The source(s) of the consumption data should be identified along with a judgement on its/their suitability for the task(s) in hand. Any weaknesses or particular strengths should be highlighted. If more than two or more sources of consumption data exist but all are not used, then reasons must be given why some were rejected. If consumption data from only one EU country is used, it is necessary to explain why it is representative for the whole of the EU or why this is irrelevant, or what assumptions have been used to try and make the data pan-European. Alternatively, it could be argued that any exposure estimate could be adjusted by a factor to cover the whole of the EU but the factor to be used must be justified
2. The packaging containing the substance(s) of interest must be identified and listed
3. Foodstuffs that could possibly be packaged in any of that packaging must be identified and listed. The information source should be indicated, e.g. expert knowledge, databases
4. How market shares for consumption of foodstuffs in the packaging of interest are allocated must be described, with supporting evidence or documentation
5. The allocation of concentration data to any foodstuff in that packaging must be described in detail, along with any assumptions used. If simulants are used instead of foodstuffs to derive concentration data, then it is necessary to describe, and justify, how the mg/dm² results were converted to mg/kg. If modelling is used, reference should be made to the model used; with any underlying assumptions. If zero concentration data are used for some foodstuffs in the packaging of interest, then it is necessary to justify the use of a true zero
6. The principle(s) of the analytical method(s) should be outlined together with the quality assurance criteria
7. The treatment of LoD and LoQ values needs to be described
8. It is necessary to demonstrate that the packaging containing the foodstuffs is representative for the whole of the EU rather than for one region. For example, fish may be packaged in different FCMs in different parts of the EU, thus, it is necessary to show how the data used either represent the EU or only a region. If the latter, it is necessary to describe and justify why that data can be used on a pan-European basis or adjust the exposure estimate accordingly
9. It is necessary to demonstrate that the packaging containing the substance of interest and the concentration data used for the exposure estimate are representative of the whole of the EU. Alternatively, the use of regional data has to be justified or a factor applied to any exposure estimate

10. It is essential to show how the links between the foodstuffs consumed, from consumption surveys, their packaging and their concentration data were established with uncertainties being identified
11. The methodology(ies) used to derive the estimate of exposure must be described. In approaches other than the EU (possibly FDA) approach, the derivation of the factors used and the underlying assumptions must be described in detail. The more refined the approach, the more important this becomes, as there is a universal mistrust of “black boxes”
12. The output(s) must be in units people understand and the population they relate to, with the percentile for that exposure estimate (if appropriate) clearly described
13. Any potential impacts of packaging loyalty, socio-economic or ethnic groups, vulnerable groups etc. must be discussed and reasons given as to why they were, or were not, considered in the estimate. The ideal situation is a comparison of the effect of both
14. Uncertainties associated with each dataset and calculation step in the exposure estimate should be described, preferably in a quantitative manner
15. Any shortcomings of the process should be included in the summary along with the application of this estimate – for example, is it restricted to a particular type of foodstuff or packaging or region.

The above list illustrates that several questions arise concerning the input data. How representative are these data? How complete is a data set? What is the quality of the data?

The representativeness of the following data for several population groups (e.g. regional vs. EU) should be expressed:

- Consumption of a type of foodstuff
- Use of packaging material for a type(s) of foodstuff
- Concentration data of the substance of interest in a food packaging.

For certain cases, it is important to have as complete as possible information on:

- Possibly affected packaging material
- Concentration data (e.g. for food categories or for regions).

Last but not least, the quality of data is of utmost importance and must be considered for:

- Concentration data
- Mathematical modelling.

To illustrate the above, one could think of the use of an unsuitable analytical method, which results in false concentration data. Another scenario would be the generation of concentration data (with a suitable method) for only a very limited range of food categories although expert knowledge might indicate a wider use of the substance under investigation in packaging material and, thus, more food categories could be affected. In the above-mentioned examples, valuable and correct consumption data would inevitably result in misleading exposure scenarios.

In those instances where the identity of the migrant(s) is (are) unknown (e.g. unknown NIAS) all of the above cannot be achieved, and so the documentation must be adjusted accordingly. In this case, unlike the former, the objective may be to determine what level of migration would exceed a threshold such as the threshold of toxicological

concern (TTC; Kroes et al. 2004, Barlow 2005) rather than the exposure from a given level of migration. The TCC concept is not accepted in Europe for chemical migration from FCMs but it can be hoped that as the science progresses then the TCC or similar concepts may be used in future. Generally, the same documentation as above is required, but as the concentration data for the unknown NIAS are either unknown or estimated the documentation has to be adjusted accordingly following the same principles of transparency.

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6 Annexes

Annex I
Questions and answers about exposure assessment

The workshop participants are asked to consider, if this section addresses all the questions in the text and to suggest what is missing or propose better answers to the questions raised. Workshop participants are also asked to give an opinion on whether the Q&A is helpful and whether it should remain in the document. Note that it is not intended to discuss all of the questions raised here in the workshop.

The questions, for which this guidance document could be used to answer, are varied; however, some of the questions that have been raised during the preparation of this report are given here with proposed answers. In some cases, the questions raised are outside the scope of this report but are given with answers in order to guide the reader. Where appropriate, reference is given in the answer to the relevant section of the text.

I.I General questions

Q1. Why is the term “exposure estimate” used instead of “exposure assessment” and what is the difference?
A1. In general, the word “estimate” is used when referring specifically to a quantitative estimate of exposure, whereas the word “assessment” is used when referring to the overall scientific consideration of exposure, which will include both quantitative estimates and qualitative evaluation of the associated evidence and uncertainties.

Q2. How is exposure assessment related to risk assessment?
A2. A risk assessment requires an exposure assessment along with the hazard characterisation.

Q3. Is the guidance document applicable to safety evaluation of not-yet-regulated substances, even if the document does not say how to do this?
A3. This guidance document will enable the exposure to any substance, new or existing, to be evaluated.

Q4. What additional certainty do we gain by the proposed approach(es) compared with the present EU approach, and why should they be followed?
A4. The present EU approach is generally conservative and it has a place as a screening phase in a tiered approach, as recommended here. It is not being replaced. Depending upon the approach used, more accurate estimates of exposure can be derived along with a better understanding of the underlying uncertainties.

Q5. How reliable is the approach and does it not generally reduce margins of safety and create a false sense of certainty and security?
A5. There are a different number of approaches outlined in this report. Exposure estimates using conservative inputs are intended to have a wide margin of safety to compensate for the uncertainty in the input data. Approaches such as probabilistic modelling enable uncertainty to be described and quantified, and if this uncertainty can be reduced then the margin of safety can be reduced accordingly. This is normal practice in all fields of life.

Q6. What data/information are needed to conduct an exposure assessment?
A6. Detail of the data required vary significantly depending upon the approach(es) being used. All need concentration data for the migrant in the foodstuffs consumed, however obtained, and all need how much foodstuffs were consumed and by whom, however derived. Section 2 details the data requirements for assessing exposure and Section 3 how these data could be used.

Q7. How can I express the uncertainty related to my data, and should I do that at all?
A7. If for any approach the data are transparent, then any associated uncertainty in that data can be shown. Some of the more simplistic and less refined techniques limit the ability to quantify the uncertainty of the data. The deterministic approach, for example, builds on a number of assumptions that should cover any uncertainty in the data. Probabilistic modelling enables the effects of the uncertainty in the data to be quantified. More discussion of the need to characterise uncertainties and a range of methods available for doing it are provided in EFSA (2006c).

Q8. Should I describe the “quality” and “representativeness” of my data?
A8. Yes. It is necessary not only to describe the sources of any data but also to give a judgement on their quality and representativeness and how that judgement was determined.

Q9. Do I have different requirements on exposure in case of assessing NIAS, or dealing with emerging safety issues (crises), or making petitions etc?
A9. In general, the purpose of an exposure assessment is to compare the actual exposure of the consumer and the health-based guidance value, e.g. TDI. The general input data are identical although the assumptions underlying these data might be different.

Q10. Can I use an exposure assessment already done for the USA, in Europe?
A10. Not automatically. It is necessary to justify that any input data and assumptions used in the USA apply to Europe, and make adjustments, if needed.

Q11. My substance is authorised only in the Warenwet and nowhere else. Can I then simply estimate exposure for Dutch consumers and use the result pan-European?
A11. This constitutes two questions. National authorisation and exposure assessment must not be confused. The national authorisation for a substance rather than a Commission authorisation will have used, if any, whatever exposure assessments were considered relevant at the time. For example, for that substance, authorisation in Warenwet will have a restriction (SML) that shall be met for compliance with Warenwet. If a substance is not authorised by Commission legislation (e.g. Plastics Directive 2002/72/EC and its amendments; European Commission 2002), of which there are many instances (coatings, paper and board, adhesives etc.), then the substance may be used provided compliance with national regulations and the Framework Regulation (EC) No 1935/2004 is met or until EU legislation is in place. As explained in §2.2 and §2.3, there are limited sources of data for assessing exposure. Hence, existing estimates of exposure can and should be used provided the sources of the data and the methodology are transparent and are of a suitable quality. Most importantly, their relevance to the rest of Europe should be either demonstrated or argued.

Q12. Only food packaging is included. How is the exposure from other FCMs addressed? How do you know if it is or is not important?
A12. This report only considers the contribution of chemicals in the diet from packaging. The contribution from other FCMs or any other source is not considered here, as the exposure from packaging is itself a difficult subject. The importance of their contribution cannot be assessed today. If, when measuring concentration data in

packaged foodstuffs, higher than anticipated values are found, then there may or may not be a contribution from other FCMs. REACH, which will catalogue all important applications of substances, could be used to identify whether other potential sources of significant exposure exist (European Parliament 2006). However, when other occurrences are known, then such data should be used in a cumulative exposure assessment.

Q13. Can exposure be used to derive modified SMLs for legislation and if so how?
A13. Yes, this argument could be made. SMLs are set by the Commission to protect consumers. However, whilst it is possible to derive exposure estimates and hence derive a risk assessment, the process of authorising and listing the substances in the legislation is beyond the scope of this report.

Q14. In the tiered approach, how do I decide when to stop if there is no toxicological limit value against which to compare the exposure estimate? Do I always have to continue to the most refined level possible?
A14. Follow the tiered approach until toxicological data support that there is no threat to human health. This may be the case when toxicological modelling shows no issues or by using structural alerts or quantitative structural activity relationships. However, if the structure of the migrant is known, it can be assessed by attributing it to defined classes of concern (Cramer Classes), which are linked to specific thresholds of no concern with exposure ranges from 1.5 to 1800 µg/person/day (Barlow 2005).

Q15. Is a separate list of authorised substances needed for the packaging of food for infants and children, because the exposure estimates for them will always be different to that for adults? Does the current legislation apply different SMLs for the packaging of food for infants?
A15. Whilst it is possible to derive exposure estimates for infants and children, and hence derive a risk assessment, the process of authorising and listing the substances in the legislation is beyond the scope of this report.

Q16. What about imports for which usage, compositional information and migration behaviour may be unknown?
A16. In the first place these food packaging materials have to comply with current EU and national legislation. Any assessment of exposure should consider sources from all packaging whether EU produced or not. If information is missing, then the assessment should make allowance for the uncertainty that this introduces.

Q17. How often do the estimates of packaging usage and food consumption have to be reviewed and updated as eating habits and markets change?
A17. This is a complex question. Many food nutritional surveys, one of the best sources of information (see §2.1), take a number of years (>5) from commissioning to reporting. The availability of data dictate at what intervals exposure estimates should be reviewed. The US FDA reviews on a regular basis the changes in the food packaging market and if considered relevant make changes to the packaging use factor (e.g. for PET, see §2.2).

Q18. For the assessment of NIAS, how can you be sure that other applications/ chemicals do not give the same substance that adds to the total exposure?
A18. This is one of the difficulties surrounding NIAS if their structure is unknown. However, industry frequently has good information about known NIAS, thus, all of these sources for potential migration could be identified.

Q19. What percentile population level should the estimates be calculated for – who and how many people are we wanting to protect?
A19. This is primarily a political or risk management decision, although there are several scientific as well as statistical aspects to be considered, in addition to understanding the impact of any safety factors applied in the exposure assessment. This report describes how to undertake exposure assessments (see §3.3). Probabilistic modelling is best suited for estimating exposure for any given percentile of the population. Several publications are available addressing this aspect but are not part of this report.

Q20. If a small sub-population of consumers has very unusual (even bizarre) habits (e.g. skewed food consumption or packaging preference) then how big or small do these groups have to be before they are included or excluded from consideration? How much trouble (time and expense) must we spend to see if these isolated social or geographical groups exist across Europe?
A20. Any group of consumers can be considered for an exposure assessment provided the relevant data exist. These include detailed consumption habits broken down into socio-economic groups etc. (see §2.1, §3.5), packaging and concentration data. If treated probabilistically, the smaller the sample size the greater the uncertainty of any outputs. The second part of the question requires a political decision.

I.II Questions linked to the hazard assessment

Q21. Should exposure assessment be conducted in parallel and in consultation with hazard identification and characterisation, or can the process operate separately until the end result is calculated?
A21. Ideally, they should run con-currently in order that any feedback from one can have the option of changing the other. However, they can be done independently, e.g. as new market use data becomes available but the toxicology data may remain unchanged.

Q22. What about chemicals that may have a common mode of action, e.g. that would have a group TDI – should they be combined together in the estimate of exposure?
A22. If there is a group TDI, this means that the respective substances in the group have the same toxicological characteristics, mostly as a result of very close chemical structures. However, the individual substances in the group may be used in significantly different applications. Whilst it is possible for a group of chemicals (e.g. bisphenol A diglycidyl ether and derivatives) to be combined in any exposure estimate, it is the decision of the risk manager or toxicologists as to what they require.

Q23. For assessment of NIAS, could not other NIAS substances act by the same mode of toxicity and so should be added together? What is the risk, if you ignore this possibility?
A23. The scope of this monograph is assessing exposure to any given migrant or group of migrants including NIAS, known and unknown. If the known NIAS have similar chemical structures, then they would be expected to behave in a similar toxicological manner. That is when toxicologists apply quantitative structure–activity relationships (QSAR).

Q24. What can be achieved without an accepted threshold being agreed?
A24. The Framework Regulation enables one to demonstrate that there is no danger to human health using internationally recognised approaches. In order for the threshold concept to be applied, which is used in the USA, a knowledge of exposure is fundamental to the process. It should be considered that frequently toxicological

information exists on known NIAS. In addition, when EFSA reviews new petitions the reaction by-products are considered. Industry also performs investigations on NIAS, including toxicological assessments.

Q25. If the hazard identification pinpoints vulnerable groups (e.g. pregnant women, young children) then should the exposure assessment focus on them – if so how much weight (emphasis) should be given to this aspect?
A25. As explained in A20, any group can be used for an exposure assessment as long as relevant data exist. It is for the risk manager to decide which groups should be emphasised, based on advice from toxicologists. The respective toxicological endpoints for such sub-groups in the population should be considered for the hazard component, which may lead to a lower toxicologically acceptable level.

Q26. If exposure estimates are used in a petition for a new substance, are the current cut-off limits (10 µg/kg, 50 µg/kg, 5 mg/kg) just migration values or can they be used unchanged as exposure cut-offs, too?
A26. The current EFSA cut-off limits can be directly related to exposure (in that e.g. 50 µg/kg equals 50 µg/person/day) because the current system taking 1 kg/day packaged food intake assumes migration equals exposure. Thus, it should be possible to use these values once the use of exposure rather than migration to set limits is accepted. This may also result in a new approach for the respective toxicological requirements for the respective exposure triggers.

Q27. The emphasis is on chronic, long-term exposure and the trick seems to be to average things out over time. What about acute events (e.g. tin migration into canned foods or latex protein allergy from cold-seal adhesives or food-handling gloves); do these cases need special consideration and how?
A27. Yes, these situations have to be treated differently, for example by comparing an acute reference dose against concentration values and quantities consumed in a single eating event. Some of these acute aspects are documented in the Note for Guidance (EFSA 2006b).

I.III Questions on migration concentration data

Q28. Which of the three possible migrant concentration data should preferably be used: analytical data in food, data in simulants or modelled concentration data?
A28. See §2.3. Legislation considers the amount in the foodstuff as the deciding factor should there be differences. Normally food is too difficult to analyse, thus food simulant data that use substances considered to mimic the migration behaviour to different foodstuffs are used. The food simulants, along with the food categories are described in the Council Directive 85/572/EEC (CEC 1985).

Q29. How do I relate migration concentration data from mathematical modelling to food?
A29. Migration modelling to food simulants is accepted for plastics (Commission Practical Guide; European Commission 2003). Migration modelling into actual foods was part of the FoodMigrosure project. In the future, modelling may be the only way that the large number of variables of time, temperature, foodstuff composition and packaging composition can be efficiently approached.

Q30. Are we confident that simulant data are reliable in estimating concentrations likely in foods?
A30. Until recently, it was generally believed that food simulants were over-conservative or at best representative of the foodstuffs they represented but recent

investigations in the FoodMigrosure project have demonstrated that for certain food categories the prescribed food simulants are inappropriate.

Q31. What about secondary packaging, prior contacts and environmental contamination, which may all give rise to a contaminant in food unconnected with the primary packaging?
Q32. These other sources of contamination can be considered in any exposure assessment provided it is known how much is transferred to the foodstuff and how much is consumed. However, this report is focussed on the migrants in food arising from primary packaging.

I.IV Questions on packaging use data
Q33. Where do I get the information on which packaging type(s) the migrant of interest is present?
A33. Today this information is not readily available and there are efforts underway to obtain more and better information. For further details of what can be used consult §2.2.2. The preferred route to obtain such information is to contact the supplier of the packaging material or article.

Q34. To get the information needed on packaging usage and composition, how does one form common interest groups to involve all parties that may use a substance?
A34. There are various options but one of the more efficient is to work through the relevant trade associations.

Q35. How can I be sure that I did not miss an important package source where the migrant of interest is present?
A35. You can never be certain that a source of a migrant has not been overlooked. However, transparency in the assumptions used and cooperation with others in relevant trade associations should highlight any major sources that have been overlooked. In the exposure assessment, assumptions can be included that the same migrant may be present in other packaging materials (e.g. it can be expected that an ethylene–octene oligomer is present in all polyolefins using these two monomers).

Q36. How do I know which packaging is used for which foodstuff?
A36. This is one of today's issues. There are initiatives and surveys underway. For further details consult §2.2.1.

Q37. My market share is 10%. How do I calculate exposure and what significance has the exposure estimate?
A37. Is this 10% of the packaging or 10% of a particular form of packaging? Is the 10% the only source of the migrant? If not then the other sources must be combined. Depending upon whether additives or monomers and starting substances are to be evaluated there may be two different approaches. Polypropylene will always contain propylene but not necessarily the same additives. The use of market share has to be carefully defined, and making the assumptions used transparent should help overcome any objections. For further details consult §2.2 and 2.3.

Q38. How do I know and how can I convince other people that my packaging usage information covers all Member States and is complete and reliable?
A38. The first step is to use existing data and ensure that it is transparent to all. It is highly unlikely that complete data sets for the different input data will exist, certainly not in the short term. By applying conservative but realistic approaches that are documented, it can be expected that the data used are acceptable.

Q39. What about the use, re-use and potential misuse of materials and articles in the home that we may not know about?
A39. This report is concerned with exposure to migrants from primary packaging. However, the use of certain types of packaging in the home, such as cling film, can be estimated. There are no surveys readily available about the use and re-use and potential misuse of FCMs. Possible misuse (e.g. at temperatures exceeding the functional performance characteristics) may result in deformation or malfunctioning. Such incidents will have a very limited effect on the exposure to a substance over a time period, but may give an excursion above an SML. In addition, there may be adverse organoleptic effects.

Q40. If exposure assessments are used to petition (and approve) a new substance, how do you deal with second and subsequent applications for the same substance? Does this mean that the first use has to be revisited, or does the first application "use-up" all of the allowance for exposure? If cumulative exposure is to be assessed then who does this – if it is the second and subsequent petitioners, then where do they get the data? If EFSA/Commission have to do it, then can they manage and resource this task?
A40. Today this is not the approach accepted by the EU. These aspects would have to be considered if exposure assessment were to be used in this way.

Q41. If exposure assessments are used to support the petition for a new substance, how does the applicant estimate the future market share? If the substance proves to be more successful than anticipated does this mean they have to tell EFSA and have the substance/exposure assessment re-evaluated?
A41. Again this is outside the scope of the monograph and the current EU approach.

I.V Questions on food consumption data

Q42. Do I need food consumption data and what do I do if I do not have them?
A42. Consult §2.1.

Q43. By how much do short-term dietary surveys overestimate long-term consumption habits?
A43. This is a frequently asked question to which there is no definitive answer, particularly as packaging usage and food consumption will change significantly over the lifetime of most individuals. Consult §2.1 for further details.

Q44. To what extent do short-term dietary surveys miss packaged seasonal items and is this important?
A44. The methodology for conducting dietary surveys is outside the scope of this report but is briefly considered in §2.1. Seasonal items can be very important as far as packaging and the consumption of these foods off-season.

Q45. What about additional exposure from restaurant meals, canteens and other eating occasions?
A45. Some surveys include consumption outside of the home. Again transparency of the data used should indicate how complete the surveys are. Consult §2.1 for some further details.

Q46. What is meant by a "lifetime exposure" (e.g. in definition of TDI)? What is the optimal timeframe for averaging exposure and should this be shorter, e.g. for infants and children in developmental stages?
A46. Lifetime exposure is for 70 years (see §3.1, 3.3.3 and 3.4). There is debate at present about suitable timeframes and the treatment of infants and children and other

vulnerable groups. The TDI assumes that the exposure for the risk assessment is for a lifetime. Eating habits and packaging may continuously change over time. These aspects are accounted for in a probabilistic exposure assessment, unlike a deterministic assessment that takes a few data points for a lifetime exposure of the consumer.

Q47. General question: If you know you have a problem with a typical package (e.g. for yoghurt) do you include or exclude sub-groups, e.g. lactose-intolerant people from your calculation?
A47. If a consumer has a problem with the food (lactose-intolerant) then the packaging used for the yoghurt is irrelevant. In a normal exposure assessment such consumers are not excluded as such data are not available. These individuals have to select their food carefully.

Annex II
Expanded description of probabilistic modelling

The following sections give an overview of probabilistic exposure modelling, and refer the reader to other sources for detail.

II.I Uncertainty and variability

Although both variability and uncertainty can be represented by distributions, there are important differences between them. Variability refers to variation that exists in the real world, e.g. body weights differ from one person to another. Uncertainty refers to limitations in knowledge, e.g. a person's weight is not known precisely due to measurement error. Variability in the factors affecting exposure determines the actual range of exposures in a population, whereas uncertainty about those factors determines how sure we are in estimating exposure. Uncertainty can be reduced by collecting more or better data, whereas variability cannot.

Most components of exposure assessment will be both variable and uncertain. For example, measured migrant concentrations for a particular food type might follow a normal distribution with a certain mean and variance; but sampling makes both the mean and variance uncertain, and this can be represented by using a second distribution for the mean and a third for the variance.

II.II Quantifying variability

Distributions like those shown in Fig. 2 (see §3.2.2) are used to quantify variation in exposure between individuals in a population. In order to quantify variation in exposure, we need first to quantify variation in the factors determining exposure – consumption, concentration and body weight. This can also be done using distributions. Consider the uncertainties and variabilities in the migrant concentration data.

Many factors contribute to variation in migrant concentration: the ratio of packaging area to food weight, composition of the food (e.g. fat content) and processing (e.g. heat treatment). Even for a specific type of packaged food (e.g. cheese in cling film), where these factors are controlled, some variation will arise between batches and between items. This variation can be quantified using a distribution. However, a single distribution may be insufficient. Often the same packaging material may be used for different foods, with differing composition, area-to-weight ratios and processing, so that several different distributions are required to describe variation for the same migrant in different types of food. Ideally, each distribution should be derived from measurements of random samples of the relevant food type. Often, however, such measurements are not available and it is then necessary to estimate the distribution by extrapolation from data for the same migrant in other types of food or in a food stimulant or from a migration model. A simple example of such an extrapolation is when measured concentrations in olive oil (simulant D) are divided by 2, 3 or 4 to estimate the levels expected in foods with lower fat contents.

The choice of input distributions to quantify variability is critical, as inappropriate choices will give misleading or invalid outputs (e.g. negative exposures). There is a wide range of options for specifying distributions and an extensive literature, including substantial chapters in publications on probabilistic risk assessment (e.g. Vose 2000, Cullen and Frey 1999, US EPA 1997). Specifying appropriate distributions requires

expertise in these statistical approaches, combined with a clear understanding of the assessment model and expert knowledge of the input in question (e.g. consumption, concentrations, etc.).

An essential first consideration when estimating a distribution from concentration or other data is to check whether the data properly represent the type of variation that is relevant to the assessment. For example, concentrations might have been measured in samples of one variety of cheese purchased in one chain of retailers but this may underestimate the true variability if the same packaging is used for other varieties and retailers.

A wide range of approaches can be used to specify distributions, depending on the amount and type of data available. For large datasets (e.g. consumption surveys), it may be best to use empirical distributions or empirical bootstrapping methods (e.g. Vose 2000), which directly reflect the sample data. For smaller datasets, or where there are reasons to expect a particular form of distribution, it may be preferable to use parametric distributions (e.g. the normal distribution). Parametric distributions are defined mathematically by parameters (e.g. mean and standard deviation) that may be estimated from the sample data in various ways. The first consideration in choosing between the many possible parametric distributions should be whether they are logically compatible with the nature of the variable in question, e.g. whether it is discrete or continuous and the existence of absolute minima or maxima. Various graphical and statistical approaches are available for assessing goodness of fit. However, goodness of fit tests can be misleading and it is generally recommended to select distributions using both statistical and graphical methods in conjunction with mechanistic criteria. Sometimes it may be appropriate to transform the sample data (e.g. to logarithms) to improve goodness of fit, or to represent a variable using a mixture of distributions instead of only one. Sometimes it may be appropriate to truncate a parametric distribution to prevent sampling of extreme values that cannot occur in reality.

Where data are very limited or only summary statistics or subjective information are available, different approaches may be appropriate. Maximum entropy approaches are intended to be conservative, since to fit the given data they select the type of parametric distribution that maximises variability. Probability bounds analysis (Ferson 2002) uses “probability boxes” to define absolute bounds within which the cumulative distribution for the variable is certain to lie, and can be defined from many types of limited input information. Finally, there are a variety of formal methods of expert elicitation that can specify distributions using only subjective expert knowledge and opinion.

Whatever methods are used, special attention should be paid to ensuring the tails of distributions are reasonable, as they are frequently critical to the outcome of exposure assessment but poorly represented by data except in very large samples.

II.III Quantifying uncertainty

In practice, each component of the exposure assessment (consumption, concentration and body weight) is affected by various types of uncertainty. For example, concentrations are subject to measurement uncertainty due to variation and bias in analytical procedures, the true values of concentrations below the limit of detection are uncertain, and sampling uncertainty arises when a small sample of food items is taken to represent a larger number. Further uncertainty arises when concentrations in one type of food are extrapolated to another type. Similarly, food and body weights in

consumption surveys are subject to measurement uncertainty and sampling uncertainty, although the latter is reduced, if the survey is large. Uncertainty is also introduced when marketing information or expert knowledge is used to estimate the proportions of foods packaged in different materials.

The importance of characterising uncertainty in risk assessment and communicating it to decision-makers, so that they can take account of it, is increasingly recognised (e.g. CAC 2003, Madelin 2004). Conservative assumptions in deterministic assessment are intended partly to allow for uncertainty. In a probabilistic assessment, uncertainty can be represented using distributions.

Statistical methods can be used to estimate distributions for measurement and sampling uncertainty and also for extrapolation where this is based on regression analysis (e.g. if migration were estimated from a calibrated relationship with area-to-weight ratio, fat content, temperature etc.). Other uncertainties have to be estimated subjectively, e.g. those associated with uncalibrated extrapolation or the use of expert judgement. For example, if the proportion of coca-cola that is in cans were estimated using expert judgement, the associated uncertainty could be represented by using a distribution rather than a fixed value (e.g. a uniform distribution between 15 and 50%, rather than a fixed value of 30%). The values used for each iteration are selected between the lower and upper limits, with a weighting around the most probable. The distribution for the weighting must be prescribed, e.g. triangular.

II.IV Dealing with dependencies between inputs

Dependencies occur when the value of one quantity in the model depends upon the value of another. They can occur between variables (e.g. body weight and food consumption, as mentioned earlier), between uncertainties (e.g. the slope and intercept of a regression relationship) or between variables and uncertainties. They can arise from a direct mechanistic or logical relationship between two quantities or indirectly when both are dependent on a third. Loyalty in dietary choices (e.g. to particular brands or types of packaging) is an important form of dependency in exposure assessment, and is discussed in more detail below.

Failing to account for important dependencies can cause major over- or under-estimation of exposure. Methods to account for dependencies in Monte Carlo assessments are discussed by Cullen and Frey (1999) and in more detail by Vose (2000). When a dependency is suspected but cannot be estimated from data, its potential importance can be investigated by trying a range of different assumed dependencies (Vose 2000, US EPA 1997). One of the advantages of probability bounds analysis (Ferson 2002) is that it can accommodate total uncertainty about dependencies by calculating bounds that enclose all possible output distributions, regardless of the dependencies between the inputs. Probability bounds can be narrowed, if some variables are known to be completely independent or perfectly correlated but cannot take account of intermediate degrees of dependency.

II.V Propagating variability and uncertainty through the exposure assessment

When distributions are used to represent variability and/or uncertainties affecting consumption, concentration or body weight, we need a way to carry or propagate them through the assessment so as to quantify variation and uncertainty in the resulting exposure estimates.

Several contrasting approaches are available for propagating variability and uncertainty. The most commonly used at present are Monte Carlo simulation and bootstrapping (e.g. Cullen and Frey 1999, Vose 2000). These both involve repeatedly recalculating exposure, using different values for the inputs that are variable or uncertain (e.g. consumption, concentration or body weight). In Monte Carlo, the input values are selected at random from distributions used to represent variability or uncertainty (see Box 6A). In bootstrapping, input values are selected at random from a set of real measurements. Several organisations have produced computer software implementing Monte Carlo and bootstrapping methods for probabilistic assessment of dietary exposure (e.g. Gibney and van der Voet 2003, van der Voet et al. 2004, Holmes et al. 2005). Slob (2006) has recently argued that Monte Carlo analysis based on consumption surveys can be misleading because the short duration of most surveys gives very uncertain estimates for the frequency of consumption. Slob proposes an alternative approach based on statistical modelling of patterns in consumption data. Other probabilistic approaches include Bayesian analysis (e.g. Vose 2000) and probability bounds (Ferson 2002). Combinations of methods are also possible, e.g. Monte Carlo simulations can include bootstrapping or Bayesian estimation for input distributions.

Box 6A. One-dimensional (1D) Monte Carlo simulation

If we know the concentration *c* in a single food item of weight *w*, then the exposure *e* from that item can be calculated as $e = w \times c$.

If the weight of food items is variable, this can be represented by a distribution for *w*. Similarly, if the concentration varies between food items, this can be represented by a distribution for *c*. Monte Carlo simulation can be used to combine the distributions for *w* and *c* and estimate the distribution for exposure, *e.*

The Monte Carlo simulation is conducted as a series of repeated steps:

1. A single weight is selected at random from the distribution for w
2. A single concentration is selected at random from the distribution for *c*
3. A single exposure is calculated as $e = w \times c$
4. Steps 1–3 are repeated many times. For example, if it is repeated 1000 times, it produces 1000 estimates for exposure *e*
5. The 1000 estimates for *e* are used to plot a distribution for exposure and to calculate any statistics that are needed, e.g. the 97.5th percentile exposure.

The above example is called “one-dimensional” or 1D Monte Carlo, because all the distributions are sampled in a single repeated loop (steps 1 to 3), producing a single distribution without confidence intervals (step 5).

Two important considerations in probabilistic assessment are whether to quantify uncertainty and whether to separate it from variability in the analysis and output:

1. When only variability is quantified, the output is a single distribution representing a “best estimate” of variation in exposure. This can be used to estimate exposure for different percentiles of the population but provides no confidence intervals and may give a false impression of certainty.
2. When input distributions representing variability and uncertainty are combined (e.g. by 1D Monte Carlo; see Box 6A and also Cullen and Frey 1999, Vose 2000), the output is again a single distribution, but now represents a mixture of

variability and uncertainty (and is therefore wider, see Fig. 3). It can be interpreted as an uncertainty distribution for the exposure of a single member of the population selected at random. This can be used to read off the probability of a randomly-chosen individual falling below any given level of exposure.

3. When variability and uncertainty are propagated separately (e.g. by 2D Monte Carlo; see Box 6B and also Cullen and Frey 1999, Vose 2000), they can be shown separately in the output. For example, the output can be presented as three cumulative curves: a central one representing the median estimate of the distribution for variation in exposure and two outer ones representing lower and upper confidence bounds for the distribution (Fig. 3). This can be used to read off exposure estimates for different percentiles of the population together with confidence bounds showing the combined effect of those uncertainties that have been quantified.

It can be seen from this that the choice of strategy depends on what is wanted as output: an estimate for a given percentile of the population with (option 3) or without (option 1) confidence bounds, or the probability of a randomly chosen individual falling below (or above) a given exposure (option 2).

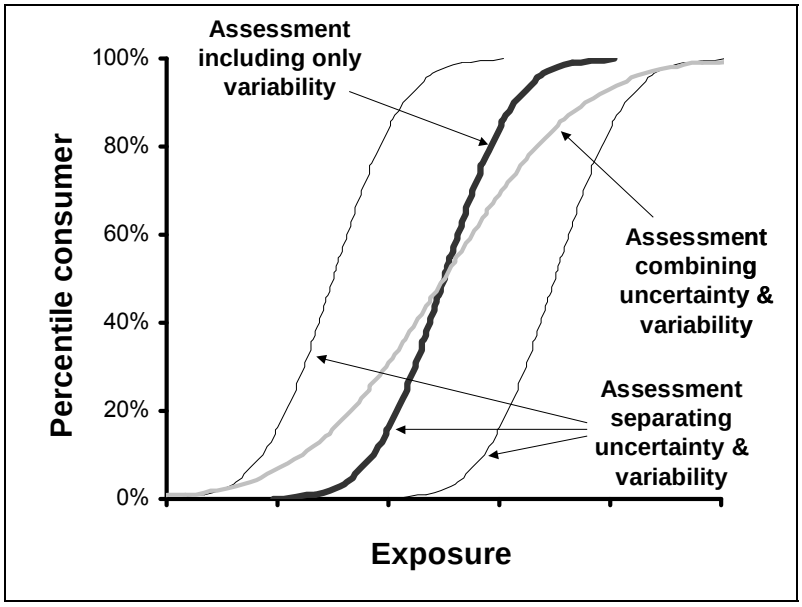

Figure 3. Diagrammatic comparison between three alternative probabilistic approaches for the same exposure assessment: option 1 – only variability quantified; option 2 – variability and uncertainty propagated together; option 3 – variability and uncertainty propagated separately. See text for interpretation

Box 6B. Two-dimensional (2D) Monte Carlo simulation

2D Monte Carlo can be used if there is uncertainty about the distributions for *w* and *c*. This uncertainty is represented using additional distributions: e.g. a distribution to represent uncertainty about the mean concentration μ, and another for its standard deviation σ. The Monte Carlo simulation is then conducted in two repeating loops:

a. Select a single value μ at random from the distribution for the mean concentration
b. Select a single value σ at random from the distribution for the standard deviation
c. Conduct steps 1–5 of the 1D Monte Carlo (above), using μ and σ to define the distribution for concentrations, and produce one distribution for exposure
d. Repeat steps a–c many times. For example, if it is repeated 1000 times it produces 1000 distributions for exposure
e. Use the 1000 distributions to produce confidence intervals for each percentile of the exposure distribution. These confidence intervals then show the effect on exposure of our uncertainty about the concentration distribution.

Annex III
Validation of probabilistic exposure models

Probabilistic models consist of multiple elements linked according to the rules of an agreed algorithm. Most but not necessarily all of these elements will have a probabilistic nature, either of the distribution of a variable or some probability distribution function that describes the variable distribution. Validation of each element can be attempted and all probabilistic models should clearly outline the efforts at validation for each element. For example, if truncation is applied to some element of the model then a check should be made that all variables generated from a probability distribution function lie within the bounds of truncation. Similarly, if rules are introduced forcing some level of correlation, that element of the process should be checked. However, whereas each element of the algorithm can be checked, validating the overall algorithm poses a greater challenge. Models that would appear to be well structured and likely to generate acceptable data often do not do so and only validation of the overall algorithm will reveal this (Gilsenan et al. 2003).

There is only one way to validate the overall algorithm of a probabilistic model and that is to remove all uncertainty from the fundamentals on which the model is built. This leads to the calculation of a deterministic (no uncertainty) exposure value. Thus, if a model uses a food consumption database, then for each individual every eating occasion should have certainty as to whether the foods eaten were packaged and have certainty of which packaging material was used and what the level of migration of the chemical was. If this “deterministic” value is known, then the probabilistic model can be populated with probabilities according to the rules of the “deterministic” database. If the mathematical assumptions of the probabilistic algorithm are correct, then the computed value should be very close to the deterministic value. If it is less than the deterministic value then rejection of the model should be considered. Of course, if all the factors for an exposure estimate are known with total certainty then there is no need whatsoever for a probabilistic model. It is precisely because the elements, on which exposure estimates are based, have uncertainty that probabilistic modelling is developed. Thus, one way to validate the model algorithm is to replace missing data in the database according to some reasonable rules. For example, if the brands and packaging of yoghurt consumed are known for 45% of the population and if within that group there are no differences in the occurrence of brands according to age and sex, then brands can be allocated to the remaining 55% for which no data exists, such that the total sample obeys the rules of the 45% for which real data exists.

It could be argued that, in the reconstruction of a database to remove all unknowns, some errors of association might be introduced. For example, some aspect of true brand loyalty or food choice correlation may not be evident in the section of the database that contains deterministic values. That is not a problem because the validation of the algorithm is based on the use of the data in the re-generated database, and if it is a valid model it should compute a value close to the deterministic value.

Ideally, all models would be validated in the sense of comparing predictions with independent data, but in practice this is not possible. For example, to validate an estimated 97.5^{th} percentile exposure it would be necessary to measure exposure for several hundred people. Firstly, it is generally difficult to measure exposure directly; biomarkers could be considered but are themselves an uncertain measure of exposure. Secondly, the number of measurements required is prohibitive, especially for validating high percentiles of the distribution of exposure.

In practice, therefore, it is necessary to identify more feasible steps to evaluate the confidence that can be placed in a probabilistic assessment. These may include:

- Literal validation or calibration of sub-components of the assessment (e.g. calibration of migration modelling with laboratory experiments or measurements in real foods)
- Partial validation of the model algorithms, by constructing hypothetical "true" exposure data and testing the ability of the model to estimate them (e.g. Gilsenan et al. 2003)
- Evaluation and documentation of the quality of input data
- Checking of computer code and sample outputs
- Peer review of the methodology, results and conclusions by relevant experts.
- Establishment of "standard" approaches. This should be based on accumulated experience over many assessments, plus in-depth peer review by a substantial number of relevant experts or expert committees and acceptance by relevant authorities.

In order to facilitate these essential processes of evaluation and peer review, probabilistic assessments must be reported clearly and in sufficient detail that every aspect can be checked and, if necessary, duplicated.

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