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D36 Exposure-Intake models

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CONTENT

1. Introduction

Intake can be considered either the next step in the source-impact chain after exposure, or as a substitute for exposure (Figure 1). The latter is particularly appropriate for the ingestion and dermal absorption pathways. For dermal absorption and inhalation intake, contact time with the contaminated media should be included. A general representation of intake is as follows:

Intake = source emission x dilution x temporal decay x removal x medium transfer x inhalation/ingestion

Intake can be quantified as a rate or a total mass amount. Many exposure models, especially those that deal with the ingestion and dermal pathways, include intake. Intake rates are usually specified as an average value. They may be further specified by age, gender, and activity level. It is also possible to derive a distribution of intake rates to be used in probabilistic modeling, although a single value is sometimes used.

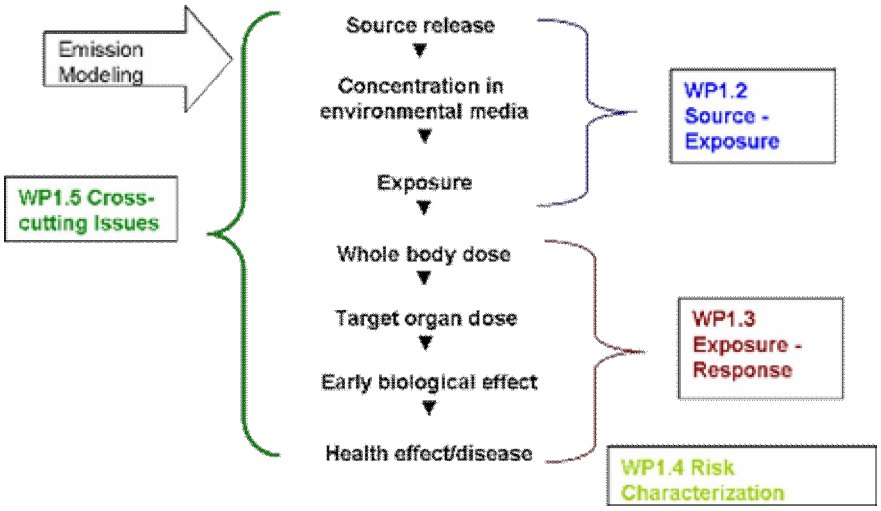

Figure 1: Steps in risk assessment chain

We can also directly relate intake to source. This provides a measure of how much of an agent that is released is taken up by the exposed population. This metric is called "intake fraction" or iF, the portion of a mass emission of a pollutant that is eventually taken in by the exposed population. Mathematically, intake fraction is the mass intake of a pollutant by a population divided by the mass emissions of that pollutant from a source. It is thus unitless, providing a metric that can be used to compare different pollutants, sources, and exposure pathways. Moreover, given certain assumptions about the dose-response of a pollutant, risk can be calculated from intake fraction. This metric can also be useful as a first-order approximation of population exposure in a situation where measurements and more sophisticated modelling has not been done, but basic information on pollutant characteristics, exposure pathways, and the population are known. This aspect of intake fraction is due to its relative robustness, at least on an order of magnitude scale, based on the consistency of estimates for certain types of pollutants from specific sources.

This report provides a review of modelling principles for three intake pathways: inhalation, ingestion, and dermal absorption. Several models will be summarized along with references to data sources.

1.1 Intake vs. Dose

A distinction should be made between intake and dose, as these two terms are related and may be confused, particularly for certain exposure pathways. *Intake* will be defined as the amount of an agent entering the body but NOT being absorbed through a protective layer (epithelial tissue of the respiratory and gastrointestinal tracts). In general, *dose,* as defined by the IPCS in its Report on Risk Assessment Terminology [1], is the "total amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub)population", which may be interpreted variously. In this document following the IPCS and Ott [2], we the process of absorption, or the crossing of an absorption barrier, can be defined as *uptake* and the resulting amount that enters the body\'s circulation is the *internal or absorbed dose*. Dose can further be subdivided into *dose to target organ*. Dose will be briefly mentioned but details on dose estimation will not be addressed in this report. Instead, this report focuses on methods for estimating intake through different exposure pathways.

1.2 Calculation of Intake for Risk Assessment

For non-cancer risk assessment, intake for risk assessment can be compared to a *tolerable intake*, which is defined as the "estimated maximum amount of an agent, expressed on a body mass basis, to which each individual in a (sub)population may be exposed to over a specified period without appreciable risk" [1]. For chronic effects, the Acceptable Daily Intake (ADI), Tolerable Daily Intake (TDI), and Reference Dose (RD) similarly refer to a daily intake amount for which an individual might be exposed over a lifetime without any noticeable increase in health risk. Intake for a particular exposure scenario may be calculated and compared to the ADI to determine whether exposure is above this threshold level. For cancer risk assessment, risk can be assessed by multiplying the cancer potency factor (mg/kg per day) by the intake rate. Here the averaging time would be a lifetime. For exposures over shorter time periods of interest, the averaging time is adjusted to the appropriate time frame. Thus, the overall intake of an agent can be defined as:

$$AverageDailyIntake = \frac{C \times IR \times ED}{BW \times AT}$$

where C = concentration in media of interest; IR = the intake rate; ED = exposure duration; BW = body weight; and AT = the averaging time of interest. Generally, intake should be in units that match the dose-response function (e.g. mg/kg per day) to provide a means of estimating health risk.

1.3 Sources of Intake Information

Ideally, intake rates and data should be specific to the population being assessed. In reality, data is likely not available in such cases. In such cases, the investigator should use the closest available data, for example, from the same country or region and (sub)population. Among the more comprehensive and internationally used sources of exposure factor data include the EXPOFACTS database, which includes data from various European countries, and the U.S. Environmental Protection Agency's (US EPA's) Exposure Factors Handbook. The latter results from a systematic

review of the literature, although it is geared towards the U.S. population. Often values from the Handbook are used as defaults in the absence of local data. The Exposure Platform [2] contains more information on sources of exposure factor data.

1.4 Variability and Uncertainty

Intake varies within and between populations, and therefore assessors should take this into consideration. In a deterministic analysis, an effort to use at least a low, middle, and high estimate of intake to examine the sensitivity of the results to intake rates. Often some aspect of the distribution is reported in studies or databases – either a mean and standard deviation or percentiles. Probabilistic analyses can also be done, and distributions have been developed for some intake rates in the Exposure Factors Handbook. Distributions from studies not included in the Handbook may be developed from reported parameters. Lognormal distributions are often assumed, but an assessment as to the validity of this assumption should be made. The Handbook has several recommendations as to the use of exposure factor data in probabilistic analyses.

There are also several sources of uncertainty related to the use of intake data. These include measurement errors in the studies, extrapolation of long-term patterns from short-term studies, and errors in characterizing the variability (across time, space, and populations). Missing data may also be a problem, and in some cases, the assessor must evaluate whether substituting data from another situation is appropriate.

2. Inhalation pathway

We can define *inhalation intake* as the mass of an agent that passes into the respiratory tract, beginning at the nose and mouth [3]. Therefore, intake is the exposure concentration (mass/volume) multiplied by the volumetric inhalation rate (volume/time). When a person breathes, air passes through several passages through which absorption through the epithelial layers of the respiratory tract is possible. The amount absorbed through this surface is the *absorbed dose*. Health effects can result from the absorbed dose or from irritation through contact of the pollutant with the boundary layer of the respiratory tract. Gaseous pollutants can reach to the smallest branches of the airways, and can diffuse into the bloodstream. Particles are subject to settling and inertial forces and thus particles deposit in the airways differentially according to size. Sequentially, the first area of the respiratory system to be crossed is the oronasal (nose and mouth), then the pharyngealCoarse particles (~ >10 μm) will generally deposit in the naso-pharyngeal region while finer particles deposit in the pulmonary regions and ultrafine particles (<0.5 μm) can also diffuse through the epithelial lining of the respiratory tract. Breathing rate and tidal volume also have an effect on particle deposition.

Breathing rates are in units of volume per time, e.g. m^3/day. Exposure factor sources, such as the U.S. EPA's Exposure Factors Handbook, report options for average breathing rate per day, stratified by gender and age, as well as activity-specific breathing rates, generally as an average per hour. These were derived from a review of the literature. These rates, however, have been acknowledged as overestimates of population breathing rates, and often a study by Layton, which provides methods for assessing breathing rates using metabolic data is used to derive rates [4]. While breathing rates are usually used as point estimates, there is a move towards incorporating population variability by generating distributions of breathing rates. The U.S. EPA has provided some guidance towards developing such distributions [5, 6].

2.1 Inhalation Models

Inhalation is generally modelled by multiplying the exposure concentration with the breathing rate. Modellers may chose a single average breathing rate or a distribution of breathing rates appropriate to the population being studied. Some existing models that calculate inhalation intake include the Stochastic Human Exposure and Dose Simulation (SHEDS) model for PM2.5 and CONSEXPO, for consumer products.

3. Ingestion pathway

The ingestion pathway includes several media, such as plant and animal food substances, water, breast milk, and non-food items, such as dust or soil and objects. The latter is particularly relevant for children, who have a tendency to crawl on the ground and put various objects into their mouths. Intake rates for these media are addressed in various databases or handbooks (e.g. EXPOFACTS and the U.S. EPA Exposure Factors Handbook) as well as studies throughout the literature. The relevant ingestion pathways depend on the agent of concern and the population of concern. Societal attributes such as cultural, national, and socio-economic may have a direct impact on the ingestion pathway, affecting the types of food ingested and cooking practices as well as rates of ingestion.

Food or dietary ingestion presents several issues for consideration. One is the composition of the diet (e.g. fruits, vegetables, meat, dairy, etc.) and the frequency of eating these foods. Another issue is that of "as consumed" versus "dry weight", which refers to the weight of the food consumed either as it is eaten, or after the moisture weight has been removed. The cooking process may either remove or increase the concentration in a food item, therefore the consumption and method of cooking food may be important for some agents. Additionally, some food items may be important sources of exposure for certain compounds. Food intake data usually come from diaries kept by study subjects, 24-hour recall, or food frequency questionnaires. These tend to only provide short-term consumption data.

3.1 Ingestion Models

Some models that address dietary exposure are the Dietary Exposure Potential Model (DEPM) from the U.S. EPA [6], and some multi-media models such as EUSES, IMPACT2000, and Caltox (??). Food chain models are further detailed in a fact sheet in D-14 of the Source -Exposure protocol. Non-dietary exposure factors for children is quantified in SHEDS-pesticide.

4. Dermal pathway

Exposure through dermal pathway is the most challenging of the three intake routes. Main issues effecting to this are the facts that several exposure media and possible exposure scenarios have to be considered and in additions the properties of the exposed chemical effects to the intake level. Exposure medium can be air, water, soil, dust or various consumer products, such as cosmetics, clothes, cleaning products etc., as liquids, creams or vaporizing fumes. As a result of this dermal intake might take place during several activities including household works, personal hygiene, hobbies, and basically during normal every day living by just wearing your clothes.

Properties of the exposed chemical and also properties of the exposed skin have a major effect in dermal intake. In order to penetrate the skin, chemical need to have ability to penetrate the skin i.e. it

needs appropriate partition capabilities. Also the condition of the exposed skin effects in this stage so that skin with some injuries might increase the level of intake.

When calculating dermal intake several factors need to be defined. These are 1) the chemical concentration in contact with the skin, 2) the extent of skin surface area exposed, 3) the duration of exposure, 4) the absorption of the chemical through the skin i.e. permeability or absorption coefficient, and 5) frequency of the exposure event. With these factors the internal dose can be calculated. In addition it's possible to calculate one step further by considering the amount of chemical that can be delivered to a target organ i.e., biologically effective dose. This is also dependable of the chemical properties, and also variable depending of the metabolism of the exposed individual.

Following equation for calculation of average daily dose through dermal intake is provided by EPA [7]:

$$ADD = \frac{DA_{event} \times EV \times ED \times EF \times SA}{BW \times AT}$$

Equation 1.

where

DA_{event} = absorbed dose per event (mg/cm^2) (see next chapter);

EV = event frequency (events/day);

ED = exposure duration (years);

EF = exposure frequency (days/year);

SA = skin surface area available for contact (cm^2);

BW = body weight (kg); and

AT = averaging time (days) for noncarcinogenic effects, AT = ED and for carcinogenic effects, AT = 70 years or 25,550 days.

4.1 Dermal absorption

Dermal absorption is defined by OECD to describe the transport of chemicals from the outer surface of the skin to the systemic circulation [8]. This is often further divided into:

- penetration, which is the entry of a substance into a particular layer or structure, such as the entrance of a compound into the stratum corneum;
- permeation, which is the penetration through one layer into a second layer that is both functionally and structurally different from the first layer; and
- resorption, which is the uptake of a substance into the skin lymph and local vascular system and in most cases will lead to entry into the systemic circulation (systemic absorption).

For calculation of absorbed dose per exposure event (equation 1; DA_{event}) following values are needed: concentration of chemical in exposure medium, permeability coefficient and duration of exposure event. Definition of these values is related to the situation so that the partitioning of chemical in exposure medium has to be taken into account with variables dependable of the situation. More guidance for this can be found from EPA's document Dermal Exposure Assessment: Principles and Applications [7].

Absorption fractions and permeability coefficients can be and have been measured for some chemicals with in vivo and in vitro studies. Some guidance on how to manage dermal absorption in dose calculations is provided in documents by World Health Organization [9] and European Commission [10]. There are also couples of web-based databases [11,12] and tools [13,14] available for defining absorption and permeability coefficients.

4.2 Other factors needed for calculations

Other factors needed for calculation of dermal intake and which are mentioned in equation 1, can be defined based on several related studies on human physiology and behavior. More detailed description of these factors with references to data sources are described in Section 6 in EPA's Exposure Factors Handbook [15]. Some links to relevant databases are also provided through External sources of Exposure Assessment Platform [16].

4.3 Models for dermal intake

Since being such a complicated issue, there are not so many models available for dermal intake. Some multimedia/multipathway models include also dermal pathway, but usually these models calculate only exposure or potential dose, not the actual intake. These models include Exposure and Fate Assessment Screening Tool Version 2.0 (E-FAST V2.0) by EPA [17], CalTOX [18], ConsExpo [19], and Euses [20], and some of them are described in more detailed in INTARESE D14.

5. References

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[8] http://appli1.oecd.org/olis/2004doc.nsf/linkto/env-jm-mono(2004)2

[9] https://www.who.int/ipcs/publications/ehc/ehc235.pdf

[10] http://ec.europa.eu/food/plant/protection/evaluation/guidance/wrkdoc20_rev_en.pdf

[11] http://rais.ornl.gov/cgi-bin/tox/TOX_select?select=csf

[12] http://www.ncl.ac.uk/edetox/theedetoxdatabase.html

[13] http://home.planet.nl/~wtberge/qsarperm.html

[14] http://www.cdc.gov/niosh/topics/skin/skinPermCalc.html

[15] http://www.epa.gov/ncea/pdfs/efh/front.pdf

[16] http://www.ktl.fi/expoplatform/external_ui

[17] http://www.epa.gov/opptintr/exposure/pubs/efast.htm

[18] http://eetd.lbl.gov/ie/ERA/caltox/index.html

[19] http://www.rivm.nl/en/healthanddisease/productsafety/Main.jsp

[20] http://ecb.jrc.it/euses/