Harmonization Project Document No. 3

PRINCIPLES OF CHARACTERIZING AND APPLYING HUMAN EXPOSURE MODELS

This project was conducted within the IPCS project on the Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals.

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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO) and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research and the Organisaion for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

Harmonization Project Documents are a new family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO) and the United Nations Environment Programme (UNEP). Harmonization Project Documents join the Environmental Health Criteria (EHC) methodology (yellow cover) series of documents as authoritative documents on methods for the risk assessment of chemicals.

The main impetus for the current coordinated international, regional and national efforts on the assessment and management of hazardous chemicals arose from the United Nations Conference on Environment and Development (UNCED) held in 1992 and was reconfirmed at the 2002 World Summit on Sustainable Development. UNCED Agenda 21, Chapter 19, the "blueprint" for the environmentally sound management of toxic chemicals under the principles of sustainable development, has guided most international and national chemical-related activities. Chapter 19 is the agreed upon, endorsed international programme of action of governments for developing and implementing national programmes for management of chemicals within the principles of sustainable development.

The IPCS project on the Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals (Harmonization Project) is conducted under Agenda 21, Chapter 19. The Intergovernmental Forum on Chemical Safety (IFCS) Forum III, held in Salvador da Bahia in October 2000, agreed on Priorities for Action Beyond 2000, which further define the actions recommended to be taken. Forum III declared that by 2004, IPCS and the Inter-Organization Programme for the Sound Management of Chemicals (IOMC, which comprises seven intergovernmental organizations) should have ensured that recommendations for harmonized assessment approaches were available for terminology, cancer, and reproductive and developmental toxicology and that common principles for the assessment approach to other specific toxicological end-points, such as immunotoxicology, endocrine disruptors and ecotoxicology, should be adopted wherever possible.

The IPCS Harmonization Project, which is ongoing, states that "harmonization," in the context of chemical risk assessment, should not simply be equated with standardization. It is not a goal of the project to standardize risk assessments globally, as that is considered to be neither appropriate nor feasible. Instead, harmonization is thought of as an effort to strive for consistency among approaches and to enhance understanding of the various approaches to chemical risk worldwide. Thus, harmonization is defined, in a step-wise fashion, as an understanding of the methods and practices used by various countries and organizations so as to develop confidence in, and acceptance of, assessments that use different approaches. It further involves a willingness to work towards convergence of these approaches or methods as a longer-term goal.

Achieving harmonization of approaches is considered to provide a framework for comparing information on risk assessment; understanding of the basis for exposure standards for specific chemicals in different countries; savings of time and expense by sharing information and avoiding duplication of work; and credible science through better communication among

organizations and peer review of assessments and assessment procedures. The stated project mission is to ensure better chemical risk assessment and hence management practices that promote the protection of human health and the environment within the framework of sustainable development.

This ongoing project is overseen by a geographically representative Harmonization Project Steering Committee and a number of ad hoc Working Groups that manage the detailed work. Finalization of documents includes a rigorous process of international peer review and public comment.

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LIST OF ACRONYMS AND ABBREVIATIONS

ADI	acceptable daily intake
AirPEx	Air Pollution Exposure Model
APEX	Air Pollutants Exposure Model
aRfD	acute reference dose
CALENDEX	advanced exposure and risk analysis tool for estimating exposure of the population of the United States and more than 30 of its subgroups to pesticides, food, air and water contaminants, and chemical ingredients in formulated products
CARES	Cumulative and Aggregate Risk Evaluation System
CHAD	Consolidated Human Activity Database
CONSEXPO	consumer exposure model designed to predict application and post-application exposure resulting from the use of consumer products
DEEM	Dietary Exposure Evaluation Model
DEPM	Dietary Exposure Potential Model
DNA	deoxyribonucleic acid
EC	European Commission
EDETOX	Evaluations and Predictions of Dermal Absorption of Toxic Chemicals
E-FAST	Exposure, Fate Assessment Screening Tool
EFCOSUM	European Food Consumption Survey Methods
EHC	Environmental Health Criteria monograph (IPCS)
EIS-ChemRisks	European Information System on "Risks from chemicals released from consumer products/articles"
EU	European Union
EUSES	European Union System for the Evaluation of Substances
ExpoFacts	European Exposure Factors
EXPOLIS	European study on air pollution exposures of adult populations in seven cities
FAO	Food and Agriculture Organization of the United Nations
GIS	geographical information system
HAPEM	Hazardous Air Pollutant Exposure Model
HAPEM-MS	Hazardous Air Pollutant Exposure Model for Mobile Sources
IFCS	Intergovernmental Forum on Chemical Safety
ILO	International Labour Organization
IOMC	Inter-Organization Programme for the Sound Management of Chemicals
IPCS	International Programme on Chemical Safety
ISC-LT	Industrial Source Complex, Long Term
ISC-ST	Industrial Source Complex, Short Term
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues

LIFELINE	software for characterizing aggregate and cumulative exposures to pesticides and dietary exposure to contaminants in food and tap water
ML	maximum level
MRL	maximum residue level
MX	3-chloro-4-dichloromethyl-5-hydroxy-2(5H)-furanone
NAAQS	National Ambient Air Quality Standards
NAPL	non-aqueous-phase liquid
NAS	National Academy of Sciences (USA)
NEM	NAAQS Exposure Model
NHANES	National Health and Nutrition Examination Survey (USA)
NHAPS	National Human Activity Pattern Survey (USA)
OECD	Organisation for Economic Co-operation and Development
PBPK	physiologically based pharmacokinetic
PC	personal computer
$PM_{2.5}$	particulate matter less than or equal to 2.5 μm in diameter
PM_{10}	particulate matter less than or equal to 10 μm in diameter
ppm	parts per million
PTWI	provisional tolerable weekly intake
QA	quality assurance
QC	quality control
QSAR	quantitative structure–activity relationship
RIVM	Rijkinstituut voor Volksgesondheid en Milieu (National Institute for Public Health and the Environment) (The Netherlands)
SCIES	Screening Consumers Inhalation Exposure Software
SHAPE	Simulation of Human Activity and Pollutant Exposure
SHEDS	Stochastic Human Exposure and Dose Simulation (model)
SIDS	Screening Information Data Set
UNCED	United Nations Conference on Environment and Development
UNEP	United Nations Environment Programme
USA	United States of America
USDA	United States Department of Agriculture
USEPA	United States Environmental Protection Agency
USFDA	United States Food and Drug Administration
VOC	volatile organic compound
WHO	World Health Organization

1. INTRODUCTION

1.1 Background and rationale

The International Programme on Chemical Safety (IPCS) Harmonization Project aims to develop consistent principles for risk assessment that are widely accepted around the world. Experts in exposure assessment (the IPCS Harmonization Project Exposure Assessment Working Group) were invited to identify issues that pose barriers to the harmonization of exposure assessment methods and to develop a plan of action. One issue that was identified is the development and application of exposure models in the exposure assessment process. The Working Group therefore designated a subcommittee to develop a state-of-the-science paper on exposure models.

1.2 Goals of this work

This report has been developed for both risk assessors who need to use exposure models and model results in their work and model developers, to help them communicate openly and effectively with each other.

Exposure models have applications to chemicals of all types and from all sources. The scope of this paper is to describe general rules for modelling exposure to substances that contaminate our air, our food and drinking-water, and our surface water, groundwater and soil. These include environmental pollutants, such as industrial chemicals, pesticides, household chemicals and combustion products (from heating, cooking, traffic, etc.), as well as food additives. The term "agents" is used for all of these environmental pollutants and food additives in this report. Exposures to radiation or microbial contaminants are not addressed.

The report provides descriptions and applications of some published exposure models to illustrate both the principles and practices of exposure modelling, but it does not attempt to provide a comprehensive list of existing exposure models. Rather, the focus of this report is on discussing general properties of exposure models and how they should be described. The characteristics of different modelling frameworks are examined, and 10 principles are recommended for characterizing, evaluating and using exposure models in order to help model users select and apply the most appropriate models. The report also discusses issues such as validation, input data needs, time resolution and extrapolation of the model results to different populations and scenarios.

This report complements several international activities that have been undertaken in the last few years in order to improve knowledge and methods of exposure assessment, as well as to harmonize exposure assessment procedures:

- A standardized format for reporting exposure data has been developed in the Organisation for Economic Co-operation and Development (OECD) project on exposure reporting formats (OECD, 2003). Three formats for reporting summary information on environmental, occupational and consumer exposure to agents are provided, together with

guidance for completing and using the formats. The formats are to be used for the reporting of post–Screening Information Data Set (SIDS) exposure information collected in the assessment of high-production-volume chemicals.

- The European Union (EU) Joint Research Centre (on behalf of DG Sanco) has started a project known as EIS-ChemRisks (EC, 2004), which is designed as a network to collect exposure data, exposure factors, exposure models and health-related data. The overall objective is to develop tools and reference data to enable harmonized exposure assessment procedures in the EU. A toolbox has been designed to collect exposure information from four reference systems to systematically support exposure assessors in the EU: 1) EU-ExpoFactors (European Reference System for Exposure Factors); 2) ExpoData (Collection of Reference Exposure Data); 3) ExpoHealthData (Reference Exposure-Associated Health Data); and 4) ExpoScenarios (Reference Exposure Scenarios). The project includes sectoral projects that are focused on specific exposure scenarios (e.g. tattoos, textiles, toys, automobiles, etc.).

- A Consumer Exposure Modelling Task Force was set up in November 2002 by the European Commission's (EC) Joint Research Centre. Its main objectives are to 1) make a web-based and managed inventory of existing consumer exposure modelling tools (Consumer Exposure Modelling Task Force, 2004); 2) identify harmonization and validation needs for these models; 3) proceed with the harmonization and validation of an appropriately selected subset of models based on specific scenarios; 4) prepare a comprehensive overview of modelling approaches to estimate consumer exposure; 5) interface with the EIS-ChemRisks project; and 6) create the Global Net on Consumer Exposure Models (Global Net on Consumer Exposure Models, 2004). Table 3 in the present report (see section 4) has been prepared in accordance with this project.

1.3 Definitions and terminology

Exposure is defined concisely as "Contact between an agent and a target" (IPCS, 2004), where an *agent* is defined as "A chemical, biological, or physical entity that contacts a target" (IPCS, 2004). To improve communication in exposure-related fields, the agent, target, exposure location and exposure duration should be clearly defined.

According to this definition of exposure, exposure occurs at a point intimately close, but external, to the exposure target. Exposure does not automatically lead to an internal dose. In line with this definition is the very simple one that states that (human) exposure is the interface between humans and the environment. This defines the position of exposure science at the interface between environmental sciences and life sciences. It studies what happens outside of humans, from the sources to the human/environment interface, because of its relevance to what may happen inside humans.

Exposure assessment is "The process of estimating or measuring the magnitude, frequency, and duration of exposure to an agent, along with the number and characteristics of the population exposed. Ideally, it describes the sources, pathways, routes, and the uncertainties in the assessment" (IPCS, 2004). Exposure assessment is used in epidemiological studies to

relate exposure concentrations to adverse health outcomes. Exposure assessment is also an integral component of risk assessment, the process that provides scientific information for risk management. Exposure assessment is based on *exposure scenarios*, which are defined as "A combination of facts, assumptions, and inferences that define a discrete situation where potential exposures may occur. These may include the source, the exposed population, the time frame of exposure, microenvironment(s), and activities. Scenarios are often created to aid exposure assessors in estimating exposure" (IPCS, 2004).

Exposure factors summarize data on human behaviours and characteristics that affect exposure to environmental contaminants (AUH, 1995; USEPA, 1997).

An *exposure model* is "a conceptual or mathematical representation of the exposure process" (IPCS, 2004). The output of an exposure model can be an exposure concentration; in practice, however, exposure often includes estimates of intake (e.g. amount of chemical inhaled or ingested) and the amount of a chemical that is absorbed into the body (e.g. amount of chemical that penetrates the skin or the lining of the lung).

1.4 Exposure model applications

Exposure models can use whatever techniques and data are available to predict the properties of the immediate environment of humans for some specified purpose or need. Only after specifying the purpose and requirements and assessing the availability of data can one define the specifications of the exposure model for an application.

Most exposure assessments rely to some extent on exposure models that combine measurements and assumptions to produce an estimate of an exposure metric, such as an intake of an environmental agent. A typical exposure model combines measurements of concentrations of environmental agents in air, water, soil and food with data on activities and inhalation and ingestion rates to produce an estimate of intake of the environmental agent. Models can be composed of a series of interconnected submodels. For example, the concentrations in environmental media can be modelled rather than measured. Exposure modelling has some advantages over monitoring. Modelling is generally cheaper and faster and can produce results for large populations and results applicable to past, future or alternative scenarios. Many scenarios are impossible to monitor, or the results would come too late to serve decision-making purposes.

Exposure modelling is often complicated, and this is well reflected in the diversity of the published exposure models. Models are developed for many purposes, ranging from the purely academic to providing support for environmental regulations and administrative permit processing. Apparently similar models can be based on fundamentally different logic and input data. For example, two inhalation exposure models may have no overlapping applicability — one might estimate long-term residential exposure to formaldehyde at the individual level, the other short-term urban exposure to traffic exhausts for a population. The purpose of the former could be to assess exposure for an epidemiological case–control study, while the latter would provide guidance for zoning of a new highway. There is a need for

agreed principles to characterize these models in a standardized and commonly understood way that would help in selecting, developing and applying a model for a given need.

There are three important applications of exposure models:

1. *Epidemiological studies*: Epidemiology is the study of patterns and distributions of disease in human populations with the aim of determining causes of disease. To investigate links between disease and exposure to environmental agents, a measure or estimate of exposure is needed for each individual in the study. Exposure metrics can be very simple. A simple categorization of subjects by whether or not one is exposed to microbes in drinking-water or lives in the neighbourhood of a steel mill may be sufficient to test a hypothesis relating to exposure and disease. However, there is often a need for more refined quantification of exposure (e.g. to develop dose–response assessments). When exposure information is based on subjects' recall and historical monitoring data, exposure models are needed to estimate individual and group exposures.

2. *Risk assessments to support risk management decisions*: Exposure assessment is an integral part of risk assessments done in support of risk management decisions. A comprehensive conceptual model or scheme for risk assessment and risk management was published by the United States National Academy of Sciences (NAS) in 1983 (NRC, 1983). The NAS Paradigm succeeded in setting a widely agreed framework for risk assessment / risk management, and it has had broad applications to environmental agents ranging from carcinogenic compounds to non-carcinogens, mixtures, radiation, microbes and other environmental agents. The EC Directive 93/67/EEC "lays down the principles for assessment of risks to man and the environment of chemicals (or substances notified in accordance with Council Directive 67/548/EEC)." According to the NAS Paradigm and the EC Directive 93/67/EEC, formal risk assessment is divided into four activities: hazard identification, dose/concentration–response/effect assessment, exposure assessment and risk characterization. In some assessments, the most exposed individual is targeted, and in other cases, it is a sensitive subgroup or the whole population. Distributions of exposure across the population are often needed. Therefore, exposure models are used widely in risk assessments to support risk management decisions. For example, when alternative future risk management approaches are being compared, exposure modelling is the only way to quantitatively estimate future exposures to support these important comparisons. The exposure models used for these comparisons must include as inputs those parameters that the policies intend to change (e.g. automobile exhausts) as well as those parameters that are expected to change as a consequence of the regulation (e.g. transportation patterns).

3. *Assessment of the efficacy of environmental risk management policies*: The efficacy of risk management policies is receiving increased attention. Governments are attempting to evaluate the public health achievements of the implemented policies against risk reduction goals. Measurement of the achieved mortality and morbidity reduction due to implementation of risk reduction policy is, however, usually impossible (with notable exceptions — e.g. Clancy et al., 2002). Implementation of regulations takes years, and other simultaneous changes in diseases, treatments, demography and other environmental

parameters will inevitably, and in many unknown ways, also change population mortality and morbidity. Regulatory targets are usually set based on reduced emissions, reduced concentrations (e.g. in air or water) or reduced exposure rather than reduction of disease, because these can be planned, modelled, managed, measured and verified independently from other developments in society. Exposure models can play an important part in assessing these changes.

2. ASPECTS OF EXPOSURE MODELLING

This section discusses some properties of models in general and brings up issues that are specific to exposure models. The topics discussed include different ways of classifying models, limitations of what can be modelled, how and to what extent models can be validated and what features of exposure models define how the models can be applied.

Exposure models can be developed to estimate exposures and doses of individuals, defined population groups or entire populations. Exposure may be estimated as a continuous variable or integrated over time ranging from minutes to a lifetime. The modelled outputs may include mean or median values, distribution parameters (standard deviations, quartiles, ranges) or complete probability density distributions. Consequently, exposure models vary widely in complexity, approach, inputs and outputs.

Having a good quality assurance (QA) plan is important for all exposure modelling projects. A United States Environmental Protection Agency (USEPA) guidance document (USEPA, 2002a) provides information about how to document QA planning for modelling. In particular, a QA project plan documents all the criteria and assumptions in one place for convenient review and referral. A QA plan can also be used to guide project personnel through the model development and application processes. It ensures that models consistent with the established objectives and project-specific requirements are selected correctly and applied properly (see section 2.5).

2.1 Conceptual models

An exposure model is a computational framework designed to reflect real-world human exposure scenarios and processes. A conceptual model is often illustrated by a block diagram (see Figure 1), and it defines the physical, chemical and behavioural information and exposure algorithms by which the model mimics a realistic exposure scenario. The elements of an exposure model include input data on product use, source strengths, environmental concentrations, exposure factors and quantitative relationships between measured or estimated exposure-related values and various measures of microenvironmental concentrations or personal exposures. An exposure model is usually based on a known or anticipated flow of events (e.g. cooking a meal on a gas stove) relevant to the exposure scenario of concern. The implementation of an exposure model should reflect the underlying conceptual model. Unfortunately, environmental exposures are often affected by many factors that are difficult to describe quantitatively, and compromises and simplifications are often necessary. Results from the implemented model may not always be reliable, even when the conceptual model behind the implementation is valid (as in the case of poor input data). Thus, proper evaluation of models is vital to ascertain their accuracy and reliability for their intended use.

2.2 Computational elements of a model

Implemented exposure models are quantitative constructs that estimate the relationships between measurable events. They are entered into the model as input variables. These inputs causally lead to other events, which are the outputs or result variables of the model. The

relationships between the inputs and outputs are described in the model using algorithms, equations and intermediate variables, as depicted in Figure 1.

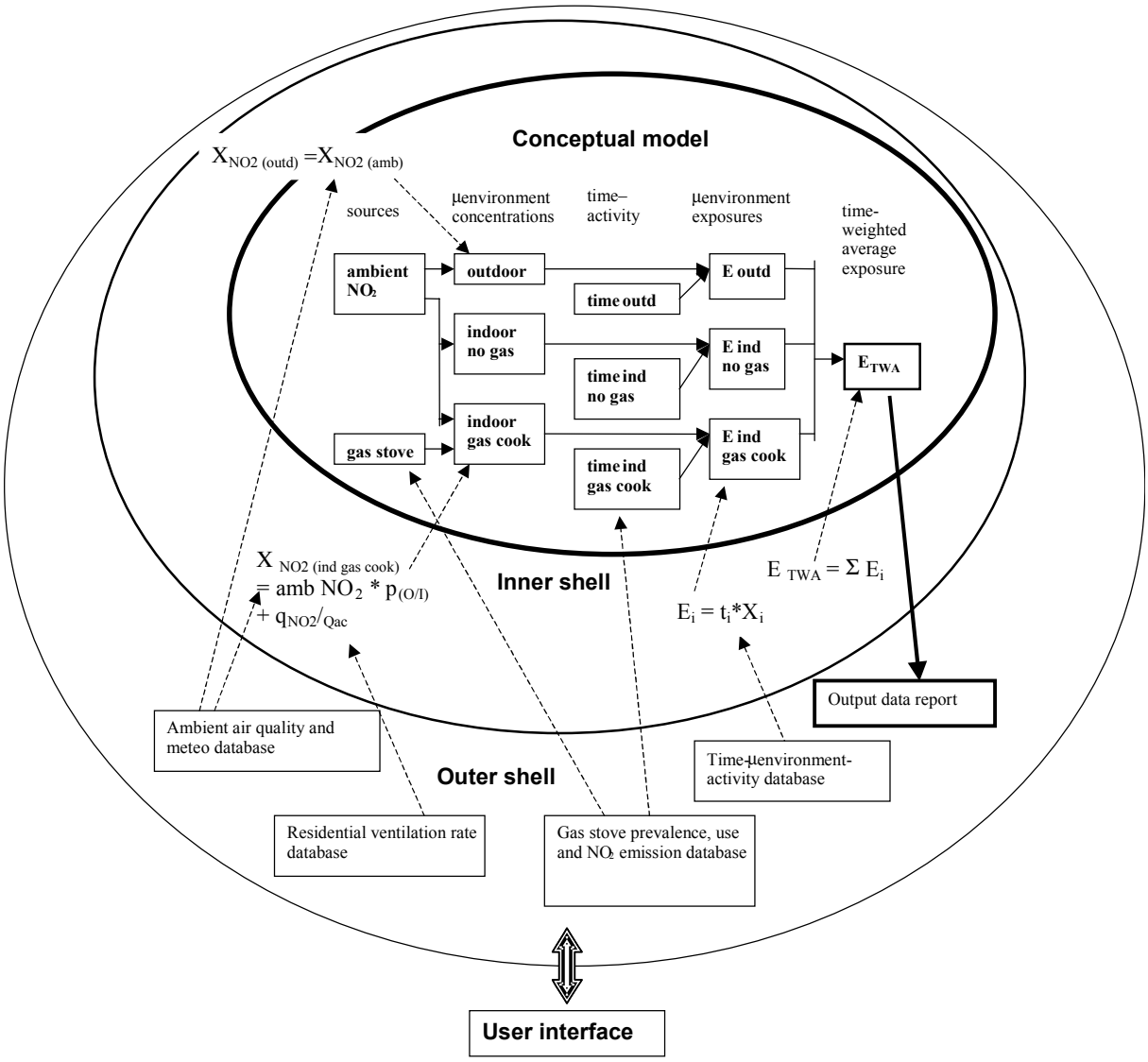

Figure 1. A simple exposure model (nitrogen dioxide exposure from ambient air and a gas stove), shown as a concentric shell structure. The **core** contains the conceptual model, the **inner shell** the used equations, program algorithms and intermediate variables, and the **outer shell** the input and output variables. Only examples of the inner and outer shell contents are shown. Abbreviations used: NO2 = nitrogen dioxide; outd = outdoors; amb = ambient; ind = indoors; μenvironment = microenvironment; TWA = time-weighted average; E = exposure; meteo = meteorological; O/I = outdoors/indoors; X = concentration; t = time; p = penetration; q = emission rate; Qac = ventilation rate.

Figure 1 presents, as an example, an extremely simple, yet realistic, nitrogen dioxide exposure modelling toolbox with only two sources of exposure — *ambient air* (for which there are many nitrogen dioxide sources) and *gas stove* — and three exposure (micro)environments —

outdoors, *indoors without gas cooking* and *indoors with gas cooking*. Often such toolboxes are called models, although they usually consist of many interlinked models. The toolbox is organized into three concentric shells. The core consists of the conceptual model, which is a logical construct describing the modelled exposure setting and defines the model components and their relations. The core is surrounded by an inner shell, which contains the equations and algorithms that are used by the conceptual model components and that can be updated one by one without altering the conceptual model. The inner shell is further surrounded by an outer shell, which contains default values, internal databases or automatic links to external databases that are used by the model, which can often be bypassed or changed by the model user or which are completely external to the modelling toolbox. Finally, a user interface enables communication between the modelling toolbox and the user.

If the events in the target system do not connect to each other logically and/or statistically, there is nothing to be modelled. Figure 2 shows different relationships between correlating variables. In case 1, there is a correlation between the two events, but the cause of the correlation is not known. In case 2, there is a cause–effect relationship. In case 3, both effects are caused by the same known cause and thus may be correlated. Models based on causal relationships (case 2) are generally more reliable than models based only on statistical associations that cannot be causally linked to each other (case 1). Statistical correlation can result from a cause affecting both of the correlating events, which, however, are independent of each other (case 3).

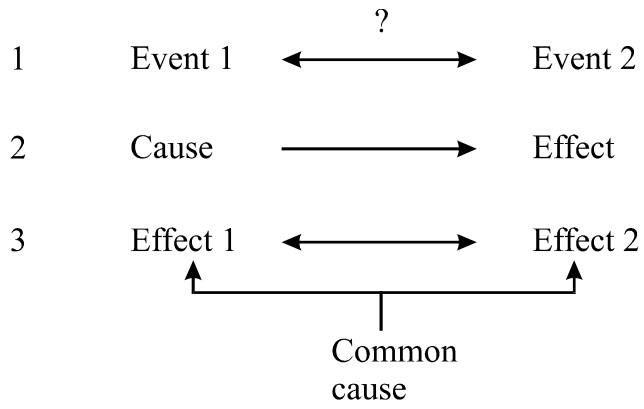

Figure 2. Different relationships between two variables (events).

Models are best suited to study how the changes in the input variables are reflected in the outputs — i.e. in sensitivity analyses. A model can be linked with other models or combined with general knowledge about how prior events are reflected in the model inputs and how the model outputs affect subsequent events. For example, an air concentration input to a model that estimates the amount of pollutant inhaled may itself be modelled using a dispersion model. An intake dose output may be used as input to a toxicokinetic model that estimates the dose to a target organ. This is shown in Figure 3. However, no model can be used to assess the effect of variables unrelated to either model inputs or model outputs. Thus, listing of the model input and output variables defines the main application domain of a model.

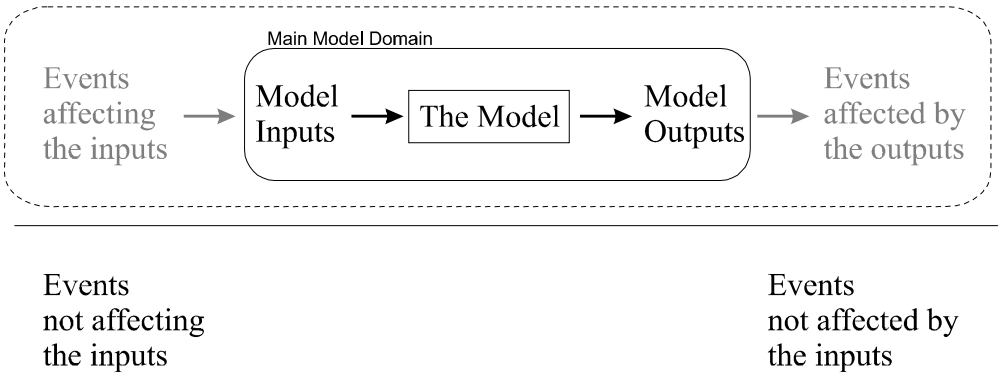

Figure 3. Relationships between input and output variables.

2.3 Approaches to exposure modelling

There are many different ways to classify models. A consensus appears to be developing around the following classification scheme, which has been adopted in this paper: 1) mechanistic or empirical; and 2) deterministic or stochastic (probabilistic) (Table 1). However, alternative classifications may be considered as well.

Table 1: Model categories.

	Mechanistic	***Empirical***
Deterministic	Mathematical constructs of physical/chemical processes that predict fixed outputs for a fixed set of inputs.	Statistical models based on measured input and output values (e.g. regression models that relate air concentrations and blood levels of a chemical or ambient pollutant concentrations with personal exposures).
Stochastic	Mathematical constructs of physical/chemical processes that predict the range and probability density distribution of an exposure model outcome (e.g. predicted distribution of personal exposures within a study population).	Regression-based models, where model variables and coefficients are represented by probability distributions, representing variability and/or uncertainty in the model inputs and parameters.

2.3.1 Mechanistic versus empirical models

The mechanistic/physical model simulates the real behaviour of an agent in the environment and in target organisms as it is transported and undergoes physical and chemical transformations. The empirical model predicts concentrations and exposures based on their statistical

associations with concentrations in the relevant media and other independent variables that are observed in measurement studies.

A mechanistic model uses process, physicochemical characteristics and mass relationships based on balance principles to predict exposures. Such a model is a mathematical construct, which attempts to mimic the physical and chemical reality relevant for the exposure of interest. A mechanistic model normally produces single point estimates of outputs by using single point values for input variables, but it can also produce distributions of output variables by sampling from distributions of input variables (i.e. the probabilistic approach).

Mechanistic exposure models are built on laws of physics and chemistry and data on behaviours and factors influencing exposures — i.e. real-world exposure phenomena that are represented by equations. Results can be calculated even when there are no measurements of the output variables. Thus, they can be applied in situations where no measured exposure data are available or where such measurements are even impossible, as in the assessment of exposures in the past and predicting exposures for future scenarios.

An empirical model is a numerical representation of the relationship between input and output variables based on historic measurements. An example of such a model is a regression between ambient air quality and personal exposure. In its simplest linear form, the empirical model contains a constant term β_0 and a coefficient term β_1. More complex multiple regression models can include the concentrations in many microenvironments and dummy variables for yes/no–type parameters, such as smoking, work on a dairy farm, connection to a municipal water supply, ethnic diet, etc. The terms of the empirical model are specific to the data set from which they have been calculated, and there are no grounds other than expert opinion or experimental confirmation with which to assess if they can be used to calculate exposures in some other system (location/population), or even in the same system at another time.

Empirical models do not require or imply any causal relationships between the model variables. While a mechanistic model would need lengthy algorithms and calculations to assess how time spent in traffic affects exposures to a traffic-originating pollutant, such a relationship, given the required data set, can be easily described by an empirical model using statistical inferences. While an empirical model often contains no construct reflecting the physical/chemical phenomena that cause the exposures, it implicitly reflects the interdependencies within the measured dependent and independent variables, regardless of whether they are known or considered by the modeller.

A weakness of empirical models is that they require both input and output variables to be known in a model development system before the model can be built.

The best area of application of empirical models is in descriptive data analysis. Statistical methods can be used to explore and identify correlating phenomena. Further studies and conceptual methods can then be used to reveal the true causal mechanisms behind the correlations. Then, when the causal mechanisms are known, process equations can be written and mechanistic models developed to describe these relationships.

2.3.2 Deterministic versus stochastic (probabilistic) models

Both mechanistic and empirical models can be classified as deterministic or stochastic (probabilistic).

A deterministic model is one in which the variables are given fixed values so that the system is at any time entirely defined by the initial/boundary conditions chosen. A given set of input variables produces a fixed output.

A stochastic (probabilistic) model is one that takes into consideration the presence of some randomness in one or more of its input parameters or variables (Swinton, 1999). It predicts the probabilities of occurrences of exposures in a population. For some simple stochastic models, outputs can be calculated analytically. For example, an exposure that is the product of lognormally distributed variables can be described exactly by a formula. A simple model that estimates intake of an airborne agent as the product of air concentration, exposure duration and inhalation rate could be such a model. Most exposure models are too complex to be solved analytically, and approaches such as Monte Carlo simulations are used to predict output distributions. Random model input variables are represented as probability density distributions from which values are selected randomly and substituted into the equations of the model to produce an output. This process is repeated, usually thousands of times, to simulate and predict a probability density function for the modelled event in a target system. Where possible, correlations in input variables must be considered. A deterministic model represents a single repetition of a stochastic model or an average of many repetitions.

Typically, stochastic models are built on a mechanistic framework, although in principle empirical models can also be stochastic. For example, a regression-based model that relates outdoor and indoor pollutant concentrations to personal exposures could be implemented stochastically by using probability density functions for model variables and normal distributions (i.e. based on mean and standard error of the estimated regression coefficients) for regression coefficients. In contrast to deterministic models, which assess the exposure to a single individual, such as the maximally exposed individual, stochastic models usually deal with the variability in exposure in a population. Individuals and events are combined into similar groups, and statistically parameterized or actual measured distributions are used to describe the input variables for each group. The output is a distribution of exposures for each group. Statistics of the distribution, such as the median, mean and 95th-percentile exposure, may be reported. Yet, especially at the high end of the distribution, where the interest is often focused, caution has to be observed in interpretation: predicted values need to be compared with actual high-end observations and, when available, with logical limits (e.g. exhaust gas concentration in air cannot exceed concentration in tailpipe). However, it is also important to recognize that measured values could be both variable (spatially and temporally) and uncertain.

Rather simple stochastic models can be powerful and accurate population exposure assessment tools if the input variables (e.g. time spent in microenvironments/activities, intake rates and exposure concentrations) are independent of each other and if the sequences of the exposure events are irrelevant to the exposure. If these conditions are violated, the models either

become more complex or may produce erroneous output (exposure or dose) distributions. More advanced probabilistic modelling techniques can also deal with intercorrelated input variables.

2.3.3 Hybrid models

Based on the definitions given above, any model, no matter how complex, can be used in either a deterministic or stochastic modelling exercise. If one or more input variables in the model fluctuate randomly within defined probability density distributions, the output will be a probability density function, and the model is stochastic by definition.

Complex models often combine aspects of empirical and mechanistic models. A complex concentration model will generally be mechanistic, but it may use empirical submodels to assign values to some of the input variables. Thus, many models are hybrids composed of empirical and mechanistic submodels.

2.4 Criteria for selecting a model

Ryan (1991) listed the following criteria affecting the selection of a model and stated that they are often in direct conflict with each other:

- mathematical simplicity
- computational simplicity
- interpretability
- consistency (the ability to use a single model for many cases)
- accuracy in prediction.

To this list we add:

- accessibility of input variables and data.

Mathematical and *computational simplicity* naturally depend on the complexity of the phenomena to be modelled. The full extent of a complex phenomenon cannot be modelled simply, unless for only limited applications. The relevance of computational simplicity, however, decreases as the power of personal computers increases. A far more important aspect of model simplicity is the requirement that the user be able to understand the model. During the past few decades, as computers have become faster and programming tools more efficient, models, including exposure models, with enormous complexity have been developed. However, it is advisable that the models be no more complex than is necessary for the sake of parsimony.

The third criterion of Ryan (1991), *interpretability*, may be a function of the complexity of the model. The model structure should reflect our understanding of the structure and workings of the target system, and it should be transparent — i.e. its assumptions and limitations should be easily seen. If the model is complete in the sense that it includes, or models, the relevant aspects of the behaviour of the target system, then it fulfils the fourth

requirement, *consistency*. Such a model can be used to answer quite different questions concerning the target system.

Accuracy in model prediction, the fifth requirement, depends on the model's construct validity (core and inner shell), but also on the validity of the model scenario, default values and the often internal (in the modelling toolbox) databases, from which many of the model input values are often drawn. Failures in each of them can alone invalidate the modelled events.

Construct validity means that the model is realistic, is logical and incorporates all relevant components needed to model the event of interest (core), that the equations used are physically and chemically correct and that the program algorithms realize these equations (inner shell).

In a very complex model, where many different submodels are put together to model a chain or network of complex phenomena, the modelling system becomes a world of its own, and it may become virtually impossible to conceptually validate the whole model. One can (should), however, still validate the constructs of its modules and submodels.

As for the validation of the outer shell model components, one could describe it instead as model evaluation (see section 2.6).

Our extra criterion, *accessibility of input variables and data*, is being increasingly met by reference materials such as the USEPA's *Exposure Factors Handbook* (USEPA, 1997), the American Industrial Health Council's *Exposure Factors Sourcebook* (AIHC, 2004), the USEPA's *Child-Specific Exposure Factors Handbook* (USEPA, 2002b) and the USEPA's Consolidated Human Activity Database (CHAD) (USEPA, 2003b).

In Europe, the *ECETOC Exposure Factors Sourcebook for European Populations, with Focus on UK Data* (Zaleski & Gephart, 2000), is the first broad compilation of European exposure factors. At a national level, for a long time, the only compilation of available exposure factors had been done in Germany (BAGS & IMDM, 1995). In 2003, the French database CIBLEX was published (IRSN & ADEME, 2003). Neither of these national data sources contains many distributional data to support probabilistic modelling.

The European Exposure Factors (ExpoFacts) database (since 2004) is a new approach for exposure factor data availability. It is a continuously updated Internet-based interactive free access database with data from 30 European countries and links to dozens of original data sources (CEFIC-LRI, 2005).

2.5 Quality assurance planning for modelling

A USEPA guidance document (USEPA, 2002a) provides information about how to document QA planning for modelling (e.g. model development, model application, as well as large projects with a modelling component). Planning for QA of modelling projects is similar to

planning for collection of exposure measurements in a field study. The planning process and the development of a QA plan incorporate the following elements:

- a systematic planning process, including identification of assessments and related performance criteria
- peer-reviewed theory and equations
- a carefully designed life cycle development process that minimizes errors
- documentation of any changes from the original plan
- clear documentation of assumptions, theory and parameterization that is sufficiently detailed that others can fully understand the model output
- input data and parameters that are accurate and appropriate for the problem
- output data that can be used to help inform decision-making.

A good QA plan is important to a modelling project in various ways. In particular, a QA project plan documents all the criteria and assumptions in one place for convenient review and referral. A QA plan can also be used to guide project personnel through the model development and application processes. It ensures that the models are selected correctly and applied properly, consistent with the established objectives and project-specific requirements.

The guidance document proposes a graded approach to a model QA project plan. In applying this approach, two aspects are important for defining the level of QA effort that a modelling project needs: intended use of the model, and the project scope and magnitude.

The intended use of the model is an important factor in the determination of the level of QA needed, because it incorporates the potential consequences or impacts that might occur due to quality issues. Typically, higher standards would be set for projects that involve potentially significant impacts, such as development of new laws and regulations. More modest levels of defensibility and rigour would be acceptable for data used for technology assessment or "proof of principle," where no litigation or regulatory action is expected (USEPA, 2002a). Even lower levels of rigour in QA may be applicable to initial or exploratory research. Nevertheless, even in this case, the modelling work has to be reviewed carefully and replicated prior to publication.

2.6 Model evaluation

Exposure modelling, like any modelling of complex physical reality, has two types of built-in error. The first is practical, based on possible errors in the selection of the model (model uncertainty) or random errors and biases in input values (data uncertainty). Such errors can be corrected for by applying more appropriate model constructs and/or better data. The second type of error is fundamental. Full validation of quantitative models in natural systems — including the relationship between a set of input parameters and exposure — is (in principle) impossible, because natural systems are never closed and model results are always non-unique. A perfect fit between the model results and the measured data does not validate the conceptual model or model algorithms, because more than one model may be able to achieve this (Oreskes et al., 1994).

Model evaluation can be seen as a three-step process:

1. The conceptual model must be validated. This is what Leijnse & Hassanizaded (1994) call "weak validation." The (causal) relationships between the model input events and the output events must be real, and the nature, or shape, of these relationships must be known — at least approximately.

2. The model implementation must follow the conceptual model. The definitions of input and output variables must effectively describe the events of the conceptual model, and the algorithms and equations must sufficiently follow the known (causal) relationships of these events.

3. Assessing the applicability of the model to a set of specific problems is possibly the most difficult step. This includes evaluating how well the input values really describe the target system. Usually the input values have been measured and contain random or systematic measurement errors. The measured input data range is a combination of data uncertainty and true inherent variability, and in some new applications it is essential to be able to differentiate between the two (e.g. when one or the other dominates the distribution). Sometimes other models, questionnaire data or expert opinions are used in place of measurements to assign values to input variables. Each of these inputs may or may not accurately describe the characteristics of the target system. Thus, even when the model is conceptually valid and carefully implemented, the model outputs may not agree with the system outputs.

The third step — called "strong validation" by Leijnse & Hassanizaded (1994) — is often thought to validate the whole model. That is, it is thought that if model outputs can be demonstrated to closely relate to outputs of a given system, the model is valid in all aspects. This view ignores the fact that even a conceptually bad model may by chance agree with a limited set of test data. In fact, while it is possible to prove that a model is not valid, it is never possible to prove that a model is universally valid. Validation of an exposure model, therefore, is limited to a demonstration that in a specific application, the model output agrees with measured data. In the absence of satisfactory validation, the most appropriate use of exposure models is for sensitivity analysis — that is, assessment of the impact of varying one, a few or all of the input parameters.

The most useful model validation attempts concentrate on the conceptual part of the model and on ensuring that the model implementation — the variables, equations and algorithms — follow the conceptual model. Application of such a validated model to a specific system or question must then be resolved on a case-by-case basis. In the case of a similar system or reliance on another data set, a model should not be extrapolated without a validation phase.

2.7 Conceptual domains in exposure modelling

Many factors affect exposure levels, including sources of environmental agents, physical and chemical processes that the agents undergo in the environment and human mobility and activity patterns that bring individuals into contact with the agents. The exposure scenario

defines the target individual or population, the time period of concern, the geographic or microenvironmental location and the expected concentrations or sources in these locations. The target populations, locations and time periods or resolutions to which the model applies define the domains of the model. When characterizing an exposure model, the model features, assumptions and limitations in each of these domains should be discussed.

The complete exposure data of a given population would contain the full lifelong time series of exposure levels via all pathways and for all possibly harmful agents for each individual of the population. Needless to say, such data are unachievable, unmanageable and unnecessary for any practical need. The exposure data that are genuinely needed are specific to each given purpose; in general, the less detailed the needed data, the cheaper they are to obtain and the easier they will be to comprehend and apply. Assuming that the agent(s), pathway(s) and effect(s) of interest have been selected, a systematic way to assess the genuine data needs is to analyse, one by one, the necessary level of data aggregation along the dimensions of group size, location, time and statistical detail, ranging from simple population mean to full frequency distribution.

Aiming at the maximum acceptable level of data aggregation that retains sufficient detail for the objectives of the particular study not only will simplify the model and reduce data needs, but will usually also improve the accuracy of the modelled results. Alternatively, one can calculate aggregated exposures from refined data, but not vice versa. As an example, the bioaccumulation and elimination rates of a chemical in the target organ determine the maximum useful exposure integration time. Above it, biologically relevant target organ dose levels cannot be determined. Similarly, exposure of a given individual cannot be derived from group- or population-averaged data.

The target population, location and time domains are described briefly below, and examples of how each of these domains is defined in exposure modelling are given in Box 1.

2.7.1 Target population domain

Every exposure assessment, or any work using exposure assessments as inputs, needs to define either target individuals or a target population.

Individual exposures

The exposure model output can be attributed to a real or a hypothetical individual. Estimates of individual exposure are needed in certain epidemiological studies in which the exposures of cases and their matched controls are compared. Individual exposure data may also be needed in the court of law, when it must be proved that certain consequences have or have not in fact been caused by certain exposures.

Regulatory agencies have created hypothetical individuals, such as the “maximally exposed person” or the “worst-case exposure.” The exposure of this hypothetical individual is modelled assuming that each input variable takes the value that will result in the highest exposure. Such estimates have been used to estimate upper-bound exposure levels. These

upper-bound estimates serve to eliminate exposure scenarios as causes of concern when the upper-bound exposure estimates are less than exposures of toxicological concern. However, such exposure estimates may be orders of magnitude higher than the most probable exposures, and they are therefore not useful for any other purpose, least of all for risk ranking or comparison.

Another kind of hypothetical individual is identified using probabilistic simulation models. In these models, input values are randomly drawn from frequency distributions and used as input to the algorithms and equations of the model. This process is repeated, and typically thousands of exposure values are randomly generated to simulate the target population and to create population-level exposure distributions. Hypothetical — or at least unidentified — individuals, such as the individual with the median exposure or the individual exposed at the upper percentile (e.g. 90th, 95th or 99th) of the distribution, can be reported.

Box 1: Examples of Domain Definitions in Exposure Modelling

- *Target population domain*: If the aggregated health statistics of all diesel locomotive operators and office workers are being compared to assess the carcinogenicity of diesel soot, modelling the exposure of each individual separately would produce unnecessary detail that would not affect the study outcome. On the other hand, more detailed job descriptions could help dose–response assessment.
- *Time domain*: If the cancer risk associated with exposure to benzene in air or with exposure to the highly mutagenic chlorinated disinfection by-product, MX, in drinking-water is studied, only annual average exposure levels are needed, and daily or hourly values contain useless information. Nevertheless, some hourly data could be helpful in identifying the sources of the agents and their contributions to total exposure.
- *Location domain*: If the daily mortality variation in a metropolitan area is being compared with variation in exposure to air pollutants, modelling of geographically detailed exposure data for each 100 m × 100 m grid cell would be wasted, because mortality data are not sufficiently refined for location.

Population exposures

Exposure assessments can be conducted for a population or a segment of a population. Such groups may range from a 10-person panel in an epidemiological study to large cohorts living in cities, regions and even countries. The target population must be clearly defined. It is not sufficient that the definition is made implicitly or hidden in a work plan. Typical target populations are groups that may have high exposures (high end of the distribution) and groups defined by gender, age (children, elderly), health status (asthmatics, individuals with cardiovascular disease), geographical location, socioeconomic conditions, occupation, diet, etc.

Whenever the exposures of different subpopulations are expected to be different from each other, the exposure assessment probably needs to treat these subpopulations separately.

2.7.2 Location domain

The location domain defines not only a geographical point in space, but also conditions for exposure concentrations and exposure factors such as demographics, activities and diets of the exposed population. Exposure can be modelled for many different types of location domains, such as:

- geographical regions of different scales
- hot spots, e.g. hazardous waste sites
- residences
- workplaces
- watersheds and stream segments.

The location domain of a model can be specified with varying degrees of refinement. A location domain may be as broad as an entire country or region. For example, a broad location domain is often used for estimating concentrations of pesticides in food items in commerce. Also, food consumption itself can be seen as a regional aspect due to regional food consumption behaviour. A location domain may also be quite specific. For example, data may be available for home-grown vegetables at individual residences surrounding a hazardous waste site, and an exposure assessment of each resident may be conducted.

Real-life exposures happen to individuals who usually divide their time between many different indoor and outdoor locations and spend on average 5–10% of their time commuting between them. Models of exposure to ambient air or drinking-water often specify a whole city as a location. Exposure at different points within the city is assumed to be similar and different from exposure in other cities.

Outdoor air concentrations (see section 3.1.1) are often modelled across a defined geographical area. For example, the expected ambient air concentrations produced by incinerators in a region can be estimated using dispersion models and stored as a grid laid over the studied area. Geographical information systems (GIS) have been developed to handle this kind of data. A GIS or proprietary modelling software can be used to combine population location information with the geographical concentration distributions to estimate potential exposures.

Concentrations in soil at hazardous waste sites are sometimes modelled across a defined area using kriging, which is a spatial prediction technique that allows the modeller to interpolate values for areas between measured concentrations. This technique produces spatial interpolations, whose results can be displayed as contour plots of equal concentration that are useful in GIS analysis.

Indoor air concentrations are often modelled using the concept of microenvironments. Microenvironments are defined as well defined surroundings such as the home, office, automobile, kitchen, store, etc. that can be treated as homogeneous (and/or well characterized) in the

concentrations of a chemical or other agent (USEPA, 1992b; IPCS, 2004). Some studies define microenvironments as areas with the same concentration, whereas others state that all locations with similar exposure patterns belong to the same microenvironment.

Based on the amount of time spent in a location, home is the most important microenvironment — approximately two thirds of the population time is spent at home. The workplace is the second most important microenvironment, representing one fifth of time activity. The other microenvironments are less important in terms of time spent; however, where they contain high concentrations of environmental agents, their contribution to exposures and especially short peak exposures can be high. Indoor microenvironments therefore usually strongly modify exposures and also have their own exposure sources that are independent of the outdoor environment and often dominate the exposures of the occupants. Sources of agents in indoor air include consumer products, building materials, drinking-water, heating and cooling equipment, cooking, etc.

2.7.3 Time domain

All exposure data are related to some point or range in time. Emissions, dispersion parameters, populations and environmental factors all change in time, and thus exposures will also change. The relationship of exposure data to the time dimension is often implicit. Limitations of data applicability are often not clearly stated or even known. For example, the EXPOLIS study measured microenvironmental and personal air concentrations in six European cities in 1996–1998 (Jantunen et al., 1998). The EXPOLIS measurements probably also describe the exposures in the six European cities for some years before and after the measurements. Expert opinion can be given as to how far in time and for which purpose the collected exposure data can be considered useful, and the limitations might be specific to a city or to a subpopulation within a specific city.

Over the years, changes in pollution sources, dispersion conditions in human-made environments and population behaviour affect at least some of the exposure patterns and thus reduce the applicability of exposure measurements collected in the past. If the changes are known and their effects on exposure concentrations are understood (e.g. impact of reduced outdoor pollution levels on indoor exposure concentrations), they can be incorporated into the model to expand its applicability in time.

Air concentration data are often recorded continuously, providing minute-by-minute levels. Alternatively, air may be sampled over a set time period, such as a day or a week, providing one average concentration. Averaging or integration time defines the shortest exposure duration that can be derived from the exposure data and used, for example, as input to biological dose–response models. Short-term peak exposure values cannot be assessed from long-term average concentrations, but it is always possible to derive long-term averages from a continuous concentration record. In Figure 4, the 1-min values are instantaneous samples, and the 1-h and 24-h values are averages calculated from the 1-min values. This figure demonstrates the decrease of the variation with the increasing averaging time.

Figure 4. Personal carbon monoxide exposure levels with 1-min sampling (unpublished EXPOLIS data).

For many exposure concentrations and factors that are expensive and difficult to measure, measurement data are available for only a day or a few days per year. Exposure analysts must often use such data to estimate exposures for longer periods of time, such as average annual exposures. A distribution of daily measurements is more variable than a distribution of average annual measurements in the same population. The issue arises of how much uncertainty in estimates of, for example, high-end exposures is introduced when using short-term measurements to estimate longer-term exposures.

Exposure data can be representative of a specific time of year (e.g. summer), day of the week (e.g. weekdays) or time of day. Seasonal, daily and hourly variations affect factors such as environmental concentrations, diet and activity patterns. This can be illustrated using food as an example. Time is an important factor in measurements of contaminants (pesticides, mycotoxins) in foods and in modelling population intakes of contaminants from food. Mycotoxin levels vary from year to year in some crops, depending on weather conditions, and pesticide levels change with usage patterns. Dietary intakes of various foods change with age (e.g. infants versus adolescents versus adults), and population dietary patterns (food preferences) change over time. Generally, exposures to contaminants in foods are estimated over long time intervals (year, lifetime), although estimates for much shorter intervals may be required when acute effects (food poisoning) are of concern. Modelling a population distribution for intake of a food contaminant over time is complicated by the lack of data on long-term dietary patterns for individuals; typically, data are available only for 1 or 2 days per year for an individual from population-based surveys — e.g. National Health and Nutrition Examination Survey, or NHANES, in the USA or European Food Consumption Survey Methods, or EFCOSUM, for review in Europe (EFCOSUM, 2002).

2.8 Linking exposure modelling to risk assessment

For some agents, only fairly long-term integrated exposures are of interest, and the only interest in the short-term peak exposures is how much they contribute to long-term exposure. At the other extreme are pollutants that at low levels are ubiquitous (e.g. carbon monoxide and nitrous oxide), but for which short high peak exposures may result in acute intoxication and even death. Still other environmental agents, such as allergens, are of primary concern only to the hypersensitive fraction of the population; for them, even quite short and low-level exposures may have serious acute consequences.

As shown in Figure 5, the risk assessment process can be represented as a continuum from source through exposure and dose to effects. An important aspect of the exposure → dose → health effects chain for the purposes of exposure modelling or monitoring is selecting the appropriate averaging time for the effect of concern. The averaging time should be selected based on the biological mechanisms that lead from exposure to the health effect, taking into account target organ dose via intake or absorption, internal dose, metabolism and the removal and accumulation mechanisms in the target organ. The exposure averaging time should be defined by considering the time scales involved in the processes of the dose–response component of the system (Georgopoulos & Lioy, 1994). This averaging time acts as a low-pass filter, removing all higher-frequency concentration information, thus reducing the data. If the averaging time is selected correctly, no health-related information is lost, yet no unnecessarily detailed (and therefore expensive) data are generated.

The actual concentration of toxicant (or its metabolites) in the target organ determines the potential effects. For example, in the presence of a fast elimination rate, a prolonged exposure to low concentrations may not result in a significant accumulated target organ dose. Yet a short exposure to high concentrations, although resulting in a much lower integrated exposure, may lead to high target organ dose and significant biological effect (Georgopoulos & Lioy, 1994). Alternatively, elimination of toxicants, such as some heavy metals, from the target organ may be very slow. Even when the toxicant is rapidly eliminated, its harmful effects may accumulate — e.g. as DNA damage. Thus, the health effects for some toxicants, including radon, asbestos and other carcinogens, as well as most heavy metals, such as mercury, cadmium and lead, can be estimated only from long-term integrated exposures. For other exposures, such as exposure to carbon monoxide and ozone, much shorter averaging times are relevant for assessing the probability of health effects. Finally, it appears that for some pollutants, such as particulate matter less than or equal to 2.5 μm in diameter ($PM_{2.5}$), which is a complex and variable mixture, both long-term and short-term exposures are relevant for health effects.

Some effects are directly linked to the route of exposure, and for these effects the cumulative systemic dose by multiple routes of exposure may not be relevant. For example, the exposure metric for eye or skin irritation from an air pollutant is related to the concentration of the irritant at the surface of the eye or on the skin, not the cumulative systemic dose (USEPA, 1992a,b). Similarly, for the nasal lesions induced in rats and monkeys by exposure to airborne formaldehyde, the relevant exposure metric appears to be the formaldehyde flux in the nasal passages, which results in the unique pattern of formaldehyde deposition and uptake

for the particular species (Kimbell et al., 2001). The induction of forestomach tumours in rats by oral dosing with ethyl acrylate is a function of the dose rate and concentration of ethyl acrylate reaching the forestomach, whereas exposure to airborne ethyl acrylate leads to nasal lesions; neither effect is related to systemic dose, although mortality from glutathione depletion at very high exposure levels is indeed a function of systemic dose (Frederick et al., 1990, 1992, 2002).

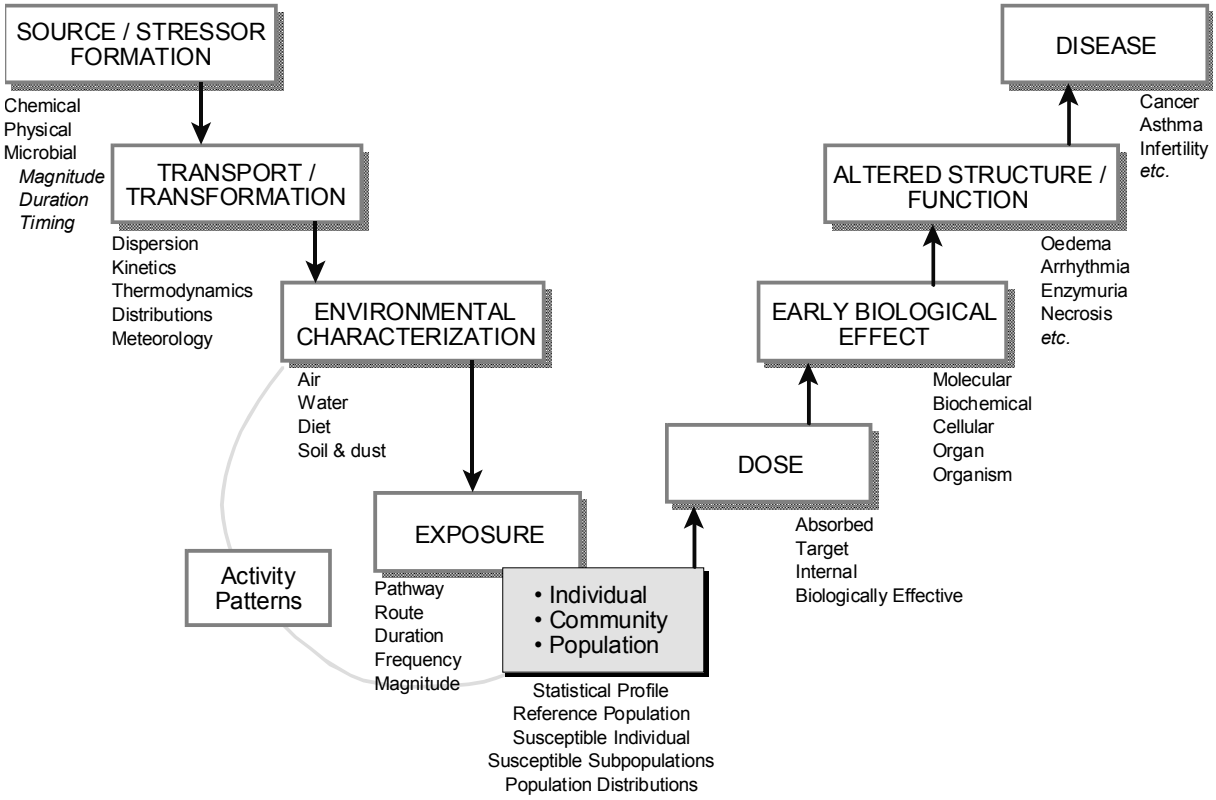

Figure 5. Scientific elements of human health risk assessment (from USEPA, 2003a).

3. CONCENTRATION, EXPOSURE AND DOSE MODELS

Concentration models estimate concentrations of environmental agents in microenvironments and environmental media. Exposure models combine measured or modelled exposure concentrations and information about the target, such as activities, times spent in locations and physiological characteristics, to estimate some measure of exposure or dose. This section summarizes the types of models that are currently used to estimate concentration and exposure. Most exposure models actually estimate some form of dose.

The exposure and concentration models discussed in this section are generally applicable to a wide range of exposure scenarios. Highly specific models have been developed for particular scenarios, such as dermal exposure models for industrial workers wearing protective clothing and multimedia exposure models for individuals exposed to pesticides in residences. Some of these models are presented as examples. The principles underlying the models are generally applicable to any scenario that leads to exposure via the route being discussed.

3.1 Concentration models

The concentrations of environmental agent in the media with which an individual is in contact are key input variables in exposure models. In many applications, measured concentration data are used directly to assess exposure. A typical example is an epidemiological study, where the exposure of a whole urban population is described by a concentration measured at one or a few central monitoring stations or water supply systems. The measured concentration is directly used as a proxy for population exposure. This simple model has worked well in many applications. Some of the most influential epidemiological results have been acquired with such approaches. Using fixed-site concentration measurements as surrogates for exposure concentrations may enable taking some population activities into account, but only very crudely via the selection of the measurement sites. The indoor sources and daily activities are ignored in such an approach and cannot affect the analysis outcomes.

Concentration models are alternatives to measured concentration data. They are used to estimate concentrations of chemical agents in environmental media, such as outdoor and indoor air, drinking-water and food, and on surfaces, such as carpets, furniture, walls and dust and soil particles. Concentration models are useful when direct measurements of exposure concentration are not feasible and for identifying sources and their contributions to exposure. Concentration models include parameters describing the sources, emissions, transport and transformation of the agent in the environment as it moves from the source to the exposure target. Concentration modelling is a complicated field, and a large number of dispersion, transformation, mass balance and other types of models are available for predicting concentrations in exposure media.

This section discusses air, surface (including soil), water and food concentration models. Since pollutants rarely remain entirely in one environmental medium, these models are overlapping. Indoor and outdoor air models, for example, usually account for deposition of pollutants on the surface, while surface water models allow for losses from volatilization to air. Some of the food concentration models combine air, water and other types of models to

estimate concentrations in foods such as home-grown produce and fish caught from contaminated surface water.

3.1.1 Air concentration models

Two general categories of air concentrations are considered in exposure assessment:

- outdoor or ambient concentrations
- indoor or microenvironment concentrations.

Outdoor or ambient air models can be used to assess the effect of different types of pollution emission sources on ambient air quality. They are typically dispersion models. These models were first developed in the 1950s, and many models used today originated in the 1970s. Examples of such models are ISC-ST (Industrial Source Complex, Short Term) and ISC-LT (Industrial Source Complex, Long Term). A large body of literature describes a multitude of such models and their validation results for different applications. One much used approach to estimating inhalation exposures is to assume exposure to ambient air levels for 24 h per day.

In addition to models that predict concentrations from specific sources, models to forecast the air quality for the next few hours up to a few days are also being developed. These models could be useful for persons having asthma or other acute health problems connected to air quality. These sensitive people could, if the expected air quality fluctuations were predicted, plan their daily activities to minimize their symptoms. Mobile communication systems (e.g. text messaging using portable phones) and personalized mass media channels on the Internet could be used to deliver such personal information effectively. Technically, these models are closely related to meteorological forecasting.

A key problem in using modelled or monitored ambient concentration data to estimate exposures is the fact that people in most societies spend most of their time indoors. Indoor environments, being closed, are partly protected from the fluctuations of outdoor air quality. More importantly, for the same reason, they may develop dangerously high concentrations of environmental agents when pollution is created inside. Smoking and some heating, lighting and cooking methods are examples of such indoor pollution sources. Ventilation systems and building structures also absorb air pollutants — from outdoor or indoor origin — and, in the absence of indoor sources, the concentrations of most air pollutants would be lower than outdoor levels. This is especially true for such reactive gaseous pollutants as ozone and nitrous oxide, as well as for coarse and ultrafine particles.

Some air quality managers reason that it is in the jurisdiction of society to control and manage only ambient air quality, and thus there is no need to try to determine total personal exposures. Only the part of exposure originating from ambient air pollution needs to be assessed. On the other hand, many exposure scientists and toxicologists argue that it is important to assess total personal exposure, because it is the total exposure that is responsible for any observed health effects of pollution. From the public health point of view, there is no difference whether the disease has been caused by pollution originating from ambient air or

from emission sources indoors. Wilson et al. (2000) discussed this issue in great detail and suggested an approach to handle it.

Many models have been developed to assess concentrations of agents in indoor air. Most of these models are based on mass balance equations, employing terms to account for air exchange with the outdoors and between rooms, infiltration, sedimentation, chemical reactions and indoor sources. The simplest steady-state indoor air models assume that the indoor environment is a single compartment and that the pollutant is well mixed and constant within the compartment. More advanced models can take partial mixing, multicompartment situations and dynamic source and dilution processes into account.

Indoor air concentration models have high data requirements. The air exchange rates vary from building to building, from room to room and from moment to moment. Whether windows are open or closed can introduce large variation within the same building. Air exchange measurement is not trivial, and it would solve only part of the problem. The sedimentation and chemical reaction rates depend on a variety of factors that cannot be measured in practice. Also, the emission rates of possible indoor sources are not constant, broadly known or easy to measure. Thus, models using mass balance equation variations must normally use many assumptions.

Subsurface groundwater and soil may be sources of indoor air contamination. Vapour intrusion models have been developed that model the transport of volatile chemicals from the air phase of soil and groundwater into the structures above via diffusion. The USEPA's waste programme, for example, recommends a screening-level model, introduced by Johnson & Ettinger (1991), that incorporates convective and diffusive mechanisms for estimating the transport of vapours from the subsurface into structures located directly above the source of the contamination (Environmental Quality Management, Inc., 2004).

Maroni et al. (1995) stated that the field on indoor air modelling has suffered from a lack of categorization and classification. Models that were developed to evaluate single rooms, multiple rooms, indoor sources, entire populations of cities and indoor/outdoor differences have all been called "indoor air models." This has led to confusion as to the applicability of each model for specific situations. This criticism is true for exposure models as well as for concentration models.

3.1.2 Surface contamination models

A surface can be defined as an area on which a chemical can be deposited. There are large surfaces, such as textiles, furniture, walls, plant leaves and fruits, but also very small ones, such as dust and soil particles. Mechanisms by which pollutants contaminate surfaces include deposition, adsorption and deliberate application.

A simple surface deposition model is displayed in Figure 6. Pollutants in the form of particles and adsorbed to particles settle on surfaces from the surrounding environment. These particles can also be released from surfaces when they are disturbed and re-entrained in air. Volatile agents can also be removed from air through interactions that bind them to surface

materials in the process of adsorption. Adsorbed agents can migrate further into the matrix. As conditions in the indoor environment change (e.g. different air concentrations, temperature and relative humidity), the process can be reversed, with compounds migrating to the surface and released back to the air through desorption and evaporation. Surface contamination is also possible from migration of a chemical from the inside of the matrix to the surface. Plasticizers, which are physically bound but not chemically incorporated in the matrix of plastic food wraps, have been shown to migrate from the matrix and enter the food.

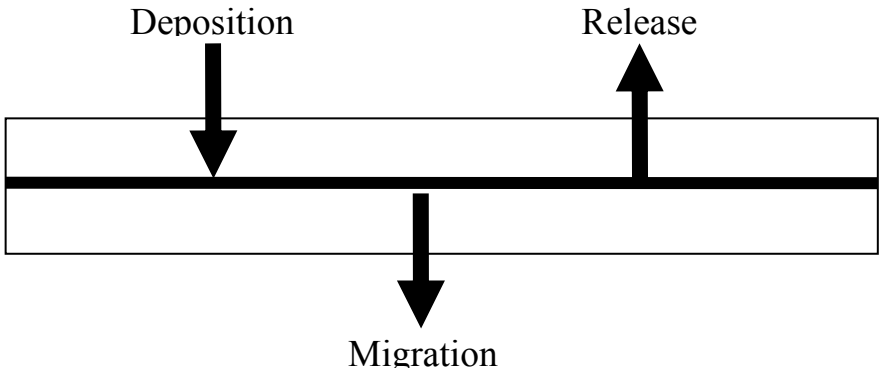

Figure 6. Transport at a surface.

The studies listed in Table 2 illustrate the many varieties of surfaces that can be contaminated. Depending on the nature of the surface, the characterization of the scenario of exposure can differ substantially. Exposure to agents on surfaces occurs by skin contact with the surface. Any type of contaminated surface, from walls, floors and large objects to small particles, can be contacted by the skin, and skin itself is a surface that can be contaminated as well as being the source that contaminates. Inhalation of pollutants adsorbed to particles that are suspended from contaminated surfaces may also occur. Oral exposure also occurs in situations where, for example, contaminated food (e.g. fruits or vegetables) or small particles with agents adsorbed to the surface are ingested. A chemical can also be ingested through contact with contaminated hands, food and other objects, a particular concern for children. Therefore, surface contamination models are often submodels of indoor and ambient air models and multimedia exposure models.

A typical indoor air model to estimate chemical concentrations, for example, consists of one or more compartments representing microenvironments such as rooms and outdoor air. The chemical is introduced to a compartment from one or more sources. Examples of sources include infiltration of the chemical in air from another compartment and release within the compartment from use of a consumer product. The surfaces in the room serve as sinks for the chemical, reservoirs where the chemical collects via adsorption and from which the chemical may be subsequently released back into the air. For the consideration of source/sink (reservoir) models, two different basic model approaches can be defined:

- *Kinetic approach*: The kinetic approach applies kinetic equations to describe the sink behaviour. Sink strength is defined as the adsorption rate of the contaminant. From

measurements, it can be concluded that the sink strength is reciprocally proportional to the vapour pressure of the contaminant (Chang & Guo, 1994). The emission rate from a sink acting as a source also depends on the contaminant vapour pressure. In some models, it is assumed that the sink strength equals the inverse of the source strength (e.g. Dunn, 1987). In general, kinetic approaches are semi-empirical models, the source and sink strengths of which are determined in chamber measurements. A number of general algorithms are applied (Dunn & Tichenor, 1988).

- *Mass transfer approach*: The mass transfer approach considers the adsorption process itself, applying a mechanistic adsorption model (see Axley, 1991). The linear isotherm adsorption model is based on simplified Langmuir adsorption kinetics. For very low concentrations of contaminant, the occupied adsorption sites are a very small fraction of the total adsorption sites. In such a case, the sink will not reach saturation, and the concentration of adsorbed contaminant will be linearly related to the concentration of "free" airborne contaminant (adapted from Axley & Lorenzeti, 1993).

Table 2. Examples of surfaces and objects that have been evaluated for surface contamination.

Surfaces and objects studied	*Compound(s) studied*	*References*
Surgical instruments	Disinfectants, cleaners	Reichl et al. (1995)
Ventilation cabins	Dust, cobalt	Melchior Poulsen et al. (1995)
Hospital surfaces	Pharmaceuticals	Simpson et al. (1988); McDevit et al. (1993)
Fruits and vegetables	Cadmium	Hovmand et al. (1983)
Sewer	Acrylamide	Cummins et al. (1992)
Pigment factory	Cadmium	Tartre (1992)
Ground	Pesticides	Yoshida et al. (1990)
Pollen	Sulfate, nitrate	Noll & Khalili (1988)
Food	Mineral hydrocarbons	Castle et al. (1993)
Paints	Solvents	Clausen et al. (1991)
Food package	Benzene	Varner et al. (1991)

3.1.3 Drinking-water concentration models

Exposure to chemicals in drinking-water occurs via direct ingestion, ingestion of foods prepared with drinking-water, inhalation and dermal contact during activities such as showering. Except for cases where bottled water is used, the exposure concentration is the concentration at the site where the water is removed for use, such as a tap or a well.

Drinking-water is obtained from surface water or groundwater. The raw surface water or groundwater may be consumed directly or after treatment to remove various classes of contaminants. Treatments may include disinfection to remove microbial contaminants, various

types of filtration to remove solids, aeration to remove volatile organic compounds (VOCs) by evaporation and biodegradation and activated carbon treatment to remove organic chemicals. The efficiency of a drinking-water treatment plant in removing a particular agent depends on the types of treatment employed and the physicochemical properties of the agent. Measurements or modelled estimates of the concentration of a substance in raw surface water or groundwater are often used as surrogates for drinking-water concentrations.

Some contaminants, notably disinfectants such as chloroform and disinfection by-products formed during the treatment process, are added to the raw water at the treatment plant. The water may be distributed through a public water system, where contaminants such as metals leach into the water supply from corroded pipes. Models have been developed to predict removal efficiencies of various types of treatment, levels of additives in treated water and fate of chemicals in distribution systems (ILSI, 1999a). These models are useful when dealing with a site-specific assessment where treatment methods are known or an assessment of a specific chemical that might be added to drinking-water during treatment. For most assessments, however, it is difficult to predict whether or how water will be treated and to what extent treatments will remove the environmental agents of interest. The concentration in the raw surface water or groundwater is the most important factor in estimating drinking-water concentrations for risk assessment, and the remainder of this section focuses on models to predict this concentration.

Many surface water and groundwater models have been developed. They are generally mechanistic and involve a mass balance around a defined system, such as an aquifer, a pond, a stream segment or a watershed. These models consider movement of the chemical through and within the system, chemical and biological reactions and partitioning processes (NRC, 1990).

Many water concentration models in widespread use are deterministic, in that a given set of inputs always produces the same outputs. Conceptual models, equations and computer codes for probabilistic models can also be developed for any surface water or groundwater modelling problem, and some models contain a software option for probabilistic modelling. However, the data requirements for probabilistic models limit their use in many cases. Surface water problems are more amenable to probabilistic modelling than groundwater problems, because surface water is more easily observed and has a more extensive database. Government agencies often keep detailed records on daily stream flow and variables (e.g. suspended sediment concentration, biomass concentration, oxygen level, pH and temperature) that can provide spatial and temporal distributions for many key input variables, but not on the drinking-water quality at the faucets within a city.

As discussed in section 2.2, while a particular model applies within a defined system, events outside the system affect the inputs and results. This is particularly true of the complex processes that provide loadings to groundwater and surface water. Sometimes the outside event is relatively simple, such as the release of a contaminant to surface water from a pipe. However, some outside events are very complex. Examples of loadings that may require modelling are leaching of agents applied to or disposed of in an aquifer recharge zone, deposition of airborne contaminants directly on the surface of streams and on surrounding

soil, and urban and agricultural runoff and soil erosion that wash agents into surface waters. Groundwater often empties into surface water, and surface water recharges groundwater. To reduce a complex system to manageable parts, modellers usually focus on either groundwater or surface water, although each type of model can usually accept agent loadings from the other medium.

The rest of this section will focus on models for estimating chemical concentrations in groundwater and surface water that are in widespread use in the exposure assessment community.

Groundwater models

The water-bearing material beneath the earth's surface can be divided into two zones: the saturated zone and the unsaturated zone. Both zones consist of soil and rock interspersed with pores and fractures. In the saturated zone, these spaces are filled with water. The top of the saturated zone, called the water table, varies with factors such as rainfall and snowmelt. The water table may be near or at the surface in low-lying areas or during rainy weather. In desert areas, the water table may be over 100 m deep. The zone between the water table and the surface is the unsaturated zone, where the spaces may contain various amounts of liquid, mainly water, and gas, mainly air.

At specific sites, groundwater models are used to estimate the travel times and concentrations of contaminant plumes from source to drinking-water well or surface water and to assess the impact on water quality of various cleanup options for wastes and spills. They are used to identify vulnerable aquifers for consideration in siting hazardous waste sites, landfills and nuclear waste repositories and to select locations for monitoring wells used to gather data for exposure assessments. They can also be used to assess the impact of use patterns such as pesticide applications on water quality. Site-specific modelling is data intensive and requires site-specific values for input data to achieve even a minimum level of predictive accuracy. Groundwater models can also be used as screening tools to identify and prioritize chemicals for further action based on their potential mobility in groundwater (ILSI, 1999b).

In the typical saturated zone model, the aquifer is assumed to be composed of a relatively homogeneous matrix of solids and pore spaces through which contaminants move in dilute solution with the flow of the water. A mass balance equation describes the water flow in terms of the permeability of the aquifer material, represented by the hydraulic conductivity, and the force of gravity, represented by the hydraulic gradient. Attenuation processes such as sorption to aquifer material, biodegradation and chemical reactions may be included.

Outputs can be presented as concentrations at points on one-, two- or three-dimensional grids describing the groundwater plume at various times after the chemical enters the system. GIS technology can be used to display the groundwater plume at various stages as it spreads and enters drinking-water aquifers, well water and surface water supplies.

In contrast to the saturated zone, the pores of the unsaturated zone are filled with a mixture of water and air. The model for solute transport in the unsaturated zone is similar to that for

saturated flow. Attenuation processes and losses of water and the chemical at the surface through runoff, soil erosion, uptake by plants and evapotranspiration may be included (NRC, 1990). Major outputs can include pore water solute concentration, depth of maximum solute concentration, maximum depth of solute penetration, volatilization losses and runoff (NRC, 1993). The output of the unsaturated zone model can be used as input to a groundwater model with the solute-containing leachate serving as recharge to the aquifer in the saturated zone model.

The saturated and unsaturated zones frequently do not have the homogeneous character assumed by many groundwater models in use today. These zones are often fractured by large pores and discontinuities that may be linked in a tortuous flow pattern. Contaminants may be delivered to unpredictable locations much more rapidly than predicted by the models. In soluble materials, such as limestone, groundwater can hollow out large caves and conduits. In such a system, groundwater flow can resemble surface water stream flow during times of high recharge. Researchers have developed models for flow in fractures. However, application of these models to predict future events at a site requires detailed data on the dimensions, orientations and connections of the fractures, information that is virtually impossible to obtain with current technology.

At waste sites and near spills and leaking storage tanks, non-aqueous-phase liquids (NAPLs) such as petroleum products and solvents may be present in both the saturated and unsaturated zones. NAPLs can be present in the subsurface as volatiles in soil gas, dissolved in water or in mobile and residual organic liquid phases (USEPA, 1994). When they reach the saturated zone, NAPLs with a specific gravity less than that of water spread across the top of the water table. NAPLs denser than water tend to pool in the aquifer when they reach impermeable material. NAPLs migrate preferentially through permeable pathways such as rock and soil fractures that provide little resistance to flow. Subsurface movement is controlled by factors such as density, interfacial tension, viscosity, the properties of the soil and aquifer media, and hydraulic forces (USEPA, 1994). Research models have been developed for NAPLs, but most groundwater models neglect multiphase flow.

Surface water models

Like groundwater models, surface water models are based on the concept of conservation of mass expressed by mass balance equations. The analyst defines a system, such as a watershed or a stream segment, and specifies its boundary conditions and the loadings of the environmental agent entering the system. The system may be divided into compartments, including, for example, the water column and the stream bed, and these compartments may be further subdivided. Chemical loadings enter the system via point source release, non-point sources such as urban and agricultural runoff and soil erosion, dry deposition of particles containing sorbed chemical, atmospheric washout with rainfall and groundwater seepage (USEPA, 2000).

A simple version of the mass balance model for a stream assumes that a chemical enters the stream at a specified point and a constant rate and is instantly well mixed. Concentration is calculated by dividing the release rate in mass per day by the stream's volumetric flow rate.

More complex models allow release rates to vary with time and allow agents to partition between sediment, water and biota compartments, volatilize from the water compartment and undergo chemical and biological processes such as aerobic and anaerobic biodegradation, photolysis and hydrolysis. Sinks such as the sediment bed may become sources when the concentration in the water column decreases or when the stream bed is disturbed.

A minimum output of a surface water model is a steady-state or average total concentration in the water column over a specified time period. The model might also report dissolved and sorbed concentrations in the water column and in the stream bed sediments as well as concentrations in fish and other biota. These values can be steady-state values, average yearly or seasonal values or a time sequence of values over the course of days or years. Other outputs might include losses from the water column via biodegradation, chemical degradation, evaporation and partitioning to sediment, as well as chemical flux out of the system.

Surface water models are generally applicable to relatively dilute concentrations of contaminants. Organic liquids that are released directly into surface water (e.g. in oil spills) may float on the surface or sink to the stream bed as immiscible liquids and serve as long-term sources of persistent organic pollutants to the water column. Most surface water models do not account for these immiscible phases.

3.1.4 Food concentration models

Studies of pesticide contamination of residential surfaces and respective aggregate exposure models (air, surfaces, water, food) are covered in section 3.2.4 on multimedia exposure models.

Exposure media include many foods that are contaminated by agents. The following are some examples commonly found in risk assessments:

- fish from consumption of algae and other fish
- residues in crops treated with pesticides and other agrochemicals
- residues from contaminated soil and air deposition in vegetables grown at home
- produce that is irrigated by untreated sewage containing heavy metals
- food products, including beef, milk, chicken and eggs, from animals that graze on contaminated soil and forage crops.

The sources of the agents can be air, water, soil or direct application of a pesticide, for example.

A food concentration model for a semivolatile organic compound might combine ambient air models with their wet and dry deposition components, surface water models, and erosion and plant uptake models, which are often components of unsaturated zone groundwater models, to predict the concentration of the chemical in food. These models are combined with models (usually empirical) that estimate factors such as concentrations in animal products grazing on pasture with soil containing a given concentration of the chemical. These food concentration

models are examples of components of the multipathway exposure models described in section 3.2.4 below.

3.2 Exposure and dose models

A general exposure model combines data on contact media (air, surfaces, water, food) concentrations with data on contact events and times to produce estimates of exposures at different routes of entry. A general dose model adds intake (e.g. inhalation or food consumption) and absorption across the contact surface into the body to the exposure model. Exposures via different routes of entry can be summed by estimating an absorbed or other internal dose. In relation to systemic health effects, the total exposure across all routes of entry is important. Many health effects, however, are specific to contact site (e.g. contact dermatitis) or exposure route (e.g. $PM_{2.5}$-induced cardiac death).

This section discusses models for single routes (inhalation, dermal contact and dietary and non-dietary ingestion) as well as exposure models that combine exposures from all three routes.

3.2.1 Inhalation models

One of the simplest ways to handle the uneven geographical distribution of human beings is to use census data and to assume that people are exposed to the air at their geographical home locations, usually using monitoring data for outdoor air from the nearest monitoring station to represent exposure concentrations. This approach ignores the fact that indoor air concentrations are often higher than outdoor air concentrations and that most people spend approximately 20% of their time at work, school or other locations away from home and about 4% in transit, both very important for the exposures to many compounds. More complex inhalation models contain many microenvironments. Concentration data for the models are obtained from the measurements or concentration models described above in section 3.1.

Inhalation models combine concentrations in outdoor and indoor air and information on human time–activity patterns to estimate inhalation exposures. Air pollutant concentrations vary in time and space, and people move within and between these changing pollution fields. The behaviours of interest are where people spend their time and the activities that bring people into contact with environmental agents. In addition to the exposure concentrations and the time spent in each microenvironment, the inhaled dose depends on the inhalation rate — i.e. age, body size and physical activity level.

Figure 7 shows a conceptual model of inhalation exposure for indoor and outdoor air, as proposed by the NAS (NRC, 1991).

Personal exposure concentration is estimated as the time-weighted average of the concentrations in the microenvironments where an individual spends time. Microenvironmental exposure models with outdoor and indoor concentrations and personal time–microenvironment–activity data as inputs perform this function.

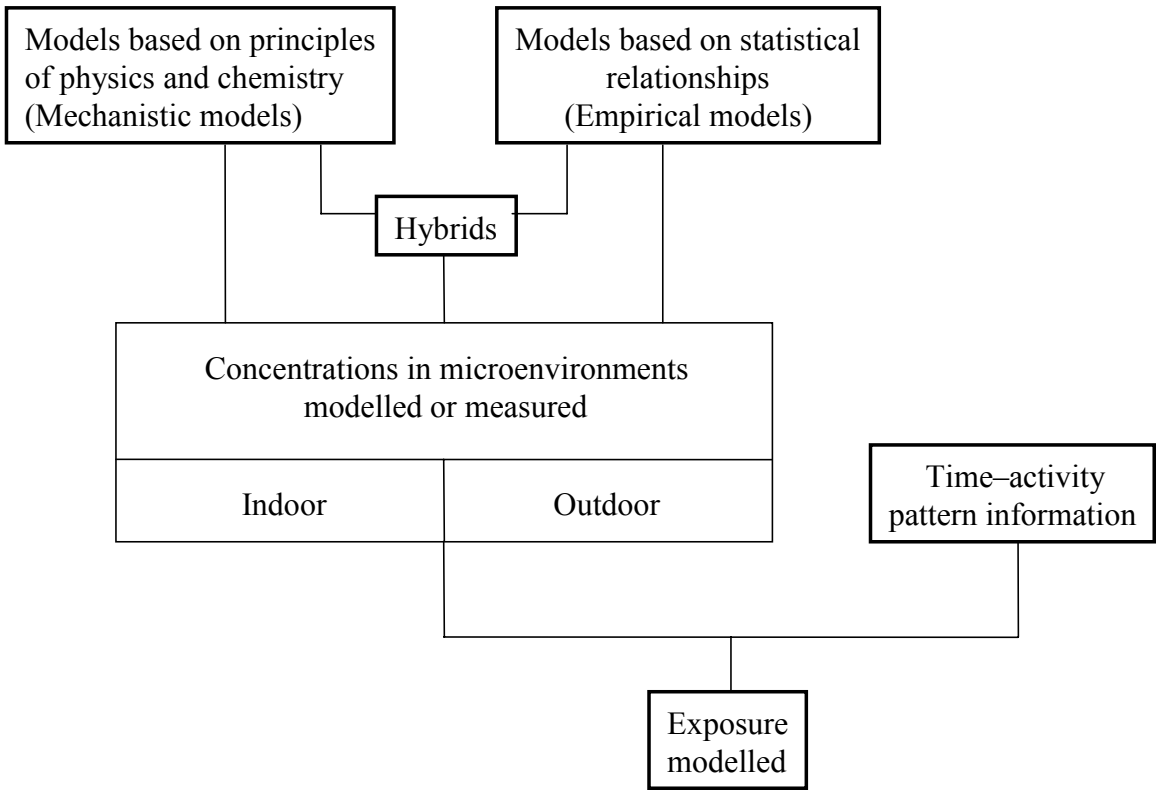

Figure 7. Schematic diagram of models used in exposure assessment.

The microenvironment concept has been developed for two different purposes. The first is to reflect the fact that the exposure concentrations of many pollutants are often more similar in two microenvironments (e.g. two residences or two offices on opposite sides of the city) than inside and outside of the same building. Consequently, the microenvironment category may be more important than the geographical location. Second, the microenvironment concept simplifies exposure modelling dramatically by reducing the millions of real microenvironments into a few classified microenvironments. In microenvironment-based exposure modelling, time–activity models that provide the sequences and distributions of the time people spend in the various microenvironments and their activities in the microenvironments are combined with concentration distribution models for each microenvironment to produce integrated exposure distribution estimates across the different microenvironments.

Probabilistic models are often used for microenvironmental modelling. The probabilistic approach, when applied to microenvironmental modelling, assumes that the concentrations in all outdoor or indoor locations can be grouped together into categorized microenvironments, each described by the same concentration distribution (e.g. category of urban homes without environmental tobacco smoke, but with gas stove). The concentrations for each microenvironment are simulated by sampling randomly from these distributions. The contribution of each microenvironment to the time-weighted average exposure is calculated using measured time–activity pattern data (e.g. AirPEx — Freijer et al., 1998; NHAPS — Klepeis, 1999;

Klepeis et al., 2001; CHAD — McCurdy et al., 2000) or a time–activity model (e.g. SHAPE — Ott et al., 1988). The former technique has the advantage that all time–activity patterns are realistic and autocorrelations are fully acknowledged, and the disadvantage that changes in the time–microenvironment–activity patterns cannot be simulated.

In SHAPE (Simulation of Human Activity and Pollutant Exposure), the detailed time–activity model contains distributions for the lengths of stay in each microenvironment as well as probabilities for the sequences in which the microenvironments follow each other in the population's time–activity profiles. Such a time–activity model can be used to create a larger variety of possible time–activity patterns. It is also useful in assessing the changes occurring in the population time–activity in the long run or after specific changes in air quality and societal behaviour.

The Air Pollutants Exposure Model (APEX) is a PC-based inhalation model developed by the USEPA's Office of Air Quality Planning and Standards. APEX is intended to be applied at the local, urban or consolidated metropolitan area scale and currently addresses only inhalation exposures (USEPA, 2005). The model simulates the movement of individuals through time and space and their exposure to the given pollutant in various microenvironments (e.g. outdoors, indoor residence, in vehicle). The user may choose the number and types of microenvironments to be included, select the time period of interest, use either monitored ambient air quality data or values provided from dispersion or other modelling runs and use either a mass balance approach or an empirical ratio-based (factor) approach to estimate indoor and/or in-vehicle concentrations.

Over the past 15 years, the USEPA's Office of Air and Radiation, in conjunction with the Office of Research and Development, developed the Hazardous Air Pollutant Exposure Model for Mobile Sources (HAPEM-MS) to assess inhalation exposure to air toxics from highway mobile sources. The USEPA has updated and improved HAPEM to predict inhalation exposure concentrations of air toxics from all outdoor sources, based on ambient concentrations from modelling or monitoring data for specific air toxics. It predicts nationwide census tract level annual average human exposure levels and can thus be used in a screening-level inhalation risk assessment. The latest version of the model, HAPEM4, has been designed to predict the "apparent" inhalation exposure for selected population groups and air toxics (USEPA, 2003c). Through a series of calculation routines, the model makes use of ambient air concentration data, indoor/outdoor concentration relationship data, population data and population activity pattern data to estimate an expected range of "apparent" inhalation exposure concentrations for groups of individuals.

The USEPA's Stochastic Human Exposure and Dose Simulation (SHEDS) model is a physically based stochastic model developed to quantify exposure (and dose) of humans to either inhalation or multimedia, multipathway pollutants (USEPA, 2004). Probabilistic inputs are combined in physical/mechanistic algorithms to estimate exposure and dose using a two-dimensional Monte Carlo methodology that quantifies variability and uncertainty in model inputs and outputs. To date, the model has focused on simulating inhalation exposures to particulate matter and air toxics, as well as for aggregate exposures (multimedia, single chemical) of children to pesticides (e.g. chlorpyrifos). The aggregate model is currently being

expanded to address cumulative exposures (multimedia, multiple chemicals), with the first application focusing on children's exposures to pyrethroid pesticides.

Some of the time–activity measurement databases and models (e.g. SHAPE, NEM — the National Ambient Air Quality Standards, or NAAQS, Exposure Model) use quite detailed microenvironmental classification of locations containing dozens of microenvironments. Detailed separation of different microenvironments is needed when exposure to pollutants with highly varying concentrations is studied. On the other hand, concentrations of pollutants like fine particulates are rather equally distributed, and much simpler microenvironmental classification can be used quite successfully (e.g. EXPOLIS Simulation Model for $PM_{2.5}$ — Hänninen et al., 2003). The health effects of air pollution are caused by the amounts of pollution entering the body — in fact, entering the most sensitive organs within the body.

3.2.2 Dermal exposure models

Dermal exposure to an agent occurs when an individual's skin comes into contact with media containing the agent. Air, water, soil, dust on household surfaces and industrial and consumer products are common media of concern to government regulatory programmes. These media are sometimes referred to as vehicles that deliver an agent to the exposed individual.

The dermal models currently in regulatory use are relatively simple. They usually estimate the amount of the agent that comes into contact with the skin and the amount absorbed through the skin over a specified period of time. Absorption models differ depending on whether the dermal contact is described as immersion of the skin in the vehicle or as deposition of the vehicle on the skin.

A critical review of methods for assessing dermal exposure has been provided by van Hemmen & Brouwer (1993). Skin permeation models have been evaluated by Wilschut and co-workers (Wilschut & ten Berge, 1995; Wilschut et al., 1995). This approach of dermal uptake has been considered, for example, in the dermal uptake models in the CONSEXPO exposure estimation tool.

Estimating dermal contact with agents

Transfer of contaminants from surfaces to skin has been studied by Brouwer et al. (1999). A single hand contact with a powdered glass surface results in transfer of 4–16% of the powdered glass to the hand. Twelve contacts result in 40% transfer to the palm surface. Contact of skin by touching solid materials, in particular textiles, paper and toys, can result in transfer of contaminants to the skin. A publication of the Ecological and Toxicological Association of Dyes and Organic Pigments Manufacturers (ETAD, 1983) deals with the extractability of dyestuffs from textiles. Adherence of soil to skin has also been studied and reviewed for applicability to modelling (McKone, 1990; McKone & Howd, 1992; USEPA, 1992a).

A simple model for estimating dermal contact with a contaminant has been proposed by the USEPA (1992a). In this model, dermal contact is estimated as the product of the surface area

of the skin exposed, the amount of medium retained on the skin (adherence) and the weight fraction of the agent in the mixture. The media that contain the agent may be soil, dust, a liquid, such as water or a liquid consumer product, or solids, such as textiles, paper and toys. In the case of some agents, such as ingredients in pesticides and cleaning products, the medium is applied and present on surfaces as part of its intended use. The EU technical guidance document for new and existing substances (EU, 1996, 2003) proposes a similar model for calculating skin contact with a liquid. This model defines a hypothetical volume on the skin, which can easily be calculated by multiplying the surface area of the exposed skin by the thickness of the liquid layer. These models can be applied for cases in which parts of the skin are covered by liquids or for application of cosmetic compounds. These simple models can be combined with models that describe volatilization losses from the skin surface to the surrounding environment to make them more realistic. Validation of these models is lacking.

Building on a conceptual model developed by Schneider et al. (1999), which systematically describes transport of contaminant from a source and impaction, deposition or transfer to skin and clothing, Van-Wendel-De-Joode et al. (2003) produced a model of dermal exposure for workers that takes into consideration the specific tasks performed. The model divides the body into nine parts and estimates exposure of the skin of each body part according to tasks performed and the presence or absence of protective clothing.

Estimating dermal absorption using the deposition assumption

The absorbed dose of agents from a solid or liquid medium deposited on the skin is often calculated as a simple percentage of the amount of agent deposited on the skin. This approach has been adopted as the only reasonable alternative given the lack of both empirical data and mechanistic understanding needed to develop more sophisticated dermal absorption models. The percentage of agent absorbed will vary with exposure conditions, such as amount of vehicle adhering to the skin, duration of contact and skin thickness. The properties of the agent and the vehicle also affect the percentage absorbed. Semivolatile organic compounds tend to be absorbed more rapidly and completely than inorganic compounds and VOCs. Inorganics are much less soluble in tissue, whereas VOCs tend to evaporate in preference to being absorbed unless they are tightly covered to prevent volatilization. Neat agents are absorbed more rapidly than agents applied to the skin in soil or dust, where binding to the medium may occur.

Experiments used to derive absorption fractions for agents are often not representative of the exposure scenarios of concern. For example, higher vehicle loadings and chemical concentrations than would be seen in the environment are often used to facilitate loading the vehicle on the excised skin sample or the experimental animal. Standard experimental protocols are needed, but little progress has been made. Data supporting development of mechanistic absorption models for soil and other media similar to the one for water described below are needed, so that permeability coefficients can be measured and used to estimate flux through the skin.

The USEPA's SHEDS model, described in section 3.2.3, applies an approach that uses exposure factors and concentrations related to specific microenvironments and microactivities to estimate children's dermal exposures (Zartarian et al., 2000).

The EC is supporting development of RISKOFDERM, a model, based on experimental data, that assesses and manages occupational dermal exposure to chemical substances. A conceptual model and a simple-to-use toolkit for the assessment and management of health risks from occupational dermal exposure are available. Major determinants of dermal hazard and dermal exposure have been analysed. The results were combined in the form of a decision tree that leads the user of the toolkit through a number of questions on the hazardous properties of the chemical in use and on the exposure situation (Oppl et al., 2003; van Hemmen et al., 2003).

Estimating absorption using the immersion assumption

When the skin is immersed in water, such as when swimming or showering, the steady-state flux (mg/cm^2 per hour) across the skin is linearly correlated with the concentration of a substance in aqueous solution (mg/cm^3). A permeation coefficient k_p can be derived to quantify the flux as a function of the concentration (McKone & Howd, 1992). Derivations of dermal absorption rates have been evaluated by Stubenrauch et al. (1995), giving data for dermal permeation coefficients for children and adults from playgrounds and in the garden, referencing primary data sources. Principles of assessing dermal exposure have also been published by the USEPA (1992a). Theoretically, this approach could be used for any medium/chemical combination. In practice, it is most often used for agents in water and, to a lesser extent, in air.

The model assumes that transport across the stratum corneum and viable epidermis is the rate-limiting step for absorption, that the transport process has reached steady state and that all of the chemical that is absorbed into the epidermis is eventually absorbed into the body, with no losses to metabolism in the skin, evaporation from the skin or stratum corneum desquamation.

Various refinements to this simple model have been proposed. For example, although the model assumes steady state, it is known that there can be a significant time lapse before steady state is reached, during which absorption is more rapid. The steady-state assumption can underestimate absorption, especially when exposure durations are short. Refinements have been made to the model to account for this lag time in aqueous systems (Cleek & Bunge, 1993). Reddy et al. (2000) developed a mathematical model to account for losses due to desquamation, which is likely to be adopted in new guidance for dermal exposure assessments being developed by USEPA's hazardous waste programmes (USEPA, 2001).

Empirical correlations have been published that predict permeability coefficients on the basis of molecular mass and octanol/water partition coefficients. The USEPA (1992a, 2001) suggests use of one by Potts & Guy (1992). While this correlation is widely used, it still has important uncertainties. The major reason why it has been difficult to improve this correlation is that the laboratory protocols used to measure permeability coefficients have varied widely.

Recently, progress has been made on this issue. In 1999, the USEPA issued the Proposed Test Rule for In Vitro Dermal Absorption Rate Testing of Certain Chemicals of Interest to Occupational Safety and Health Administration (USEPA, 1999b). Since then, the OECD (2004) has issued test guidelines for in vitro skin absorption. These rules should significantly improve the degree of standardization in these data. One limitation is that these recently proposed methods are primarily oriented towards testing pure compounds. Further research is needed to determine if the permeability coefficients derived from testing pure compounds can be adjusted to represent aqueous and other solutions.

The EDETOX (Evaluations and Predictions of Dermal Absorption of Toxic Chemicals) Program is a three-year research programme funded by the fifth framework of the EU. EDETOX evaluates the usefulness of in vitro models to deliver relevant data on percutaneous penetration of chemicals. Its major objective is to develop validated in vitro experimental strategies for the quantitative measurement of the dermal absorption of chemicals and corresponding predictive computational models so that the use of animal testing will be greatly reduced in these risk assessment procedures. A series of important environmental and occupational contaminants are investigated to improve knowledge on dermal penetration, which may play an important role in the total internal exposure. Prediction of the rates of absorption and the subsequent disposition of dermal penetrants is evaluated by testing in vitro and in vivo experimental data generated in the project and existing quantitative structure–activity relationships (QSAR) and physiologically based pharmacokinetic (PBPK) models.

3.2.3 Ingestion models

One type of dietary ingestion model combines data on dietary intake of food types with data on chemical residues in each food type consumed to produce an estimate of total residue intake via the food pathway. Intake and residue data for these models are usually collected over a wide geographic area. Another type of dietary model examines specific, often localized, chemical residues, such as residues in fish caught in a particular contaminated stream or exposure to agents in home-grown vegetables and fruits contaminated by fallout from an incinerator. Exposure models have also been developed to estimate ingestion via non-dietary pathways, where individuals are exposed through accidental or intentional consumption of items such as contaminated soil or through mouthing of fingers or objects such as toys.

Dietary exposure models

Assessment of dietary exposure considers intake of substances in foods, beverages and water, which will hereafter be referred to as "food." A dietary exposure model, in its simplest form, calculates an intake of a contaminant as the product of the mass of the food item consumed during the exposure duration of interest and the average concentration of the contaminant in the item. More complex models also use this basic approach and sum the contributions of various food items and food types. Dietary exposure models have been developed that combine human food consumption data obtained from surveys with chemical residue data for the foods consumed to estimate daily intake of chemical residues from all dietary sources.

A comprehensive overview of food exposure estimation has recently been reported by the International Life Sciences Institute project "Food Safety in Europe" (Kroes et al., 2002). A common method of measuring intake of chemical residues in the diet is to collect and analyse duplicate samples of all foods and beverages consumed during the study period. If a particular food type such as home-grown produce is of interest, that food type would be collected and analysed separately. Another widely used approach is the total diet study, which uses information on both consumption and food preparation to prepare food composite samples, which are then analysed. These duplicate diet and total diet protocols are expensive and difficult to administer. Thus, models are used to predict dietary exposures as an alternative or supplement to specifically measuring residues in duplicate food samples. Models are particularly useful in estimating possible exposure to a chemical during its pre-market review (e.g. pesticides and food additives).

Food consumption surveys typically obtain diaries from a population-based probability sample of respondents who report detailed breakdowns of food consumption by type. Another approach to obtaining intake data is to have participants fill out a checklist of common food items. A common type of checklist indicates a typical serving size and asks the respondent to record the number of servings of that size consumed per day, per week or per month. Twenty-four-hour recalls ask the participant to recall his or her food consumption on the previous day, and the dietary history method is used to find out the participant's usual food consumption during longer periods in the past (Willett, 1998; Margetts & Nelson, 2003).

The number of days of data obtained in such studies is limited, with 1–7 consecutive days of data being typical. Examples of such surveys in the USA include the Continuing Survey of Food Intake by Individuals, conducted by the United States Department of Agriculture (USDA), and NHANES, conducted by the United States Department of Health and Human Services. In Europe, several countries have conducted their own nutrition surveys. For example, in Germany, there are the German National Food Consumption Study (food record; 1985–1988; on behalf of the German Federal Ministry of Research and Technology; Adolf et al., 1995) and a nutrition survey conducted by the Robert Koch-Institut (dietary history; Mensink et al., 1998). A special German survey (VELS; 2001–2002; Heseker et al., 2003) determined the nutrition of children in the age range 6 months to 4 years using a food record.

Each food type in the food consumption survey is matched with its corresponding food type in a database of chemical residue data obtained from monitoring programmes. In the USA, for example, USDA, USEPA, the United States Food and Drug Administration (USFDA) and the State of California monitor pesticide residues in food. In Germany, the federal government has conducted, together with the federal states, a monitoring programme for pesticides, heavy metals, mycotoxins and other objectionable substances in foods every year since 1995 (BgVV, 2003). Typically, the information from these studies represents residues found on raw agricultural commodities during routine monitoring, enforcement monitoring or import monitoring. The exception in the USA is data from the USFDA Total Diet Study, which include residue levels measured on a market basket of foods purchased from retail outlets and prepared for consumption following standard recipes. Each source of chemical residue information has a unique bias or limitation (e.g. geographic limitation, limited number of raw

agricultural commodities, analytical method with high limit of detection, small sample size), depending on the purpose of the monitoring programme.

Computer models are used to combine dietary intake and residue data. In the USA as well as in other countries (e.g. Germany), dietary intake and residue data come from different monitoring programmes that use different methods of coding the food types. Developing a consistent set of codes has been a major hurdle to implementing the dietary model.

One example of such a model is the Dietary Exposure Evaluation Model (DEEM), a computer-based model developed by Novigen Sciences, Inc. to estimate dietary intake of chemical residues. DEEM is used for exposure and risk assessments conducted by the USEPA's Office of Pesticide Programs. DEEM output includes dietary exposure estimates over alternative averaging times (acute and chronic) and on a population (e.g. mean) and individual level (e.g. population distribution).

The Dietary Exposure Potential Model (DEPM) is another USEPA dietary model. Food consumption in DEPM is expressed in terms of 800 exposure core foods selected in a manner to facilitate matching between food consumption data and chemical residue data (Tomerlin et al., 1997). Food consumption data are not available in DEPM at the level of the individual; rather, the model contains per capita food consumption rates for the 800 exposure core foods for the population in the USA and approximately 24 subpopulations defined by demographic factors such as geographic region, gender, age and ethnicity. DEPM is run by selecting a food consumption database, a chemical residue database and a population. Model output is average daily intake of a chemical for a hypothetical person with the average diet for the selected population. DEPM does not estimate the distribution of exposure for a population or exposure for any individuals of a population. A special feature of DEPM allows a user to specify a diet in the form of exposure core foods that can be matched with residue data and used to estimate exposure.

At the international level, two joint committees of the Food and Agriculture Organization of the United Nations (FAO) and WHO have, over a period of four decades, evaluated more than 1500 food chemicals and 300 pesticides. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluates food additives and veterinary drug residues, and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) evaluates pesticide residues. Recommendations for use are made on the basis that the model exposure assessment does not exceed the established acceptable daily intake (ADI). The models used differ for each type of chemical, with pesticides and veterinary drug residues based on maximum residue levels (MRLs) in raw commodities and food additives based on maximum levels (MLs) in processed food categories. In the case of contaminants, JECFA may establish a provisional tolerable weekly intake (PTWI) to protect consumers against the chronic health hazards usually associated with the long-term intake of these chemicals. Depending on where the contaminant occurs, different models are used. JECFA and JMPR may also establish an acute reference dose (aRfD) for a chemical that may cause adverse health effects after short-term exposure, such as one meal or one day. In these cases, the food consumption model uses a high-percentile approach for both residue and consumption rather than the mean or median.

Non-dietary ingestion exposure models

Ingestion of agents in non-food items can be an important exposure pathway, particularly for small children. Items that may be ingested include soil and dust, paint chips and grass treated with pesticides. Pollutants adhering to hands, toys, food and other objects may be transferred to the mouth either deliberately or inadvertently and subsequently ingested. The general pathway-specific algorithms for non-dietary ingestion of agents in media such as soil and paint chips are similar to those for dietary ingestion and involve combining medium-specific ingestion rates over the exposure duration with concentrations of agent in the ingested medium.

Non-dietary ingestion of hazardous substances may also occur in occupational settings and may become more important as employers increase efforts to control inhalation and dermal exposures. Systematic investigation to correlate airborne or dermal exposure to metals in the workplace with biological indicators has sometimes shown poor correlation (Kiilunen et al., 1997; Cattani et al., 2001; Enander et al., 2004). It has been suggested that this may, in part, be due to incidental ingestion.

For estimating non-dietary ingestion of chemical residues on indoor surfaces from hand-to-mouth transfer, a different approach has been used. The loading of a residue on a surface ($\mu g/cm^2$) is multiplied by the surface area of hands that contact indoor surfaces and then transfer residues to the mouth in a given event (cm^2/event), the frequency of hand-to-mouth events (events/h) and the exposure time (h/day).

Several aggregate exposure models (e.g. CALENDEX, CARES [Cumulative and Aggregate Risk Evaluation System], LIFELINE, SHEDS) are being developed to address non-dietary exposure. These models aggregate the exposures to pesticides incurred by simulated individuals using actual human activity data. The USEPA's SHEDS model, for example, preserves the sequence of location–activity combinations (macroactivities) from sampled individuals' diaries and simulates, for each macroactivity, non-dietary hand-to-mouth ingestion by combining residue loading on the hands with the fraction of hands containing residue entering the mouth, frequency of hand-to-mouth activity, duration of the macroactivity and saliva removal efficiency. Object-to-mouth transfer is simulated by combining surface residues on objects with object-to-mouth contact frequency, surface area of objects touching surfaces, then entering the mouth, duration of macroactivity and saliva removal efficiency.

The USEPA is developing a physically based probabilistic model to quantify and analyse children's dermal and non-dietary ingestion exposure to and dose of pesticides. The Residential-SHEDS model for pesticides simulates the exposures and doses of children contacting residues on surfaces in treated residences and on turf in treated residential yards. The simulations combine sequential time–location–activity information from children's diaries with micro-level videotaped activity data, probability distributions of measured surface residues and exposure factors and pharmacokinetic rate constants. Model outputs include individual profiles and population statistics for daily dermal loading, mass in the blood compartment, ingested residue via non-dietary objects and mass of eliminated

metabolite, as well as contributions from various routes, pathways and media (Zartarian et al., 2000).

3.2.4 Multimedia models

For government agencies charged with chemical safety, the most pressing exposure questions often relate to exposure of the groups they are charged to protect and the sources or exposure media that fall within their authority. This has led many government programmes to focus their assessments on single media, such as air, water or food, and specific segments of the population, such as workers in the chemical industry, pesticide applicators and consumers. Single-pathway and single-medium assessments are useful to decision-makers because they can provide quantitative risk estimates on which to base risk management decisions. However, such assessments do not provide an estimate of the baseline exposure in the absence of the pathway of concern. Therefore, risk managers do not know the extent to which mitigation of the risk associated with that pathway will lower the total risk.

Multimedia exposure assessments that estimate total exposures via all pathways and routes are more complex and costly than single-medium assessments. They require the collection of data and development and implementation of models for the additional pathways and sometimes for additional groups of people to serve as control groups for comparison with the subgroup of interest.

Due to the evolution of exposure and risk assessment science and to new laws, regulations and policies that recognize the importance of understanding the contributions to exposure from all sources, there is now a trend towards total exposure assessments that include all potential exposure pathways. For example, the *Food Quality Protection Act* in the USA mandates the USEPA to make a determination that there is a reasonable certainty of no harm from aggregate exposure to pesticide chemical residues, including dietary exposures and all other exposures, except for occupational exposures, which are addressed elsewhere. As a result, pesticide assessments, which previously addressed dietary, drinking-water and residential exposure pathways separately, now also provide an estimate of total exposure via food, drinking-water and residential pesticide use (USEPA, 1999a).

The first deterministic (mechanistic) method of conducting a total exposure assessment for a chemical is source (or exposure)-to-dose modelling. The following are the steps in such an assessment:

- Formulate the assessment questions that need to be answered. In this step, the exposure assessor should consult with a toxicologist to identify the toxicological end-points for each exposure route and the appropriate exposure duration to correspond with the end-point.
- Identify the populations of interest.
- Identify exposure pathways.
- Determine exposure concentrations in environmental media. This can be done through measuring or modelling exposure concentrations.

- Estimate aggregate intake or uptake for each route (inhalation, ingestion and dermal) via all pathways separately.
- Convert intakes and uptakes to a common dose or risk (response) metric suitable for summing contributions across routes, and sum across routes.
- If necessary, convert the summed dose to the dose used in the toxicity study that will be used to estimate risk.

Measurements of exposure biomarkers, such as concentrations of a chemical in blood or urine, provide a more direct measurement of aggregate exposure than source-to-dose modelling, since they reflect contributions for all pathways. These exposure biomarkers are useful measurements of total exposure in epidemiological studies in which the investigator is studying the relationship between dose and adverse effect. However, this method is not widely used by regulatory agencies to develop risk management approaches, because it does not provide information about the sources of exposure.

One issue in total exposure assessment is whether high exposure via one pathway is correlated with high exposure via other pathways. Worst-case analysis is a deterministic approach to the question of correlations among exposures. In assessment terminology, the worst case refers to the maximum possible exposure, dose or risk that can conceivably occur, whether or not it actually does occur. The worst case assumes that an individual who is highly exposed via one pathway will also be highly exposed via all others. A government programme may decide to take no action based on a worst-case estimate of risk that is below its concern level, but generally would not regulate a chemical based on such an estimate. If the worst-case estimate is above a designated concern level, the assessment is usually refined.

Other types of deterministic scenarios have been developed that produce what is believed to be a more realistic estimate of a high exposure, such as reasonable worst-case and high-end estimates (USEPA, 1992a). Instead of assuming the combination of values that produces the highest possible aggregate exposures, these scenarios use a combination of high and mid-range values to aim for an estimate in the actual top 10% of the population. The extent to which these scenarios are successful is difficult to verify because of lack of data with which to test them.

In the 1990s, with increased computer capabilities, probabilistic or stochastic models (described above in section 2.3) came into greater use. The output of a probabilistic model allows a decision-maker to base regulatory decisions on exposures and risks at policy-determined percentiles, such as the 90th, 95th or 99th percentile. The probabilistic model does not in itself solve the problem of correlation among exposure pathways. If the probabilistic assessment assumes that all pathways and input variables are independent, when some in fact are correlated, some of the simulated individuals will have sets of characteristics that are physically impossible or highly improbable.

If quantitative values of correlations are known, they can be built into the probabilistic sampling scheme. If only qualitative information on correlations is available, a widely used approach is to construct the probabilistic analysis around hypothetical individuals. Using census data, the modeller randomly assigns an age and sex to each simulated individual.

Other traits can also be randomly assigned. Examples are geographic location, ethnicity and pesticide use within the past year. Then, values for the other input variables are assigned to the individual by drawing from distributions for the particular age, sex or other traits assigned to that individual. This approach introduces correlation between age- and sex-related factors such as height and weight, skin surface area, activity patterns and drinking-water and food intakes and avoids many incongruities in the output distributions.

A total exposure assessment often requires the summing of doses across multiple routes and pathways. This usually requires that each dose be converted to a common dose or risk metric. The metric serves to convert the multiroute exposures to a common quantity that can be added. Examples of dose metrics include the absorbed dose (the amount of agent that enters a target by crossing an absorption barrier, such as the skin and the linings of the lung and gastrointestinal tract) and the concentration of the chemical or its metabolite in blood or a target organ. An example of a risk metric is an estimate of cancer risk, which is estimated separately for each route and then added.

The second approach is statistical. For agents that have been intensively studied in human populations, it may be possible to develop regression equations that relate environmental concentrations or intakes of the agent to concentrations in human tissue and fluids, such as blood and urine, that serve as integrators of aggregate exposure. This approach requires large numbers of data, and the results are often applicable only to the small subgroups that are the subjects of the studies (e.g. occupational groups, groups residing near smelters).

A third approach is the use of PBPK models, which is discussed below in section 3.2.6.

3.2.5 Multichemical exposure models

Multichemical exposure models can have components that include all of the different types of models described so far. In addition, multichemical exposure models need to provide a method for summing the contributions of each chemical to the risk. To achieve a meaningful quantitative estimate of exposure, dose and response or risk from two or more agents, it is necessary to take the relative toxicities of the agents into account.

There are complications in source-to-exposure-to-dose modelling for multiple agents that do not exist in assessments of single agents. The environmental fate and hence the exposure concentrations and toxicity of the mixture will depend on the constituent congeners. The relative concentrations of congeners making up an emission are likely to change as the releases move through the environment

Another type of exposure assessment considers the combined impacts of chemical and other stressors on an individual or a community. For example, in assessing risks associated with the siting of an incinerator, a regulatory agency might consider the impact of catastrophic releases and increased noise, dust and traffic, in addition to stack emissions of toxic agents. Such an assessment is likely to consider multiple effects as well as multiple stressors. In trying to answer questions related to the high frequency of adverse health conditions in a community, one might need to consider nutrition, smoking habits, presence of environmental

tobacco smoke and access to medical care, as well as exposure to environmental agents released from the stack. There is a need for research and methods development in this area. No models are available for this type of assessment that could be considered exposure models.

3.2.6 Biologically based models of internal dose

Risk assessors employ a variety of models to estimate internal doses of chemicals to target organs. These models estimate the dose to a target tissue or organ by taking into account rates of absorption into the body, metabolism, distribution among target organs and tissues, storage and elimination. Such models are not strictly speaking exposure models, but they are included here because they are at the interface between the exposure assessment and the dose–response assessment and are essential for incorporating more biological data into risk assessments and reducing reliance on default values. They are useful in extrapolating between humans and test animals and between children and adults because they allow consideration of species- and age-specific data on physiological factors that affect dose levels and data on biological responses that are different or more intense in certain subpopulations such as children. They are also useful in extrapolating between routes of exposure, allowing toxicity data generated in an oral exposure study, for example, to be used to estimate the response to an inhalation exposure that produces the same internal dose. For example, complex computational dosimetry models have been developed to address dose to nasal cavity and critical regions of the lung for purposes of interspecies extrapolation, taking into account factors such as inhaled particle size distribution, structure of the nasal compartments of humans and animals, fluid dynamics and properties of the environmental agent (Bogdanffy et al., 1999; Robinson, 2005).

PBPK models depict the body as a series of compartments. The toxicant enters the body and is transported through circulation in the blood to the target organ or organs. Mass balances are developed for each organ, taking into account toxicant flow into and out of the compartment and losses within the compartment due to reactions.

A basic mammalian PBPK model for inhalation exposure to a VOC (Figure 8) includes a lung compartment where exchange occurs between the alveolar air and the capillaries of the lungs, a fat compartment where lipophilic compounds accumulate, a compartment for poorly perfused tissues, including the bones and muscles, and a compartment for richly perfused tissues where metabolism is most likely to occur. In more complex models, separate compartments can be added for administration by ingestion and through dermal absorption. For example, the gut compartment can be used to provide a more detailed description of absorption of agents from food and drink. Compartments can also be added to account for elimination processes in addition to gas exchange in the alveolar region — the kidney for urinary elimination, the gut for direct desorption into faeces and the liver for biliary excretion.

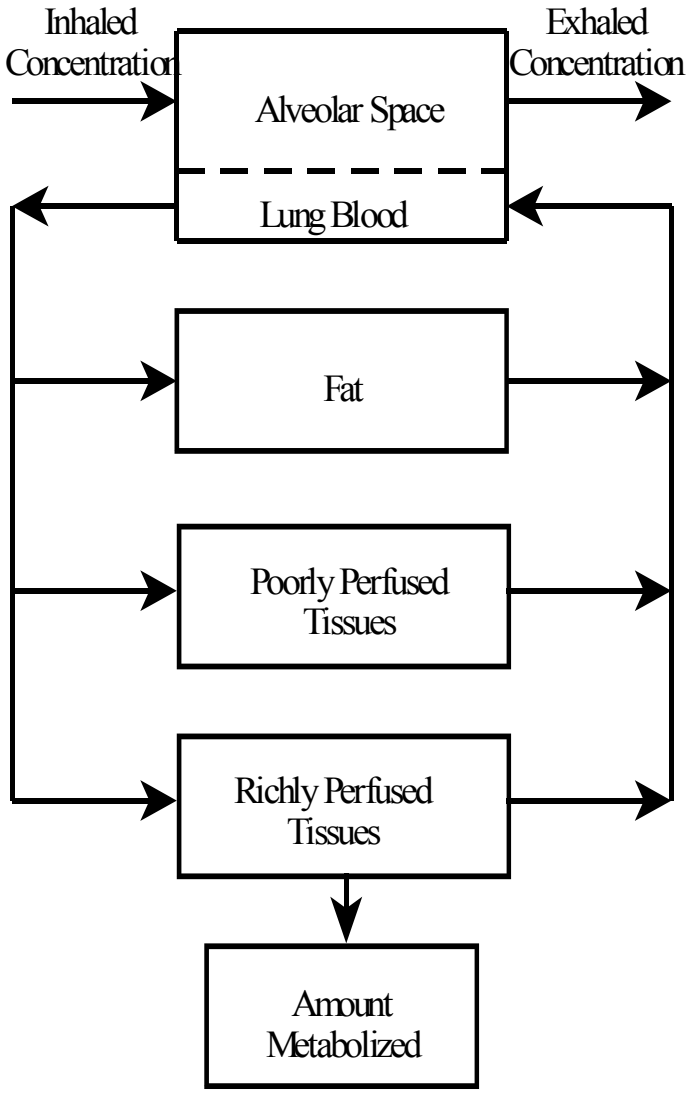

Figure 8. Simple physiological model for a VOC with a single route of exposure (inhalation).

3.2.7 Source apportionment models

All pollution (or precursors of pollution) originates from sources. These can be natural processes, such as forest fires and volcano eruptions, they can be human activities, such as traffic, farming and industry, or they can be a combination of both, such as flooding of industrial, urban or agricultural areas. Source apportionment models and analysis methods are used to study how the total measured concentrations or exposures split into fractions caused by different sources and source categories (Cooper & Watson, 1980; Henry et al., 1984).

The task of environmental health authorities is to keep the ambient air, drinking-water, food and indoor air quality in such a clean state that it does not harm public health. From this point

of view, the knowledge of pollution sources is essential as soon as any problems emerge. Ability to apportion the exposures to sources (as specifically as possible) allows for maximizing the exposure reduction while minimizing the cost and the necessity for government control. In some cases, apportioning the exposure to sources may be quite obvious and simple. Source apportionment of exposure to particulate matter less than or equal to 10 μm in diameter (PM_{10}) in urban air is a much more demanding task due to the complexity of the PM_{10} itself and the multitude of local, remote, indoor, occupational and personal sources that contribute quite variably to the exposures of the citizens (Turnbull & Harrison, 2000).

The source apportionment techniques that have been used include different factorial analysis techniques that statistically divide the exposures to mutually independent factors, which presumably represent different sources (e.g. Henry et al., 1984; Song et al., 2001). The more identically collected and analysed samples one has, the better one can identify the sources and apportion their contributions to exposure. Statistical source apportionment methods do not require a priori knowledge of the source emissions, but they can be applied only for a fairly large set of samples, not for a single sample.

Another method is to use chemical mass balance analyses, such as source reconstruction (e.g. Malm et al., 1994; Schauer et al., 1996). When the chemical compositions (the spectra and relative proportions of compounds and/or elements) of the most significant source emissions are known, the best fit of the proportions of the source compound spectra to the exposure compound spectrum reveals the contributions of each source. Chemical mass balance analysis can be made from one sample — i.e. specifically and separately for one study subject — but it does require (usually quite demanding) a priori analyses of the source emissions.

Source apportionment methods can be applied either to concentration or to exposure data. It has also been suggested that exposure models could be built to model the exposures from different sources separately. In fact, such a technique is directly built into the ambient dispersion models, which use the emission rates of individual sources as inputs and can be applied to output either the source contributions separately or the total concentrations originating from all sources together.

4. RECOMMENDATIONS FOR CHARACTERIZING EXPOSURE MODELS

The information provided in this report is intended to serve both the developers and users of concentration, exposure and dose models by summarizing features of these models and providing guidance in documenting their intended applications and limitations. For proper use of these models, it is recommended that a variety of technical details be provided in the documentation, including a general model description and information on inputs, model processes and algorithms, and outputs. A clear and transparent documentation of the models used to assess exposures will ensure correct and easy application of these models for a selected scenario.

Ten characteristics of the models (also referred to as "10 principles") that need to be provided by the model developer and considered by the model user are summarized below and in Table 3. Details on these various model elements are covered in the previous sections of this report.

4.1 General model description

1. *General description of the purpose of the model and its components*: The basis for any model should be a clear theoretical description of the situation using a conceptual model. This will ensure that the model can be easily understood. Assumptions should be explicitly stated. The developers of the model should provide a clear description of the model, including its intended use; the exposure media, routes and pathways considered; and the structure of the model (e.g. single medium or multimedia, single or multiple agents, etc.). The framework of the model, including key modules and important assumptions, should also be described. The selection of a specific exposure model should be based on the technical and regulatory requirements of a particular application. In general, less detailed (Tier 1) exposure models are selected for screening-level analysis. These models rely upon fewer inputs and basic exposure algorithms and provide daily or annual average exposure estimates for an entire population. More detailed (Tier 2) models incorporate more details in concentration and time–activity profiles of study populations. For example, Tier 2 models incorporate distributions for times spent indoors and outdoors and real-time concentration values. On the other hand, Tier 3 models use more complex exposure algorithms and detailed time–activity diaries (such as the ones included in the USEPA's CHAD). Tier 3 model predictions are temporally and spatially resolved and provide individual-level exposure estimates for the study populations. Tier 3 model results are presented in terms of probability density functions and cumulative distribution functions to allow for quantifying high (e.g. 90th-percentile) or low (e.g. 10th-percentile) exposure estimates to the individuals in a study population. Tier 3 models are typically used in regulatory analysis.

2. *Individual- or population-level analysis*: Exposure models provide either individual- or population-level estimates, or both. Other characteristics of the target individuals/population may also be important for model selection. The model documentation should

describe the types of population and individual analysis that the model can support. These include exposure estimates for individuals and exposure statistics and exposure distributions for populations and subpopulations as defined by demographic features, including age, gender, ethnicity, socioeconomic status, geographic or spatial analysis scales (e.g. local, regional, national or global scale) and other factors, such as residence or occupation.

3. *Modelled time resolution*: Exposures often vary considerably over time and location for most regulated air pollutants, such as ozone and carbon monoxide, but also for some multimedia pollutants, such as residential use pesticides and air toxics. In addition, the physiological averaging period of concern varies for each pollutant type or class, depending on its toxicity in the body. Consequently, both the developers and the users of concentration and exposure models have to ascertain the applicable time resolution for each model and selected pollutant. The following temporal characteristics of the model should be considered for each particular application: capability to provide real-time concentration estimates (typically, minute-by-minute measurements or hourly averages); capability to provide integrated long-term concentration estimates (daily, seasonal, annual or lifetime averages); and capability to perform short-term, intermittent and long-term or event-related exposure analyses in order to support acute, subchronic or chronic risk assessments.

4. *Applicability to diverse exposure scenarios*: Exposure scenarios are characterized by sources or activities responsible for the exposure, microenvironments where the exposure takes place, properties of the agents that are released and contacted, and the roles and characteristics of the individuals of concern. The model developer should provide information on the exposure scenarios for which the model has been intended and the data used to develop the model and should describe the pollutants and pollutant classes to which the model is most applicable. The model developer should also describe the limitations of the model for its secondary or non-targeted applications.

4.2 Model inputs

5. *Description of data inputs*: Available exposure models vary in their demand for detailed input data. Screening-level models often require fewer inputs than more complex stochastic exposure and dose models. It is necessary that the model documentations and user manuals list the types and format of the input data required (e.g. emissions or concentration data, time–activity or questionnaire data on source use and building characteristics, census data, food or water consumption surveys, etc.). The format for these inputs is also critical for model users who must gather or select the inputs required for analysing each type of exposure scenario. Some inputs are chosen as deterministic single values, whereas others are probabilistic distributions representing variability in the input values across different subjects or households. The user has to specify the distributions for the probabilistic inputs to the exposure models, such as the SHEDS model. These distributions incorporate both variability and uncertainty. Compatibility with the survey data required by the model may also restrict its application to other intended applications of the model (e.g. multimedia analysis of a persistent pollutant may be limited if time–

activity surveys used by the model do not effectively capture dermal contact or the dietary and the non-dietary ingestion activities of the age groups of interest). Finally, the temporal resolution and the level of input data quality (including availability and completeness) needs for selected model applications have to be specified to allow better interpretation of the accuracy and precision of the model results. Models may depend on the availability of specific databases, from which they draw values, or even include the database in the model package. These should be spelled out in the model documentation, and possibilities/requirements for using alternative databases (e.g. time–activity database) should be described.

4.3 Model processes

6. *Modelling tool methodology*: The logic and methodology used in the design of the model (i.e. mechanistic or empirical, deterministic or stochastic) have to be identified and discussed by the model developer.

7. *Model code and platform*: The model description should also include an explanation of the model algorithms, with references to the published reports and articles describing them or appendices providing full description. The model hardware and software requirements and other computational system or platform needs should also be presented early in model user manuals and other accompanying documentations of the code.

8. *Model performance and evaluation summaries*: Models are used to provide estimates of concentrations, exposures, intakes or internal doses for realistic exposure scenarios. Confidence in the results obtained from these models depends on how well the models have been evaluated against actual field data. Thus, model users need to provide information on model performance and summaries of findings from any evaluation studies performed by either the model developers or other users of the model — in the format of peer-reviewed reports or articles.

4.4 Model outputs

9. *Description of model outputs*: The description of the type and form of model outputs should be specified in detail, along with pertinent examples to facilitate the evaluation, selection and application of the model by its intended users. Model outputs can vary substantially. Typical displays of model results range from tabular outputs to graphical displays, showing key model inputs as well as estimated outputs. Depending on the model and the objectives of the exposure analysis, model outputs can apply to individuals or populations and may include concentrations of environmental agents in different environmental media, route- and pathway-specific exposure concentrations, rates of inhalation and ingestion of the agent, internal doses for individuals and populations, and contributions of sources to exposures. The form of the outputs may be single numbers, statistics for a population or distributions across a population. Histograms, pie charts and frequency distributions, such as probability or cumulative distribution functions, are commonly used by recent models, as well as various percentiles of the predicted exposure or dose metrics

(e.g. mean, 50th percentile, 90th percentile, etc.). Export capabilities of the model outputs for post-processing are also essential for model users and should therefore be described.

10. *Model sensitivity and uncertainty analysis*: In addition, error estimates or confidence intervals associated with the key output variables may be available and are recommended for use in quantitative uncertainty analysis of the exposure-related results. Model sensitivity and uncertainty analysis is a critical component of identifying key inputs and parameters that influence the predicted exposures. A number of statistical methodologies, both parametric and non-parametric, can be used to determine and present the variability and uncertainty in modelled results. Some exposure models internally provide both diagnostic and prognostic tools that will allow the user to implement these statistical procedures directly. In other cases, the users are encouraged to save model inputs and outputs to perform quantitative sensitivity and uncertainty analysis using a variety of available commercial or free statistical software packages.

Table 3. Set of characteristics of a model that should be provided by the model developer and considered by the model user.

General model description

- Model name
- Full model name
- Program version, last update, next expected update, expected update features
- Responsible institution(s)
- Contact person(s)
- Contact address(es)
- E-mail(s)
- Availability

1. General description of the purpose of the model and its components

- What is the intended use of the model?
- What are the technical and regulatory requirements of the application (e.g. screening-level assessment, regulatory analysis)?
- Which exposure routes (dietary and non-dietary ingestion, inhalation, dermal) and pathways are considered?
- What is the scope of the basic model structure: single medium or multimedia, single or multiple chemical analysis?
- Outline the framework of the model, including key modules and analyses toolboxes.
- What are the important assumptions of the model (default values, etc., not covered in subsequent questions)?

Table 3. (contd)

2. Individual- or population-level analysis (level of aggregation)

- Is the model developed for individual, cohort, population or population subgroup assessment?
- Which sociodemographic definitions are required: age, gender, socioeconomic status, ethnicity, body weight, life expectancy, etc.?
- What are the relevant subject/cohort characteristics of the model — urban, rural, residence, workplace, occupation, building type, product use and other personal habits (e.g. smoking, cooking, etc.) — influencing exposures, etc.?
- What is the spatial resolution: grid size, local, regional, national?

3. Modelled time resolution

- Is the model intended for real-time exposure assessment: minutes to hourly calculations?
- Is the model developed for integrated exposure average: daily, seasonal, annual average or lifetime calculations?
- Does the model have the capability to model single event, intermittent event and/or continuous exposures?

4. Applicability to diverse exposure scenarios

- What is the model's applicability for different population groups (e.g. workers/labourers, consumers/users, residents/occupants, bystanders, vulnerable groups, etc.)?
- What is the model's applicability for different agents: phase (liquid/solid/gas; in air, gas/vapour/particles), organic/inorganic, reactivity?
- What is the model's applicability for different sources and activities?
- What is the model's applicability for different types of environments (e.g. residential indoor, workplace, recreational, etc.)?

Model inputs

5. Description of data inputs

- Which types of data are needed (measurements, physical and chemical characteristics of the agents, estimates from other models, questionnaires, time–activity data, etc.)?
- Which are the formats of data inputs (e.g. point estimates, variation, statistical distributions, original survey data)?
- Is the model connected to existing databases? If so, what are the database availabilities?
- How does the model treat input data limitations (data uncertainty, sparse data, missing data, non-representative, expert judgements, etc.)?

Model processes

6. Modelling tool methodology

- Is the model deterministic (physical/mechanistic)?
- Does it incorporate probabilistic (stochastic) simulation capabilities?
- Is it centrally based on statistical (empirical, e.g. regression analysis–based) components?
- Does the model incorporate other logics, e.g. Bayesian?

7. Model code and platform

- What is the programming software?
- What are the main model algorithms?
- What are the model's system requirements?

Table 3. (contd)

8. Model performance and evaluation summaries

- Availability of the model's quality assurance / quality control (QA/QC) documentation
- Model evaluation report(s)
- Verification and validation study results
- Other references (e.g. peer-reviewed publications)

Model outputs

9. Description of model outputs

- What are the model output formats: tables, figures, histograms and pie charts, distributions (e.g. probability/cumulative density functions)?
- What are the model output dimensions: media concentrations, intakes, doses?
- Does the model output data uncertainties?
- What are the post-processing/export capabilities of outputs?

10. Model sensitivity and uncertainty analysis

- Does the model provide identification of key inputs and parameters influencing results?
- Does the model output display predicted exposure profiles and associated uncertainties (variability and uncertainty analysis)?

An earlier version of these 10 principles for model characteristics description has been applied by the EC Joint Research Centre's Consumer Exposure Modelling Task Force to collect information about existing consumer exposure models worldwide (Consumer Exposure Modelling Task Force, 2004). The present formulation of the principles takes into account the experience gained in this exercise. Some principles underwent fundamental changes, others were just edited without changing the objectives and most were changed into the format of questions.

The consumer exposure models (i.e. models for exposures as a result of contact with consumer products) that were collected and reviewed by the EC Joint Research Centre's Consumer Exposure Modelling Task Force using the modified template included the following:

- CONSEXPO-3, National Institute of Public Health and the Environment (RIVM), The Netherlands
- PROMISE, American Chemistry Council
- E-FAST, Versar for USEPA
- SCIES, USEPA / Office of Prevention, Pesticides, and Toxic Substances
- DERMAL, USEPA / Office of Prevention, Pesticides, and Toxic Substances
- MCCEPA, USEPA / Office of Research and Development
- SHEDS, USEPA / Office of Research and Development
- DERM, Stanford University, USA
- AirPEx, National Institute of Public Health and the Environment (RIVM), The Netherlands
- BEAT, Health and Safety Laboratory, United Kingdom

- (CALENDEX, Novigen Science, Inc., database not available)
- CARES, CropLife America
- LIFELINE, LifeLine Group
- EUSES, National Institute of Public Health and the Environment (RIVM), The Netherlands, for Joint Research Centre / European Chemicals Bureau

The result of this ongoing consumer exposure model evaluation and intercomparison exercise will be published separately by the Consumer Exposure Modelling Task Force of the EC's Joint Research Centre (Institute for Health and Consumer Protection, Physical and Chemical Exposure Unit, Exposure Modelling Sector) in Ispra, Italy, in 2005.

REFERENCES CITED

Adolf T, Schneider R, Eberhardt W, Hartmann S, Herwig A, Heseker H, Hünchen K, Kübler W, Matiaske B, Moch KJ, Rosenbauer J (1995) *Ergebnisse der Nationalen Verzehrsstudie (1985-1988) über die Lebensmittel- und Nährstoffaufnahme in der Bundesrepublik Deutschland*. Niederkleen, Wissenschaftlicher Fachverlag Dr. Fleck (VERA-Schriftenreihe Band XI).

AIHC (2004) *Exposure Factors Sourcebook.* Washington, DC, American Industrial Health Council.

AUH (1995) *Standards zur Expositionsabschätzung*. Hamburg, Ausschuss für Umwelthygiene, Behörde für Arbeit Gesundheit und Soziales (http://www.uke.uni-hamburg.de/zentren/experimentelle_medizin/biometrie/publikationen/berichte/auh/index.de.html).

Axley JW (1991) Adsorption modeling for building contaminant dispersal analysis. *Indoor Air*, 1: 147–171.

Axley JW, Lorenzeti D (1993) Sorption transport models for indoor air quality analysis. In: Nagda NL, ed. *Modeling of Indoor Air Quality and Exposure*. Philadelphia, PA, American Society for Testing and Materials, pp. 105–127 (ASTM Special Technical Publication 1205).

BAGS, IMDM (1995) *Standards zur Expositionsabschätzung.* Hamburg, Behörde für Arbeit, Gesundheit und Soziales and Institut für Mathematik und Datenverarbeitung in der Medizin (http://www.uke.uni-hamburg.de/zentren/experimentelle_medizin/biometrie/publikationen/berichte/auh/index.de.html).

BgVV (2003) *Handbuch Lebensmittel-Monitoring.* Berlin, Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin (Federal Institute for Health Protection of Consumers and Veterinary Medicine).

Bogdanffy MS, Sarangapani R, Plowchalk DR, Jarabek A, Andersen ME (1999) A biologically based risk assessment for vinyl acetate–induced cancer and noncancer inhalation toxicity. *Toxicological Sciences*, 51: 19–35.

Brouwer DH, Kroese R, van Hemmen JJ (1999) Transfer of contaminants from surface to hands: experimental assessment of linearity of the exposure process, adherence to the skin, and area exposed during fixed pressure and repeated contact with surfaces contaminated with a powder. *Applied Occupational and Environmental Hygiene*, 14: 231–239.

Castle L, Kelly M, Gilbert J (1993) Migration of mineral hydrocarbons into foods. 3. Cheese coatings and temporary casings for skinless sausages. *Food Additives and Contaminants*, 10(2): 175–184.

Cattani M, Krzysztof C, Edwards J, Pisanielle D (2001) Potential dermal and inhalation exposure to chlorpyrifos in Australian pesticide workers. *Annals of Occupational Hygiene*, 45(4): 299–308.

CEFIC-LRI (2005) *ExpoFacts Sourcebook*. Brussels, European Chemical Industry Council, Long-Range Research Initiative Program (http://www.ktl.fi/expofacts).

Chang JCS, Guo Z (1994) Modeling of the fast organic emissions from a wood stain. *Indoor Air*, 4: 35–39.

Clancy L, Goodman P, Sinclair H, Dockery DW (2002) Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study. *The Lancet*, 360: 1210–1214.

Clausen PA, Wolkoff P, Holst E, Nielsen PA (1991) Long-term emission of volatile organic compounds from waterborne paints — methods of comparison. *Indoor Air*, 4: 562–586.

Cleek RL, Bunge AL (1993) A new method for estimating dermal absorption from chemical exposure, general approach. *Pharmacological Research*, 10: 497–506.

Consumer Exposure Modelling Task Force (2004) *Consumer Exposure Modelling Tools*. Ispra, European Commission, Joint Research Centre, Institute for Health and Consumer Protection, Physical and Chemical Exposure Unit, Exposure Modelling Sector (http://cem.jrc.it/cemdb/qstart.php).

Cooper JA, Watson JG (1980) Receptor oriented methods of air particulate source apportionment. *Journal of the Air Pollution Control Association*, 30: 1116–1125.

Cummins K, Morton D, Lee D, Cook E, Curtis R (1992) Exposure to acrylamide in chemical sewer grouting operations. *Applied Occupational and Environmental Hygiene*, 7(6): 385–391.

Dunn JE (1987) Models and statistical methods for gaseous emission testing of finite sources in well-mixed chambers. *Atmospheric Environment*, 21: 425–430.

Dunn JE, Tichenor BA (1988) Compensating for sink effects in emission test chambers by mathematical modeling. *Atmospheric Environment*, 22: 885–894.

EC (2004) *European Information System on Risks from Chemicals Released from Consumer Products/Articles*. Brussels, European Commission, Joint Research Centre (http://www.jrc.cec.eu.int/eis-chemrisks/).

EFCOSUM (2002) European Food Consumption Survey Method. *European Journal of Clinical Nutrition*, 56(Suppl. 2): S1–S96.

Enander RT, Cohen HJ, Gute DM, Brown LC, Desmaris AMC, Missaghian R (2004) Lead and methylene chloride exposures among automotive repair technicians. *Journal of Occupational and Environmental Hygiene*, 1: 119–125.

Environmental Quality Management, Inc. (2004) *User's Guide for Evaluating Subsurface Vapor Intrusion into Buildings.* Research Triangle Park, NC, United States Environmental Protection Agency.

ETAD (1983) *Final Report on Extractability of Dyestuffs from Textiles*. Basel, Ecological and Toxicological Association of Dyes and Organic Pigments Manufacturers (Project A 4007).

EU (1996) *Technical Guidance Document in Support of Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances and Commission Regulation (EC) No 1488/94 on Risk Assessment for Existing Substances (Part I) (1996).* Luxembourg, Office for Official Publications of the European Communities.

EU (2003) *Technical Guidance Document on Risk Assessment in Support of Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances & Commission Regulation (EC) No 1488/94 on Risk Assessment for Existing Substances*. European Union, European Chemicals Bureau, Institute for Health and Consumer Protection (http://europa.eu.int).

Frederick CB, Hazleton GA, Frantz JD (1990) The histopathological and biochemical response of the stomach of male F344/N rats following two weeks of oral dosing with ethyl acrylate. *Toxicologic Pathology*, 18: 247–256.

Frederick CB, Potter DW, Chang-Mateu MI, Andersen ME (1992) A physiologically based pharmacokinetic and pharmacodynamic model to describe the oral dosing of rats with ethyl acrylate and its implications for risk assessment. *Toxicology and Applied Pharmacology*, 114: 246–260.

Frederick CB, Lomax LG, Black KA, Finch L, Scribner HE, Kimbell JS, Morgan KT, Subramanian RP, Morris JB (2002) Use of a hybrid computational fluid dynamics and physiologically based inhalation model for interspecies dosimetry comparisons of ester vapors. *Toxicology and Applied Pharmacology*, 183: 23–40.

Freijer JI, Bloemen HJT, deLoos S, Marra M, Rombout PJA, Steentjes GM, van Veen MP (1998) Modelling exposure of the Dutch population to air pollution. *Journal of Hazardous Materials*, 61: 107–114.

Georgopoulos PG, Lioy PJ (1994) Conceptual and theoretical aspects of human exposure and dose assessment. *Journal of Exposure Analysis and Environmental Epidemiology*, 4: 253–286.

Global Net on Consumer Exposure Models (2004) *Minutes of the 1st Global CEM Net Workshop on Consumer Exposure Models Inter-comparison Exercise (Phase A).* Ispra, European Commission, Joint Research Centre, Institute for Health and Consumer Protection, Physical and Chemical Exposure Unit, Exposure Modelling Sector (http://cem.jrc.it/cemdb/qstart.php).

Hänninen O, Kruize H, Lebret E, Jantunen M (2003) EXPOLIS simulation model: $PM_{2.5}$ application and comparison to measurements. *Journal of Exposure Analysis and Environmental Epidemiology*, 13: 75–85.

Henry CR, Lewis CW, Hopke PK, Williamson HJ (1984) Review of receptor model fundamentals. *Atmospheric Environment*, 18: 1507–1515.

Heseker H, Oepping A, Vohmann C (2003) *Verzehrsstudie zur Ermittlung der Lebensmittelaufnahme von Säuglingen und Kleinkindern für die Abschätzung eines akuten Toxizitätsrisikos durch Rückstände von Pflanzenschutzmitteln (VELS)*. Paderborn, Universität Paderborn, Forschungsbericht.

Hovmand MF, Tjell JC, Mosbaek H (1983) Plant uptake of airborne cadmium. *Environmental Pollution (Series A)*, 30(1): 27–38.

ILSI (1999a) *Exposure to Contaminants in Drinking Water: Estimating Uptake through Skin and by Inhalation.* Washington, DC, International Life Sciences Institute, CRC Press.

ILSI (1999b) *A Framework for Estimating Pesticide Concentrations in Drinking Water for Aggregate Exposure Assessments: An ILSI Risk Institute Working Group Report*. Washington, DC, International Life Sciences Institute, ILSI Press.

IPCS (2004) IPCS glossary of key exposure assessment terminology. In: *IPCS Risk Assessment Terminology*. Geneva, World Health Organization, International Programme on Chemical Safety (Harmonization Project Document No. 1).

IRSN, ADEME (2003) *Base de données CIBLEX.* Institut de Radioprotection et de Sureté Nucléaire and l'Agence de l'environnement et de la maîtrise de l'énergie.

Jantunen MJ, Hänninen O, Katsouyanni K, Knöppel H, Künzli N, Lebret E, Maroni M, Saarela K, Srám R, Zmirou D (1998) Air pollution exposure in European cities: the EXPOLIS-study. *Journal of Exposure Analysis and Environmental Epidemiology*, 8: 495–518.

Johnson PC, Ettinger RA (1991) Heuristic model for predicting the intrusion rate of contaminant vapors in buildings. *Environmental Science and Technology*, 25: 1445–1452.

Kiilunen M, Aitio A, Tossavainen A (1997) Occupational exposure to nickel salts in electrolytic plating. *Annals of Occupational Hygiene*, 41(2): 189–200.

Kimbell JS, Overton JH, Subramaniam RP, Schlosser PM, Morgan KT (2001) Dosimetry modeling of inhaled formaldehyde: Comparisons of local flux predictions in the rat, monkey, and human nasal passages. *Toxicological Sciences*, 64: 100–110.

Klepeis NE (1999) An introduction to the indirect exposure assessment approach: Modeling human exposure using microenvironmental measurements and the recent National Human Activity Pattern Survey. *Environmental Health Perspectives*, 107: 365–374.

Klepeis NE, Nelson WC, Ott WR, Robinson JP, Tsang AM, Switzer P, Behar JV, Hern SC, Engelmann WH (2001) The National Human Activity Pattern Survey (NHAPS): a resource for assessing exposure to environmental pollutants. *Journal of Exposure Analysis and Environmental Epidemiology*, 11(3): 231–252.

Kroes R, Müller D, Lambe J, Löwik M, van Klaveren J, Kleiner J, Massey R, Mayer S, Urieta I, Verger P, Visconti A (2002) Assessment of intake from the diet. *Food Chemistry and Toxicology*, 40: 327–385.

Leijnse A, Hassanizaded SM (1994) Model definition and model validation. *Advances in Water Resources*, 17: 197–200.

Malm WC, Sisler JF, Huffman D, Eldred RA, Cahill TA (1994) Spatial and seasonal trends in particle concentration and optical extinction in the United States. *Journal of Geophysical Research*, 99: 1347–1370.

Margetts B, Nelson M (2003) *Design Concepts in Nutritional Epidemiology*, 2nd ed. Oxford, Oxford University Press.

Maroni M, Seifert B, Lindvall T, eds. (1995) *Indoor Air Quality. A Comprehensive Reference Book*. Amsterdam, Elsevier Science.

McCurdy T, Glen G, Smith L, Lakkadi Y (2000) The National Exposure Research Laboratory's Consolidated Human Activity Database. *Journal of Exposure Analysis and Environmental Epidemiology*, 10: 566–578.

McDevit JJ, Lees PSJ, McDiarmid MA (1993) Exposure of hospital pharmacists and nurses to antineoplastic agents. *Journal of Occupational Medicine*, 35(1): 57–60.

McKone TE (1990) Dermal uptake of organic chemicals from a soil matrix. *Risk Analysis*, 10: 407–419.

McKone TE, Howd RA (1992) Estimating dermal uptake of non-ionic organic chemicals from water and soil: I. Unified fugacity-based models for risk assessments. *Risk Analysis*, 12: 543–557.

Melchior Poulsen O, Olsen E, Molin Christensen J, Vinzent P, Holm Petersen O (1995) Geltape method for measurement of work related surface contamination with cobalt

containing dust: Correlation between surface contamination and airborne exposure. *Occupational and Environmental Medicine*, 52(12): 827–833.

Mensink GBM, Hermann-Kunz E, Thamm M (1998) Der Ernährungssurvey. *Gesundheitswesen*, 60(Special Issue 2): S83–S86.

Noll KE, Khalili E (1988) Dry deposition of sulfate associated with pollen. *Atmospheric Environment*, 22(3): 601–604.

NRC (1983) *Risk Assessment in the Federal Government: Managing the Process*. Washington, DC, National Research Council, National Academy Press.

NRC (1990) *Ground Water Models: Scientific and Regulatory Applications*. Washington, DC, National Research Council, Commission on Physical Sciences, Mathematics, and Applications, National Academy Press.

NRC (1991) *Human Exposure Assessment for Airborne Pollutants: Advances and Opportunities*. Washington, DC, National Research Council, National Academy Press, 321 pp.

NRC (1993) *Ground Water Vulnerability Assessment: Contamination Potential Under Conditions of Uncertainty*. Washington, DC, National Research Council, Committee on Techniques for Assessing Ground Water Vulnerability, Water Science and Technology Board, Commission on Geosciences, Environment, and Resources, National Academy Press.

OECD (2003) *Guidance Document on Reporting Summary Information on Environmental, Occupational and Consumer Exposure*. Paris, Organisation for Economic Co-operation and Development, Environment Directorate, Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology, December (http://www.olis.oecd.org/olis/2003doc.nsf/LinkTo/env-jm-mono(2003)16).

OECD (2004) *Test Guideline 428: Skin Absorption: In Vitro Method*. Paris, Organisation for Economic Co-operation and Development.

Oppl R, Kalberlah F, Evans PG, van Hemmen JJ (2003) A toolkit for dermal risk assessment and management: an overview. *Annals of Occupational Hygiene*, 47: 629–640.

Oreskes N, Shrader-Frechette K, Belitz K (1994) Verification, validation, and confirmation of numerical models in the earth sciences. *Science*, 263: 641–646.

Ott W, Thomas J, Mage D, Wallace L (1988) Validation of the Simulation of Human Activity and Pollutant Exposure (SHAPE) model using paired days from the Denver, CO, carbon monoxide field study. *Atmospheric Environment*, 22: 2101–2113.

Potts RO, Guy RH (1992) Predicting skin permeability. *Pharmacological Research*, 9: 663–669.

Reddy MB, Guy RH, Bunge AL (2000) Does epidermal turnover reduce percutaneous penetration? *Pharmacological Research*, 17(11): 1414–1419.

Reichl R, Inacker O, Roth K, Schrimm H, Sieber JP, Heeg P, Buess G (1995) Identification and quantification of surface contamination on surgical instruments with surface analytical methods after cleaning procedures. *Minimally Invasive Therapy*, 4(5–6): 325–327.

Robinson RJ (2005) Carcinogen specific dosimetry model for passive smokers of various ages. *The Science of the Total Environment*, 338(3): 201–212.

Ryan PB (1991) An overview of human exposure modeling. *Journal of Exposure Analysis and Environmental Epidemiology*, 1(4): 453–474.

Schauer JJ, Rogge WF, Hildemann LM, Mazurek MA, Cass GR, Simoneit BRT (1996) Source apportionment of airborne particulate matter using organic compounds as tracers. *Atmospheric Environment*, 30: 3837–3855.

Schneider T, Vermeulen R, Brouwer DH, Cherrie JW, Kromhout H, Fogh CL (1999) Conceptual model for assessment of dermal exposure. *Occupational and Environmental Medicine*, 56: 675–773.

Simpson AE, Roberts PJ, Christmas P, Woods MJ (1988) The accuracy of surface contamination measurements; survey of U.K. hospitals, 1986. *Applied Radiation and Isotopes*, 39(10): 1103.

Song X-H, Polissar AV, Hopke PK (2001) Sources of fine particle composition in the northeastern US. *Atmospheric Environment*, 35: 5277–5286.

Stubenrauch S, Hempfling R, Simmleit N (1995) Abschätzung der Schadstoffexposition in Abhängigkeit von Expositionsszenarien und Nutzergruppen. *Zeitschrift für Umweltchemie und Ökotoxikologie*, 7: 37–45.

Swinton J (1999) *A Dictionary of (Ecological) Epidemiology*. Cambridge, University of Cambridge (http://www.swintons.net/jonathan/Academic/glossary.html).

Tartre A (1992) Investigation of surface contamination in a cadmium pigment factory. *Applied Occupational and Environmental Hygiene*, 7(5): 318–322.

Tomerlin JR, Berry MR, Tran NL, Chew SB, Petersen BJ, Tucker KD, Fleming KH (1997) Development of a dietary exposure potential model for evaluating dietary exposure to chemical residues in food. *Journal of Exposure Analysis and Environmental Epidemiology*, 7(1): 81–101.

Turnbull AB, Harrison RM (2000) Major component contributions to PM_{10} composition in the UK atmosphere. *Atmospheric Environment*, 34: 3129–3137.

USEPA (1992a) *Dermal Exposure Assessment: Principles and Applications*. Washington, DC, United States Environmental Protection Agency (EPA/600/6-88/005Cc).

USEPA (1992b) Final guidelines for exposure assessment. *Federal Register*, 104: 22888–22938. Washington, DC, United States Environmental Protection Agency.

USEPA (1994) *Quick Reference Fact Sheet: DNAPL Site Characterization*. Washington, DC, United States Environmental Protection Agency (EPA/540/F-94/049).

USEPA (1997) *Exposure Factors Handbook*. Washington, DC, United States Environmental Protection Agency (http://www.epa.gov/ncea/pdfs/efh/front.pdf).

USEPA (1999a) *General Principles for Performing Aggregate Exposure and Risk Assessments*. Washington, DC, United States Environmental Protection Agency, Office of Pesticide Programs (Docket No. OPP-00732).

USEPA (1999b) Proposed Test Rule for In Vitro Dermal Absorption Rate Testing of Certain Chemicals of Interest to Occupational Safety and Health Administration. 40 CFR Part 799. *Federal Register*, 64(110): 31073–31090. Washington, DC, United States Environmental Protection Agency.

USEPA (2000) *Exposure Assessment Modeling System (EXAMS): User Manual and System Documentation*. Research Triangle Park, NC, United States Environmental Protection Agency (EPA/600/R-00/081, Revision B).

USEPA (2001) *Risk Assessment Guidance for Superfund, Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment), Interim.* Washington, DC, United States Environmental Protection Agency (EPA/540/R/99/005; http://www.epa.gov/oswer/riskassessment/ragse/index.htm).

USEPA (2002a) *Guidance for Quality Assurance Project Plans for Modeling: EPA QA/G-5M*. Washington, DC, United States Environmental Protection Agency, Office of Environmental Information (EPA/240/R-02/007).

USEPA (2002b) *Child-Specific Exposure Factors Handbook (Interim Report)*. Washington, DC, United States Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment (EPA-600-P-00-002B; http://fn.cfs.purdue.edu/fsq/WhatsNew/KidEPA.pdf).

USEPA (2003a) *Human Health Research Strategy*. Washington, DC, United States Environmental Protection Agency, Office of Research and Development (EPA/600/R-02/050).

USEPA (2003b) *Consolidated Human Activity Database (CHAD)*. Washington, DC, United States Environmental Protection Agency (http://www.epa.gov/chadnet1/).

USEPA (2003c) *Further Technical Details about HAPEM4*. Washington, DC, United States Environmental Protection Agency (http://www.epa.gov/ttn/atw/nata/modelexp.html).

USEPA (2004) *Report on the Model SHEDS-PESTICIDES.* Washington, DC, United States Environmental Protection Agency (http://cfpub.epa.gov/crem/crem_report.cfm?deid=75824).

USEPA (2005) *Human Exposure Modeling — Air Pollutants Exposure Model (APEX/TRIM.Expo$_{Inhalation}$)*. Washington, DC, United States Environmental Protection Agency (http://www.epa.gov/ttn/fera/human_apex.html).

van Hemmen JJ, Brouwer DH (1993) Predictive exposure modelling for pesticide registration purposes. *Annals of Occupational Hygiene*, 37(5): 541–564.

van Hemmen J, Auffarth J, Evans PG, Rajan-Sithamparanadarajah B, Marquart H, Oppl R (2003) RISKOFDERM: Risk assessment of occupational dermal exposure to chemicals. An introduction to a series of papers on the development of a toolkit. *Annals of Occupational Hygiene*, 47: 595–598.

Van-Wendel-De-Joode B, Brouwer DH, Vermuelen R, Van Hemmon JJ, Heederik D, Kromhout H (2003) DREAM: A method for semi-quantitative dermal exposure assessment. *Annals of Occupational Hygiene*, 47(1): 71–87.

Varner SL, Hollifield HC, Andrzejewski D (1991) Determination of benzene in polypropylene food-packaging materials and food-contact paraffin-waxes. *Journal of the Association of Official Analytical Chemists*, 74: 367–374.

Willett W (1998) *Nutritional Epidemiology*, 2nd ed. New York, NY, Oxford University Press.

Wilschut A, ten Berge WF (1995) Two mathematical models for skin permeation. In: Brain KR, James VJ, Walters KA, eds. *Proceedings of the Fourth International Prediction of Percutaneous Penetration Conference, La Grande Motte, April*. European Union, EDETOX.

Wilschut A, ten Berge WF, Robinson PJ, McKone TE (1995) Estimation of skin permeation. The validation of five mathematical skin permeation models. *Chemosphere*, 30: 1275–1295.

Wilson WE, Mage DT, Grant LD (2000) Estimating separately personal exposure to ambient and nonambient particulate matter for epidemiology and risk assessment: Why and how. *Journal of the Air and Waste Management Association*, 50(7) (http://www.awma.org/journal/ShowAbstract.asp?Year=2000&PaperID=155).

Yoshida K, Fuzesi I, Suzan M, Nagy L (1990) Measurements of surface contamination of spray equipment with pesticides after various methods of application. *Journal of Environmental Science and Health, Part B*, 25(2): 169–183.

Zaleski R, Gephart L (2000) *Exposure Factors Sourcebook for European Populations, with Focus on UK Data*. Brussels, European Centre for Ecotoxicology and Toxicology of Chemicals (Report 79).

Zartarian VG, Ozkaynak H, Burke JM, Zufall MJ, Rigas ML, Furtaw EJ Jr (2000) A modeling framework for estimating children's residential exposure and dose to chlorpyrifos via dermal residue contact and non-dietary ingestion. *Environmental Health Perspectives*, 108(6): 505–514.

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