Exposure Modeling and Measurement: Exposure Factors

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Abbreviations

PBPK physiologically based pharmacokinetic
SOP standard operating procedure

Introduction

Exposure Factors and Their Impact on Risk Assessment

Common daily activities, such as eating, showering, commuting, hobbies, and exercising, bring everyone into contact with potentially hazardous chemical and biological agents. The overall goal of risk analysis is to assess the health impact of these agents, and the risk assessment process combines estimates of exposure and potency of agents to develop qualitative and quantitative estimates of the potential health risks. The estimation of potency of an agent is typically derived from dose–response functions developed using data from experimental animal or human studies. For many activities, however, the exposure assessment process is complex and the estimation process uncertain because of a lack of understanding of human characteristics and behaviors that drive exposures in the most highly exposed or vulnerable populations. The lack of well-characterized scenarios, measurement data, and adequately detailed models describing the magnitude, frequency, and duration of exposure is a major impediment to understanding and developing exposure reduction, elimination, or risk management strategies.

The term ‘exposure factors’ has evolved to define disparate types of data that describe human characteristics and behaviors that are essential for the estimation of human exposure to environmental chemical, biological, and physical agents. Exposure factors include media-specific intake rates, human body characteristics and behavior patterns, and chemical-specific data that are required to estimate exposures under specific scenarios. Intake rates include dietary factors (e.g., food and water consumption rates, and percentage of diet from homegrown foods), inhalation rates, and dermal permeation coefficients for specific chemicals or classes of compounds. Human body characteristics include bodyweight or skin surface areas, time–activity patterns, and frequency of mouthing behaviors. Exposure factors are also data that pertain to specific scenarios, such as soil adherence factors, consumer product use, and residential characteristics (e.g., duration of home ownership).

Exposure factors are important because they link measurements and models to actual human exposure. Both measurements and models are used to trace a chemical’s movement through the environment and ultimately to human contact (Figure 1). In this process, different types of models (e.g., fate and transport, exposure, and physiologically based pharmacokinetics (PBPK)) are used to estimate concentrations in environmental media, various pathways, and ultimately humans. Probabilistic models that link human behavior and activities to specific exposures are increasingly being developed to help answer risk assessment and management questions. Although measurements serve as the basis for all models, it is increasingly clear that models to predict human exposure and risk need to address the variability in exposure to multiple chemicals. This process has come to be called aggregate and cumulative exposure and risk assessment: in this context, aggregate means adding up exposure to a single chemical by all relevant routes (inhalation, ingestion, and dermal absorption) and cumulative describes the process of summing the effects of all compounds with a similar mechanism of action. Models to estimate aggregate and cumulative exposures and risks meld chemical measurements and assumptions to develop exposure estimates that typically vary over a wide range of values with a large confidence interval due to the nature and quality of the underlying data and judgments. This makes substantive characterization of the underlying variability and uncertainty and their effects on model outputs important. Models are typically validated, to the extent possible, using sensitivity analysis, by comparing results of multiple models, or doses derived from biomonitoring in an attempt to understand the ‘true’ exposure.

This article describes the exposure assessment process, with a focus on the human exposure factor data used to model exposures. It describes the basic underlying equations, approaches, and the interplay between measurements and models that is essential to conduct quantitative exposure assessment. It also summarizes the main uses of exposure factors in modeling exposure, and highlights the impact of assumptions, variability, and uncertainty on the exposure estimation process. Examples from the field of children’s exposure to pesticides are used to demonstrate some of the key concepts and illustrate the complexities of the process.

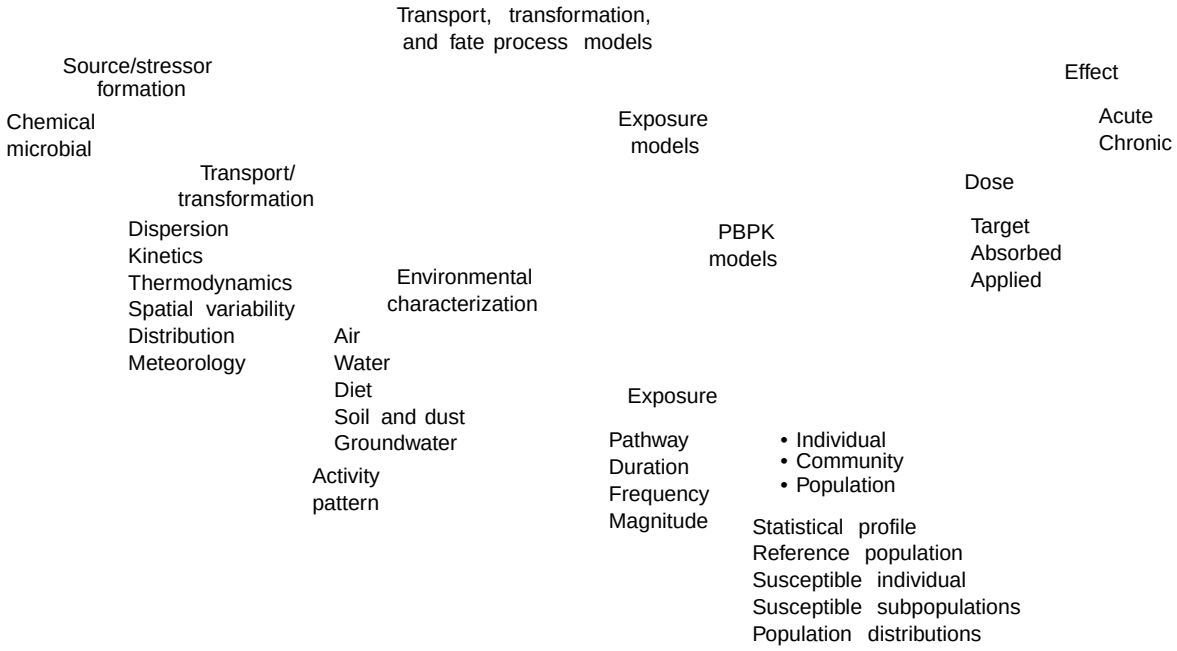

Figure 1 The environmental health paradigm illustrating the source to dose continuum, showing the importance of media measurements, activity patterns, and other exposure factors, and models for estimating exposure and health effects From WHO (2007) Principles for evaluating health risks in children associated with exposure to chemicals. In: Environmental Health Criteria, vol. 237. IPCS, WHO.

Exposure Assessment Process

Basic exposure equations

The exposure assessment process identifies potential exposed populations, pathways, and exposure conditions, and quantifies the magnitude of chemical intakes and potential doses (PDs). Exposure is commonly defined as contact between an agent and a target, individual, or population, taking place at a specified surface over a defined interval. Dose refers to the mass of a chemical or agent that crosses an organism's external boundaries, and is dependent on the concentration in environmental media, the rate of intake (e.g., inhalation rate), and uptake (e.g., absorption rate). PD is the mass that potentially could be inhaled, ingested, or deposited on the skin, and absorbed dose is that which passes through the exposure boundary layers (e.g., surface of the lung or gastrointestinal tract) and into the body. PD is typically calculated using the following formula:

$$PD = C \quad IR \qquad [1]$$

where PD is the potential dose (mg or mg per day), C the contaminant concentration in a specific environmental media (mg m^{3}, mg l^{1}, mg g^{1}, or mg cm^{2}), and IR the media intake or contact rate (m^{3} per day, l per day, or m^{2} per day).

PD is dependent on both concentration and exposure factors that influence intake rates and contact opportunities. The media-specific concentration for any pathway of exposure may be measured or modeled, depending on the scenario of interest and the availability of relevant data. The contact rate may also be expressed as the product of more than one term, such as dermal contact with soil, which is the product of skin surface area in contact in square centimeters per day times the soil adherence factor in milligrams per square centimeter. Although models to predict concentrations in specific media at particular times are important in the calculation of PD, it is clear from eqn [1] that exposure factors can strongly influence the magnitude of PD, especially if they have large uncertainties.

A PD is typically normalized to bodyweight (or in some cases surface area) to obtain dose in units of milligrams per kilogram bodyweight per day (mg per kg bodyweight per day) by multiplying exposure factors that express duration and frequency to yield time-averaged potential daily dose:

$$ADD_{(pot)} = \frac{PD \quad ED \quad EF}{BW \quad AT} \qquad [2]$$

where $ADD_{(pot)}$ is the potential average daily dose (mg kg^{1} per day), ED the exposure duration (days per year), EF the exposure frequency (years), BW the bodyweight (kg), and AT the averaging time (days).

Although days have been used in the aforementioned example, hours can be substituted for days for cases where acute exposure is the concern and the IR and the PD are adjusted to be consistent with this shorter timeframe. Thus, with adjustments, eqn [2] can be used to

(LADD) by varying the AT. The ADD is typically used for assessment of noncancer health effects, whereas the LADD is used for calculation of lifetime excess cancer risk, even though the exposure does not necessarily occur over the entire lifetime (typically 70 years).

Absorbed doses are calculated by multiplying an absorption factor:

$$\mathrm{ADD}_{\mathrm{abs}} = \mathrm{ADD}_{\mathrm{pot}} \times \mathrm{ABS} \quad (3)$$

where ABS is an absorption factor (unitless).

The use of an absorption factor is less common and may not be necessary in screening assessments for some routes (e.g., inhalation and ingestion) but is often necessary for a realistic assessment of dermal exposures when the contaminant in question is present in a large volume of media, for example, dermal exposure to trihalomethanes in a contaminated pool.

Populations and exposure factors

Exposure assessments are typically done for a defined population, for example, the general population of individuals in a country, adults of working age, or children less than 10 years old. In many cases, defined subpopulations have activities or behaviors that make them more likely to be in contact with an agent, such as households that use pesticides frequently or individuals who raise some of their own food. Children have become a source of special attention because normalized to bodyweight, they have higher intakes of air, water, and food than adults, may be more sensitive to the effects of exposures, and have more years ahead to develop disease. As a consequence, exposure factor databases have been developed for children summarizing their special characteristics and behaviors that may lead them to be more highly exposed (Table 1), typically through techniques that quantify typical behaviors, such as hand–to–mouth ingestion, that may drive exposure in young children.

Exposure assessment approaches

Exposure assessment for environmental agents involves use of both qualitative and quantitative data to describe contact with and entry into the human body. The quantitative estimation of chemical exposure can be approached in three ways: personal measurements, biomonitoring, or scenario–based assessment. Although these three methods are used to assess exposures, scenarios are central to the exposure assessment process in environmental decision making because they underlie the deterministic and probabilistic models used to make decisions about potential risk of new products or aggregate or cumulative risk of existing hazardous materials.

Personal measurements and biomonitoring are complementary methods, based on direct measurements of media or the tissues of an exposed population. Both

Table 1 Examples of authoritative exposure factor databases available online

Author (source)	Title	Main variable categories	Data examples
Joint Research Centre of the European Commission (http://cem.jrc.it/expofacts/index.php)	ExpoFacts: Exposure Factor Sourcebook for Europe	Countries	Air exchange rates
		Housing	Housing tenure
		Ingestion	Food consumption (by EU nation, age)
		Nondietary ingestion	Water source, ingestion rates
		Physiology	Energy expenditure
		Population	Birth rates, marital status
		Time–activity patterns	Time use, physical activity level
US Environmental Protection Agency (USEPA) (http://www.epa.gov/ncea/pdfs/efh/front.pdf)	Exposure Factors Handbook (EPA/600/P–95/002Fa–F)	Physiology	Bodyweight, height, skin surface area
		Time–activity	Time spent indoors, hours at home/work, work tenure, shower duration, time use patterns
		Receptor contact rates	Soil consumption rates
			Dietary composition: home–produced food, fat consumption, serving size, fish intake rates
			Drinking water intake, sources
			Inhalation rates
USEPA (http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=458966)	Child–Specific Exposure Factors Handbook (EPA/600/R/06/096A)	Breast milk	Intake rates, lipid and fat content, nursing infant population characteristics
		Food intake	Age–specific food intake distributions
		Fish consumption	Native American subsistence population consumption rates
		Total dietary intake	Fat intake, total dietary intake
Conversion factors		Wet to dry weight conversion	
		Meat and dairy fat content	

methodologies are increasingly used, but are still less common than scenario−based methods because of costs involved in their collection and because necessary data, measurement devices, and models are not available to provide interpolation of the health implications for all the situations and populations of interest with sufficient temporal and spatial specificity. Nonetheless, biomonitoring is increasingly used to characterize exposures, to track trends in populations over time, and as benchmarks for interventions. Although biomonitoring has long been used to estimate effects of compounds for which there is a substantial database on both exposure and effect levels, such as lead, in the past decade it is only beginning to be used to relate body burden of other chemicals to health−related benchmarks through a variety of methods.

Thus due to a lack of data, the most common approach to estimating exposure is scenario−based exposure assessment, which requires the analyst to use available information (e.g., environmental measurements and exposure factors), in combination with inferences and professional judgment, to construct a plausible set of assumptions (i.e., a scenario) that describes quantitatively how contact occurs between people and chemicals.

A typical scenario−based approach estimates pesticide exposure by merging the two main components of exposure: (1) concentration of the chemical in an environmental media, estimated by using monitoring data or models that quantify the relationship between sources, pathways, and media concentrations; (2) people's contact time with the carrier medium, estimated by using existing demographic, geographic, and time–activity data or by making reasonable assumptions about population or individual activity patterns, proximity to sources, and other factors. PDs estimated using this method incorporate data and assumptions about relevant intake and uptake processes. Two variations in the scenario−based approach are: (1) 'microenvironmental' methods, which combine measurements in important microenvironments (e.g., inside the residence and outdoors in the community) with data on time–activity patterns, and (2) macroactivity methods, which combine measurements in important environmental media (e.g., air, water, food, soil, and dust) with default exposure factors and assumptions about time use for an entire population (e.g., volume of air breathed or water consumed per day, bodyweight, and skin surface area). Examples of different types of route or chemical−specific data and both behavioral and activity exposure factors used in constructing exposure scenarios are shown in Figure 2.

The primary advantage of scenario−based approaches is that they enable assessors to estimate exposures and doses when data are limited, which is commonly the case. The uncertainties introduced by the need to make assumptions and inferences due to inadequate information are also their major disadvantage. When used in deterministic models, scenario−based assessments typically do not include a complete description of the exposure and dose distribution for the population of interest: typically they provide only a single−point estimate along a hypothesized population distribution of exposures. The main points of interest on the exposure distribution are typically the central tendency (median or average) exposures, the 'high−end' exposure (typically the 90th percentile and above), and the most exposed individual in the population. Although the scenario−based approach is frequently used, it is most scientifically defensible when the analyst has some insight into the validity of underlying assumptions and judgments. Despite these limitations, scenario−based approaches remain the only viable method for estimating exposure and dose in the absence of extensive personal or direct measurements and comprehensive aggregate and cumulative models.

Scenario−based deterministic approaches are specified, for example, in the US Environmental Protection Agency's standard operating procedures (SOPs) for pesticide exposure assessment in residential settings, which provide standard default methods for assessment of both handler (i.e., the individual applying the pesticide) and postapplication exposures when chemical or site−specific data are limited. These SOPs are for deterministic 'high−end' exposures so that the residential lawn scenario, for example, outputs a point estimate or range that is assumed to represent the upper end of the distribution of exposures that could occur from lawns, parks, playgrounds, recreational areas, athletic fields, and other turf areas. These scenarios typically rely on one or more upper percentile assumptions, such as the 90th percentile value for exposure duration and the 90th percentile value for skin surface area exposed. They are intended to represent 'tier 1' assessments that can be used to indicate whether a more detailed assessment is warranted, possibly including collection of chemical− or site−specific data. A tier 1 assessment uses a 'conservative' screening scenario to make 'worst case' or 'bounding' estimates (e.g., maximum pesticide application to 100% of turf). If this analysis suggests a possible problem, estimates can then be refined in subsequent tiers using progressively more realistic assumptions and values (e.g., average pesticide residues on percentage of turf actually treated). These 'high−end' deterministic models produce point estimates or a range of point estimates, but cannot present any distribution of exposures or statistical error term because they have no way to propagate measurement error or underlying uncertainty.

Variability/uncertainty analysis

Efforts to address these underlying uncertainties, which are often driven by incomplete or undercharacterized exposure factors, involved developing models that pro−

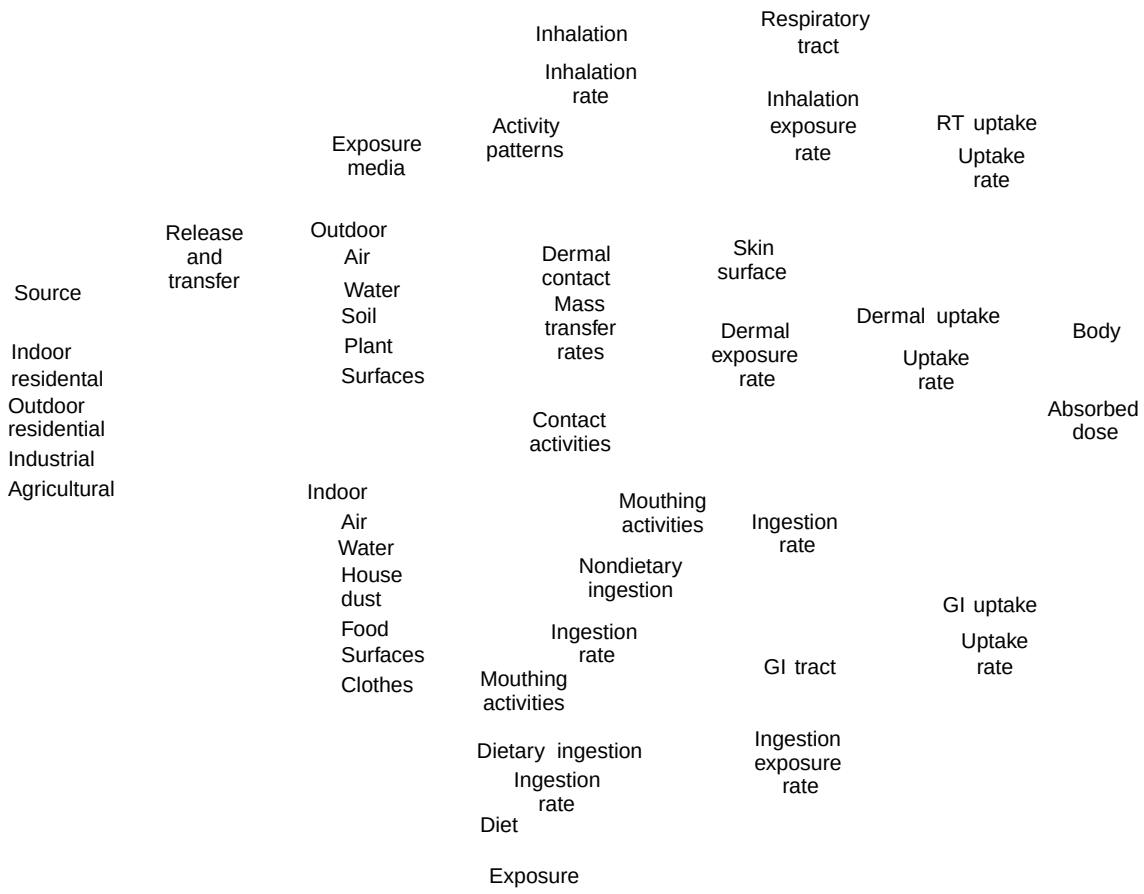

Figure 2 The major exposure pathways and the importance of both route or chemical−specific (inverted triangles) and behavioral and activity exposure factors (ovals) in estimating exposure. Reproduced from Cohen Hubal EA, Sheldon LS, Zufall MJ, Burke JM, and Thomas K (2000b) The challenge of assessing children's residential exposure to pesticides. Journal of Exposure Analysis and Environmental Epidemiology 10: 638–649, with permission from Nature Publishing group.

around exposure estimates. The most common way by which this is accomplished is using stochastic models (e.g., Monte Carlo methods) that use a large number of trials to develop probabilities of an event as outputs provide distributions of exposures within a defined population. A number of different commercial (DEEM, Calendex, and CARES) and noncommercial models or modeling frameworks (SHEDS and Mentor) have been developed to address these issues. These models attempt to address the impact of both uncertainty and variability on model outputs.

There are three main categories of uncertainty in exposure factor measurement studies:

1. natural variation in the levels of some quantity, for example, children's water intake over time and space and between individuals;
2. sampling and analytical variability, or random errors in the collection or analytical method used to measure some parameter, for example, error associated with quantification of children's hand−to−mouth behaviors;
3. incomplete scientific or technical knowledge, that is, the inability to measure pesticide loading on a hand

Although variability in a parameter can be characterized using sampling statistics, in many instances uncertainty arises because 'we do not know what we do not know.' In many exposure assessment scenarios, this uncertainty dominates the overall uncertainty. Often classical stat−istics is unable to cope with such situations, and Bayesian approaches are increasingly being used to address this problem.

In contrast to uncertainty, variability is the real dif−ference among individuals, cases, or categories of some parameter, and it is a property of the population of things studied. In this context, variability is distinct from the population characteristics. For example, if one measures drinking water consumption rates of 25 children, the differences in intake rates are real, independent of the precision of the tools used to measure the volumes consumed. In contrast, uncertainty is due to imperfect knowledge of the true value of the parameter being measured.

There are at least three features of variability and two of uncertainty that are underappreciated in the context of exposure and risk modeling. First, for variability, the use

to overstate the true underlying variability, because they include measurement error of the parameter in question. Second, a nonrepresentative sample for any parameter reduces the overall accuracy of any assessment, especially since factors are often multiplied, which expands the impact of errors. Last, in exposure assessment, the magnitude of variability is strongly influenced by averaging time, with longer times tending to reduce observed variability by diluting short-term fluctuation. The two features of uncertainty that are not fully appreciated in the context of exposure and risk assessment are the following:

1. the use of the standard error statistic to describe a data set or sets tends to understate uncertainty, because it excludes unsuspected systematic error that affects all data points, such as an unrepresentative sampling frame for a population parameter;
2. an incomplete tabulation and appreciation of model errors reduced the accuracy of model predictions.

The new generation of exposure models attempts to compensate for the shortcomings through systematic variability and uncertainty analysis.

Overall, use of exposure factors in exposure modeling is complex and limited by available data and models that can be used to assess variability and uncertainty. As a consequence, statistical models and judicious assumptions are necessary to address this problem, because it is not possible to measure all possible exposure pathways or all parameters necessary to develop a comprehensive exposure or risk profile across the affected population(s). Understanding the impact of expert judgment on the selection of parameters is crucial to understanding the uncertainties inherent in exposure and risk assessment.

Further Reading

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Relevant Websites

www.who.int/ipcs
International Programme on Chemical Safety.

www.epa.gov
United States Environmental Protection Agency.