
Guidelines for

# good exposure assessment practice for human health effects of chemicals

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The Interdepartmental Group on Health Risks from Chemicals aims to stimulate the development of new, improved approaches to the assessment of risks to human health from chemicals.

The Steering Committee of the Interdepartmental Group on Health Risks from Chemicals comprises participants from the Department for Environment, Food and Rural Affairs, the Department of Health, the Department of Trade and Industry, the Home Office, the Environment Agency, the Health and Safety Executive, the Food Standards Agency, the Medicines and Healthcare Products Regulatory Agency, the Pesticides Safety Directorate, the Veterinary Medicines Directorate, the Biotechnology and Biosciences Research Council, the Medical Research Council, and the Natural Environment Research Council.

The Secretariat is based at the Medical Research Council's Institute for Environment and Health.

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# Foreword

This document has been produced by the Interdepartmental Group on Health Risks from Chemicals (IGHRC) as part of its Phase I work programme (October 1999–September 2003), and is informed by a workshop on Human Exposure Assessment of Chemical Substances in the UK, held in November 2001. Following initial drafting, we consulted Government departments, agencies and their advisory committees in order to obtain as broad an input and consensus as possible. The following provided input to the document:

- Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
- Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment
- Advisory Committee on Pesticides
- Veterinary Products Committee
- Advisory Committee on Hazardous Substances
- Pesticides Safety Directorate
- Air Quality Modelling and Assessment Unit in the Environment Agency

While these committees and advisory groups gave input, responsibility for the content of the document remains entirely with IGHRC.

This document is intended to provide general guidance to assist those having to undertake or evaluate chemical exposure assessments. We hope it will be read as a useful introduction and a worthwhile attempt to clarify what is a complicated area of science.

**Dr David R Harper**
**Chairman of the IGHRC**
**Chief Scientist, Department of Health**

# Contents

# Executive summary

Good exposure assessment practice is essential for (i) effective assessment and management of health risks from chemicals, and (ii) effective monitoring, control and enforcement of regulatory standards in various environmental media. Government departments and agencies assess exposure of humans to chemicals by a variety of routes and environmental media and their needs will differ depending on the purpose for which the exposure information is required. Some key areas in which exposure assessment plays an essential role are: risk assessment; epidemiological research; health impact assessment; and standards setting and compliance checking.

The aim of this document is not to prescribe what each UK Government agency or department should do to undertake an exposure assessment, but to provide guidance that will assist those having to undertake or evaluate exposure assessments. These guidelines will enable those individuals inexperienced in exposure assessment to familiarise themselves with the underlying principles and to gain an insight into the information required to conduct an exposure assessment. They are also aimed at risk assessors and risk managers who need to understand the process involved in obtaining the output from an exposure assessment to assist them in making more confident and informed decisions when characterising and evaluating risks to human health from exposure to chemicals.

Aspects to be considered in an exposure assessment include the sources and pathways of exposure, the magnitude, duration and frequency of exposure and population variability. Populations are exposed to chemicals from a range of different sources including industrial materials, agrochemicals, household products and environmental contamination. Chemicals can be transferred to the human individual (the receptor) through many possible environmental media including food, air, soil and water. One of the most effective approaches for conceptualising exposures is to identify whether potential source–pathway–receptor linkages exist.

Exposures to chemicals are rarely regular, uniform events and, since the degree of exposure often varies with time, the period over which an exposure estimate is based can have a large influence on the result. It is also necessary to consider the target population (for example, infants or the elderly) and the natural variability of that population. For populations of individuals exposed to a chemical, there will be a distribution of possible exposure levels, each associated with a probability of occurrence determined by individual exposure patterns, influenced by factors such as lifestyle, occupation, diet.

This document suggests a stepwise approach to exposure assessment that includes four main steps:

- problem formulation;
- data gathering;
- data analysis; and
- exposure characterisation.

Each of these steps may be further subdivided. Problem formulation includes determination of the purpose, scope and level of detail of the exposure assessment, the development of a conceptual model and consultation. Data gathering comprises literature review, preparation of sampling plans, exposure measurement, and modelling. Data analysis covers statistical analysis, treatment of data gaps, outliers and limits of detection, modelling, and quality assurance. Exposure characterisation consists of a summary of estimates of exposure and evaluation of the quality of the data.

The step-wise approach begins with problem formulation, leading to the development of a conceptual model that describes the exposure situation. In developing a model, all potential links between sources, pathways and receptors should be considered and a series of exposure scenarios may be established on which the assessment will be based. It may be necessary to determine exposure levels at more than one point in the source–pathway–receptor chain, particularly if links in the chain are uncertain. The conceptual model should be revised as necessary as data are gathered and analysed and more information becomes available.

The final stage of an exposure assessment is the exposure characterisation, without which the assessment would be merely a collection of data, calculations and estimates. The exposure characterisation represents the output of the exposure assessment and draws together the results of the steps outlined above, presenting a balanced representation of all the available data and identifying key assumptions and major areas of uncertainty. Exposure characterisation provides an opportunity to review the results in the context of the conceptual model and this may indicate that reappraisal of the model or further monitoring is required.

Following the production of the exposure assessment report, the assessment must be critically evaluated before recommendations are made. Frequently the person called upon to interpret the results of an exposure assessment in the context of compliance checking, risk assessment or epidemiology is not the same as the person who was responsible for the production of the exposure data. An evaluation might comprise a completeness check to ensure that the exposure assessment report contains the elements defined above.

Auditability is an essential requirement for the documentation of an exposure assessment. Reviewers of exposure assessments are usually asked to identify inconsistencies in the underlying science, methods, models and assumptions used and to assess the effect these inconsistencies might have on the results and conclusions. In particular, a reviewer should consider whether the inconsistencies or deficiencies would result in underestimation or overestimation of exposure.

Finally, this guidance document provides a suggested checklist which will assist evaluators and auditors in assessing whether or not all the key steps in an exposure assessment have been undertaken.

# 1 General introduction

## 1.1 Background

The Interdepartmental Group on Health Risks from Chemicals (IGHRC[a]) is an informal group of representatives from the main UK Government departments, agencies and research councils with an interest in chemical risk assessment in relation to human health. IGHRC aims to reduce the uncertainties and limitations in the process of assessing risks to people's health by stimulating the development of new, improved methodology (IGHRC, 2000)[b]. IGHRC also aims to promote coherence and consistency in the practice of chemical risk assessment in the UK.

In taking forward these aims, a workshop was held at the Institute for Environment and Health (IEH) in November 2001 to agree the content and format of a guidance document to promote coherence and consistency in human exposure assessment of chemicals in the UK. Representatives of a number of government departments and agencies, academia and expert committees attended the workshop (Annex E). A draft document was prepared and, following consultation, comments from all the workshop participants, government departments, agencies and expert committees were incorporated.

The purpose of this document is not to prescribe what each UK Government department should do in order to undertake an exposure assessment, but to provide guidance that will assist, but not constrain, those having to undertake or evaluate exposure assessments. It contains the underlying principles of exposure assessment and, where appropriate, supporting science, but not extensive detail, that is applicable to all government departments that undertake exposure assessments of chemical substances as part of their responsibility.

These guidelines will enable those individuals inexperienced in exposure assessment to familiarise themselves with the principles of exposure assessment and to gain an insight into the information required to conduct an exposure assessment. They are also aimed at risk assessors and risk managers who need to understand the process involved in obtaining the output from an exposure assessment to assist them in making more confident and informed decisions when characterising and evaluating risks to humans from exposure to chemicals. The guidelines will also assist those who are undertaking exposure assessments for presentation to, or on behalf of, government departments, agencies or expert committees to appreciate and understand the nature and form of presentation required.

## 1.2 Definitions of exposure and exposure assessment

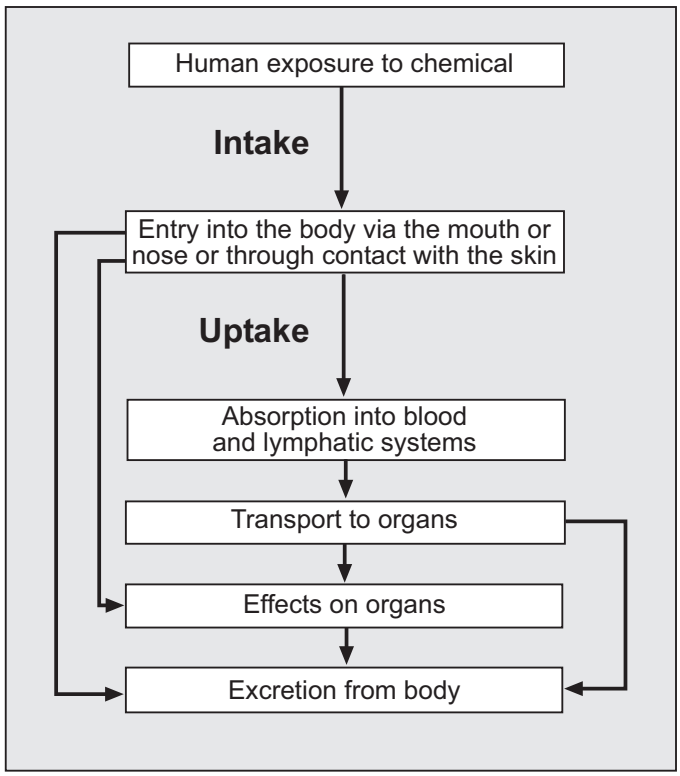
Professionals and organisations using exposure assessments, both within the UK and worldwide, tend to use the term **exposure** to represent slightly different concepts. There is a broad consensus that exposure means contact between a chemical and an individual or population (WHO, 2000a). Ambiguity may arise, however, as to whether this means contact with:

- the body exterior, or
- internal exchange boundaries such as the lungs or the gastrointestinal tract, or
- target organs like the liver, or
- biological receptors within target organs.

[a] Formerly the Risk Assessment and Toxicology Steering Committee

[b] Available [December 2003] at http://www.le.ac.uk/ieh/ighrc/igpublications.html#IGHRCtitles

**Figure 1.1 Simplified diagram of the relationship between exposure, intake and uptake**




Defra & Environment Agency (2002a), copyright Environment Agency, reprinted with permission

The relationship between the amount of a chemical in the external environment and internal exposure has been described in connection with contaminants in soil (Defra & Environment Agency, 2002a) (Figure 1.1).

For the purpose of this document exposure is defined as 'contact over time between a chemical and an individual or population'. Exposure assessment is defined as 'the measurement, estimation or prediction of intake or exposure to a chemical, in terms of magnitude, duration and frequency, for the general population, for subgroups of the population, or for individuals' (Risk Assessment and Toxicology Steering Committee, 1999a). The principles of exposure and exposure assessment are described more fully in Sections 2 and 3.

Terminology for other concepts can also be confusing. Outlined below are definitions of frequently occurring terms as used in this document. Variations of these definitions can be found in Defra & Environment Agency (2002a), WHO (2000a) and a glossary of exposure-related terms can be found at http://www.ipcsharmonize.org/documents/exp-gloss-comp.pdf.

The term **intake dose** is generally defined as the amount of a chemical entering or contacting the human body at a point of entry (i.e. mouth, nose or skin) by ingestion, inhalation, or skin contact (Defra & Environment Agency, 2002a). Intake dose is frequently referred to as just 'intake'.

**Uptake dose** is usually defined as the amount of a chemical that reaches the circulating blood having been absorbed by the body through the skin, the gastrointestinal system and the pulmonary system, expressed in terms of mass of substance per unit volume of blood (Defra & Environment Agency, 2002a).

**Acute exposure** is contact between a chemical and an individual or population over a short time period.

**Chronic exposure** is a continuous or intermittent long-term contact between a chemical and an individual or population.

The words used to describe the duration of exposure, whether of exposed individuals, populations or duration of sampling periods, can vary depending on the different disciplines undertaking exposure assessment. This can cause confusion and it is thus imperative to verify the nature of the time-base in question. As an example, the terms 'acute' and 'short-term' are often used interchangeably to describe a relatively limited

period of exposure or sampling period. However, the word 'acute' can also be used in the medical or toxicological sense to describe harmful effects that develop rapidly, regardless of the duration of exposure that may have led up to the effect. Similarly, the terms 'chronic' and 'long-term' are also used interchangeably to describe a length of time of exposure that can vary between one month and one year to describe either true exposure or sampling duration. Again, confusion can be caused because of the medical use of the word 'chronic', which is used to describe a condition that is slowly developing and usually irreversible, but again independent of duration of the exposure that may have caused it, although in many cases chronic health effects are related to 'long-term' or 'chronic' exposure.

As indicated above, the terminology used varies among departments, agencies and organisations, often to reflect the legislative/regulatory context in which the term is applied. Exposure assessors should ensure that, when interpreting information, they are using the same terms and concepts applied by those conducting the exposure assessment or at least are aware of the variations in interpretation.

## 1.3 Applications of exposure assessment

Exposure assessments are undertaken to obtain exposure information for:

- assessing and managing health risks; and
- monitoring, control and enforcement of regulatory standards in various media.

Government departments and agencies assess exposure of humans to chemicals by a variety of routes and media (Table 1.1). Exposure information needs will differ from department/agency to department/agency because:

- departments/agencies operate within different legislative and regulatory frameworks;
- degree of protection sought will differ;
- risk/benefit or exposure/risk considerations may differ;
- intrinsic hazard potential of groups of chemicals differs;
- routes of exposure will differ;
- populations/subgroups/individuals most at risk may differ;
- the degree of confidence/level of precision required in exposure estimate will vary;
- the exposure assessment may be amenable to a tiered approach; and/or
- ready availability of exposure data will vary.

The following sections (1.3.1 to 1.3.4) illustrate some key areas in which exposure assessments play an essential role.

### 1.3.1 Risk assessment

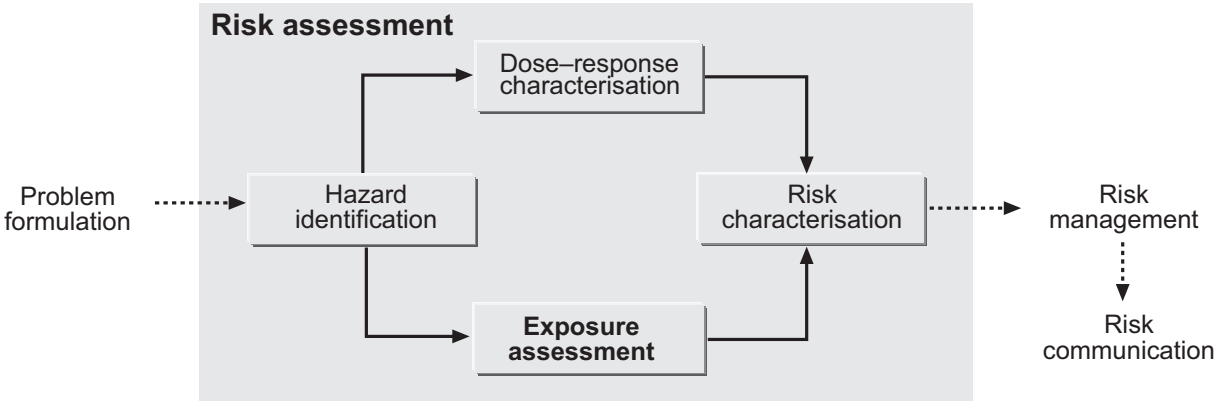
In human health **risk assessment,** for **regulatory** or other purposes, the aim of exposure assessment is to characterise source–pathway–receptor linkages (in this context, the receptor is the person/individual exposed to the chemical) and

**Table 1.1 Principal sources of chemical exposures and departments and agencies primarily responsible for assessing risks**

| Source of exposure | Department/agency |
|---|---|
| Food | FSA |
| Plant protection products | DH/PSD/FSA/HSE |
| Biocides | DH/PSD/HSE |
| Veterinary products | VMD/FSA/HSE/Environment Agency |
| Occupational exposures | HSE/PSD |
| Consumer products | DTI/DH |
| Air quality | Defra/Environment Agency/DH/SEPA |
| Water quality | Defra/Environment Agency/DH/SEPA |
| Land quality | DH/Defra/Environment Agency/FSA/SEPA |
| Human medicines | MHRA |

Based on Risk Assessment and Toxicology Steering Committee (1999a)
Defra, Department for Environment, Food and Rural Affairs; DH, Department of Health; DTI, Department of Trade and Industry; EA, Environment Agency; FSA, Food Standards Agency; HSE, Health and Safety Executive; MHRA, Medicines and Healthcare Products Regulatory Agency; PSD, Pesticides Safety Directorate; SEPA, Scottish Environmental Protection Agency; VMD, Veterinary Medicines Directorate

**Figure 1.2 Elements of risk assessment and management**




Based on Risk Assessment and Toxicology Steering Committee (1999a)

ultimately to provide an estimate of dose (usually represented by intake) that can be related to the dose–response relationship of a chemical. The aim may be to identify whether the exposure of individuals or groups exceeds a recommended level or to estimate population risks from exposure to particular amounts of a chemical.

The risk assessment is used to develop and evaluate risk management strategies, such as introducing measures to control the use or release of the chemical, restricting human contact, or introducing compliance testing or surveillance.

Approaches to risk assessment have evolved over the last few decades. However, most currently used models include four key elements (Risk Assessment and Toxicology Steering Committee, 1999a) whose relationships are described in Figure 1.2.

**Hazard identification** is the identification, from animal and human studies, *in vitro* studies and structure–activity relationships, of adverse health effects associated with exposure to a chemical.

**Dose–response characterisation** is the quantitative (potency) evaluation of the observed adverse effects of a chemical, usually by dose–response analysis, and the evaluation of mechanisms of action and species differences in response.

**Exposure assessment** is the measurement, estimation or prediction of intake or exposure to a chemical, in terms of magnitude, duration and frequency, for the general population, for subgroups of the population, or for individuals.

**Risk characterisation** is the integration of hazard identification, dose–response characterisation and exposure assessment in order to:

- predict whether or not effects in humans are likely to occur;
- predict the nature and severity of adverse effects that may occur in a given population exposed to a given concentration;
- predict the proportion of the population that may be affected;
- identify any vulnerable subpopulations; and/or
- estimate the likelihood of an event (such as accidental release of a toxic chemical) giving rise to an exposure of a particular level and duration associated with a specified level of effect upon the exposed population.

Exposure assessment provides a vital element in risk assessment because it defines the magnitude, duration, frequency, geographical and demographic extent, etc. of the risk. Without such information it is impossible for government departments and agencies to judge whether risk management actions are required or to identify what action is appropriate. For more information on risk assessment principles generally applied across government departments/agencies see EPA (1992)[a], Risk Assessment and Toxicology Steering Committee (1999a)[b], Defra *et al.* (2000)[c], WHO (2000a), and EC (2003)[d].

### 1.3.2 Epidemiological research

Epidemiological studies investigate the relationships between the incidence or prevalence of particular

[a] Available [June 2003] at http://www.epa.gov/ncea/pdfs/guidline.pdf
[b] Available [December 2003] at http://www.le.ac.uk/ieh/ighrc/igpublications.html#RATSCtitles
[c] Available [December 2003] at http://www.defra.gov.uk/environment/eramguide/index.htm
[d] Available [May 2003] at http://ecb.jrc.it/tgdoc

diseases in specified populations with environmental, occupational, dietary or other potential causative factors, thus enabling direct associations between human exposure and health effects to be established. Exposure assessment is thus a crucial element of epidemiological research. In investigations into long-term health effects of 'low dose' environmental exposures, epidemiological studies are probably the only practicable approach (WHO, 1999, 2000a; Kroes *et al*., 2002; Van den Brandt *et al*., 2002). Approaches to exposure assessment in epidemiological studies can range from qualitative, 'exposed' *versus* 'non-exposed' or 'low', 'medium', 'high', to quantitative measurements, depending on the available data.

### 1.3.3 Health impact assessment

Health impact assessment is a methodology that aims to identify, predict and evaluate the likely changes in health risk, both positive and negative (single or collective), of a policy programme, plan or development action on a defined population. Ideally, health impact assessments should always include consideration of physical, mental and social impacts (BMA, 1998). For example health impact assessments may be required when it is necessary to evaluate the potential effect on health of some significant proposed environmental change such as the construction of a waste treatment facility (WHO 2000b)[a] or the building of an airport. Exposure assessment in this case involves prediction of the levels of a chemical that will result from the development. These values can then be compared with the appropriate standards.

Sections 1.3.1 to 1.3.3 above relate to assessing and managing health risks and Section 1.3.4 below relates to monitoring, control and enforcement of regulatory standards in various media.

### 1.3.4 Standards setting and compliance checking

Many regulatory authorities manage potential risks from exposure to chemicals by setting standards or maximum levels of a chemical that should not be exceeded. These standards or recommended maximum levels may be expressed either as a concentration of a chemical in a medium, such as air, water or food, or may be expressed as an upper limit for human intake (e.g. amount ingested from food and/or water, or inhaled from the air). The status of the standards may vary; in some cases they may be advisory, such as soil guideline values, certain air or water quality standards or Acceptable or Tolerable Daily Intakes (ADIs and TDIs) for additives and contaminants in food. Alternatively, they may be mandatory and form part of a regulatory framework such as occupational exposure limits, or maximum residue levels for pesticides or veterinary medicines in foodstuffs.

The scientific derivation of standards varies, reflecting historical and regulatory approaches. As an example, an ADI or TDI is obtained from the output of a hazard assessment (e.g. the No Observed Adverse Effect Level (NOAEL) for critical effect to which has been applied a number of uncertainty factors) to arrive at a given standard. Alternatively, in situations where NOAELs are not considered to be appropriate, as is the case for genotoxic carcinogens, pragmatic standards may be set that are based on best achievable control or best practice. In the case of carcinogens in the workplace, best practice would include strict controls for the use of that chemical so that exposure is kept as low as is practicable; the backup of an air standard may also be used.

Compliance checking usually involves the collection and analysis of samples in a prescribed fashion and comparison of the measured concentrations with the appropriate standard. The value from the exposure assessment data is compared with the standard (e.g. the ADI, TDI, water quality standard or occupational exposure limit) to assess how well it relates to the standard. If, for example, the value from the exposure assessment is higher than the standard, this indicates that the exposure to the hazard needs to be reduced; if the value is far lower then no immediate action need be taken to instigate a reduction strategy. A simplified compliance check can also be used to determine whether further, more refined data collection and/or exposure assessment is necessary. This check may form part of an initial tier in the exposure assessment process and will be discussed in Section 3.

## 1.4 Structure of these guidelines

These guidelines have been designed so as to take the reader through a logical series of steps in exposure assessment. They are not intended to be a comprehensive treatise on exposure assessment nor a simple checklist. Information and references have been chosen so as to provide a stand-alone guidance document for those who need to understand the background, logic, and scope of exposure assessment.

[a] Available [December 2003] at http://www.who.dk/document/e71393.pdf

- Section 2 presents the basic principles of exposure assessment.

- Section 3 outlines the strategy for conducting an exposure assessment.

- Section 4 briefly addresses the models that may be used in exposure assessments.

- Section 5 describes how to conduct the exposure characterisation.

- Section 6 gives a brief introduction to critical reviewing and auditing of an exposure assessment.

Annexes provide further supporting information, including a glossary of terms, additional detail on concepts of exposure, additional detail on exposure assessment models, a number of case studies and a list of workshop participants.

# 2 General principles of exposure assessment

This section briefly outlines the general principles of exposure assessment. It considers sources and pathways of exposure, magnitude, duration and frequency of exposure and population variability in exposure assessment.

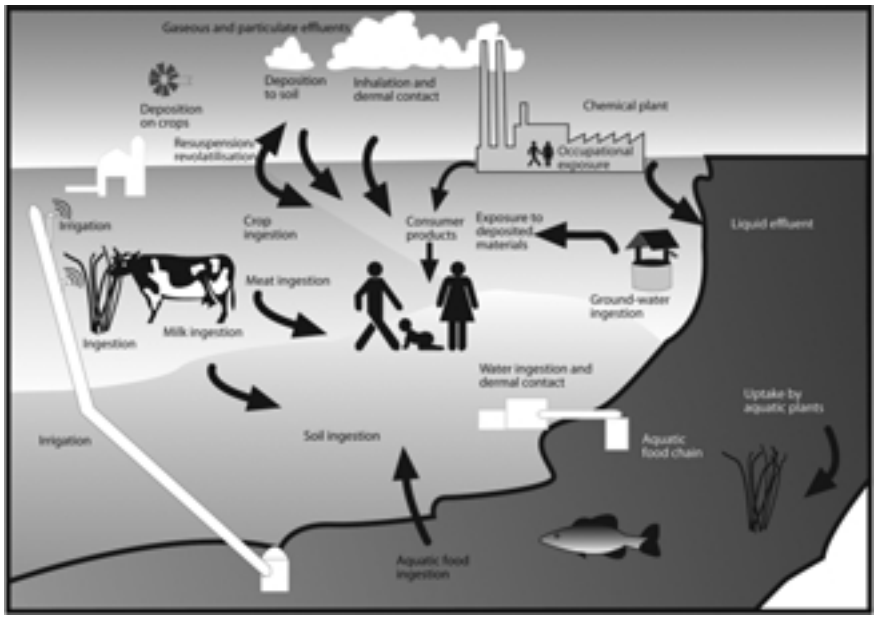
## 2.1 Sources and pathways of exposure

Populations are exposed to chemicals from a range of different sources including industrial materials, agrochemicals, household products, environmental contamination and natural sources such as the production of Ochratoxin A, from strains of fungal genera *Penicillium* and *Aspergillus* found in a variety of foods, red wine and beer. Chemicals can be transferred to the human individual (**the receptor**) through many possible pathways including food, air, soil and water. Some of these are illustrated in Figure 2.1 although in reality the relationships between sources, pathways and receptors can be far more complex than this simple model indicates.

One of the most effective approaches for conceptualising exposures is to identify whether potential **source–pathway–receptor** linkages exist (Defra *et al*., 2000). For example, if the source of a chemical is a chemical plant (Figure 2.1) then there are several possible exposure pathways affecting different potential receptor groups such as:

- Direct occupational exposure of those who work in the plant.
- Inhalation from dust and gaseous exposures of populations (infants, children, adults, the elderly) living near the plant.
- Material leached from the plume by rain might pollute surface waters, which, if used as drinking water, could affect a wider receptor population.

**Figure 2.1 Some typical sources and pathways of human exposure to chemicals**




Adapted from ECETOC (1994)

- If the chemical accumulates in soils then crops grown in those soils or animals fed on those crops might become contaminated.

In the last two cases, the receptor population might have no link with the industrial plant other than through the water supply or food chain and might live many miles away. The particular circumstances, such as the chemical composition of the plume, topography, wind direction, land use, soil pH, etc. that prevail in a particular location will determine whether each source–pathway–receptor linkage is relevant.

Graphical representation of the conceptual model allows determination of the source–pathway–receptor linkages to enable the key pathways to be identified before a more detailed exposure assessment is undertaken. Conceptual models will be discussed further in Section 3.

## 2.2 Magnitude, duration and frequency of exposure

Exposures to chemicals are rarely regular, uniform events and so exposure assessment needs to take account of the frequency, duration and level (magnitude) of exposure (Nieuwenhuijsen, 2003). Since the degree of exposure often varies with time, the period over which an exposure estimate is based can have a large influence on the result (Benford & Tennant, 1997). In some cases, such as exposure to an acutely and highly toxic chemical, only a single dose might be required to result in an adverse effect. At the other extreme, for a chemical that bioaccumulates in body tissues such as fat or that has a cumulative toxic effect, such as cadmium in the kidney, it may be necessary to estimate the cumulative dose over periods of up to a lifetime. Selection of the period over which exposure is integrated must take into account the relevant human health effects and the dose–response relationship (Renwick, 1999). For example, when estimating exposures for investigations into effects on the fetus, it is important to assess exposures during the relevant critical period of pregnancy, that is the 1st, 2nd or 3rd trimester, depending on the chemical and the effect.

### 2.2.1 Peak and acute exposures

In many situations, exposures may be continuous but fluctuate in level according to, for example, various stages in an industrial production process or, in the case of traffic exhaust pollutants, according to time of day and traffic flow. Many acute harmful effects, such as irritancy, are related to the short-term peaks in exposure and thus it may be very important, either from an exposure assessment point of view or in the setting of regulatory standards to be aware of such short-term or 'peak' exposures. It is thus important to be able to measure such short-term peaks, which would be missed if one only undertook long-term sampling that measured only the average exposure. In the occupational setting, direct reading instruments can measure peak exposures in air for periods as short as 15 seconds and these are often expressed as mg/m$^3$ or ppm; for regulatory or compliance purposes substances which can cause known harmful acute effects from peak (short-term) exposures normally have a 15 minute short-term exposure limit (STEL) set (HSE, 2002). Often the occurrence of these peak exposures (high but short-term) in the occupational setting is the result of accidents, malfunctioning of process or poor work practice. Outside the occupational setting, the terms peak exposure, acute exposure and short-term exposure can have other time-related bases and can vary from a few hours to a few days. As an example of the latter, one could imagine the high consumption of a particular food item which is only consumed (due to availability) for a few days in the year.

The Pesticides Safety Directorate routinely carries out estimates of short-term dietary intake for certain types of pesticide product to address the concern that consumers may occasionally be exposed to high residues in food items which may exceed reference levels for acute toxic effects (PSD, 1999). These estimates, termed the National Estimate of Short Term Intake (NESTI), are derived for individual food commodities (e.g. apples, potatoes, grapes) using the highest residue levels detected in field trials (conducted in accordance with Good Agricultural Practice and single day consumption data at the 97.5th percentile level (see Annex C).

### 2.2.2 Chronic exposures

Exposure averaged over a prolonged period of time may be the relevant measure for exposure assessment because the onset of ill health may be a consequence of a long-term exposure to a chemical or mixture of chemicals. Chronic exposures are typically exposures over periods of months or years or even a lifetime. In an occupational setting an 8 hour **time-weighted average** (TWA) limit is a surrogate for a working lifetime (up to 40 years, i.e., 8 h/day, 5 d/week, 52 weeks/year) and the 8 hour TWA (mg/m$^3$ or ppm) is intended to prevent chronic ill-health effects. Exposure assessors are sometimes obliged to use exposure data that do not

include information about fluctuations that may be relevant to the risk assessment. This can be an important source of uncertainty in exposure assessment (see Section 5).

In many circumstances, it will be important to take into account the frequency of peak exposures over time as it may affect both the nature and degree of the harmful effect. As an example, a series of high intermittent exposures may cause greater damage to a tissue or organ than the same total dose received on a steady-state basis over the same time period.

The use of **integrated exposures** over time allows for factors such as seasonal variations in chemical concentrations, for example, in air pollutants or pesticide use, to be taken into account. Regular repeated measurements are often taken over the relevant time period so that the total exposure can be estimated by integration of the area under the time–exposure curve (WHO, 2000a).

For certain chemicals that accumulate in the body the cumulative dose is the critical factor (Tennant, 2001). Cumulative dose represents the total quantity of chemical an individual has received over a given period of time. Cumulative doses are sometimes measured using biomonitoring techniques, such as determination of urinary cadmium levels since the half-life of cadmium is so long (seven years) that excretion in the urine remains constant and thus a representative urine sample can be taken at any time (Delves, 1995). However, many potential biomarkers for substances with a short half-life only represent body burden over a relatively short recent exposure period and so the results should be interpreted with caution (see Section 3.3.3).

## 2.3 Population variability in exposure assessment

The previous section has described some ways of measuring exposure of individuals taking into account the health end-points. However, when considering the magnitude, duration, and frequency of exposure, it is also necessary to consider the target population and the natural variability of that population. For populations of individuals exposed to a chemical, there will be a distribution of possible exposure levels, each associated with a probability of occurrence determined by individual exposure patterns, such as lifestyle, occupation, diet. It is rarely possible to measure exposure for every single individual in a population unless exposure is limited to very small groups. When undertaking risk assessments it is usually considered necessary to estimate the exposure for individuals at the high end of the overall exposure distribution in order to protect the majority of individuals within the population (Pascal, 1995).

It is also frequently important to take into consideration variations of both exposure and risk within populations, such as for young children or the elderly (Risk Assessment and Toxicology Steering Committee, 1999b). The case study of phthalates described in Annex D is a good example of an exposure analysis aimed at a particular subpopulation — in this case young children. In contrast, the case study of benzene, also described in Annex D, included the whole population, which was divided into subpopulations to estimate the risk to the general population but also to investigate whether one subpopulation was at a higher risk.

Often the most susceptible population is used when estimating exposure to ensure stringent protection of the population as a whole. For example, the exposure of infants and children to pesticides may differ considerably from that of adults, both qualitatively and quantitatively (National Research Council, 1993). Infants and children take in more calories from food per unit of body weight than do adults, and also eat a narrower range of foods (National Research Council, 1993). They spend more of their time in proximity to floors, carpets, and other surfaces with a greater proportion of their body surface area in contact with surfaces than adults; they also have more frequent and greater duration of hand-to-mouth activity than do adults (Lu *et al*., 2001). The breathing zone of a child is also much closer to the ground than that of adults (Bearer, 1995). Overall, these factors result in an increased likelihood that children will receive higher exposures to pesticides, on a mg/kg body weight basis, than adults. The elderly may be susceptible for different reasons. For example, the added effects of reduced liver size and liver blood flow with age contribute to reduced clearance of drugs from the liver (Rawlins *et al*., 1987).

Another example of a susceptible group would be a group with pre-existing disease such as asthma. This group would be more susceptible than the general population to severe episodes of air pollution or high pollen counts.

**Population risk** describes the extent of harm for a given population or subpopulation, for example, the proportion of the population that exceeds a given safety standard (WHO, 2000a). When the exposure of a proportion of the population exceeds a safety limit, it may be necessary to extend the exposure analysis by characterising that subgroup by geographical location, age, sex, ethnicity etc., so that risk management actions can be targeted more effectively.

# 3 Exposure assessment strategy

Exposure assessments can be undertaken to fulfil a variety of needs as illustrated in Section 1 and so must be carefully planned in order to ensure that they produce results relevant to those needs. The specific data requirements will thus depend on the purpose for which the exposure assessment is being undertaken. Accurate estimates of human exposure to chemicals may be necessary for a realistic appraisal of the risks these chemicals pose and for the design and implementation of strategies to control and limit those risks. In other situations, rough estimates or 'worst case' estimates of exposure may suffice.

It should be borne in mind that those who provide exposure data are often remote from those who are responsible for its interpretation in an exposure characterisation and/or risk characterisation. It is therefore vital that the latter are familiar with approaches used for making exposure measurements or estimates, since the methods applied, assumptions made and errors introduced can have a major impact on the interpretation of results. Situations where, for example, a data set has been edited to remove apparent outliers when such data would have been critical to the risk characterisation can be prevented if **data providers know what information to report** and **risk assessors know what information to expect**. That is, it is a two way process and it is important that the data providers provide information that is presented clearly.

This section outlines an exposure assessment strategy and has a dual purpose. It provides guidance on both good exposure assessment practice and on clear and transparent reporting of the exposure assessment.

## 3.1 Stepwise approach to exposure assessment

There are four main steps in the exposure assessment process (Figure 3.1), namely:

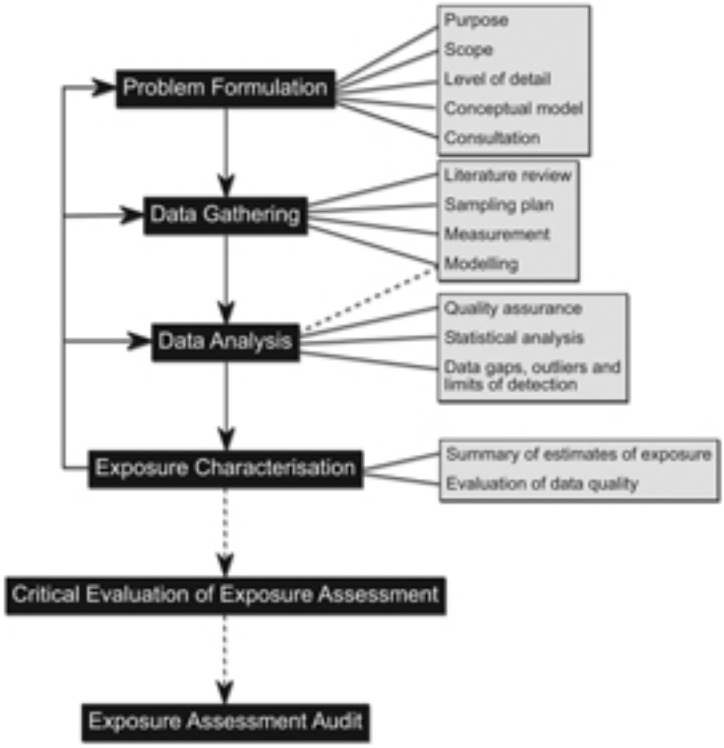
- problem formulation;
- data gathering;
- data analysis; and
- exposure characterisation (Section 5).

Each of these steps (described in detail in Sections 3.2 to 3.4 and Section 5) may be subdivided, as outlined in Figure 3.1. The step-wise approach begins with problem formulation, leading to the development of a conceptual model that describes the exposure situation. In developing a model, all potential links between sources, pathways and receptors should be considered and a series of exposure scenarios may be established on which the assessment will be based. It may be necessary to determine exposure levels at more than one point in the source–pathway–receptor chain, particularly if links in the chain are uncertain. The conceptual model, including source–pathway–receptor links, should be kept under review as the data are gathered and analysed, as adjustments to the model may be necessary as more information becomes available. Exposure characterisation (see Section 5) provides an opportunity to review the results in the context of the conceptual model and this may indicate that reappraisal of the model or further monitoring is required.

## 3.2 Problem formulation

Describing the problem in clear and unambiguous terms is important in deciding how to undertake an exposure assessment and what methodology to use.

**Figure 3.1 Step-wise approach to exposure assessment**




The dotted line between modelling and data analysis indicates that modelling can be used for both data gathering and data analysis. The dotted line from exposure characterisation to critical evaluation of exposure assessment and to exposure assessment audit indicates that, although the compilation and evaluation of the exposure assessment is complete at exposure characterisation stage, the exposure assessment should be critically evaluated and audited. This procedure will ensure consistency in the underlying science, methods, models and assumptions used and will identify the effect any inconsistencies might have on the results and conclusions (discussed in Section 6).

A clear statement at the outset can also provide a baseline should the ensuing assessment process or risk management decision be challenged or audited, that is, it will make clear exactly what was and was not taken into account.

A useful approach to problem formulation is to consider the purpose, scope and level of detail required in the exposure assessment (EPA, 1992). These aspects are best addressed through consultation with others involved in the execution and interpretation of the assessment.

### 3.2.1 Purpose

The purpose of an exposure assessment is a fundamental consideration in problem formulation, as the approach followed will ultimately depend on the purpose of the assessment. For risk assessors concerned with a particular issue, it is easy to make implicit assumptions or take account of knowledge that will not be known to all who use the exposure assessment. Consequently, recording the purpose from the outset provides significant benefits by making clear to anyone using the assessment exactly what was taken into account. A clear statement of intent will also facilitate monitoring and feedback and help to determine whether discrepancies between forecasts and outcomes were caused by poor judgement, lack of knowledge or other factors.

The purpose of exposure assessments will vary. A number of examples are outlined below.

- When used as part of **risk assessment**, the purpose of exposure assessment is to characterise source–pathway–receptor linkages and ultimately to provide an estimate of dose (usually represented by intake) that can be related to the dose–response relationship. The aim may be to identify individuals or groups whose intake exceeds a safety threshold or to estimate population risks.

- In **epidemiological studies** the emphasis is on using the exposure assessment to establish whether there is an association between exposure to a chemical and the incidence or prevalence of adverse health effects. It may also be used to quantify an exposure–response relationship.

- If the exposure assessment is intended to support **regulation** of specific chemical sources such as point emission sources, consumer products or pesticides, then establishing the pathway between the source and the exposed or potentially exposed population becomes essential.

- For **compliance testing** the purpose is to investigate whether exposure concentrations in the relevant medium exceed prescribed limits.

- Exposure assessment may be used **to inform risk management decisions**.

- Exposure assessment may form part of a **health impact assessment** of the potential effects of a proposed new development.

### 3.2.2 Scope

An important requirement for any exposure assessment is ensuring that the boundaries or scope of the assessment are clearly and logically selected (EPA, 1992). Three aspects of exposure are important for determining related health consequences:

- **Magnitude**. What is the concentration of the chemical and the intake into the body of any carrying medium?

- **Duration**. How long does the exposure last?

- **Frequency**. How often do exposures occur? Is there a pattern to the exposure?

A number of other important questions may also be asked.

- Should all **media** be investigated or is one medium of particular importance?

- What are the **physical properties** of the chemical (e.g. particle size, solubility, volatility, lipophilicity, etc)?

- If there is more than one **chemical species**, should one or all of the species be examined?

- Are there any **subgroups** of the population that should be studied separately?

- What sort of exposure **measurements** (if any) should be made?

- Should **sampling** be conducted at an international, national or local level?

- Is it necessary to obtain samples throughout the year or working day or some other relevant **time interval**? Does sampling need to be seasonal or timed to coincide with particular events?

- Are **other relevant data** available on which a reliable exposure estimate can be based? It may not always be necessary or appropriate to take any exposure measurements if relevant data are already available from the scientific literature or from other sources.

The design of an exposure study specifies the procedures that will be used to answer these questions. It is important to document the reasons for selecting the boundaries for an assessment to avoid what others might see as omissions. It is also sometimes helpful to document what is beyond the scope of an exposure assessment exercise. Quality assurance procedures (see Section 3.4.2) should be considered at this stage.

### 3.2.3 Level of detail

Exposure data collection is often conducted using an iterative or tiered approach with the first stage involving a simple **qualitative** or semi-quantitative screening method in which the level of detail is relatively low. Screening allows the identification of the most important sources, pathways or receptors so that resources (including time, data collection, personnel and equipment) can be focused on providing a more detailed assessment of the most important of these. Such qualitative screening methods can allow a more thorough understanding of the problem without providing any immediate answers.

Once a potential link has been established between the source and the receptor, a tiered approach to exposure data gathering and analysis can be adopted, with the initial application of a **worst case** or a **reasonable worst case** estimation or conservative screening method. If this indicates that exposures could exceed acceptable levels, then estimates can be gradually and continually refined, as more data are gathered, until a more reliable estimate is obtained. These estimates are often used as a quick check for exceedances of standards in compliance checking.

The worst-case scenario usually refers to a hypothetical situation in which everything that can plausibly happen to maximise exposure does in fact happen (EPA, 1992). A worst-case estimate usually overestimates exposure in a specific situation. The worst-case scenario is a useful device when a combination of low probability events may result in

a catastrophe that must be avoided even at great cost. In most health risk assessments, the worst-case scenario is used to give a bounding estimate (i.e. 'exposures are less than …'), typically applied for screening purposes. An example of a worst case scenario for the benzene case study in Annex D is that of the smoker who spends eight hours a day working close to heavy traffic. This individual would be exposed to benzene in the course of his normal home life, travel to and from work, via his occupation and through smoking. Reasonable worst case scenarios are an example of a method originally used in occupational settings to define high-end exposures that do not exceed the maximum exposure that would be likely to occur in reality (EC, 1996[a]). This approach has now been adopted in other exposure contexts. The reasonable worst case is regarded as the level of exposure that is exceeded in a small percentage of cases over the whole spectrum of likely circumstances of use for that particular scenario. It excludes accidents, extreme use or misuse.

The next step in the assessment is to collate enough data to refine the assessment and to make realistic estimates of exposure; these can be in the form of a mean and range or as distributions, where information (modelling or otherwise) allows for this. The more data that are gathered the more accurate the estimates will be.

Level of detail is also determined by the **precision** that is required in the results. For example, when determining whether an exposure is in compliance with an exposure standard, more information and measurements may be required if the exposure is near the standard than if it is far below or far above the standard. In the case of the assessment of chemical levels in contaminated land, levels of a compound measured in soil may be compared with Soil Guideline Values (SGVs), which indicate the level of a contaminant that does not pose an unacceptable health risk for a particular land use (Defra and Environment Agency, 2002b). If levels of the chemical of concern are significantly below the SGV then no further assessment is necessary. If levels are close to, or exceed the SGV, then a more refined assessment (e.g. taking into consideration soil type and local conditions) may be required.

### 3.2.4 Developing a conceptual model

Conceptual models are useful tools in problem formulation (Defra *et al.*, 2000). They are a way of representing in visual and/or written form the hypothesised relationships between sources, pathways and receptors. For example, Figure 3.2 illustrates a simple, conceptual model for exposure to hydrocarbon fuels at petroleum retail sites and Table 3.1 presents the same conceptual model in text format. This example illustrates general population environmental exposure to hydrocarbon fuels (those exposed occupationally would be, for example, tanker drivers or forecourt attendants). The level of detail required in the conceptual model will differ depending on the complexity of the exposure assessment. A conceptual model can be highly specific and concentrate on just one facet of a large project, or it may be possible to embody the entire question or problem in one model. For a single chemical affecting a single receptor the conceptual model will probably be simple; in the case of multiple sources and multiple receptors the model will be more complex.

Conceptual models can be a crucial step in identifying an appropriate measurement strategy and exposure metric. In addition, models can often be developed from measurement data (e.g. the EASE model used for occupational chemical exposure by HSE and other national authorities — see Annex C) or model predictions can be updated in the light of subsequent measurement, using Bayesian techniques (Schneider *et al.*, 1999).

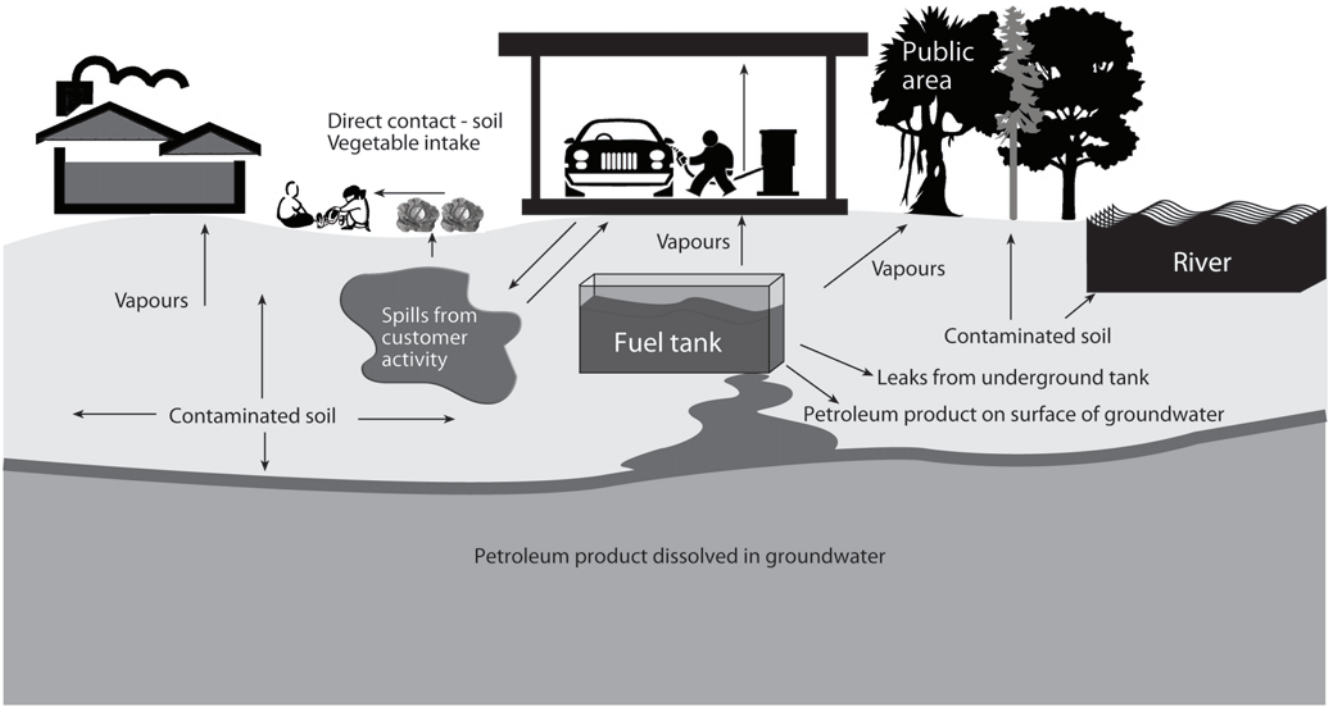
Uncertainty in developing conceptual models arises from a lack of data, failure to identify hazards, failure to consider the boundaries of the exposure assessment correctly, or failure to consider direct or indirect effects. As data gathering and analysis progress and knowledge of the situation increases, the uncertainties will decrease but other questions may be raised. Therefore it is important to revisit, and where necessary revise, the conceptual model to ensure the underlying rationale is correct (Figure 3.1). Initial models are often wide-ranging but as further information is accrued certain hypotheses may be discarded. This should result in an assessment focusing on only the most significant aspects of exposure. Exposure assessment is an iterative process.

### 3.2.5 Consultation

Because of the complex nature of many exposure assessments, a multidisciplinary approach may be adopted and, where possible, scientists, statisticians, regulators, planners, and social issues officers may be consulted. The individuals consulted with will depend on the purpose and nature of the exposure assessment. The following are examples of the types of experts who might be consulted.

[a] This document has now been updated to EC (2003)

**Figure 3.2 Illustrative conceptual model (non-occupational) of exposure to hydrocarbon fuels at petroleum retail sites**




The Institute of Petroleum (1998), reproduced with the kind permission of the Energy Institute (formerly the Institute of Petroleum). For more information visit www.energyinst.org.uk

**Statisticians** should be consulted as early as possible in an exposure assessment. At the problem formulation and data gathering stage, statistics aids in the design of the sampling plan, in establishing the power of the study (the ability to detect a difference of a given size) and in determination of the amount and form of data to collect (Lang & Secic, 1997). Following data collection, statistical description of the results aids in an understanding of the basic characteristics of exposure and its determinants. Statistical inference also allows generalisation of observations derived from a sample to the wider population from which the sample was drawn. Statisticians can advise on detailed analysis of data and its use in relation to health outcomes.

**Analytical chemists** may have information about the presence of a chemical in a particular medium and other sources of exposure, anticipated concentrations, analytical detection limits, or be able to assist with advice on targeting and timing of sampling.

**Toxicologists** might be familiar with the toxicodynamics (the relationship between the internal dose and effect) of a particular chemical and could advise on issues such as the duration of sampling and whether the measurement of fluctuations in exposure is relevant to the exposure assessment. For example, for chemicals known to have developmental effects following exposure during pregnancy, a short-term exposure during a particular time window might be relevant.

**Chemists** and toxicologists may also be able to provide advice on issues such as the speciation of the substances to be assessed and whether a mixture of chemicals or isomers should be considered.

**Occupational hygienists** and **air pollution scientists** will give advice on means to collect and analyse airborne contaminants in relation to specific health end-points.

Other stakeholders, for example employers, employees, residents, consumers and others may have valuable first-hand information about exposure patterns not immediately evident to the exposure assessor, in particular, the time–activity patterns of people on whom the exposure assessment is being carried out.

**Table 3.1 Simplified, conceptual model (non-occupational) for exposure to hydrocarbon fuels at petroleum retail sites**

| Primary source | Secondary source | Hazard | Transport mechanism | Pathway | Medium of exposure | Receptor |
|---|---|---|---|---|---|---|
| Fuel tank | None | Dizziness, CNS depression, potential carcinogenicity | Vapour transport through air | Inhalation of vapours | Air | Humans (forecourt users) |
| Fuel tank | None | Vegetative die back, damage to leaf function | Vapour transport through unsaturated zone | Absorption of vapours | Air | Adjacent vegetation (trees) |
| Fuel tank | None | Reduction of groundwater quality | Product loss and vertical migration to water-table | Dissolution in groundwater | Water | Groundwater aquifer |
| Fuel tank | None | Reduction of surface water quality | Product loss and dissolution in groundwater | Base flow and discharge to adjacent surface water body | Water | Adjacent river |
| Fuel tank | Contaminated soils | Dizziness, CNS depression | Vapour transport through unsaturated zone | Inhalation of vapours | Air | Humans (recreational users) |
| Fuel tank | Contaminated soils | Skin irritation, contact dermatitis in extreme cases | Direct contact with contaminated soil | Dermal contact at surface | Soil | Humans (recreational users) |
| Fuel tank | Contaminated soils | Flammability | Vapour transport through unsaturated zone | Vapour build-up in basement void | Air | Humans (residential) |
| Fuel tank | Contaminated soils | Flammability | Vapour transport through unsaturated zone | Vapour build-up in basement void | Air | Property |
| Fuel tank | Contaminated soils | CNS depression, asphyxiation | Vapour transport through unsaturated zone | Vapour build-up in basement void | Air | Humans (residential) |
| Fuel tank | Contaminated soils | Reduction of surface water quality | Bulk fluid transport through unsaturated zone | Free product flow to adjacent river | Water | Adjacent river |
| Fuel tank | Free product on water-table | Reduction of soil quality | Evaporation to overlying soils | Vapour phase | Soil vapour | Soil |
| Fuel dispenser | None | Reduction of soil quality | Spillage and percolation through cracked hardstanding | Leaching | Soil | Soil |
| Fuel dispenser | None | Various, potential carcinogenicity | Vapour transport through air | Inhalation | Air | Humans (forecourt users) |
| Spills from customer activity | None | Vegetative die back | Vapour transport through unsaturated zone | Absorption of vapours | Soil gases | Adjacent vegetation (home grown produce) |
| Spills from customer activity | None | Various, potential carcinogenicity | Vapour transport through unsaturated zone | Consumption of contaminated produce | Vegetable produce | Humans (residential consumers of home grown produce) |
| Spills from customer activity | None | Various, potential carcinogenicity | Vapour transport through air | Inhalation | Air | Humans (forecourt users) |
| Spills from customer activity | Contaminated soils | Dizziness, CNS depression | Vapour transport through unsaturated zone | Inhalation of vapours | Air | Humans (forecourt users) |

DETR *et al.* (2000), ©Crown Copyright material is reproduced with the permission of the Controller of HMSO and Queen's Printer for Scotland

## 3.3 Data gathering

Once problem formulation has been completed, the process of data gathering can begin. Data gathering may comprise four steps:

- literature review;
- sampling plans;
- exposure measurement, and
- modelling.

Exposure modelling may be used to facilitate both data gathering and data analysis. However, as it is a complex subject that requires some detailed explanation, it is considered separately from data gathering and data analysis, in Section 4.

The undertaking of sampling and exposure measurements is not always necessary or desirable in an exposure assessment. Information on sampling plans and exposure measurements is provided to enable those conducting the exposure assessment and those using the results to appreciate how these tasks are approached and conducted and to enable them to put the appropriate weight on, and know how much confidence to have in, the data.

### 3.3.1 Literature review

The first step in any data gathering exercise is to review the literature to obtain information on previous exposure studies, and on analytical and sampling techniques that might be useful in addressing the problem. A literature review can be divided into two stages: literature search and evaluation of the data.

#### Literature search

The selection of appropriate search terms is crucial to retrieving relevant information. On-line database interrogation systems have selection tools available that help in identifying which databases are appropriate for detailed searching. A record of the searching strategy used should be included in any report. Good practice in optimising search strategies has been developed as part of the 'evidenced-based' approach applied to medical sciences and is documented in *Cochrane Reviewers' Handbook Version 4.1.6*[a].

[a] Chapter 5.2.1: Developing a search strategy, in *Cochrane Reviewers's Handbook Version 4.1.6*, available [13 Nov 2003] at http://www.cochrane.dk/cochrane/handbook/hbook.htm

It is important to be aware of reports and other documentation containing relevant exposure data that may not be in the public domain. Such unpublished or 'grey' literature may provide monitoring data held by specific industries or government agencies and may often be obtained by direct contact with the relevant government department, agency or industry.

#### Evaluation of the data

Often a particular chemical exposure situation will have been encountered and studied before and in such cases it may be possible to base an exposure assessment on the results of previously published reports or use the information to help design a new strategy. Particular attention should be paid to judging whether all of the relevant parameters in the reported exposure scenarios are consistent with the current situation. This will largely depend on the level of detail provided in the report. In many cases space will have prevented large amounts of data from being provided and only summaries will be available. Hence, it may be necessary to identify and approach the authors of earlier reports in order to obtain clarification and further detailed information.

It may also be possible to use data from closely analogous substances when exposure data are not available for the chemical of interest. These may be chemicals that have a similar physico-chemical structure and are known to behave in a similar way. The data used for 'read across' must come from validated and reliable data sources. The use of 'read across' should be explained clearly in the document to facilitate confidence and clarity in all stages of the risk assessment.

The types of information that are available in the literature are very variable. In some cases a directly corresponding exposure situation may be identified where it will be possible to draw immediate conclusions. However, it is more common to find that the available data are incomplete or the scope of the study varies from the original. For example, exposure concentrations need to be combined with additional data on human exposure factors or time–activity patterns. Any decisions made about which data to use should be explained in the report.

Combining information from different sources can allow a set of scenarios to be established and used as the basis for exposure estimates. This approach was applied to generate the estimates of benzene exposure described in Case Study 2 of Annex D. In this example data on benzene concentrations in urban or rural environments, in the presence

or absence of tobacco smoke, were used to create a series of exposure scenarios.

When utilising data from the literature or any other source, it is necessary to be confident in the quality of the data. The following sections in this chapter give some guidance on data quality.

### 3.3.2 Sampling plans

Ideally one would like to measure the personal exposure of every person in an investigation at every possible time period. As this is not possible, a limited number of samples or measurements, either from personal or from fixed positions, are taken, which are intended, by extrapolation, to represent the whole population or exposure situation. Sampling plans are thus essential when estimating exposure to ensure that the measurements are truly representative of the current situation. An inadequate plan can lead to biased, unreliable or meaningless results, whereas good planning makes optimal use of resources and is more likely to produce valid results.

A good sampling plan should consider:

- sampling strategy;
- number and location of samples;
- scenarios; and
- quality control (see Section 3.4.2).

#### Sampling strategy

If, after problem formulation and the literature review have been completed, it is decided that sampling is necessary, a sampling strategy must be devised to obtain data relevant to the purpose of the exposure assessment.

Some regulatory frameworks for evaluating the safety of chemicals provide clear guidelines on the generation of data for exposure assessment. For example, guidelines provided in association with the European Commission Directive 91/414/EEC for evaluating the safety of crop protection products, give recommendations for the design and preparation of residue trials and for data sampling and data processing in exposure assessment[a].

[a] *Guidelines: Appendix B – General Recommendations for the Design, Preparation and Realisation of Residue Trials; Appendix D – Comparability, Extrapolation, Group Tolerances and Data Requirements.* Available [19 June 2003] at http://www.europa.eu.int/comm/food/fs/ph_ps/pest/index_en.htm

The design of sampling strategies is a complex subject (Keith, 1991, 1996; Crosby, 1995; Quevauviller, 1995; Manly, 2001) and a number of different approaches are possible.

- **Comprehensive sampling** includes all members of the population of concern and so will rarely be practical or feasible on cost grounds. However, there may be circumstances where the risk is considered to justify the need, e.g. film badges worn by all radiation workers.
- **Probability sampling** uses population demographics to ensure that the number of samples taken from a particular age, sex, geographical location, etc. represents the proportion of individuals in that category in the population.
- **Simple random sampling** ensures that each member of the population has an equal probability of being selected.
- **Directed sampling** is targeted to specific individuals or situations and is thus designed to obtain exposure information about a particular issue.
- **Composite sampling** combines a number of different samples into one data point. However, the resulting loss of precision may be unacceptable.

Each approach should be considered in the light of the purpose and scope of the assessment being conducted. The reasons for selecting an approach should be explained in the report.

#### Number of samples and sampling location

Estimates of the number of samples to be taken and/or measurements to be made should ideally be based on expected sample variability. Sample size/power calculations (taking into account various sources of variability) can be used to estimate the number of samples required (Hallenbeck, 1993; Nieuwenhuijsen, 2000; Armitage *et al.*, 2001). However, the number of samples that can be taken is frequently restricted by budget constraints and it is then necessary to decide how to deploy limited resources in the optimum way to generate maximum information. It is also necessary to balance the benefits of increasing the number of repeated measurements on the same individuals or samples (to assess within subject variability) or increasing the number of individuals or samples included in the study. A preliminary survey or pilot investigation is often a good way to generate information about factors that influence variability

so that the optimum number, spacing, and sampling frequency can be estimated more reliably.

Similarly, the location for the sampling must be carefully considered as personal sampling of individuals may be impracticable and fixed point sampling is often used. It is essential that the sampling location is representative of the exposure of concern. It is necessary to be aware that where sampling is based at least in part on observation of man or animals, there are several potential sources of bias. For example, people responding to questionnaires on food intake may respond that they eat more fruit than they actually do because they think they should. Another type of bias would be where samples of fish are taken to estimate exposure to polybrominated diphenyl ether (PBDE). If high concentrations of PBDE make the fish unhealthy these unhealthy fish might be more likely to be caught during sampling thus biasing the concentrations of PBDE observed towards higher levels.

#### Scenarios

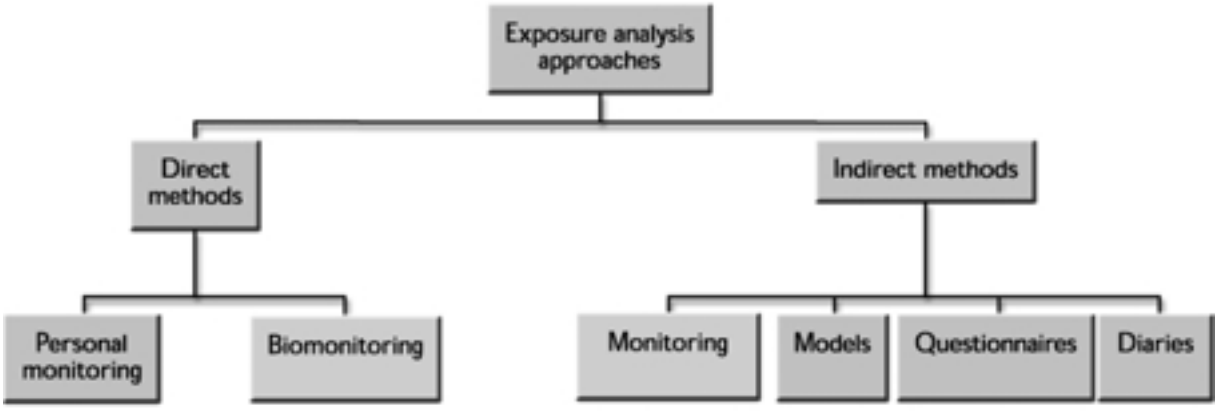
Limited resources can mean that standard randomised sampling across the whole population would not produce meaningful results because a large number of samples where exposure was minimal (at or below the detection limit of the method for the substance of concern) might be included. However inclusion of a large number of non-detects would not be a problem if it truly reflected the underlying distribution. Thus, in such a situation, where it is still necessary to estimate the population exposure, a better approach is to identify a series of scenarios designed to represent various subpopulations categorised according to their potential exposure, which can be based upon, for example, geography, location, lifestyle, diet, method of transport. For example, if exposure was known to be related to particular sources then scenarios could be set up to characterise individuals with high, typical and low exposures to each source or combination of sources. The set of scenarios would then represent all possible exposure situations. Case Study 2 in Annex D represents a good example of the use of scenarios in assessment of benzene exposure. The exposure of the whole population can then be estimated by weighting the exposure values for each scenario group according to the number of individuals expected to fall into each group.

### 3.3.3 Exposure measurement

Where and how the actual exposure measurements are made can have a major bearing on the results obtained. A number of approaches to exposure measurement are possible (outlined in Figure 3.3) and should be considered carefully before selecting the appropriate approach for a particular investigation:

- **direct measures**: measurements taken at the point of contact while the exposure is taking place;
- **indirect measures**: extrapolation from data about exposure concentrations, intakes of media and patterns of exposure to estimate intakes; and
- **laboratory-based methods.**

**Figure 3.3 Summary of approaches to determining personal exposure to air pollutants**




Adapted from Risk Assessment and Toxicology Steering Committee (1999c)

**Direct methods of exposure measurement**

Direct methods measure the exposure at the environment/person interface at the moment that it occurs (WHO, 2000a). These methods are frequently used for checking compliance with exposure limits and in other situations where it is necessary to record the actual exposure concentration. For example, personal exposure monitors (worn on the lapel) that take air samples from the breathing zone are ideal for providing measurements of individual exposures, although identification of sources of elevated exposures may require information about the environmental setting. In occupational monitoring, where the source is already known, personal monitoring (within the breathing zone) is the generally accepted method.

Direct methods have the advantage of providing relatively specific information about exposures of individuals but may be of less value when considering populations of heterogeneous individuals if the number of observations that can be made is limited. However, the methods may provide useful information about specific sources of high exposures and insight into the influence of certain time–activity patterns. There can be practical and cost considerations in taking large numbers of personal samples.

An important factor when using direct methods is to consider the degree to which the investigation may alter the normal behaviour of study participants and thus bias the results. For example occupational workers may only wear personal protective equipment when they know they are being monitored, or people may tend to eat more healthy foods when their diet is being monitored.

*Occupational monitoring*

There are two main types of inhalation exposure monitoring used in the workplace: personal and static (fixed place). The purpose of personal monitoring is to establish the concentration of the airborne substance in a person's breathing zone. Static monitoring can be carried out anywhere in the workplace. Occupational exposure limits relate to personal exposure and results from static monitoring should not be used to check compliance. Static monitoring is often used to identify emission sources, check effectiveness of controls and when continuous monitoring alarm systems are installed.

The behaviour, deposition and fate of any particle after entry into the human respiratory system, and the response it elicits, depend on the nature and size of the particle. Most industrial dusts contain particles of a wide range of sizes, therefore it is important to consider the concentrations of dust present in different size fractions. The size fractions most commonly measured are the inhalable and the respirable. To do this different sampling instruments are needed. Further information can be found in MDHS 14/3 (HSE, 2000). Analysis for specific substances can also be carried out. Details of methods can be found in HSE's *Methods for the Determination of Hazardous Substances* publication series (HSE Books, Sudbury, Suffolk, UK)[a].

There are a number of methods available for dermal monitoring but in general they are not as well developed as for inhalation monitoring. Further information can be found in Ness (1994).

*Biomonitoring*

Biomonitoring can be an important method of monitoring exposure and uptake of either individuals or groups as it can provide information on exposure that could not be provided, for example, by air or water monitoring alone. It is usually described as the measurement of a particular chemical of concern, or a metabolite of that chemical, in a suitable biological matrix such as urine, blood or other tissues such as hair, sweat or even in exhaled breath. Biomonitoring uses measurements in body tissues or excreted material as a means of assessing total uptake rather than exposure, over a period of time. It can also be used as another means of assessing exposure if the sources of the substance are known.

The application of biomonitoring is frequently limited by the availability of biomarker materials. In particular, the duration of exposure that the biomarker represents should be relevant to the dose–response characterisation of that substance if the effect is known. Many biomarkers will only reflect recent exposure and not cumulative or chronic exposure. Thus, it is crucial to understand the half-life of the substance or its metabolite in the body in deciding on an appropriate sampling strategy. Another concern regarding the use of biomarkers is that invariably it will be necessary to obtain ethical approval for the sampling if conducted for research purposes, and in particular, methods involving invasive sampling such as blood or tissue sampling. In addition, the handling of any biological specimen will involve health and safety issues.

Biomonitoring has been most successfully applied in the field of occupational health, where the concentration of certain chemicals in biological

[a] Complete list of the series on *Methods for the Determination of Hazardous Substances* available [5 December 2003] at http://www.hsebooks.co.uk/books/

materials such as lead in blood, or red-cell cholinesterase can be directly related to known health end-points (WHO, 2000a). There are a few biological exposure limits set for occupational health, some of which are statutory, such as lead, and some advisory.

Biomonitoring techniques, often using blood or urine, can also be used to assess early biological or physiological changes which are correlated with the uptake of a substance; these are called biological effect markers. An example of this is the reduction in red-cell acetylcholinesterase levels (an enzyme that, in nerve cells, is important to nerve conduction) in people exposed to organophosphate pesticides. More recently, molecular biomarkers have been developed, primarily for research purposes. However, there are practical applications in biomonitoring populations exposed to certain chemicals, such as carcinogens or their metabolites, that are able to bind to DNA or some other protein such as haemoglobin. The resulting covalently bound product is known as an adduct and can be measured by extremely sensitive techniques (a few adducts per human cell). As an example, it has been shown that smokers have higher levels of polycyclic aromatic hydrocarbon DNA adducts than non-smokers.

#### Indirect methods of exposure measurement

Indirect exposure measurement methods link information about the concentration of the chemical in a medium or location (microenvironment) with information about the duration and intensity of contact with the medium by different individuals or population groups (WHO, 2000a). Such measures of exposure include estimates based on environmental monitoring (e.g. measurements made in locations frequented by the study population) and the use of exposure factors and time–activity survey data. Indirect methods of exposure measurement are frequently used in risk assessments where it is necessary to adopt a population-based approach to potential exposure scenarios. Different sets of assumptions about concentrations, durations of exposure or population parameters such as age group can be used to develop exposure scenarios that relate to particular subpopulations. A good example of the indirect approach using scenarios is provided by the assessment of benzene exposure described in Case Study 2 of Annex D. For the exposure assessments for children, scenarios included: rural infant; urban infant; urban infant/passive smoker; rural child; urban child and urban child/passive smoker. In comparison with the direct approach, individual personal exposure measurements are not determined.

##### *Microenvironmental monitoring*

Microenvironmental monitoring is based on the idea that individuals are exposed to a series of specific environments, each with its own pre-determined chemical concentration and the individuals will move between the environments during their daily activities. Table 3.2 lists some

**Table 3.2 Potentially important microenvironments for air pollution assessment**

| Microenvironment | Comments |
|---|---|
| **Outdoor** | |
| Urban | Metropolitan areas where are pollution levels are high as a result of high density of mobile and stationary sources |
| Suburban | Small- to medium-sized communities where pollution levels tend to be lower than in metropolitan areas although transport of urban pollution can affect local air quality under certain conditions |
| Rural | Agricultural communities and small towns with few major anthropogenic sources of air pollution. Air pollution levels tend to be low, although transport of urban and suburban pollution can affect local air quality under certain conditions |
| **Indoor — occupational** | |
| Industrial | Manufacturing and production processes, such as those in petrochemical plants, pulp mills, power stations and smelters |
| Non-industrial | Primary service industries where workers are not involved in manufacturing and production processes, such as insurance companies, legal offices and retail sales outlets |
| **Indoor — non-occupational** | |
| Residential | Single-family houses, flats, mobile homes |
| Commercial | Restaurants, retail stores, banks, supermarkets |
| Public | Post offices, courtrooms, sports arenas, cinemas |
| Institutional | Schools, hospitals, convalescent homes |
| **Indoor — transportation** | |
| Private | Cars, private aeroplanes |
| Public | Buses, underground trains, railways, commercial aircraft |

WHO (2000a) reprinted with the kind permission of the World Health Organization

typical examples of microenvironments that could be included in an investigation. The time spent in each microenvironment is often based on information recorded in a time–activity diary.

The microenvironment model is based on three key assumptions (WHO, 2000a):

- the concentration in each microenvironment is constant;
- the concentration within each microenvironment and the time each subject spends in contact are independent; and
- the number of microenvironments necessary to characterise personal exposure adequately is small.

Given the potential diversity of microenvironments that individuals may move through each day, this method is likely to be limited by the ability to obtain monitoring data from a sufficient number of microenvironments.

Environmental monitoring is also an important aspect of compliance checking. For example, certain outdoor air quality standards are monitored in the UK through an automatic compliance network.

*Food monitoring*

Food monitoring is carried out indirectly to gauge the UK population's exposure to food additives using *per capita* estimates (SGCAFS, 1993). Such estimates are made by combining manufacturer's production data, import information and by removing additive that is exported out of the country. This method is useful where it is impracticable to obtain detailed information on a large number of food chemicals and provides a logical basis for identifying the potential need for more detailed studies.

*Exposure factors*

Exposure factors are those variables that relate to human activities (e.g., time indoors *vs* outdoors, weekly hours at work) and biological characteristics (e.g., inhalation rates, body weight, skin surface area). Exposure estimates that are based on environmental concentrations combined with duration of human contact can make use of published exposure factors. For example, in the benzene case study described in Annex D, estimates of children's exposure took into account exposure factors such as body weight, inhalation rate, rural or urban location and exposure or not to passive smoking. It is important to note that exposure factors may vary with time, age of the individual, etc. and so a range of values may need to be applied. In the UK occupational context exposure factors may relate to how often a task is conducted per day and/or how much of a compound is produced (1 tonne or 10 tonnes).

Many examples of exposure factors (and default values[a] for exposure factors) relevant to the UK are provided in an ECETOC sourcebook (ECETOC, 2001). For each exposure factor, a point value representative of the central tendency (i.e., mean or median) is given. Upper and lower values are also presented when available. For exposure factors with sufficient data, appropriate data distributions are also provided. The information provided in the sourcebook can be used to develop more realistic estimates of exposure than those calculated using single point values based upon extreme exposure scenarios, if this is required. The ECETOC sourcebook focuses heavily on risk assessment of chemically contaminated sites. The data contained therein might therefore be insufficient for other exposure assessment applications.

Some other useful UK data sources are available in a series of Department of Trade and Industry (DTI) publications: CHILDATA (DTI, 1995); ADULTDATA (DTI, 1998); Strength Data (DTI, 2000a); OLDER ADULTDATA (DTI, 2000b), which provide data including body measurements, strength and performance expressed by age-bands. Most of the data are presented with distributional statistics (i.e. mean, standard deviation, 5th percentile and 95th percentile).

*Activity surveys*

Observation and recording of all individual activities, including location–time data, are likely to provide the most accurate source of information for indirect exposure assessment. However, such data may be impractical or technically impossible to obtain. A common alternative is the use of time–activity surveys or video visualisation.

In an exposure context, data about human time use and activity patterns (time–activity data) have four related purposes (WHO, 2000a) outlined briefly below.

- Knowledge of the activities performed while a study participant carries a personal monitor can aid in identifying the determinants of exposure, that is, 'what did this person do that led her/him to have such a high exposure?'

[a] A default value is a preassigned value used in the absence of real information

- Time–activity data allow modelling of human exposure to pollutants for which personal monitors are not yet available, or are very expensive, or for which exposure is a function of multiple pathways.

- From an epidemiological perspective, activity patterns can be used to assess the relationship between exposure and health status, that is, 'do those who engage in potentially high-exposure activities experience more frequent or severe illness?'

- Another purpose of time–activity data is to describe patterns of population behaviour.

Approaches used in activity surveys can range from the use of simple diaries to questionnaires and video monitoring. The diary approach, probably the most powerful method for developing individual activity patterns, provides a sequential record of a person's activities during a specified time period. Occupational hygienists often develop qualitative exposure categories based on workplace observations, job descriptions, employment duration and local environmental conditions such as ventilation and type of machinery.

Questionnaire surveys provide qualitative and quantitative, frequently retrospective, information that may be used to categorise subjects into groups corresponding to their respective levels of exposure (e.g. low, medium, high). In designing a questionnaire survey it is essential to have first established the potential association between the activity to be investigated and anticipated exposures. Other variables that might influence the results, such as age, income level, smoking, must be carefully considered and accounted for in the questionnaire design.

#### Laboratory-derived exposure data

The general lack of availability of exposure data, particularly in the case of consumer products, is a frequent problem and remains a critical research need. Where such data are unavailable, 'best' or 'worst case' exposure estimates may need to be generated; the emphasis is usually on the latter in the first instance with subsequent refinement in the event of any identified concern. Default assumptions should be made where applicable and available. Exposure modelling is discussed in more detail in Section 4.

However, laboratory-based studies may also be used to overcome difficulties associated with the absence of exposure-related data. Literature and information review may be used to establish appropriate exposure parameters and scenarios and to derive relevant criteria for exposure assessment. Existing candidate laboratory studies can then be reviewed or new studies derived and the limit values produced can be used as part of a risk assessment.

These laboratory-based studies may produce, or be refined to produce, limit values in line with toxicologically acceptable measured or estimated exposure limit values obtained from other sources on a known product. Through validation by collaborative trial, the values obtained from these laboratory-based studies can then be considered against limit values. Statistical analysis of data is shown in Section 3.4. Method uncertainty can be expressed for the studies — see Section 5.1.

An example of the derivation and use of laboratory-based studies is shown in Case Study 1 of Annex D, which estimates the exposure of young children to phthalate plasticisers from soft PVC toys and child use and care products.

## 3.4 Data analysis

Analysing and evaluating the exposure data is an essential part of exposure assessment. As indicated in Section 3.2.5, statistical description of the results, following data collection, aids in the understanding of the basic characteristics of exposure and its determinants. Statistical inference also allows generalisation of observations derived from a sample to a wider population from which the sample was drawn. Furthermore statistics plays an important role in quality assurance programmes.

The application of descriptive and inferential statistics is beyond the scope of this document and detailed descriptions of such applications can be found in WHO (2000a) and Armitage *et al.* (2001).

Also, as indicated in Section 3.3, exposure modelling is used to facilitate data analysis but as it requires some detailed explanation it is covered separately in Section 4.

### 3.4.1 Data gaps, outliers and limits of detection

Statistical analysis of exposure measurement data can be carried out to produce summary measures such as means, medians, percentiles, and estimates of variability and also to provide relational models for prediction purposes. Statistics selected to represent the data should be clearly described. This is particularly important for very skewed distributions where a single statistic (such as the mean, median or mode) is insufficient or even

misleading as a description of the entire data set. Clear distinctions should be made between conclusions that are drawn from the data in hand and those that are based on inferences from them.

Statistical analysis will highlight both gaps in the data and unusual values or outliers. The treatment of both data gaps and outliers, for example, by checking, replacing, removing or ignoring the latter, should be carefully reported and possible explanations of anomalies provided.

Resource constraints mean that it is often necessary to use a limited number of measurements (typically over a period of one per day to one per week) on a limited section of the population when generating exposure data for use in long-term exposure assessments which are intended to cover several years or even a lifetime for the whole population. In such circumstances, it is crucial to consider how well such 'snap-shots' truly represent the longer-term scenario or the whole population. An appropriate example would be the National Diet and Nutrition Survey conducted by the Food Standards Agency, which is a programme of cross-sectional dietary surveys, each focussing on a specific population age group, carried out at two to three year intervals. Around 2000 people take part in each survey and keep a record of food consumption, usually for seven days. The information derived from the dietary surveys is taken to be representative of the whole UK population.

The use of limited sampling data taken over a short period of time to estimate long-term exposure can lead to under- or overestimating exposure. As an example, the use of average long-term data for estimating short-term exposure can miss significant variations by smoothing out important short-term fluctuations. The magnitude of peaks and troughs in exposure may be particularly important, especially when dealing with dose rate-dependent effects, or estimating exposures that may be time related. For example, if one is interested in peak concentrations when measuring air concentrations of pollutants near road sites it would be necessary to have a series of short sampling periods over the day.

#### Managing outliers

Certain data sets may contain outlier data points that do not appear to follow the distribution of values that would be expected from the majority of the data. Outliers should only be removed from data sets where there is strong evidence that they are erroneous. If possible, the site or sample should be re-tested. In some cases the result is so low or so high that the exposure conditions necessary to achieve such a result are not feasible, in which case it may be justifiable to ignore the data point. In cases where an outlier is realistic but unexpected the possibility that it reflects a subset not characterised by the other data points should be considered. The presence of unexpected outliers may also raise doubts about the validity of the entire data set. The management of outliers should be discussed in the report.

#### Limits of detection and quantification

The **limit of detection** (LOD) is the smallest measure that can be detected (i.e. distinguished from zero) with reasonable certainty for a given analytical procedure. The **limit of quantification** (LOQ) is the minimum concentration or amount of an analyte that a procedure can measure with a specified degree of confidence (Manly, 2001). When the measured exposure concentration of a chemical in a medium is less than the analytical LOD or LOQ employed by the analyst, the chemical may be reported as 'not detected'. Analytical chemists use such reporting limits because measurements taken close to the baseline are subject to the greatest uncertainty. Some statisticians argue that an uncertain measurement is better than none at all and that analysts should report all of the results. Analytical uncertainties can then be reported and included in the discussion of uncertainties.

The presence of 'non-detects' can have significant effects on calculated statistics, particularly statistics such as geometric mean, or lower percentiles. When high-end exposures are being assessed, they may have minimal effect on estimating upper percentiles. If significant numbers are present however they can introduce difficulties in estimating the mean and standard deviation of a distribution. Several approaches are available for handling such data, ranging from simple substitution with zero or half the LOD to complex parametric models (Manly, 2001). The Food Standards Agency often provides two sets of values in its food surveys, for example, when values are <LOD it is assumed that levels are either equal to 0 or are equal to the LOD.

In preparing a sampling plan, it is important to collate information on analytical methods and LOD for specific compounds to ensure that the sampling period (and quantity) is long enough to ensure that the minimum number of samples fall below the LOD. Often high levels of non-detects are a reflection of the use of inappropriate sampling and/or analytical techniques. Such problems could have been spotted by the use of a short 'pilot study' as discussed in Section 3.3.2. If samples contain very small amounts of the

contaminant of interest, then it is important to consider, for example, sampling for longer periods (air), taking larger samples (e.g. foodstuffs/water) and/or bulking samples (e.g. blood samples from different individuals to get an average blood concentration).

### 3.4.2 Quality assurance

**Quality assurance** refers to overall management and organisational systems put in place to assess and maintain the integrity of the study. Human exposure studies are complex, involving large amounts of data. Consequently, quality assurance should be applied to all aspects of the exposure assessment, including its design, implementation and reporting to ensure the reliability and reproducibility of the results. Independent monitoring ensures that facilities, equipment, personnel, methods, practices, records and controls conform to accepted quality management principles. An effective quality assurance programme provides confidence that the overall study meets the pre-established standards of accuracy, precision, completeness and clarity (WHO, 2000a).

**Quality control** is a valuable and commonly used quality assurance tool applied to individual components of the study. Examples of such components are selection of study participants, collection of environmental samples, chemical analysis and analysis of data. The quality of an analytical measurement may be evaluated, for example, by comparing analytical results against a known standard, determining the sensitivity, accuracy, and precision of the analysis and ensuring that the analytical equipment has been properly maintained.

All measurements are subject to variability, which can be a major contributor to uncertainty in exposure assessments. It is important to be able to distinguish between natural variability and variability introduced by sampling and analysis (see Section 5.1).

Lack of information about quality assurance procedures can also make data extremely difficult to interpret since it is not known how much reliance can be placed on the results. Even when duplicate sampling and analysis have been used to control some aspects of measurement uncertainty, some ambiguity between inherent variability and measurement uncertainty may remain. The problem may be exaggerated when high-end exposures are being estimated because they are frequently based on relatively few data. One method for addressing this problem is to calculate confidence intervals around exposure estimates. However, high-end estimates that include consideration of uncertainty should be presented with both the upper and lower uncertainty bounds.

Questionnaire and survey data can provide other sources of error and may require different quality assurance techniques such as the use of independent observers and retrospective verification or validation.

A detailed account of quality assurance procedures can be found in WHO (2000a).

# 4 Modelling in exposure assessment

A variety of approaches are used within UK Government departments to assess human exposure to chemicals as part of risk assessments or for other purposes. Many of these approaches involve the design and application of an appropriate exposure model. An exposure model can simply be described as 'a conceptual or mathematical representation of exposure' (WHO, 2001)[a]. Section 3 provides information on the measurement of exposure by direct or indirect methods. The use of exposure factors and previously published data to make estimates of exposure was also described. Such methods can be thought of as simple models. Exposure models range from very simple multiplicative models containing few inputs to extremely complex structures. As well as numerical models, decision-tree type models are also used.

Exposure models provide an analytical structure for combining data of different types and from different studies so as to make more complete use of existing information than is possible from direct exposure measurements (WHO, 2000a). Models can also provide useful tools for predicting exposures to new substances or new population groups where no direct data are available. Properly validated models, when available, can also reduce the need for resource-intensive exposure monitoring programmes for existing exposure situations. Some models are designed to predict the exposure concentration part of an exposure assessment while others are designed to model human contact. More sophisticated models may predict intake by single or multiple routes.

When using models it is important to ensure that the data, default values, algorithms and assumptions are valid and that the overall structure is relevant to the purpose of the exposure assessment. It is generally assumed that exposure measurements are more reliable than modelling but this may not always be the most practicable approach. In most cases some form of modelling is required unless it is possible to make direct measurements of the populations at risk at the time of exposure.

A variety of models are used by UK Government departments and agencies (Table 4.1). Some of these models are commercially available, others have been developed by the departments/agencies themselves for a specific purpose and some are developed in conjunction with consultants for

A classic example of a simple exposure model is one that is often used to calculate potential daily dose for chronic health effects, where risk is assumed to be linearly associated with dose:

$$\text{Dose} = \frac{\text{IR} \times \text{C} \times \text{ED}}{\text{BW} \times \text{LT}}$$

| | | |
|---|---|---|
| Dose | = | lifetime average daily dose (mg of chemical per kg bodyweight per day) |
| IR | = | Intake rate: for inhalation, this is typically expressed as litres per minute |
| C | = | Concentration of chemical in environmental medium (e.g., micrograms per cubic metre of air) |
| ED | = | Exposure duration (e.g years) |
| BW | = | Bodyweight (kg) |
| LT | = | Lifetime (years) |

[a] WHO (2001) *Glossary of Exposure Assessment-Related Terms: A Compilation*, available [19 June 2003] at http://www.who.int/pcs/harmon_site/harmonize/docs/Expo_Assess_Compil.pdf

**Table 4.1 Examples of exposure assessment models used by different UK Government departments**

| Model | Intended use | Exposure route | Government Department | Availability |
|---|---|---|---|---|
| New generation atmospheric dispersion models (e.g. ADMS and AERMOD) | To simulate the dispersion of a wide range of buoyant and passive releases to the atmosphere | Inhalation | Environment Agency | Proprietary |
| American Pesticide Handlers Exposure Database (PHED) | To predict level of exposure likely to be experienced by operators applying pesticides under American conditions | Dermal<br>Inhalation | PSD | Currently available, but replacement anticipated |
| Bayesian Exposure Assessment Toolkit (BEAT) | Predicts occupational exposure to chemicals based on the task tool and expert judgement | Dermal | HSE | Under development (this model will be free, and is expected to be released by the end of 2004) |
| Contaminated Land Exposure Assessment (CLEA) Model | To estimate child and adult exposures and risks from soil contaminants for those potentially living, working and/or playing on contaminated sites over long periods of time | Dermal<br>Ingestion<br>Inhalation | Environment Agency | Free to download from the Defra website |
| Consumer Exposure and Uptake Model (CONSEXPO) | To assess human exposure to and uptake of chemicals used in consumer products | Dermal<br>Ingestion<br>Inhalation | HSE | Full model is proprietary but generic deterministic version available free from HSE |
| Contaminated Land Exposure Assessment (ConSim) | To predict the impact of leaching contaminants from land contamination on the quality of controlled waters (particularly groundwater) | Dermal<br>Ingestion | Environment Agency | Available free from the Environment Agency |
| Estimation and Assessment of Substance Exposure (EASE) | To assess the exposure of workers to substances hazardous to human health in the workplace | Dermal<br>Inhalation | HSE | Proprietary — intended to be made freely available |
| European Union System for the Evaluation of Substances (EUSES) | To produce quantitative assessments of the risks posed by new and existing chemicals to man and the environment | Dermal<br>Ingestion<br>Inhalation | DTI, Environment Agency | Proprietary — available for a charge from the European Chemicals Bureau |

| Model | Intended use | Exposure route | Government Department | Availability |
|---|---|---|---|---|
| German Operator Exposure Model | To predict levels of exposure likely to be experienced by operators applying pesticides under German conditions | Dermal Inhalation | PSD | Published by German regulatory authority |
| HSE Pesticide Model | To predict level of exposure likely to be experienced by operators applying biocides or those handling treated materials under UK conditions | Dermal Inhalation | HSE | Published by the HSE |
| INTAKE Program | To assess the exposure of the general UK population and specified subpopulations to single contaminants via the dietary ingestion route | Ingestion | FSA, PSD | Proprietary — used in-house by the FSA |
| Landfill Simulation Model (LandSim) | To predict the impact of pollutants in a landfill site on the quality of controlled waters (particularly groundwater) | Dermal Ingestion | Environment Agency | Available free from the Environment Agency |
| Predictive Operator Exposure Model (POEM) | To predict the level of exposure likely to be experienced by operators preparing and applying pesticides in the UK under UK conditions | Dermal Inhalation | HSE, PSD | Available from PSD free of charge |
| RISC Human — Risk Integrated Software for Cleanups | To assess the potential for adverse human health impacts due to exposure to contaminated soil, water and air, to calculate target cleanup levels for these media, and to estimate the cross-media transport of chemicals in the environment | Dermal Ingestion Inhalation | Environment Agency | Proprietary |
| SeedTropex | To predict level of exposure likely to be experienced by operators applying seed treatments or those handling treated seed under UK conditions | Dermal Inhalation | PSD, HSE | Proprietary |

specific projects. A comprehensive directory of environmental exposure assessment tools is available in the Environment Agency's Risk Portfolio (Duarte-Davidson and Pollard, 2000). In certain circumstances, such as when complying with European regulations concerning new and existing substances, modelling may be a regulatory requirement (EC, 1996[a]).

This section gives a brief overview of the types of models available for exposure assessment. Further details of particular models can be found in Annex C.

## 4.1 Modelling exposure concentration

Models to estimate the concentration of chemicals in the environment to which people may be exposed incorporate physical and chemical information about a specific substance into a mathematical model that simulates transfer between, and behaviour in, environmental compartments so that the concentrations in media such as air, water, soil, plants and animals can be predicted (WHO, 2000a). Numerous mathematical equations (algorithms) are used to describe the various transport, transformation and partitioning processes that affect a chemical's concentration in the environment.

Some of the most commonly used distribution models are air dispersion models and these have achieved a high degree of sophistication. Air models use meteorological data to predict plume behaviour from point sources to estimate concentrations at ground level that can be directly compared with air quality standards (Beychok, 1994; Arya, 1999; CERC, 2002[b]). Dispersion models can combine measured data with modelling results to predict concentrations at other points under the plume (Paustenbach, 2000). The air concentration predicted by numerical dispersion models is frequently considered as a 'given value' in risk assessments. However, there is a level of uncertainty associated with such modelling which increases in the presence of buildings and/or significant terrain variations in the vicinity of the point source. The deposition of particulate matter is treated in a highly simplistic manner within exposure models. In general, a particle size distribution is assumed, but it is unlikely to be well defined for a particular process. The quantification of the source of the chemical of potential concern may also be uncertain. However, in most cases the emission rate of a pollutant is assumed to be at its permitted limit.

Dispersion models are also available to predict chemical behaviour and concentrations in water, soil and groundwater. Water models range in complexity from basic, large-scale distribution models to detailed site-specific models and models that deal with specific types of chemicals. For example, the GREAT-ER model has been developed to simulate the fate of (organic) chemicals discharged from point sources into rivers (Verdonck *et al*., 1999). Numerous models exist to predict the fate of chemicals in soil and groundwater, an example being the ConSim model[c], which is designed to assess the risk posed to groundwater by contaminants leaching from contaminated land. This is important as a large amount of drinking water is abstracted from groundwater aquifers.

## 4.2 Modelling human contact

Human contact models use data such as daily activity patterns or food consumption together with exposure concentration data to predict intake or uptake of chemicals. Simple models consider one potential exposure route at a time, whereas more complex models may consider multiple routes (Douglass & Tennant, 1997). The Pesticides Safety Directorate (PSD) has published simple human contact models that enable prediction of consumer intakes of pesticide residues under approved usage conditions (Annex C; PSD, 1999). CONSEXPO, a more complex human contact model, allows the specification of contact, exposure and uptake parts of an analytical framework to predict consumer exposures (Annex C; Veen, 2001[d]). Sometimes it is necessary to combine a practical and theoretical approach, such as when modelling exposure of small children to chemicals from chewing toys (Annex D, Case Study 1).

## 4.3 Taking variability into account in modelling

Environmental concentration data and human contact data are both subject to natural variability. This means that exposure parameters in the real world can seldom be represented by single fixed values. Instead there is usually a distribution of

[a] Now updated (EC, 2003)
[b] Available [June 2003] at http://www.cerc.co.uk/software/pubs/ADMS%203.pdf
[c] Available free from the (UK) Environment Agency
[d] Software available [Dec 2003] at http://arch.rivm.nl/index_en.html

possible values with each value having a probability of occurrence associated with it. For example, concentrations of chemical contaminants in environmental media are frequently found to be log-normally distributed with many low values and few high or very high values. Variability and uncertainty are discussed in greater detail in Section 5.

Provided sufficient samples are obtained, this natural variability will also be measured when direct exposure measurements are taken in the environment. When indirect measurements, default data and models are employed it is necessary to consider incorporating information about variability. Single data points, such as maximum values, can be used to represent distributions in worst case or screening analyses but if these produce indications of unacceptably high exposures then the effect of combining maximum values on the exposure estimate should be examined.

Providing details on all the exposure models currently in use is beyond the scope of this report. This section provides an introduction to deterministic and probabilistic exposure modelling approaches, which are commonly applied as part of exposure assessments, giving an overview of the underlying concepts and discussing their relative strengths and weaknesses. For the purpose of promoting understanding, these approaches are discussed in the context of their application to exposure assessment as part of human health risk assessment (see Section 1.3). The concepts behind these approaches are, however, generic and can be applied to exposure assessment in a broader sense.

### 4.3.1 Point estimate or deterministic modelling approaches

Chemical risk assessments are designed primarily to characterise risks to groups of individuals such as the general population of a country or potentially vulnerable subgroups such as children, infants or the elderly. Many of the factors than can affect risks from exposure to chemicals vary from one individual to another. Bodyweight, inhalation rate, frequency and duration of contact with contaminated media and genetic predisposition can lead to different risks among individuals, even if the concentration of chemical to which they are exposed is the same (variability and uncertainty are discussed in greater detail in Section 5). Theoretically, there is no single risk for a particular exposure circumstance, but as many different risk values as there are individuals. To overcome the problem of addressing variability in exposure and risk assessment, regulatory authorities have traditionally characterised the risks to individuals in a population who are likely to encounter the greatest exposure. The approach they have used, frequently referred to as a **'point-estimate'** or a '**deterministic'** approach, uses single values to represent each exposure variable and produces a single risk estimate. In chemical risk assessments, initial screening of potential human health risks from chemicals of concern is often carried out by calculating 'worst-case', (or 'high-end' or 'upper bound') point estimates of exposure using maximum or upper percentile values for exposure variables. In risk characterisation, these point-estimates of exposure are then combined with an appropriate toxicological end-point to determine whether a hypothetical 'worst' case individual exceeds the regulatory threshold of concern (or other calculated margins of safety). Where worst-case exposure estimates exceed regulatory thresholds, refined point-estimate exposure estimates (or 'best-case' estimates), are sometimes derived using average, mean or median values for exposure variables to provide a more realistic estimate of exposure.

The Pesticides Safety Directorate uses a tiered deterministic approach to estimate chronic and acute dietary exposure to pesticide residues (PSD, 1999) as part of the approvals process for the authorisation of use of pesticide products (described in Annex C).

The main advantages of using deterministic approaches for modelling exposure are that these are generally simple, quick and inexpensive and can be used as a screening tool for assessing chemical health risks. These approaches are, however, associated with a number of disadvantages, which can undermine their use in regulatory decision making. Deterministic approaches provide little information on the extent to which exposure or risk varies within a population or subgroup under investigation; certain models are inflexible and do not allow different assumptions or scenarios to be considered and they can provide conservative or unrealistic exposure estimates. For example, it is not possible to determine from a 'worst-case' point estimate whether this represents an exposure likely to be encountered by the 95th, 99th or 99.999th percentile individual in a given population or is so extreme that it is unlikely ever to take place. If a high-end point estimate significantly exceeds the maximum (100th percentile) exposure likely to be encountered by a real population, it is likely to be highly unrealistic and provide an extremely conservative basis upon which to regulate safety to chemicals.

### 4.3.2 Probabilistic modelling

Probabilistic analysis is an alternative approach used in chemical risk assessment which addresses the shortcomings of deterministic, point-estimate methods in terms of variability and uncertainty and enables risk analysts to produce more accurate and realistic estimates of risk across populations under investigation. The term 'probabilistic risk assessment' is commonly used to describe chemical risk assessments in which probabilistic exposure modelling techniques are used to generate exposure estimates across an entire exposed population that incorporate the probabilities of these exposures being encountered. The output of this approach, often given as an exposure distribution, can be used in different ways to inform the risk characterisation stage of a risk assessment. In contrast to deterministic risk assessments, which generate single risk estimates, often based on worst case scenarios to protect the whole population, probabilistic risk assessments generate a range of risk estimates enabling risk to be characterised across a whole population.

In probabilistic exposure modelling, distributions of exposure variables (also referred to as the exposure model input distributions) are used rather than single values. For example, instead of using a single adult bodyweight of 70 kg in an exposure calculation, a distribution of bodyweights is used which reflects the variability in bodyweight in the exposed population. Depending on the availability and quality of data, distributions for any exposure variable relevant to a given exposure assessment scenario can be used in a probabilistic exposure model.

In probabilistic modelling, distributions of exposure variables are combined in such a way as to give an exposure distribution. Exposure variables are also sometimes combined with toxicological endpoint levels to give risk distributions. Although, there are several ways to combine exposure input distributions, the most common approach involves the use of a mathematical sampling technique called Monte Carlo simulation. The Monte Carlo technique, as applied to exposure assessment, involves combining the results of hundreds or thousands of random samplings of values from input distributions to produce an output distribution, which reflects the expected range and frequency of exposures. A detailed description of the Monte Carlo technique, including a description of the fundamental assumptions involved is provided by Vose (1996) and IEH (2000).

As a simple example, a probabilistic modelling approach can be used to determine the daily dietary intake of chemical X from oranges consumed by children. Intake of chemical X can be determined using the simple exposure model:

$$\mathbf{I = C \times F / BW}$$

I = intake of chemical X (mg/kg bodyweight/day)

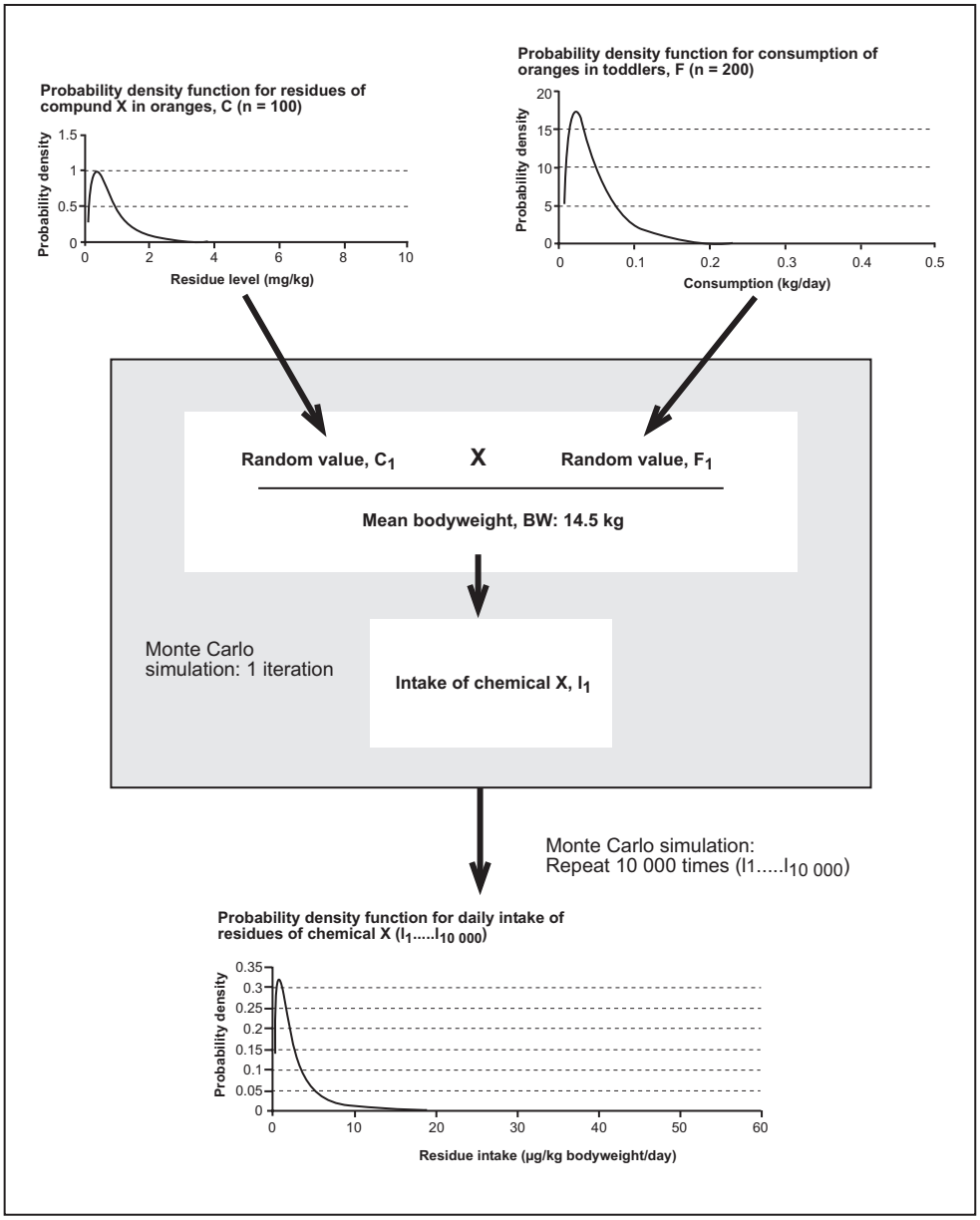
C = concentration of chemical X in oranges (mg/kg)

F = amount of oranges consumed by a child in 1 day (kg/day)

BW = bodyweight of child (kg)

In this example, the concentration of chemical X in oranges (i.e. variable **C** in the exposure model) was measured experimentally in a sample of 100 individual oranges treated with chemical X in field trials. The set of 100 residue measurements for 100 oranges was then used to construct a distribution graph of residues in oranges (see Figure 4.1). In probabilistic modelling, distributions of input variables are often illustrated as a 'probability density function' or PDF distribution (PDF distributions are also referred to as probability functions or frequency functions). A PDF is a graphical representation of the relative likelihoods with which a variable may obtain various values. In this example, the PDF for residues of chemical X in oranges shows the relative likelihood with which residues in oranges can obtain values between 0 and 10 mg/kg, based on experimental measurements in 100 oranges. Orange consumption in kg/day in toddlers (i.e., variable **F** in the exposure model) was obtained from a dietary survey of 200 toddlers. The set of 200 consumption data points was used to construct a distribution graph (see Figure 4.1). In this example, a single value of 14.5 kg representing the mean bodyweight in 200 toddlers included in the survey was used to represent the exposure variable **BW**, used in the exposure model. This was included to demonstrate that single values as well as distributions are sometimes used in probabilistic exposure modelling (for example, when data for a given exposure variable are limited).

**Figure 4.1 Example of probabilistic modelling of dietary intake of residues of chemical X from oranges consumed by toddlers**




Toddler consumption data from Gregory *et al.* (1995)

In Monte Carlo simulation, a random value is selected from the distribution of residues of chemical X ($\mathbf{C_1}$) and multiplied by a random value selected from the distribution of orange consumption in toddlers ($\mathbf{F_1}$). The product is then divided by the fixed bodyweight to give a value for the intake of chemical X ($\mathbf{I_1}$). The step in the Monte Carlo simulation, which generates an output value (i.e., $\mathbf{I_1}$) is frequently referred to as one iteration. In this example, the process is repeated 10 000 times (i.e. 10 000 iterations are performed). The Monte Carlo simulation generates 10 000 values for the daily intake of chemical X in toddlers, which can be presented graphically as a probability density function, which represents the exposure distribution for the toddler population.

The sequence and frequency of Monte Carlo simulations can vary depending on the exposure scenario under investigation.

Input data for a given exposure scenario can be represented in different ways in probabilistic modelling. The data values themselves can be used directly in the Monte Carlo simulation. In this technique, values from the raw input data are repeatedly selected at random and used to calculate the model outputs. Distributions of 'raw' data are sometimes referred to as an empirical distribution function (EDF). Input data can also be used to define a non-parametric EDF where the data values themselves are used to specify a cumulative distribution and the entire range of values

(including intermediate points) is used as model inputs. With this technique, any value between the minimum and maximum observed values can be selected and model input is not limited to the specific values present in the measured data. Finally, as illustrated in the example above, an assessor can attempt to fit a theoretical or parametric distribution (a PDF) to the data using standard statistical techniques. The input value used in the model is selected at random from these fitted distributions. Normal and log-normal distributions are examples of theoretical distributions which are sometimes fitted to data used in exposure modelling.

There is currently no consensus among risk analysts as to which is the best technique to use for selecting representative distributions in probabilistic exposure modelling. In general, the use of parametric theoretical distributions may be preferable to the use of empirical distributions when data are limited; when the fit of the theoretical distribution is shown to be good using statistical tests or when there is a theoretical or mechanistic basis which supports the chosen parametric distributions. Ultimately, the technique selected depends on the quality and quantity of exposure data and the judgement used to assess the variability and uncertainty inherent in the risk assessment problem. Issues relating to distribution selection and Monte Carlo analysis more generally have been addressed by the US Environmental Protection Agency in the report *Guiding Principles for Monte Carlo Analysis* (EPA, 1997).

Probabilistic modelling can be carried out using distributions for all input variables in a given exposure model or using combinations of single values and distributions. The FSA's INTAKE program (Annex C) is an example of a model that usually uses distributional data for an individual's food consumption patterns with fixed values for concentrations of chemicals in food. Another example is provided by the Contaminated Land Exposure Assessment model, CLEA (Defra & Environment Agency, 2002b). CLEA combines information on a measure of the toxicity of soil contaminants with estimates of potential exposure by adults and children to land affected by contamination, over long periods of time. Predicted exposure is compared with health criteria values, such as TDIs, to derive Soil Guideline Values that are protective of human health. CLEA employs elements of probabilistic modelling in that eight parameters for estimating exposure are selected from a range of possible values rather than just one. Probabilistic parameters in CLEA include body weight, respiration rate, vegetable consumption and the mean daily soil ingestion rate by children aged 0–6 years.

For many purposes, the simplest way to carry out probabilistic exposure modelling is by using a spreadsheet add-in such as @RISK (http://www.palisade.com) or Crystal Ball (http://www.decisioneering.com). Both of these products use spreadsheets (such as Microsoft Excel or Lotus 1,2,3) as the basis for calculations, adding extra facilities for Monte Carlo simulation (see Annex D).

Probabilistic modelling techniques are discussed in various textbooks. A good introduction to the use of the technique in exposure assessment is provided by *Probabilistic Techniques in Exposure Assessment: A Handbook for Dealing with Variability and Uncertainty in Models and Inputs* (Cullen & Frey, 1999).

## 4.4 Modelling multiple pathway and multiple chemical exposures

Until recently it was common practice within Government agencies and departments to consider each chemical, source and pathway of exposure separately. Thus, for example, a chemical that could be present in occupational settings, in drinking water, food and as an airborne environmental contaminant would have a separate exposure assessment for each source and pathway and the total exposure of populations and individuals, known as **aggregate exposure**, would not be considered. Similarly, chemicals that had a similar toxicological effect would be considered separately and the combined effects from simultaneous exposures, known as **cumulative exposure** ignored. In this context the term cumulative exposure, coined in US Food Quality Protection Act documentation, does not refer to long-term accumulation. Instead, cumulative exposure refers to combined exposure to a chemical and to all other substances with a common mechanism of toxicity, regardless of their source and pathway of exposure. A frequently cited example of such substances is the class of structurally related potential carcinogens such as dioxins and dioxin-like compounds (polychlorinated dibenzofurans and polychlorinated biphenyls). Dioxin-like compounds are those having a similar mode of action to the parent compound 2,3,7,8-tetrachloro-*para*-dibenzodioxin (TCDD), which is commonly known as dioxin. Estimates of the total dose can be derived by adjusting the relative doses of

different chemicals by using toxicity equivalence factors (TEFs). TEFs represent the relative potency of dioxins and dioxin-like compounds in comparison with that of TCDD. The toxic equivalent quantity (TEQ) is the sum of all the individual dioxin-like congeners multiplied by their specific TEFs.

Government departments and agencies are increasingly working together to bring multiple pathways and multiple chemicals into the risk assessment process. For example, the FSA established a working group on risk assessment for mixtures of pesticides and veterinary medicines (WiGRAMP) under the auspices of the Committee on Toxicity of Chemicals in Food Consumer Products and the Environment (COT, 2002). The aims of the committee were:

- to assess the potential for multiple residues of pesticides and veterinary medicines in food to modify individual toxicity in chemicals in humans — the so-called 'cocktail' effect;
- to evaluate what assumptions can be made about the toxicity of pesticides in combination;
- to consider the potential impact of exposure to pesticides and veterinary medicines by different routes; and
- to formulate advice on the standard risk assessment procedures applied to the safety evaluation of individual pesticides and veterinary medicines in the light of the above considerations.

In its report the Committee noted that exposure assessment of mixtures would be extremely difficult because of the poor quality and availability of data on levels in food and environmental media (COT, 2002). Deterministic methods of risk assessment were considered to be highly conservative and probabilistic methods would be more appropriate for both multiple pathway and multiple chemical risk assessment.

## 4.5 Model selection and validation

There has been a proliferation of models designed to predict environmental concentrations, model human contact or estimate exposure, dose or risk. Some of these are commercial proprietary software, some are derived from academic research projects and others have been developed through government and/or industrial initiatives. Selection of an appropriate model is essential for successful estimation of chemical exposures. There may be no ideal model for use in any particular study. There are, however, several factors that will help in selecting the most appropriate model.

The primary consideration in selecting a model is a clear understanding of the purpose of the exposure assessment. The associated schedule, budget, and other resource constraints may also affect model selection. Models are available to support both screening-level and more detailed studies. Screening methods based on conservative default assumptions can be used to eliminate the need for further enquiry. More sophisticated models are able to take into account more detail, such as spatial and temporal distributions of chemicals (Price *et al.,* 2001).

The technical capabilities of a model determine its ability to simulate the relevant processes occurring within the specified environmental setting for the conceptual model. It should be possible to examine all of the mathematical formulae, default assumptions and underlying structures of any model so that its relevance to the particular task can be assessed. Models that contain hidden elements ('black boxes') that cannot be evaluated by the user should be avoided unless they have undergone thorough independent evaluation.

Comparing predicted values with those measured in the field can validate the prediction accuracy and precision of models. For some models, authenticated test data sets may be available to help with model validation. When comparison with measurements is not possible (such as in retrospective analyses), comparison of results from different assessment methods and models can be used to provide evidence of validity or at least agreement. Complete model validation is seldom attainable because of practical limitations such as situations where the collection of direct samples is impossible. In such cases it may be necessary to rely on independent expert evaluation of the model.

The Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE, 2001) has recommended six criteria, outlined below, that an exposure assessment model should fulfil and that can be followed in an expert evaluation.

- The model must be properly documented and analysed.
- The model should have an appropriate time and spatial scale.

- The application range of the model and other limitations must be complied with.

- The mathematical relations and the conceptual and theoretical background must be known.

- The expected degree of uncertainty and the sensitivity of the model to input must be known.

- There should be support for the assumptions made and for the values of the default parameters used.

# 5 Exposure characterisation

The final stage of an exposure assessment is the exposure characterisation, without which the assessment would be merely a collection of data, calculations and estimates. The exposure characterisation represents the output of the exposure assessment and draws together the results of the steps outlined in Sections 1–4, presenting a balanced representation of all the available data and identifying key assumptions and major areas of uncertainty. It should be noted that when an exposure assessment is conducted as part of a risk assessment, quite often the exposure characterisation is undertaken during the risk characterisation. It is at the risk characterisation stage that the exposure data and the health effects data are integrated to assess the overall risk of a chemical to human health.

Before the approach to, and content of, an exposure characterisation is outlined, two important components of exposure assessment, uncertainty analysis and sensitivity analysis will be discussed.

## 5.1 Uncertainty analysis

Any exposure assessment will be subject to some degree of uncertainty, which is derived from the decisions, judgements and actions taken during the planning and execution stages. Uncertainty should be distinguished from natural or 'true' variability within parameters that contribute to exposure. **Variability** in exposure assessments arises from true heterogeneity across people, places or time whereas **uncertainty** is the lack of knowledge about factors affecting exposure, such as the correct value for a specific measurement or estimate (WHO, 2000a). Thus variability can affect the precision of estimates of exposure and the degree to which they can be generalised, whereas uncertainty can lead to inaccurate or biased estimates. Exposure assessment reports should include a discussion of sources of uncertainty and their potential effects on the outcome of the assessment.

Professional judgement is a key element in virtually every aspect of the exposure assessment process, from defining the appropriate exposure scenarios, to selecting appropriate models, to determining representative environmental conditions, etc. Variability in professional judgement is thus a potential source of uncertainty as often there is no clear 'correct' choice, e.g. of distribution curve, and hence professional judgement is used. Alternative choices may be equally supportable, but one might be less accurate than the other, introducing uncertainty or variability into the model.

Uncertainty analyses can be performed at differing levels of sophistication depending on the types and amounts of data available. For simple exposure assessments **uncertainty characterisation** can be used to provide a qualitative discussion about sources of uncertainty, such as the selection or rejection of certain data or the adequacy of the scenarios employed, sampling strategies, chemical analysis, etc., and the likely effect on the overall results. More sophisticated analyses, particularly those where extensive modelling has been applied may in addition require **uncertainty assessment**, which applies a more quantitative approach. The discussion of the uncertainty characterisation or assessment should allow the reader to make an independent judgement about the validity of the conclusions reached, describing the uncertainty associated with any inferences, extrapolations, and analogies used and the weight of evidence that led the assessor to particular conclusions.

Uncertainty in exposure assessment can be classified into the following three broad categories: scenario uncertainty, parameter uncertainty and model uncertainty (EPA, 1992).

### 5.1.1 Scenario uncertainty

The sources of scenario uncertainty include failure to take account of all uses of a chemical when determining the source–pathway–receptor links. Scenario uncertainty might also arise from assuming that populations are homogeneous in their exposure patterns when in fact they include significant subgroups, or from assuming steady-state conditions in a system that is undergoing change.

### 5.1.2 Parameter uncertainty

Sources of parameter uncertainty include measurement errors, sampling errors, and use of inappropriate generic or surrogate data.

Sampling error concerns the representativeness of the sample with regard to the true distribution of values. Typical problems include taking samples too close together either temporally or spatially so that the full range of values is not obtained or taking too few samples. Other parameter errors might be due to using data from previous exposure assessments, or other sources, that are not relevant to the current exposure. Random sampling error occurs when statistics derived from the sample are not equal to the underlying population parameters because, by chance, members of the sample do not accurately represent the population as a whole.

The use of published data sources for the basis of exposure estimates can provide a particular problem for exposure assessors since there is not always sufficient detailed information to judge whether the estimate is relevant to the current situation.

### 5.1.3 Model uncertainty

Apart from the selection of an inappropriate model, relationship errors and modelling errors are the primary sources of uncertainty associated with models. Relationship errors include errors in associations between chemical properties and environmental fate models. Modelling errors result from models being simplified representations of reality, for example by assuming steady-state conditions when exposures are really fluctuating or by ignoring associations between input variables (see Section 4). The effects of model uncertainty are difficult to detect and evaluate and so are best avoided, if possible, by using some form of model validation (see Section 4.5).

## 5.2 Sensitivity analysis

Sensitivity analysis is not an essential prerequisite of an exposure assessment but can provide additional information to inform risk management.

Sensitivity analysis is a technique that allows determination of the effect on the overall outcome of altering the value of one variable. The relative importance of each variable in determining the values of the output distribution can then be independently assessed. This in turn allows the identification of the input variables for which the most benefit would be derived from further research to reduce or better quantify uncertainty. If only limited or uncertain data were available for the exposure variables responsible for most of the variation in output values then confidence in the results would be poor. Conversely, if robust data had more importance, then confidence in the overall results would be greater.

In simple sensitivity analyses the procedure involves fixing each variable, one at a time, at its credible lower bound and then its upper bound (while holding all others at their medians or at their measured value), and then computing the outcomes for each combination of values (EPA, 1992). A more quantitative approach is to estimate the sensitivity of the output to each input variable in turn by increasing the variable by, as an example, 10% increments and then re-calculating the exposure estimate and recording the change in the value. The sensitivity analysis should cover the range of uncertainty in the parameter under investigation.

An excellent example of the method has been published by the Scottish Environmental Protection Agency (McCaffery & Earl, 2000). A sensitivity analysis is described that considers the effects of varying input parameters including the tolerable daily intake, exposure duration, averaging time, intakes from other sources, site-specific parameters and chemical-specific parameters on a framework for deriving numeric targets for minimising adverse human health effects of long-term exposure to contaminants in soil.

Sensitivity analysis also provides powerful information for risk managers. They can use the relationships to investigate the most cost-effective solutions if the exposure assessment indicates that control measures are required. The outcome of a sensitivity analysis can also be used to test the boundaries of a resulting decision using a ‘what if?’ approach. For example, ‘what if parameter X were

ten times as high as that used in the model?' 'How would that affect the outcome of the assessment and would it alter the conclusion?' Such approaches encourage more robust decision-making.

## 5.3 Key elements of an exposure characterisation

An exposure characterisation should:

- provide a brief statement of the purpose, scope, level of detail and approach used in the assessment, including key assumptions;
- present the estimates of exposure and dose by pathway and route for individuals, population subgroups and populations in a manner appropriate, for example, for an intended risk characterisation;
- provide evaluation of the overall quality of the assessment and the degree of confidence in the estimates of exposure and dose and the conclusions drawn;
- interpret the data and the results;
- identify key data gaps, if applicable; and
- communicate the results of the exposure assessment to the intended audience.

In addressing the purpose, the exposure characterisation explains the reasons for, and the purpose of, the investigation, and the questions asked. It considers whether the questions were answered sufficiently well or, if new questions were raised during the exposure assessment whether the new questions were answered adequately and with what degree of confidence.

The statement of scope covers the geographical or demographic boundaries. The populations and subpopulations of interest are clearly identified, and the reasons for their selection and any exclusions are discussed, for example children are the subgroup of interest when considering phthalates in toys since adults are unlikely to mouth or suck plastic toys. Vulnerable groups with particularly high or unusual exposure patterns are highlighted. The characterisation discusses whether the scope and level of detail of the investigation were sufficient to answer the question being addressed and whether any limitations in scope and level of detail were the result of technical, practical or financial constraints. The implications of such limitations for the quality of the conclusions are also discussed.

The strengths and weaknesses of the particular methods used to quantify exposure and dose are described (models and/or measurement), and compared and contrasted with alternative methods, if appropriate. In presenting the exposure and dose estimates, the important sources, pathways, and routes of exposure are identified and quantified, and reasons for excluding any from the assessment are discussed. For example, the exposure assessment of benzene (IEH, 1999) identified three routes of exposure to benzene: inhalation, ingestion and dermal contact. However, inhalation accounted for over 95% of the total exposure in the UK, therefore inhalation was the only route considered in the risk characterisation. How exposure is distributed across the population or subpopulations and how the variability in population activities influences this distribution, is also discussed.

A discussion of the quality of the exposure and dose estimates is essential for the credibility of the assessment. This will include discussions on uncertainty analysis and, possibly, sensitivity analysis. Where one set of data has been used in preference to another, the reasoning should be given clearly and logically.

Following all of the above, it is necessary to interpret the data and results on the basis of the information presented in the exposure assessment. If there is insufficient information for a clear interpretation then a description of the additional research and data needed to improve the exposure assessment is necessary. When a decision has to be made on the basis of the available information, the uncertainties and data gaps should be made apparent. Following the interpretation, a brief summary or conclusion should be presented. Table 5.1 summarises the key components of an exposure characterisation.

Guidance on exposure characterisation is also published by the EPA (1992) and the WHO (2000a).

## 5.4 Reporting an exposure assessment

Once the exposure assessment is complete it is necessary to communicate the results to the appropriate audience, for example, risk assessors, who may then use the exposure characterisation, along with the characterisations of the other risk assessment elements (outlined in Section 1.3.1) to develop a risk characterisation. This is usually

**Table 5.1 Summary of key components of exposure characterisation**

| General components | Specific components |
|---|---|
| What are the most significant sources of environmental exposure? | • Are there data on sources of exposure from different media?<br>• What is the relative contribution of different sources of exposure?<br>• What are the most significant environmental pathways for exposure? |
| What populations were assessed? | • General population, highly exposed groups, highly susceptible groups?<br>• Number of people likely to be exposed in a population? |
| What was the basis for the exposure assessment? | • Monitoring, modelling, or other analyses of exposure distributions such as Monte Carlo simulation or kriging[a]? |
| What are the key descriptors of exposure? | • What is the range of exposures to average individuals, high-end individuals, general population, high exposure groups, children, susceptible populations?<br>• How were the central tendency and high-end estimates developed?<br>• Is there information on highly exposed subgroups? Who are they and what are their levels of exposure? How are they accounted for in the assessment? |
| Is there a reason to be concerned about cumulative or multiple exposures? | • Does the chemical belong to a wider group with common mechanism of action? |
| What are the conclusions of the exposure assessment? | • What are the results from different approaches (i.e. modelling, monitoring, probability distributions)?<br>• What are the limitations of each approach and the range of most reasonable values?<br>• What is the level of confidence in the results? |

From Williams and Paustenbach (2002); reproduced with kind permission from Taylor & Francis Ltd, http://www.tandf.co.uk/journals
[a] A type of statistical approach used to characterize spatial data or interpolate between known sample points using random search procedures.

accomplished via a written report. The emphasis of this report should be to make explicit exactly what was done, using a variety of means including charts and tables to aid communication. Sections 3–5 of this document provide guidance as to how the assessment should be reported as well as conducted. Typically the report should contain the following sections.

- Executive summary: describes all the main points.
- Introduction: describes problem formulation, the physical characteristics of the chemical and the study design, sampling approach and use of scenarios.
- Methods: includes a description of how the data are gathered including sampling and analytical methods together with their performance characteristics. Modelling methods should be described including justification for choice of model, formulae used and assumptions and default values applied.
- Results: includes statistical summaries of measured and modelled data, with graphical representations where possible, and a description of the analysis of the data (including uncertainty and sensitivity analysis).
- Exposure characterisation: presents estimates of exposure and dose by pathway and route, in the context of the purpose, scope and approach adopted; evaluates the overall quality of the assessment, interprets the data and results and identifies any data gaps.
- Conclusion: clearly describes the main outputs from the exposure assessment and their interpretation in the context of compliance checking, risk assessment or epidemiology.
- Annexes: include all background material and raw data necessary to allow the exposure analysis to be repeated.

# 6 Critical evaluation and auditing of exposure assessments

## 6.1 Critical evaluation of exposure assessments

Frequently the person called upon to interpret the results of an exposure assessment in the context of compliance checking, risk assessment or epidemiology is not the same as the person who was responsible for the production of the exposure data. It is then necessary for that person to critically evaluate the data and any conclusions before recommending any actions arising from its interpretation.

An evaluation might comprise a completeness check to ensure that the exposure assessment report contains the elements defined in Sections 3, 4 and 5. The report should provide a clear explanation of the problem being addressed, the approach adopted, the assumptions and default values applied, the results obtained and the uncertainties encountered. The conclusions drawn should be consistent with the information provided.

Some examples of questions an evaluator might ask to identify the more common problems associated with exposure assessments are listed in Table 6.1 together with the section of these guidelines in which they are discussed.

## 6.2 Auditing

An essential requirement in the documentation of an exposure assessment is that of auditability. A complete and clear account should be given of what was done, the results and how inferences were made. Interested parties should be able to rely on the documentation, so that they can scrutinise, check and, if desired, repeat what was done without having to seek any further information. This normally means including all of the raw data used in the assessment in annexes to the main report.

The audit procedure often proves to be the means whereby problems are first revealed. There is therefore much to be gained from arranging an independent review of the report before publication. It is also good practice to submit the report for internal review before sending to the external reviewer. The reviewer should be a suitably qualified person who has had no direct involvement in the exposure assessment up to that point.

Reviewers of exposure assessments are usually asked to identify inconsistencies in the underlying science, methods, models and assumptions used and to assess the effect these inconsistencies might have on the results and conclusions. In particular the reviewer should consider whether the inconsistencies or deficiencies would result in underestimation or overestimation of exposure. The reviewer might also consider the checklist provided in Table 6.1. This checklist is for illustrative purposes only and will therefore not necessarily include all issues/points that should be considered in the exposure assessment process.

**Table 6.1 Example of items in an exposure assessment evaluation and audit checklist**

| | |
|---|---|
| Has the **purpose** of the exposure assessment (EA) been clearly stated? Is the approach relevant to the current application? | The EA could be targeted at checking regulatory compliance, risk assessment or for some other purpose such as an epidemiological investigation. The purpose of the EA will have a critical bearing on the way the assessment is carried out and affect its usefulness for other purposes (3.2.1)[a] |
| Are any **published data** used relevant to the current situation? | The use of published data sources for the basis of exposure estimates can provide a particular problem for exposure assessors since there is not always sufficient detailed information to judge whether the estimate is relevant to the current situation (3.3.1). |
| Is the **scope** of the EA adequately defined? | Temporal and spatial limits, specific subpopulations or whether typical or high-end exposures are being assessed, will have an effect on the results obtained and should be clearly expressed (3.2.2). |
| Is any **reasonable worst case** adequately defined? | Reasonable worst case estimates should fall within the bounds of reality while not under-estimating true high-end exposures (3.2.3). |
| Is the **level of detail** applied in the EA clearly stated? | EA methods can range from very simple screening to highly sophisticated surveys and models. The level of detail can have a high impact on the results obtained. In general, simpler methods should be expected to be more conservative (3.2.3). |
| What was the **duration of exposure** applied in the EA? Is this time period relevant to the hazard characterisation? | Different durations of exposure from peak exposures to exposures averaged over many years can be applied in an EA. It is essential that the period chosen should be relevant to the toxicological properties of the chemical and the health end-point of concern (2.2). |
| Has a valid **conceptual model** been presented? | The specific problem that the EA is designed to address should be clearly defined, usually in a graphical form (3.2.4) |
| Have all potential **sources** of exposure been considered? | Although not all EAs are designed to include multiple routes other significant sources of exposure should be considered and recorded in the report (2.1). |
| Has a **pathway** analysis been conducted and is it broad enough to avoid overlooking a significant pathway? | All possible pathways from the source to receptor should be identified and discussed (2.1). |
| Have **receptor** populations been adequately identified and defined? | The receptor population should usually represent the most susceptible group both in terms of receiving the highest potential exposures but also in respect of their personal characteristics such as age, sex, etc (2.1). |
| Has the **sampling plan** for the exposure measurements been adequately described? | Methods used for selecting samples, particularly whether random or weighted schemes are used, can have a significant impact on the results obtained (3.3.2). |
| Is the **number of samples** taken sufficient to achieve the desired degree of statistical confidence? | Frequently, limited resources and other factors mean that the number of samples that can be obtained is relatively small. The number of samples taken should be sufficient to support the EA's conclusions (3.3.2). |
| Have relevant exposure **scenarios** been used in the EA? | The choice of exposure scenarios, in particular the degree of aggregation of subgroups, will affect the results obtained. All exposure scenarios should be realistic (3.3.2). |
| Has an adequate **quality assurance** scheme been included in the EA? | Replicate samples, blank samples and the use of certified reference materials could provide good evidence about the accuracy and precision of an EA (3.4.2). |

| | |
|---|---|
| Is the EA based on a **limited data set**? | Incomplete data sets can arise for a variety of reasons and if not corrected for can lead to misleading results (3.4.1). |
| Have missing data points been produced by **extrapolation** or **interpolation**? | If missing data have been estimated from other data points or data sets the assumptions used must be stated (3.4.1). |
| Have **outliers** been edited? | The removal of outliers can affect results and their treatment must be fully justified in the EA (3.4.1). |
| How have **less than LOD** data been managed? | The presence of data that are below limits of detection (LOD) and quantification (LOQ) can be managed in different ways that can affect results (3.4.1). |
| Was **model selection** appropriate? | It should be possible to determine from the information provided whether the model is suitable for the application and likely to produce valid results (4.5). |
| Have **models** used been adequately described? | All of the assumptions, algorithms, default values and other factors contained within a model that could affect the result should be fully described, if necessary by reference to a published source (4.5). |
| Were **associations** between input distributions investigated and properly accounted for? | Probabilistic and parametric methods often assume that input variables are independent. However input variables, such as time–activity data, are not necessarily independent since if an individual is engaged in one activity they cannot be simultaneously engaged in another (4.3.2). |
| Was **model validation** adequate? | Where validation data sets are available the results should be reported. Otherwise any other validation undertaken should be described (4.5). |
| Does the EA include an analysis of **uncertainty**? | The EA should report all sources of uncertainty and discuss their potential impact on results (5.1). |
| Is there any **bias** affecting the study that could cause misleading results. | The report should indicate the sampling strategy that was employed together with other potential sources of bias and consider whether this would limit the applicability of the results (3.3.2). |
| Does the EA include a **sensitivity analysis**? | For EAs based on many factors the effect of altering each factor in turn can be investigated to determine its effect on the overall result (5.2). |
| Does the EA include an **exposure characterisation** that draws together all of the data, uncertainties and other factors into an overall conclusion. | The person producing an exposure assessment is in the best position to consider the effect of uncertainties and variability on the results obtained and to draw conclusions about their reliability and applicability (5.3). |

[a] Number in brackets refers to the appropriate sections of text

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# Annexes

## Annex A
## Glossary of terms

The following glossary is included to provide the reader with a convenient set of definitions of exposure assessment terms used in government departments and agencies. The list is not intended to be exhaustive but to provide a level of inclusion sufficient to allow a clear understanding of terms and expressions used in this document or in common use in the field of exposure assessment. Not all of the terms are used within all government departments and agencies and in a small number of cases there may be subtle differences in the precise interpretation of certain terms.

The definitions of terms are largely based on those provided in government publications and in particular the *Contaminated Land Exposure Assessment Model* (Defra & Environment Agency, 2002). Further definitions have been adapted from other relevant publications (EPA, 1992; Paustenbach, 2000).

| Term | Definition |
|---|---|
| Absorbed dose | See internal dose. |
| Absorption barrier | Any of the exchange barriers of the body that allow differential diffusion of various substances across a boundary. Examples of absorption barriers are the skin, lung tissue, and gastrointestinal tract wall. |
| Accuracy | The measure of the correctness of data, as given by the difference between the measured value and the true or standard value. |
| Acute exposure | Short-term or one-off exposure to, or contact with, a chemical. |
| Aggregate exposure | Multiple pathway exposure to a chemical from all sources and by all routes. |
| Ambient | The normal conditions surrounding a person, i.e. sampling location. |
| Applied dose | The amount of a substance in contact with the primary absorption boundaries (e.g., skin, lung, gastrointestinal tract) and available for absorption. |
| Average daily exposure | The average daily amount of a chemical to which a critical human receptor is exposed over the duration of exposure. |
| Averaging time | Time period over which exposure is aggregated and averaged. This varies with the conceptual model and the toxicological end-point of the chemical assessed. |
| Auditability | The presentation of sufficient data and other information in a report to allow another investigator to repeat and confirm the exposure characterisation. |
| Bias | A systematic error inherent in a method or caused by some feature of the measurement system. |
| Bioavailability | The fraction of the chemical that can be absorbed by the body through the gastrointestinal system, the pulmonary system or the skin. |
| Biomarker | Any substance, structure or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease. Biomarkers can be classified into markers of exposure, effect and susceptibility. |

| Term | Definition |
|---|---|
| Biomonitoring | Analysis of the amounts of potentially toxic chemicals or their metabolites present in body tissues and fluids, such as blood, hair, breath, urine or faeces, as a means of assessing exposure to these chemicals. |
| Body burden | The amount of a particular chemical stored in the body at a particular time, especially a potentially toxic chemical, as a result of exposure. |
| Bounding estimate | An estimate of exposure or dose that is higher than that incurred by the person in the population with the highest exposure or dose. Bounding estimates are useful in developing statements that exposures or doses are 'not greater than' the estimated value. |
| Breathing zone | A zone of air in the vicinity from which respired air is drawn. |
| Chemical exposure rate | The amount of a chemical in water, food, air, or soil that enters the human body in a specified time period. |
| Chronic exposure | Long-term or repeated exposure to, or contact with, a chemical. |
| Conceptual exposure model | A textual or graphical representation of the relationship(s) between source(s), pathway(s) and receptor(s) for an exposure situation. |
| Cumulative dose | The accumulated amount of a specified chemical received by an individual over a given period of time. |
| Cumulative exposure | Exposure to a chemical and to all other substances with a common mechanism of toxicity regardless of their source and pathway of exposure. Multiple chemical exposure. |
| Deterministic model or parameter | The traditional approach to modelling where in any calculation a single value is assigned to each variable. |
| Delivered dose | The amount of the chemical available for interaction with any particular organ or cell. |
| Dose | The amount of a substance available for absorption and subsequent interaction with metabolic processes or biologically significant receptors after crossing the outer boundary, i.e. skin. See also: potential dose, applied dose, absorbed dose, internal dose and delivered dose. |
| Empirical distribution | A frequency distribution derived from actual measurements and not fitted to a particular parametric distribution. |
| Frequency distribution | A graph, table or plot that shows the number of observations that occur within a given interval; usually presented as a histogram. |
| Dose–response assessment | The quantitative (potency) evaluation of the adverse effects observed; the evaluation of mechanisms of action and species differences in response. |
| Dose–response curve | A graphical representation of the quantitative relationship between administered, applied, or internal dose of a chemical or agent, and a specific biological response to that chemical or agent. |
| Dose–response relationship | The resulting biological responses in an organ or organism expressed as a function of a series of different doses. |
| Dose rate | Dose per unit time, for example in mg/day, sometimes also called dosage. Dose rates are often expressed on a per unit body weight basis, yielding units such as mg/kg/day. They are also often expressed as averages over some time period, for example a lifetime. |
| Environmental fate | The destiny of a chemical or biological pollutant after release into the environment. Environmental fate involves temporal and spatial considerations of transport, transfer and transformation. |
| Environmental fate model | A computer program incorporating mathematical relationships to predict the concentration of a compound in environmental compartments, as influenced by processes such as dilution, partitioning and degradation. |
| Environmental medium | Material found in the physical environment that surrounds or contacts organisms, e.g., surface water, ground water, soil, food or air, through which chemicals or pollutants can move and reach the organisms. |
| Exposure | Contact between a chemical and an individual or population. |

| Term | Definition |
|---|---|
| Exposure assessment | The measured, estimated or predicted intake/exposure to a chemical in terms of its magnitude, duration and frequency, for the general population, for different subgroups of the population, or for individuals. |
| Exposure characterisation | The output of the exposure assessment, which includes a summary of the results, discussion of reliability and uncertainty and conclusions that draw together all of the information collected in the exposure assessment. |
| Exposure concentration | The concentration of a chemical in its transport or carrier medium at the point of contact. |
| Exposure duration | The specified period of exposure over which the intake rate for a receptor is accumulated. |
| Exposure factors | The parameters that relate to human activities (e.g., time indoors *vs* outdoors, weekly hours at work) and physiological parameters (e.g., inhalation rates, body weight, skin surface area). |
| Exposure frequency | The number of events in a specified time period when a receptor is exposed to a chemical at the intake rate. |
| Exposure pathway | The physical course a chemical or pollutant takes from the source to the receptor exposed. |
| Exposure route | The way a chemical or pollutant enters the body after contact, e.g. by ingestion, inhalation, or dermal absorption. |
| Exposure scenario | A set of facts, assumptions, and inferences about how exposure takes place that defines a specific population or sub-population. |
| Hazard identification | The identification, from animal and human studies, *in vitro* studies and structure–activity relationships, of adverse health effects associated with exposure to a chemical. |
| High-end exposure (dose) estimate | A plausible estimate of individual exposure or dose for those persons at the upper end of an exposure or dose distribution but not higher than that of the individual in the population who has the highest exposure or dose. |
| Intake (dose) | The amount of a chemical entering or contacting the human body at the point of entry (i.e. mouth, nose or skin) by ingestion, inhalation, or skin contact. |
| Internal dose | The amount of a substance penetrating across the absorption barriers (the exchange boundaries) of the body, *via* either physical or biological processes. For the purpose of these Guidelines, this term is synonymous with absorbed dose. |
| Kriging | A type of statistical approach used to characterise spatial data or interpolate between known sample points using random search procedures. |
| Limit of detection (LOD) | The minimum concentration of an analyte that, in a given matrix and with a specific method, is statistically significantly greater than zero. Also known as Limit of Quantification (LOQ). |
| Microenvironment method | A method used in predictive exposure assessments to estimate exposures by sequentially assessing exposure for a series of well-characterised locations (microenvironments). |
| Microenvironments | Well defined surroundings such as the home, office, car, kitchen, shop, etc. that can be treated as homogeneous (or well characterised) in the concentrations of a chemical or other agent |
| Monte Carlo sampling | A computational technique to select a random or pseudo-random value from a distribution of specified values. |
| Nonparametric statistical methods | Methods that do not assume a functional form with identifiable parameters for the statistical distribution of interest (distribution free methods). |
| Parametric techniques | Fitting known statistical distributions to empirical data. |
| Pathway | The physical course a chemical or pollutant takes from the source to the receptor exposed. |

| Term | Definition |
|---|---|
| Percentile | One of 99 actual or notional values of a variable dividing its distribution into 100 groups with equal frequencies; the 90th percentile is the value of a variable such that 90% of the relevant population is below that value. |
| Personal monitoring | A measurement collected from an individual's immediate environment using active or passive devices to collect the samples. |
| Pharmacokinetics | The study of the time course of absorption, distribution, metabolism, and excretion of a foreign substance (e.g., a drug or pollutant) in the body. |
| Potential dose | The amount of a chemical contained in material ingested, breathed in, or bulk material applied to the skin. |
| Precision | A measure of the reproducibility of a measured value under a given set of conditions. |
| Probabilistic exposure modelling | A repeated random sampling from the distribution of values for each of the parameters in a generic exposure or dose equation to derive an estimate of the distribution of exposures or doses in the population. |
| Probability samples | Samples selected from a statistical population such that each sample has a known probability of being selected. |
| Quality assurance (QA) | An integrated system of activities involving planning, quality control, quality assessment, reporting and quality improvement to ensure that a product or service meets defined standards of quality with a stated level of confidence. |
| Quality control (QC) | The overall system of technical activities whose purpose is to measure and control the quality of a product or service so that it meets the needs of the users. The aim is to provide quality that is satisfactory, adequate, dependable, and economical. |
| Random samples | Samples selected from a statistical population such that each sample has an equal probability of being selected. |
| Range | The difference between the largest and smallest values in a measurement data set. |
| Reasonable worst case | The level of exposure that is exceeded in a small percentage of cases over the whole spectrum of likely circumstances of use for that particular scenario. |
| Receptor | The entity (e.g. human, animal, water, vegetation, building services etc.) which is vulnerable to the adverse effect(s) of a hazardous substance or agent |
| Representativeness | The degree to which a sample is, or samples are, characteristic of the whole medium, exposure, or dose for which the samples are being used to make inferences. |
| Risk | The probability of an adverse effect arising from a specified exposure to a given hazard. |
| Risk characterisation | The description of the nature and often the magnitude of human risk, including uncertainty. |
| Route | The way a chemical or pollutant enters the body after contact, e.g., by ingestion, inhalation, or dermal absorption. |
| Sample | A small part of something designed to show the nature or quality of the whole. Usually samples of environmental or ambient media, exposures of a small subset of a population, or biological samples, for the purpose of inferring the nature and quality of exposure parameters. |
| Sampling frequency | The time interval between the collection of successive samples. |
| Sampling plan | A set of rules or procedures specifying how a sample is to be selected and handled. |
| Source characterisation measurements | Measurements made to characterise the rate of release of agents into the environment from a source of emission such as an incinerator, landfill, industrial or municipal facility, consumer product. |
| Standard operating procedure (SOP) | A procedure adopted for repetitive use when performing a specific measurement or sampling operation. |

| Term | Definition |
|---|---|
| Surrogate data | Substitute data or measurements, i.e. on one substance used to estimate analogous or corresponding values of another substance. |
| Tiered approach | Initially applies a conservative screening method and, if this indicates that exposures could exceed acceptable levels, then gradually refines this with more detail until a more reliable exposure assessment is obtained. |
| Uncertainty | Lack of knowledge about variability in specific parameters in an exposure assessment. |
| Variability | Natural or inherent differences within a sample population. If not evaluated, may contribute to uncertainty. |
| Uptake (dose) | The amount of a chemical that reaches the circulating blood having been absorbed by the body through the skin, the gastrointestinal system and the pulmonary system. |
| Worst case exposure | A semi-quantitative term referring to the maximum possible exposure that can conceivably occur, whether or not this exposure actually occurs or is observed in a specific population. |

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# Annex B
# Concepts of exposure

### Introduction

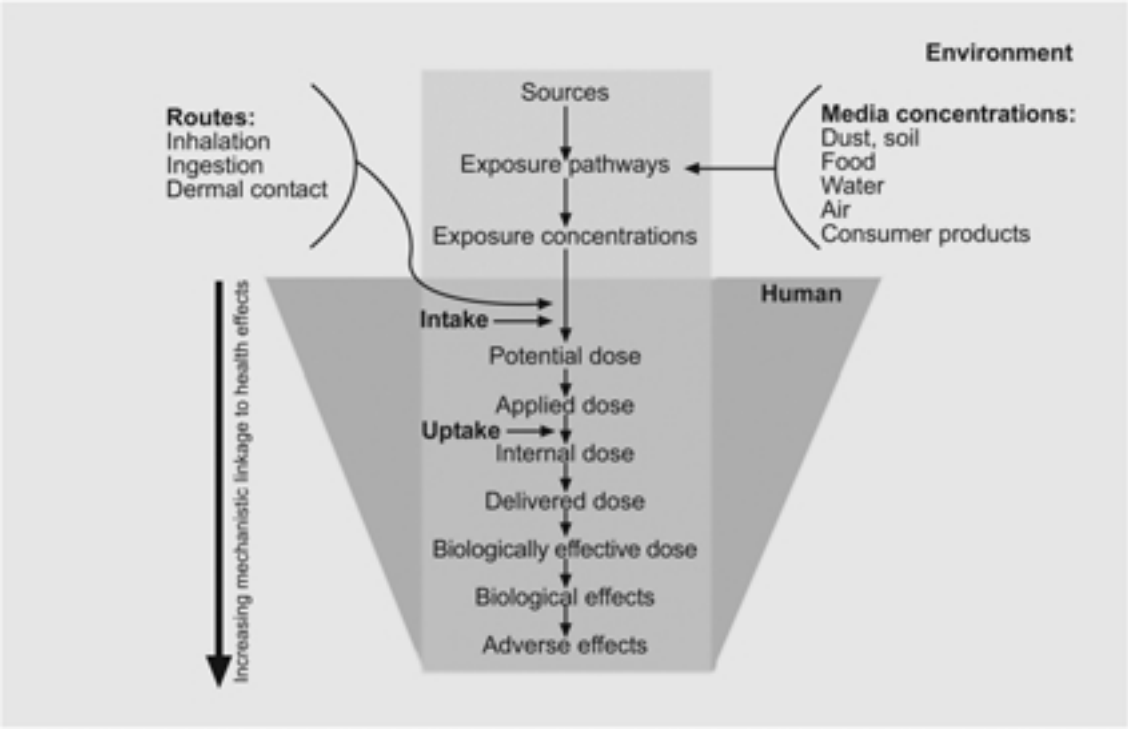
In Section 2 of these guidelines the use of the term **exposure** is discussed in the context of good exposure assessment practice for human health effects. For some professionals in the field exposure relates to a chemical's presence in the external environment surrounding a subject, while for others it is the amount of a chemical that enters the body (regardless of the amount subsequently expelled). Other professionals focus on that part of the amount entering the body that is retained, while still others are concerned only with the part that enters the bloodstream. Finally, there are exposure professionals who are concerned only with the amounts that enter the organs and cells or that interact with the specific molecules that determine biological effects. These different concepts are illustrated in Figure B1.

The definitions provided in Section 2 are intended to allow everyday use of the terms exposure, intake and uptake. This Annex provides a deeper analysis of the terminology used to describe the process of transfer of chemicals from the external environment to the internal organs and toxicologically specific sites within the body that might be applicable in different kinds of exposure assessment conducted at different points on the exposure–intake–uptake–interaction spectrum.

### External exposure

The human body can be visualised as possessing a hypothetical outer boundary separating the inside of the body from the external environment. Chemicals can be present in media such as air, food, water, soil or consumer products that exist on the exterior of this barrier. **External exposure** is considered to be contact between the chemical and the outer boundary and is the product of chemical concentration in the external environment and extent of contact with the external environment. For example, for exposure via inhalation, external exposure is the product of mass per unit air volume, inhalation rate, and duration of contact with air. External exposure represents the potential dose and internal exposure cannot exceed this. This is particularly true where protective measures, such as breathing apparatus, are used. In other circumstances an individual may not choose to use or consume a product containing the chemical so that while the external exposure may be high the internal exposure is zero.

**Figure B1 Exposure pathways, routes and absorption**




WHO (2000) reprinted with kind permission from the World Health Organization
Adapted from WHO (1993), Sexton *et al.* (1995)

The chemical concentration in the medium at the point of contact is the exposure concentration. Exposure over a period of time can be represented by a time-dependent profile of the exposure concentration. The area under the curve of this profile is the magnitude of the exposure, in concentration–time units:

$$\textbf{External exposure} = \int_{t_1}^{t_2} C(t)\, dt$$

Where C(t) is the exposure concentration as a function of time and $t_1$–$t_2$ is the **exposure duration**.

### Intake *versus* uptake

External exposure does not necessarily lead to internal exposure unless the chemical crosses the outer boundary into the body. **Intake** is the physical transfer of the chemical through a body opening (usually nose or mouth) through the processes of breathing, eating and drinking. The chemical is usually present in a medium such as air, food or drinking water and the amount of the chemical entering the body is thus the product of the concentration of the chemical in the medium and the amount of the medium that enters the body.

In the majority of situations the duration of exposure should also be taken into account. The amount of the chemical that enters the body per unit time is the **chemical intake rate**. The chemical intake rate is the product of the level of chemical in the medium and the rate and frequency at which the medium enters the body:

| **Intake rate** | = exposure concentration | × contact with medium | × contact rate |
|---|---|---|---|
| e.g. (mg/day) | (mg/g) | (g) | /day |

**Uptake** is the direct absorption of the chemical by the skin or other body tissue and passage into body fluids. This includes absorption through the internal surface of the lung and gastro-intestinal tract following intake. Although the chemical may be contained in a carrier medium such as air or water, the chemical is not necessarily absorbed at the same rate as the medium and so uptake is dependent on the concentration of chemical in the medium and on other physicochemical parameters. Dermal absorption is the result of diffusion across the skin barrier and can be expressed as a function of the exposure concentration, permeability coefficient, and surface area exposed. The **chemical uptake rate** is the amount of chemical absorbed per unit time.

### Applied and potential dose

The **applied dose** is that part of the external dose that is available for absorption at a barrier such as the skin, lung or gastrointestinal tract surface. It is therefore necessary to take into account the amount of medium being taken in, the exposure concentration and any residual chemical in the medium that does not contact the absorption medium (e.g. that which is present in exhaled air or faeces). Applied dose is extremely difficult to measure since information about dynamics around the barrier interface is required and so the potential dose is estimated in its place.

The **potential dose** is the total quantity of a chemical that is available from intake at the absorption barrier. It is analogous to the administered dose in a dose–response study and so is frequently used in risk assessments.

In intake processes the potential dose is the integration of chemical intake rate, which is a function of the concentration of the chemical in the medium (C) and the intake rate of the medium (IR) over time:

$$\textbf{Potential dose} = \int_{t_1}^{t_2} C(t)\ IR(t)\ dt$$

Where IR(t) is the ingestion or inhalation rate as a function of time and $t_1$–$t_2$ the exposure duration. The exposure duration may reflect periods of continuous exposure or may include periods of intermittent exposure with no exposure in between. Doses are normally presented as doses over time (e.g. mg/person/day) or on a per unit bodyweight basis (e.g. mg/kg bw/day) depending on the presentation of hazard characterisation data.

The applied and potential doses do not take bioavailability into account. However, if data on bioavailability are available then they can be used to convert the measured potential dose into an estimate of internal dose.

### Internal dose

Not all of the applied or potential dose will be absorbed and the quantity of material that crosses the absorption barrier (uptake) is the internal dose. The **internal dose** is that part of the applied or potential dose that is available for metabolism, storage or transport. The amount of chemical that reaches the tissues where adverse effects might occur is the **biologically effective dose**.

The absorption efficiency is a product of the bioavailability (i.e. how readily the chemical is released from the matrix *via* which exposure occurs (carrier medium)) and how effectively the chemical is transferred across exchange boundaries, for example the gastrointestinal tract. The former depends on physical location and efficiency of incorporation of the chemical within the carrier, whereas the latter is dependent on such factors as the concentration gradient across the boundary.

Both bioavailability and the effectiveness of transfer across exchange boundaries may be measured (with some difficulty) by a range of *in vivo* and *in vitro* methods. Examples of the former include intake *versus* output studies or intake of a radiolabelled analogue of the chemical under study. *In vitro* methods include model systems in which metals are incubated under simulated gastrointestinal tract environments.

In uptake processes the internal dose can be estimated using the chemical uptake rate in place of the chemical intake rate:

$$\textbf{Internal dose} = \int_{t_1}^{t_2} C(t)\ K_p\ SA(t)\ dt$$

Where $K_p$ is the permeability coefficient and SA the surface area exposed. While C and SA may vary over time, K cannot although it can vary between different parts of the body.

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# Annex C
# Exposure assessment models

### Introduction

Section 4 of these guidelines describes the use of modelling in exposure assessment. Exposure modelling is frequently used by government departments and agencies since it is often impracticable to obtain data through the use of direct or indirect environmental measurements. This annex describes some models that are routinely used by government departments in executing their regulatory functions. The examples are intended to provide an illustration of the different kinds of models that are available, not a comprehensive inventory of exposure assessment models. Useful descriptions of the wide range of environmental exposure assessment models used by the Environment Agency can be found in Duarte-Davidson and Pollard (2000).

### EASE (Estimation and Assessment of Substance Exposure)

The UK EASE (Estimation and Assessment of Substance Exposure) system is a knowledge-based exposure concentration model (see Section 4.1) developed by the Health and Safety Executive (HSE) in conjunction with the Artificial Intelligence Applications Institute (AIAI) at the University of Edinburgh (HSE, 1997). EASE was developed as a tool to assist both regulatory authorities and industry during the risk assessment process for new substances.

The EASE model assesses the exposure of workers to substances hazardous to human health in the workplace. Daily exposures are predicted based on a standard 8-hour working day. Shorter duration, acute exposures cannot be assessed using EASE. The model considers dermal and inhalation exposures to substances, which may be present as solids, liquids or gases or vapours in the workplace. There are no restrictions placed on which substances the EASE model is applicable to but the model does focus on pure substances and cannot deal expressly with mixtures. The model is able to consider a range of workplace activities, control strategies, and maintenance and sampling procedures. Where exposures are potentially widespread and adequate control measures are not in place, EASE may be applied to predict exposure levels for other, non-process workers at the site, and even for the general public. The EASE model is deterministic in nature and is unable to perform aggregate or cumulative assessments.

EASE is a key element in meeting the requirements concerning human exposure assessment of the European Commission's technical guidance document on chemicals regulation (EC, 1996).

### Consumer exposures to pesticides — deterministic modelling

The Pesticides Safety Directorate (PSD) uses simple contact models (see Sections 4.2 and 4.3.1) to predict consumer intakes of pesticide residues under approved usage conditions (PSD 1999). Exposure concentrations are drawn from the results of supervised field trials or, where such data are unavailable, maximum residue limits (MRLs) proposed or in legislation are used. Food consumption data are taken from the National Diet and Nutrition Surveys (http://www.foodstandards.gov.uk /science/101717/ndnsdocuments/) for adults and pre-school children with additional data for schoolchildren and infants.

#### Chronic dietary intake

In order to protect the population as a whole, the PSD derives chronic dietary intake estimates for 'high level' rather than 'average' consumers. The PSD uses the 97.5th percentile to define the 'high level' consumption (i.e 97.5% of consumers will eat amounts equivalent to this or below), making the assumption that consumption of foods at levels greater than the 97.5th percentile is unlikely to be maintained over an individual's lifetime.

Estimates of chronic dietary intake of pesticide residues from one food commodity (i.e the part consumed or used to make food) for each population group are derived using the basic equation:

$$TMDI_c = \frac{F_{97.5th} \times MRL}{BW}$$

TMDI = Theoretical Maximum Daily Intake (mg/kg bodyweight/day)

$F_{97.5th}$ = 97.5th percentile consumption of food commodity (kg/day)

MRL = Maximum residue level (mg/kg)

BW = Bodyweight (kg)

When evaluating the chronic dietary intake of pesticide residues, the PSD routinely derives a

TMDI based on a combination of foods using the equation

$$TMDI_T = [\ \Sigma\ (\text{two highest } TMDI_c \text{ values} + \text{average intakes from other foods})\ ] / BW$$

Where $TMDI_T$ is the total theoretical maximum daily intake for that chemical. The $TMDI_T$ is based on the assumption that consumers are unlikely to consume more that two commodities at the 97.5th percentile level, each day over a lifetime.

In the risk characterisation step of this approach, the $TMDI_T$ is usually compared with the Acceptable Daily Intake (ADI) derived from toxicological studies of chronic effects.

The TMDI is based on very conservative assumptions and, as such, is likely significantly to overestimate actual exposure. In deriving the TMDI, it is assumed that all produce eaten has been treated and contains residues at the MRL and there is no loss of residue during transport, storage, processing or preparation of foods prior to consumption. When the $TMDI_T$ is found to exceed the ADI, a more realistic estimate of chronic dietary intake is usually derived using additional data. This estimate, termed the National Estimated Daily Intake (NEDI) is derived using the equation:

$$NEDI = [\ \Sigma\ (F \times RL \times K)\ ] / BW$$

NEDI = National Estimated Daily Intake (mg/kg bodyweight/day)

F = Food consumption (kg/day)

RL = Appropriate residue level (i.e Supervised Median Trial Residue or STMR, mg/kg)

K = Processing factor

BW = Bodyweight (kg)

#### Acute dietary intake

Dietary risk assessment has traditionally focused on chronic dietary risk based on lifetime exposure scenarios. Recently, potential acute toxicity associated with short-term dietary intake of pesticides has become a concern. Residues were found to vary between units for certain commodities and occasional high residues could lead to acute dietary intake. The PSD now routinely carries out acute dietary risk assessments for pesticide products. The approach considers the highest residue levels measured in field trials; the high-level 97.5th percentile consumption in recorded eaters only, and takes into account the variability between residues in individual commodity units. Acute intake is normally derived for adults aged 16–64 years and children aged 1.5–4.5 years and only one commodity at a time is considered.

Acute dietary exposure is expressed as the National Estimate of Short-Term Intake (NESTI) and is derived using the basic equation:

$$NESTI\ (mg/kg\ body\ weight/day) = \frac{Residue\ (mg/kg) \times Single\text{-}day\ high\ level\ consumption\ (kg/day)}{Bodyweight\ (kg)}$$

In practice, three different NESTI models are used (shown below). These relate to different commodity types and make different assumptions about residue variability in the commodity.

**Case 1:** Small or blended commodity units
Many (4 or more) consumed in 1 meal or day
Variability is not considered
E.g. strawberries; wheat

$$NESTI = \frac{LP \times HR}{BW}$$

**Case 2a:** Larger units
4 or less consumed in 1 meal or day
1 unit is assumed to have high residues
E.g. apples; potatoes

$$NESTI = \frac{[U \times HR \times v] + [(LP\text{-}U) \times HR]}{BW}$$

**Case 2b:** Large units
1 or less consumed in 1 meal or day
Amount consumed is assumed to have high residues
E.g. cauliflower; lettuce

$$NESTI = \frac{LP \times HR \times v}{BW}$$

BW = bodyweight; HR = highest residue derived from supervised field trials; LP = 97.5th food consumption; U = unit weight; V = variability factor

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#### CONSEXPO (Consumer Exposure)

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CONSEXPO comprises a complex framework of models that enables assessment of the exposure of consumers to chemicals released by consumer products, via the inhalation, dermal and oral routes. For each component, the user selects a model from the available set and provides its parameters. Together, these components are claimed to form a full, multi-route exposure and uptake model to assess exposure and uptake of a single compound from consumer products ranging from shoe polish to household detergents or

pesticides against aphids. However, the accuracy of the results depends heavily on the accuracy of the model parameters.

In order to cope with the diversity in consumer products, CONSEXPO provides for widely differing exposure situations. The exposure component, for example, contains models that range from screening models to more realistic models with a mechanistic basis. Exposure includes the inhalation, dermal and oral routes and it is possible to model exposure through multiple routes. The program also allows for the input of stochastic parameters, in order to propagate the effects of variability to the final exposure and uptake estimates.

Several exposure variables can be reported, in particular the per event concentration, the yearly averaged concentration, the fraction taken up, the amount taken up during a year (per route and summed) and the uptake per kilogram body weight per day.

**Food Standards Agency INTAKE program**

The INTAKE program of the Food Standards Agency is a distributional model (see Section 4.3.2) for determination of acute or chronic intake of chemicals from food that uses distributional data for one input variable. The system contains raw data about food consumption from the National Diet and Nutrition Surveys. If information about the concentration of a chemical in foods is available, a concentration value can be assigned to each relevant food description in the database. The system is usually run with fixed values for exposure concentrations or normal, lognormal or empirical input distributions. Acute or chronic chemical intake can be calculated for each individual in the survey based on their personal food consumption records and the concentration data, which can be corrected for that person's bodyweight. After calculation of the intake for each individual, statistics for the population, including mean values and upper percentiles, can be estimated. A crude estimate of the confidence interval around the percentiles can also be provided.

**CLEA (Contaminated Land Exposure Assessment Model)**

The computer-based application CLEA 2002, developed by the Environment Agency, combines information on the toxicity of soil contaminants with estimates of potential exposure by adults and children living, working and/or playing on land affected by contamination, over long periods of time. It predicts the amount of a contaminant to which people might be exposed based on a given soil contaminant concentration. The model focuses on pathways relevant to direct human health risks arising from exposure to contaminated land, consistent with the 'suitable for use' approach. By comparing predicted exposure with health criteria values on tolerable or acceptable contaminant intakes (see below), the model is used to generate assessment criteria that establish a contaminant concentration in soil that is protective of human health. The term *health criteria value* introduced in CLR 10 represents the toxicological guideline value against which human exposure to soil contamination is ultimately compared. (Derivation of the main such criteria, tolerable daily soil intakes (TDSIs) and Index Doses, is discussed in CLR 9.) A critical assumption in the development of CLEA 2002 is that human exposure to a soil contaminant at a level that exceeds a relevant health criteria value is at best undesirable and in many cases not acceptable on the grounds of increased risk to human health.

Human exposure to contaminants in soil is a highly complex process that demands not only an understanding of the fate and transport of chemicals in the environment but also the social aspects of human behaviour. Quantifying risk and exposure gives rise to several different areas of uncertainty and variability whose impact on any assessment should be evaluated.

CLEA 2002 is a probabilistic exposure model (see Section 4.3.2): some single-value parameters from an exposure assessment are replaced with data from a family of values selected from a defined probability distribution. Each time the model estimates exposure, it selects a value from this family. By repeating the assessment, a probabilistic model builds a range of predicted exposures rather than providing a single outcome. This allows the assessor to gain a better understanding of the sensitivity of the assessment to parameter uncertainty and variability, and allows more informed judgements about its degree of conservatism. There are eight parameters in the CLEA 2002 model, which are selected from a range of possible values rather than being represented by a single value. The model uses the computational technique known as the Monte Carlo method to select a random or pseudo-random value for each probabilistic parameter from a range of specified values. CLEA 2002 does not model the possible impact of soil contaminants on groundwater or surface water quality, on buried services and construction materials, or on soil ecosystems, nor does it model transient risks to site workers during redevelopment or other construction works.

### POEM (The Predictive Operator Exposure Model)

The Predictive Operator Exposure Model (POEM) is used by the PSD and HSE to estimate the level of exposure likely to be experienced by operators applying pesticides (Martin, 1990). It is essentially a collection of data points on dose from pesticide spray operator exposure studies that are grouped according to different tasks and types of equipment, for example loading liquids onto spray tanks, applying by hand held equipment or applying by tractor mounted boom sprayers. For these data sets various potential exposure values have been identified and the model enables estimation of the amount reaching the skin for varying levels of potential exposure.

The dose of pesticide absorbed by a spray operator is determined by a number of factors that are independently variable. The major factors were identified as being the volume of external contamination, the extent to which this external contamination penetrated clothing to reach the skin and the rate at which a chemical in direct contact with the external skin surface was absorbed percutaneously.

POEM operator exposure calculations are divided into two parts: contamination from handling the concentrated product and contamination during actual application of the dilute spray. These are dependent on product-specific and technique-specific data, respectively. In addition to these data it is necessary to make a number of 'semi-quantitative value judgements'. These assumptions may be based on data, but in the absence of data conservative estimates have to be made.

The input data required to generate a POEM estimate include:

- active ingredient, and concentration;
- formulation type;
- main solvent, and concentration;
- container size and design (neck width);
- methods of application;
- protective clothing recommendations;
- maximum application rate; and
- minimum label spray application volume.

There are similar German and Dutch models as well as the harmonised EURO-POEM, which is under development.

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# Annex D
# Worked examples

## Introduction

In order to demonstrate some of the principles of exposure assessment, worked examples are provided in this Annex.

## Case Study 1 — Phthalate plasticiser migration from soft PVC toys and child–use and care articles

### Background

Phthalate plasticisers are added to polymers to give them specific properties, e.g. flexibility. They are used extensively in PVC at levels as high as 40% or more. They may also be present in glues and varnishes, and in lubricants at far lower levels, e.g. 2%.

Guidelines concerning plasticiser migration have traditionally been based on static tests to assess migration from materials and articles in contact with food. However, testing that provides data under more realistic (dynamic) conditions of exposure is more appropriate for assessing indicative plasticiser release from articles that are intended to be, or which may be, mouthed.

However, achieving a predictive laboratory-based (*in vitro*) method for use in determining the potential impact on health from exposure of young children to phthalate plasticiser migration from such products has been limited by the lack of validated oral contact time and *in vivo* migration exposure data as reference points.

### Approach

The approach adopted to develop the test method is shown in Figure D1.

*Literature studies*

A literature review of recent publications indicated several phthalate exposure studies, but few of the available data are actual measurements, the rest being results of different calculations or models. Many of these contribute to the indirect exposure assessment route provided by the food-chain. However, one addresses factors that affect exposure to a particular phthalate from children's products (Little, 1985). There are a number of determinations of phthalates leached from toys, but very few concerning child use and care articles. Most of these reports describe the methodology very briefly, making it difficult to judge the significance of the data.

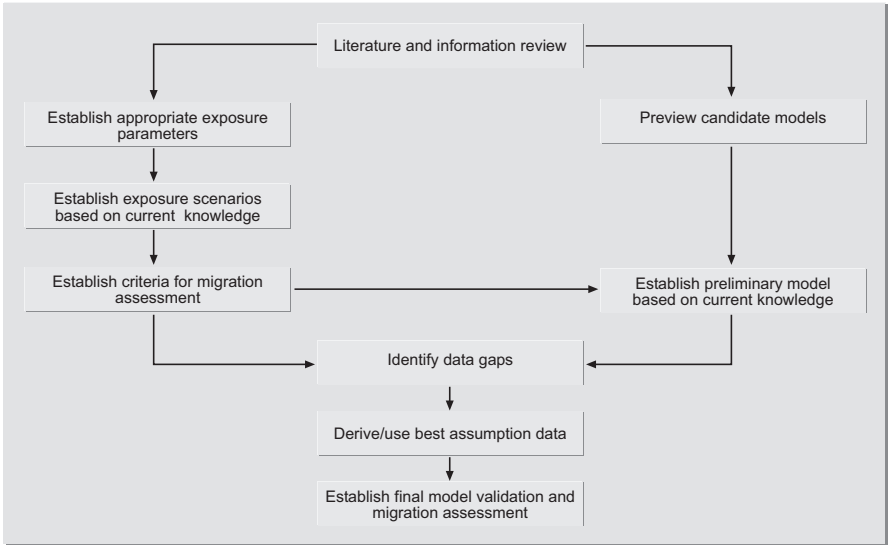
However, a few recent studies have reported oral exposure levels to adults through chewing studies (RIVM, 1998; Steiner *et al*., 1998) whilst others report oral exposure times (Groot *et al*., 1998; Juberg *et al*., 2001; DTI, 2002).

*Exposure parameters and scenarios*

The first step in the exposure assessment was to identify the parameters relevant to young children, and those relevant to the product.

- Parameters relevant to users — normal and foreseeable behaviours, age and weight ranges and abilities of users (population characteristics), usage patterns and mode of use, pre-conditioning requirements, contact areas and environment between products and users, contact intervals, and intake proportions from product.

**Figure D1 Flow chart of the approach to develop a test method for plasticiser migration**



- Parameters relevant to products — sizes and compositions of products, volumes and compositions of salivas, solubilities of plasticisers in salivas, and boundary conditions at interfaces of products/salivas.

The inherent vulnerability of young children, combined with their different stages of development and learning, exposes them to potential chemical risk from the constantly changing range and variety of toys and child use and care articles to which they have access, either intended or not. Their acknowledged early sensorimotor actions, that is use of their senses to learn to see, hear, taste, smell and feel, mean that the major exposure route to plasticisers is mouthing (although it becomes redundant with time, being replaced by indirect exposure through the food-chain). Any dermal and inhalation exposure is considered to be limited.

*Assessment criteria and candidate models for migration tests*

The next step was to consider parameters relevant to the testing method, which would depend upon the model selected.

Various test models were considered: static, stirring, ultrasonic agitation, tumbling (head over heels) and horizontal shaking (linear or rotation).

Parameters considered relevant to the model included: shape and dimensions of test article, pre-conditioning, dimensions of vessel, volume and composition of saliva (simulant), temperature, replenishment of saliva (simulant), means and frequency of mechanical agitation, amplitude of motion and contact interval.

It was also necessary to identify a suitable analytical methodology (normal or reverse phase High Performance Liquid Chromatography (HPLC), Gas Chromatography-Flame Ionisation Detection (GC-FID) or Gas Chromatography-Mass Spectrometry (GC-MS)) with an appropriate limit of detection.

**Results**

Analysis of the oral exposure studies is summarised in Tables D1–D3. The studies show a marked variation in duration of mouthing with some children consistently not mouthing any objects and some mouthing objects for significantly longer times. Mouthing behaviour is dependent on age and types of items available for mouthing. Children in the 6–12 months range tend to mouth toys longer than their peers, but significant mouthing appears to continue beyond the currently accepted 3 year 'cut-off' time, albeit predominantly the use of fingers.

**Table D1 Estimated maximum daily mouthing time (hours:minutes) for all items mouthed**

| | Age group (months) | | | |
|---|---|---|---|---|
| Item mouthed | 3–6 | 6–12 | 12–18 | 18–36 |
| Dummy/ Soother | 3:34 | 1:53 | 1:35 | 2:35 |
| Toys for mouthing | 0:12 | 0:40 | 0:01 | 0:00 |
| Other toys | 0:27 | 1:41 | 0:10 | 0:04 |
| Non toys | 0:07 | 0:26 | 0:50 | 0:12 |
| Fingers | 0:51 | 0:42 | 0:52 | 0:26 |

Data from Groot *et al.* (1998)

**Table D2 Estimated mean daily mouthing time (hours:minutes) for all items mouthed**

| | Age group (months) | |
|---|---|---|
| Item mouthed | 0–18 | 19–36 |
| Dummy/ Soother | 3:41 | 7:42 |
| Teether | 0:20 | 0:30 |
| Plastic toy | 0:28 | 0:11 |
| Other objects | 0:22 | 0:15 |

Data from Juberg *et al.* (2001)

**Table D3 Estimated maximum daily mouthing time (hours:minutes) for all items mouthed**

| | Age group | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Months | | | | | | | | Years | | | |
| Item mouthed | 1–3 | 3–6 | 6–9 | 9–12 | 12–15 | 15–18 | 18–21 | 21–24 | 2 | 3 | 4 | 5 |
| Dummy/Soother | 2:55 | 2:33 | 1:40 | 5:23 | 3:32 | 3:40 | 5:18 | 1:55 | 3:37 | 5:04 | 5:22 | 0:08 |
| Fingers | 0:51 | 1:36 | 1:17 | 1:39 | 0:36 | 0:39 | 1:20 | 1:53 | 2:28 | 3:19 | 2:51 | 9:03 |
| Toys | 0:01 | 2:35 | 3:47 | 1:05 | 0:44 | 0:58 | 0:33 | 1:42 | 2:06 | 1:35 | 0:21 | 0:11 |
| Other objects | 0:28 | 0:37 | 1:10 | 1:31 | 1:03 | 1:38 | 1:06 | 0:40 | 2:58 | 1:25 | 1:17 | 0:53 |

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Analysis of anthropometric data for open mouth dimensions (DTI, 1995) suggests that the area of the open mouth (and hence surface area of an article available for mouthing) is 10 $cm^2$. For articles with a smaller surface area, it is proposed that twice this value (i.e. 20 $cm^2$) is used as the maximum surface area available for mouthing (Little, 1985). Analysis of body weight charts suggests that 8 kg is the mean body weight of a young child 6–9 months old.

The Technical Guidance Document to the Commission Regulation (EC) No. 1488/94 on Risk Assessment for Existing Substances (EC, 2003) suggests performance of a quantitative risk characterisation. This includes comparison of quantitative information on exposure with the identified no/lowest observed adverse effect level (N/LOAEL). Using this approach the EC Scientific Committee for Toxicity, Ecotoxicity and the Environment (CSTEE) provided its opinion on acceptable guidance values for maximum tolerable extractable amounts of phthalates (Table D4).

Analysis of oral exposure level data (RIVM, 1998; Steiner *et al*., 1998) indicated maximum phthalate plasticiser release levels of 8.9 µg/min DINP in their respective adult 'chew and spit' studies using a known (reference) PVC disc. This data corresponds to the EC CSTEE maximum guidance value of 6.6 µg/min with an approximate 30% standard deviation (a value typically acceptable for migration-based test methodologies) and was accepted by the CSTEE as the target value for migration test methodology.

Use of 'natural' saliva in the laboratory is not feasible on both practical, and health and safety grounds. Selection of suitable and accepted saliva simulant solution is limited to BS, DIN or Dutch Consensus Group solutions. The BS simulant has a lower pH and contains an organic component, the Dutch simulant is a near neutral pH salt solution and the DIN simulant is a carbonate solution found to yield low release levels in this case (LGC, 1998). Saliva pH varies from 4.5–6.7 depending on state of hunger and represents an important factor.

Analysis of adult saliva production levels indicates 0.5 ml/min in 'resting' and 1.5 ml/min under 'active mouthing' (chewing) conditions giving approximately 100 ml/h. Equivalence was assumed for young children with continual replenishment of saliva. Replenishment studies led to the observation that at short time intervals (up to 30 min), a cumulative linear phthalate plasticiser release profile was achievable (LGC, 1999). The same study also showed that increasing the temperature resulted in near exponential plasticiser release under agitation conditions for short time intervals.

#### Conclusion

The LGC set out to establish an agitation-based test method that would allow meaningful determination of the release levels of at least six specified phthalate plasticisers from toys and child use and care articles.

Through a structured approach of assessment of existing exposure data and of laboratory method validation and uncertainty analysis, a suitable method for determining the release of all commonly used phthalates in saliva simulant solution from such articles has been provided (Earls *et al*., 2003). The migration results obtained from use of this *stringent* method may be compared directly with the guidance migration levels recommended by the CSTEE.

**Table D4 Acceptable guidance values for maximum tolerable extractable amounts of phthalates**

| Phthalate | Critical effect | NOAEL value (mg/kg/day) | Tolerable daily intake (µg/kg/day) | Guidance value (µg/10 $cm^2$ and 3 h and 8 kg) |
|---|---|---|---|---|
| DINP | Increased liver and kidney weight | 15 | 150 | 1200 |
| DnOP | Microscopic liver and thyroid changes | 37 | 370 | 3000 |
| DEHP | Hepatic peroxisome proliferation | 3.75 | 37.5 | 300 |
| DIDP | Increased liver weight | 25 | 250 | 2000 |
| BBP | Increased liver weight | 40 | 200 | 1600 |
| DBP | Reduced F2 pup weights | 52 | 100[a] | 800 |

Adapted from CSTEE (1998) The Scientific Committee on Toxicity, Ecotoxicity and the Environment, available [March 2004] at http://europa.eu.int/comm/health/ph-risk/Committees/sct/docshtml/sct_out19_en.htm

[a] Additional uncertainty factor of 2* incorporated as based on LOAEL value

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## Case Study 2 — Total personal exposure to environmental benzene

### Background

Benzene has long been recognised as a genotoxic carcinogen and has caused great concern historically as an occupational health hazard. Current concern, however, is centred on the effects of continuous low-level exposure to benzene both occupationally and environmentally. In response to this concern the Department of the Environment, Transport and the Regions (DETR) commissioned the MRC Institute for Environment and Health (IEH) to evaluate any potential risk to the health of the general population from exposure to environmental levels of benzene.

### Approach

The study was focussed on non-occupational exposure and considered consumers' exposure through normal use of benzene-containing products and indirect exposure through contaminated air, soil, water and via the food-chain. A literature review of recent publications was used to identify:

- sources of benzene and annual emissions;
- current legislation and estimated future emissions;
- environmental fate and behaviour; and
- environmental concentrations to produce 'typical' concentrations for key environmental compartments.

It was found that benzene emissions to air in the UK are predominantly derived from road transport, mainly petrol; the most important sources include evaporative losses, refuelling emissions and combustion of petrol. Benzene may also enter the environment through fugitive emissions from chemical manufacturing and processing operations and from refining and distribution of fuels, principally petrol. As benzene is primarily found in the atmosphere, human exposure is mainly through inhalation, which accounts for >95% of the total daily intake. Given the minor contribution that non-inhalation sources make to the overall daily intake of benzene to humans, only exposure via inhalation was considered when estimating the daily exposure of the general population to benzene. Ambient benzene concentrations in urban, rural, industrial and roadside environments were taken from the 1995 data from the automatic hydrocarbon

monitoring network and passive monitoring networks and were combined with other published data to derive typical environmental concentrations. These were applied with time–activity data to derive a series of exposure scenarios for adults and children:

Adult exposure scenarios:

- a non-smoker who lives in a rural environment;
- a non-smoker who lives in an urban environment;
- a non-smoker who lives in an urban environment in a house where at least one member of the family smokes;
- a smoker who lives in an urban environment; and
- a smoker who spends 8 hours/day actively working close to heavy traffic (e.g. a road worker on a busy city-centre road.

Children's exposure scenarios:

- an infant or child who lives in a rural environment;
- an infant or child who lives in an urban environment; and
- an infant or child who lives in an urban environment in a house where at least one member of the family smokes.

**Results**

The analysis showed that infants (<1 years old), children (11 years old) and non-occupationally exposed adults receive average daily doses of 15.3–25.9 (Table D5), 29.3–49.3 (Table D5) and 70–522 μg (Table D6) of benzene, respectively, which corresponds to an average exposure range to benzene in air of 3.4–5.67 μg/m$^3$ for infants and children (Table D7) and 3.75–26.1 μg/m$^3$ for adults (Table D8). Infants and children exposed to environmental tobacco smoke have benzene exposure levels comparable to those of an adult passive smoker. This is a significant source of exposure as a 1995 UK survey has shown that 47% of children aged 2–15 years live in households where at least one person smokes. The consequence of benzene exposure in infants is more significant than for children or adults owing to their lower body weight; this is reflected in their higher daily intake (2.40–3.07 μg/kg bw/day) when compared with children (0.71–1.29 μg/kg bw/day) or non-smoking adults (1.06–2.43 μg/kg bw/day). The worst-case scenario for benzene exposure in the general population is that of an urban smoker who works adjacent to a busy road for 8 hours/day (e.g. a maintenance worker) who can receive an average daily exposure of approximately 819 μg. This represents a physically active individual whose inhalation rate is higher than that of a person in a more sedentary occupation.

**Uncertainty analysis**

The monitoring campaigns that were used to obtain exposure concentrations were designed for specific research activities with clearly defined objectives; they may therefore not be typical or take full account of temporal/spatial variability in scenarios. Combining data from different sources that involved numerous sampling and analytical methods (e.g. passive or active sampling or continuous automatic monitoring; GC-FID, GC-ECD or MS) and therefore differences in quality assurance or quality control procedures could affect the accuracy of measurements. Information provided in the published literature may be insufficient to evaluate the significance of the results; for example the mean and/or range of concentrations with no information on frequency, duration or number of samples collected.

**Conclusion**

The study approach has generated estimates of exposure under various scenarios that appear to follow expected patterns. However, uncertainties derived from the methods used to obtain data mean that the values may not be representative of real situations, either because they are not sufficiently conservative or because significant exposure scenarios may not have been identified and included.

This case study is based on a detailed report on the risk assessment of benzene published by IEH (1999).

**References**

ICRP (1975) *Report of the Task Group on Reference Man*, Oxford, UK, Pergamon Press

IEH (1999) *Benzene in the Environment: An Evaluation of Exposure of the UK General Population and Possible Adverse Health Effects,* (Report R12), Leicester, UK, MRC Institute for Environment and Health

Layton DW (1993) Metabolically consistent breathing rates for use in dose assessments. *Health Phys 64,* 23–36

**Table D5 Estimated benzene absorbed daily doses (µg/day) for infants and children under different exposure scenarios**

| Activity | Rural infant | Urban infant | Urban infant passive smoker | Rural child | Urban child | Urban child passive smoker |
|---|---|---|---|---|---|---|
| Indoors | 10.2 | 14.3 | 20.5 | 19.6 | 27.4 | 39.1 |
| In-vehicle | 5.0 | 5.0 | 5.0 | 9.5 | 9.5 | 9.5 |
| Outdoors, pleasure | 0.1 | 0.4 | 0.4 | 0.2 | 0.7 | 0.7 |
| Total daily dose | 15.3 | 19.7 | 25.9 | 29.3 | 37.6 | 49.3 |

**Table D6 Estimated absorbed daily doses of benzene (µg/day) for members of the general public under different exposure scenarios**

| Activity | Rural non-smoker | Urban non-smoker | Urban passive smoker | Urban smoker | Extreme case |
|---|---|---|---|---|---|
| Indoors | 45.5 | 63.7 | 91 | 91 | 58 |
| In-vehicle | 22 | 22 | 22 | 22 | 22 |
| Refuelling[a] | 1.9–7.4 | 1.9–7.4 | 1.9–7.4 | 1.9–7.4 | 1.9–7.4 |
| Outdoors, pleasure | 0.5 | 1.6 | 1.6 | 1.6 | 1.6 |
| Outdoors, work[b] | - | - | - | - | 330 |
| Smoking | - | - | - | 400 | 400 |
| Total daily dose | 70–75 | 89–95 | 116–122 | 516–522 | 814–819 |

[a] The lower of the reported range refers to whether vapour recovery equipment has been fitted in filling necks and petrol pump nozzles. As these are still not required by UK or EU legislation, the higher value of this range will reflect current exposure more accurately and therefore this value is used for evaluating benzene exposure to the general UK population. With the implementation of controls to reduce emissions from this source, there should be a gradual reduction of exposure to benzene from this source (down to an estimated daily absorbed dose of 1.5 µg) over the next few years (IEH, 1999).

[b] Breathing rate for heavy activity is 2.5 $m^3$/hour (Layton, 1993)

**Table D7 Summary of estimated absorbed doses of benzene for infants and children under different exposure scenarios**

| | Daily dose (µg/day) | Daily intake (µg/kg bw/day)[a] | Equivalent atmospheric concentration[b] (µg/$m^3$) |
|---|---|---|---|
| Rural infant | 15.3 | 1.68 | 3.40 |
| Urban infant | 19.7 | 2.16 | 4.38 |
| Urban infant, passive smoker | 25.9 | 2.55 | 5.76 |
| Rural child | 29.3 | 0.71 | 3.37 |
| Urban child | 37.6 | 0.91 | 4.32 |
| Urban child, passive smoker | 49.3 | 1.20 | 5.67 |

[a] Values converted from daily doses by assuming that the average infant (<1 year old) weighs 9.1 kg and the average child (11 years old) weighs 41.1 kg; there will be a progression in ranges so that on average a 1 year old weighs 11.3 kg, a 5 year old weighs 19.7 kg, an 8 year old weighs 28.1 kg and so on

[b] Values converted from daily doses by assuming that the average infant and child inhales a volume of air of 4.5 and 8.7 $m^3$/day, respectively

**Table D8 Summary of estimated absorbed doses of benzene for adult members of the general public under different exposure scenarios**

| | Daily dose (µg/day) | Daily intake (µg/kg bw/day)[a] | | Equivalent atmospheric concentration (µg/$m^3$)[b] |
|---|---|---|---|---|
| | | Females | Males | |
| Rural non-smoker | 75 | 1.29 | 1.07 | 3.75 |
| Urban non-smoker | 95 | 1.64 | 1.36 | 4.75 |
| Urban passive smoker | 122 | 2.10 | 1.74 | 6.10 |
| Urban smoker | 522 | 9.00 | 7.46 | 26.10 |
| Urban smoker who works adjacent to busy road for 8 hrs/day | 819 | 14.12 | 11.70 | 41.95 |

[a] Values converted from daily doses by assuming that the average UK female and male weigh 70 and 58 kg, respectively (ICRP, 1975)

[b] Values converted from daily doses by assuming that the average individual inhales 20 $m^3$ of air per day

## Case Study 3 — Probabilistic modelling of acute pesticide intake

### Background

Deterministic methods for estimating pesticide intakes are described in Annex C. Combining single figures to represent pesticide concentrations or food consumption can provide reliable estimates of average or high level intakes but gives no information about the likelihood of occurrence of such levels of intake. Probabilistic modelling provides an alternative approach that makes use of all of the available data. In this example a simple probabilistic model is described that considers only one residue in one type of food (apples). More sophisticated probabilistic models can take account of other residues with the same mechanism of toxicity, consumption of all affected foods and other sources and pathways of exposure.

### Approach

Simple probabilistic modelling can be illustrated by the estimation of acute intakes of a pesticide from individual apples by children. The model can be run in a conventional spreadsheet using data analysis commands and tools such as Crystal Ball. Figure D2 shows the distribution of residues of an organophosphate pesticide in individual apples harvested after treatment with a crop protection agent. The distribution is skewed with a relatively small proportion of residues that are significantly higher than the majority of samples. Figure D3 shows the distribution of apple consumption by occasion by UK pre-school children aged 1.5 to 4.5 years. Note the relatively high number of consumers of 100 g per day. This could be a genuine figure although probably represents rounding up or down by the person recording the data.

In the probabilistic analysis samples are drawn at random from the residue distribution and then from the apple consumption distribution to provide the data points for the intake distribution. This sequence is repeated several thousand times until a smooth intake distribution curve is produced.

### Results

The intake distribution shown in Figure D4 represents 20 000 samples drawn from each of the pesticide residues (Figure D2) and apple consumption (Figure D3) distributions. The bars represent the relative frequency of each intake level. The distribution is very skewed and it can be seen that the cumulative frequency is nearing 100% when only the mid-point of the distribution is being approached. This means that very high intakes are very infrequent when compared with the majority of intakes.

Upper percentiles (95th, 97.5th or 99.9th) can be derived from the cumulative frequency distribution:

| | |
|---|---|
| Mean value | 0.044 mg/day |
| 95th percentile | 0.130 mg/day |
| 97.5th percentile | 0.171 mg/day |
| 99.9th percentile | 0.491 mg/day |
| Maximum | 0.667 mg/day |

### References

Gregory JR, Collins DL, Davies PSW, Hughes JM & Clarke PC (1995) *National Diet and Nutrition Survey; Children aged $1^1/_2$ to $4^1/_2$ years*, London, HMSO

PSD (1998) *The Occurrence of Unit to Unit Variability of Pesticide Residues in Fruit and Vegetables*, York, UK, Pesticides Safety Directorate

## Case Study 4 — Spreadsheet probabilistic modelling

### Background

The availability of spreadsheet add-ins for probabilistic modelling makes the technique available for use on any personal computer with Microsoft Excel, Lotus 1,2,3, or any other suitable spreadsheet installed. Such systems are extremely versatile and are best illustrated with a simple example.

### Approach

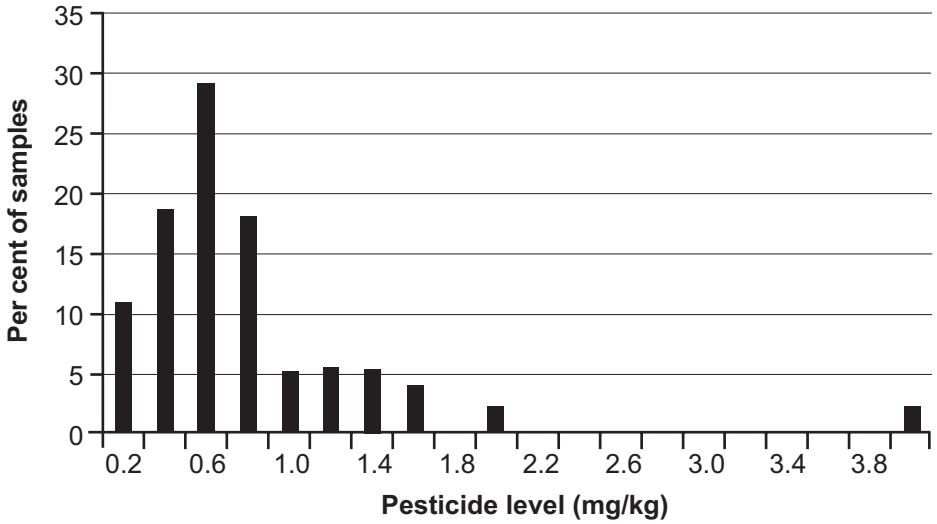
In this hypothetical example the distribution of intakes of a chemical element, chemical X, from milk consumption by small children is being investigated to define the proportion that might suffer from either deficiency or toxicity. The principal source of chemical X for infants is milk and in this analysis it is assumed that all infants drink milk. The levels of chemical X in samples of milk have been measured and can be represented by a histogram function in a spreadsheet add-in such as @RISK as:

**RISKHISTOGRM**(0.5,1.0,{2,3,4,8,20,38,18,12,7,4,1})

This input distribution is represented in Figure D5. Note that @RISK automatically reallocates the distribution from 11 to 20 classes in this example.

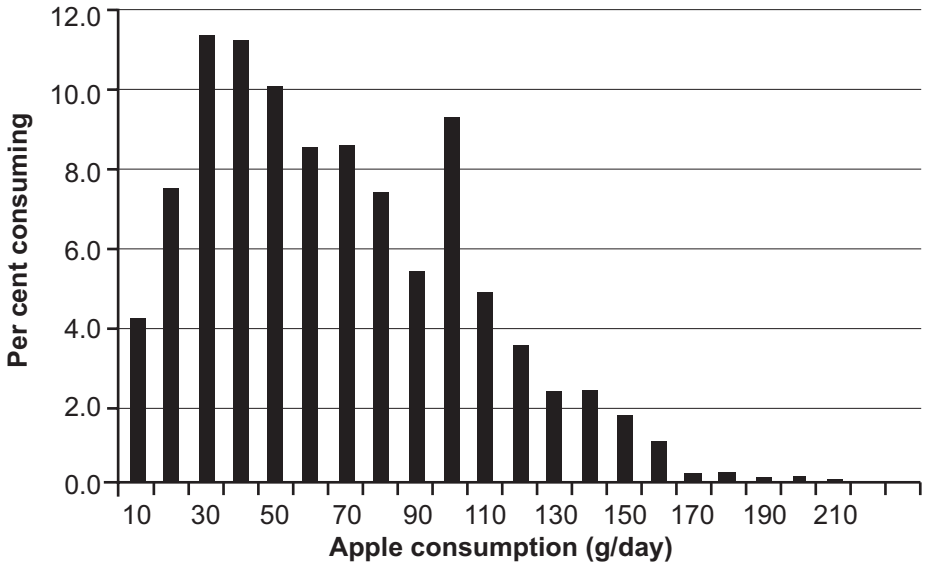
Similarly infants' consumption of milk has also been studied and been found to be log-normally distributed with an arithmetic mean of 2.9 litres per week and standard deviation of 0.7.

**Figure D2 Frequency distribution of pesticide residues in apples**



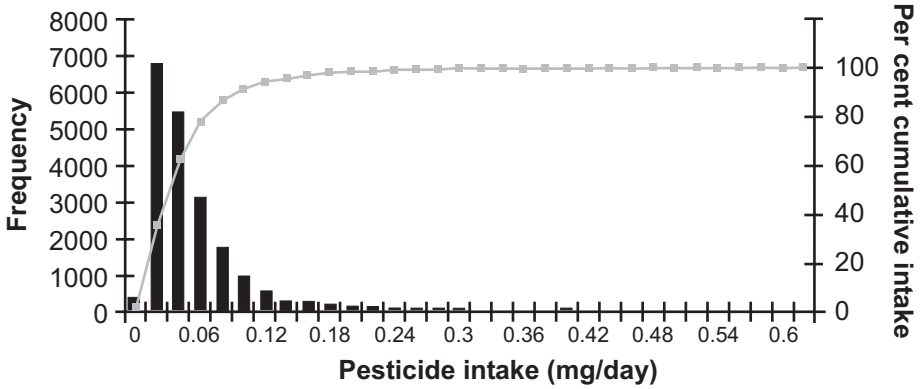

Based on data from PSD (1998)

**Figure D3 Frequency distribution of apple consumption by UK pre-school children**




Based on data from Gregory *et al.* (1995)

**Figure D4 Probabilistic distribution of pesticide residue intakes from apples**

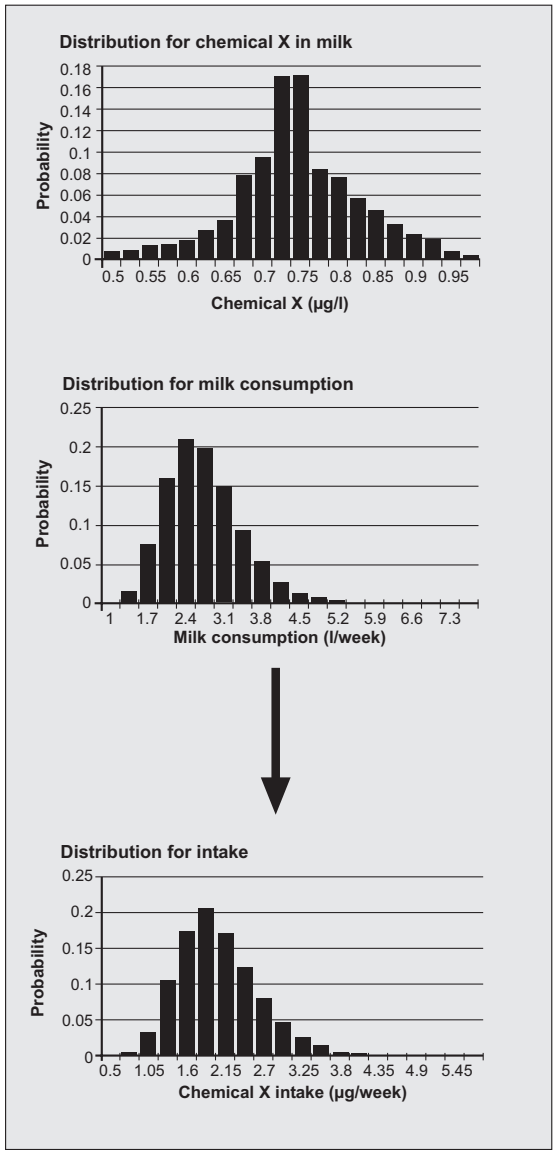


This distribution can be represented by a lognormal function in @RISK and Excel as:

**RISKLOGNORM**(2.9,0.7)

This input distribution is also shown in Figure D5. Note that the distribution permits milk consumption in excess of three times the average level. If this was an unrealistic scenario the log-normal distribution could be truncated to prevent such high values being included.

**Figure D5 Example of predicting intakes of chemical X**




| Variable | Data | Formula |
|---|---|---|
| Chemical X in milk | 0.76 | = RISKHISTOGRM, (0.5,1.0{2,3,4,8,20,38,18,12,7,4,1}) |
| Milk consumption | 2.90 | = RISKLOGNORM(2.9,0.7) |
| Intake | 2.19 | = D13*D14 (from Output Statistics) |

**Results**

The example was run through 10 000 iterations and the chemical X intake distribution depicted in Figure D5 generated. While this graphical representation provides a useful preliminary indication of the results, @RISK can also provide a detailed results summary (Table D9). Detailed statistics are provided for both input distributions and the output distribution. Note that the system allows target values to be entered. In this example if it is assumed that children with intakes less than 1.0 µg chemical X per week are at risk of deficiency and those with intakes greater than 4.0 µg chemical X per week at risk of toxicity, these values can be entered as target values. In this hypothetical model, 0.35% of the population would be at risk of chemical deficiency and 0.81% at risk of toxicity.

**Uncertainty and sensitivity analysis**

This analysis is highly dependent on the reliability of the input data, for example whether sufficient samples of milk have been analysed for chemical X and whether they reflect a representative sample, whether concentrations of chemical X vary seasonally and whether these variations have been taken into account. Model uncertainties can include whether the statistics used to represent milk consumption are accurate, particularly at the extremes. Table D9 shows that the range of values used in the model range from 11 per week to over 71 per week. Are these values realistic?

The output distributions can be further analysed using sensitivity analysis to determine the input variables that have the greatest statistical influence on the derived output distribution. A distribution with a large spread of values will have a greater effect on the distribution of output values than an input distribution with a narrow spread. In this simple hypothetical example chemical X intakes correlate more strongly with the consumption of milk than with the concentrations of chemical X in the milk (Table D10). This type of information may be of value when planning risk management strategies.

**Conclusion**

Spreadsheet probabilistic models are relatively easy to set up and use. However, the validity of the results is highly dependent on the quality of the input data and on assumptions applied within the model.

**Table D9 Output statistics for chemical X example**

| @RISK Simulation of Chemical-X.xls | Run on 25/01/02, 14:30:09 | Simulations = 1 | Iterations = 10 000 |
|---|---|---|---|
| Name | Intake/Data | Chemical X in milk/Data | Milk consumption/Data |
| Description | Output | Histogrm(0.5,1,{2,3,4, 8,20,38,18,12,7,4,1}) | Lognorm(2.9,0.7) |
| Cell | D11 | D9 | D10 |
| Minimum = | 0.7107468 | 0.5002568 | 1.120307 |
| Maximum = | 5.585615 | 0.9995274 | 7.087778 |
| Mean = | 2.191401 | 0.7554392 | 2.899978 |
| Std Deviation = | 0.5892581 | 8.53E-02 | 0.6998277 |
| Variance = | 0.3472252 | 7.28E-03 | 0.4897588 |
| Skewness = | 0.7833976 | -0.122341 | 0.7348667 |
| Kurtosis = | 4.129443 | 3.534204 | 3.95231 |
| Errors Calculated = | 0 | 0 | 0 |
| Mode = | 2.173186 | 0.7690851 | 2.678623 |
| 5% Perc = | 1.35806 | 0.6005256 | 1.905813 |
| 10% Perc = | 1.500181 | 0.651692 | 2.077802 |
| 15% Perc = | 1.608456 | 0.6830524 | 2.202806 |
| 20% Perc = | 1.689556 | 0.6963616 | 2.30737 |
| 25% Perc = | 1.770751 | 0.7096388 | 2.400902 |
| 30% Perc = | 1.842097 | 0.7229498 | 2.488163 |
| 35% Perc = | 1.912781 | 0.7319961 | 2.572003 |
| 40% Perc = | 1.987074 | 0.7389941 | 2.654081 |
| 45% Perc = | 2.052569 | 0.7459854 | 2.735963 |
| 50% Perc = | 2.12158 | 0.7529865 | 2.818976 |
| 55% Perc = | 2.194194 | 0.7599841 | 2.904603 |
| 60% Perc = | 2.273042 | 0.7669852 | 2.994211 |
| 65% Perc = | 2.35519 | 0.775358 | 3.089745 |
| 70% Perc = | 2.437846 | 0.7901446 | 3.193623 |
| 75% Perc = | 2.529108 | 0.804917 | 3.309817 |
| 80% Perc = | 2.639848 | 0.8204473 | 3.444114 |
| 85% Perc = | 2.777933 | 0.8426116 | 3.607256 |
| 90% Perc = | 2.954231 | 0.8655243 | 3.823759 |
| 95% Perc = | 3.265331 | 0.9035507 | 4.169163 |
| Target #1 (Value) = | 1 | | |
| Target #1 (Perc%) = | 0.35% | | |
| Target #2 (Value) = | 4 | | |
| Target #2 (Perc%) = | 99.19% | | |

**Table D10 Sensitivity analysis for chemical X in milk**

Example Simulation Sensitivities for Intake/Data in Cell D11 (from @RISK Simulation of VitMilk.xls; Run on 25/01/02, 14:30:09, Simulations = 1, Iterations = 10 000)

| Rank | Cell | Name | Sensitivity (RSqr = 0.9900618) | Rank Correlation Coefficient |
|---|---|---|---|---|
| #1 | D10 | Milk consumption/Data | 0.897193 | 0.8927082 |
| #2 | D9 | Chemical D in milk/Data | 0.420663 | 0.4118245 |

# Annex E
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## Risk Assessment and Toxicology Steering Committee publications

cr 1 Developing New Approaches to Assessing Risk to Human Health from Chemicals

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