

Chapter 21 Ingestion Toxicity Assessment

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21.1 Introduction

As described previously in Chapter 12, the purpose of the toxicity assessment is to weigh available evidence regarding the potential for toxicity in exposed individuals (**hazard identification**) and to quantify the toxicity by deriving an appropriate dose-response value (**dose-response assessment**). Toxicity assessment is the second part of the general risk equation. The toxicity assessment is accomplished in two steps: **hazard identification** and **dose-response assessment**. Although

the toxicity assessment is an integral and important part of the overall air toxics risk assessment, this is usually accomplished prior to the risk assessment. EPA has completed the toxicity assessment for all HAPs and has made available the resulting toxicity information and dose-response values, which have undergone extensive peer review (see Appendix C).^(a)

This chapter focuses on toxicity assessment for the ingestion (oral) pathway. Dermal toxicity assessment is described in detail in several EPA guidance documents.⁽¹⁾ The ingestion pathway uses the same general types of studies, hazard and dose-response information, and dose-response methods to assess toxicity as those used for the inhalation pathway (see Chapter 12). The discussion in this chapter focuses on the unique features of toxicity assessment for the oral pathway.

Risk = f (metric of exposure, measure of toxicity)

Toxicity Assessment is a Two-Step Process:

1. **Hazard Identification** – What types of effects does the chemical cause? Under what circumstances?
2. **Dose-response Assessment** – How potent is the chemical as a carcinogen and/or for noncancer effects?

Ingestion Dose-Response Values^(a)

Oral Cancer Slope Factor (CSF): An upper bound, approximating a 95 percent confidence limit, on the increased cancer risk from a lifetime exposure to an agent. For ingestion, this estimate is usually expressed in units of amount of risk per amount of intake and is written as risk per mg/kg-day or simply (mg/kg-d)⁻¹.

Reference Dose (RfD): An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive sub-populations) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Generally used in EPA's noncancer health assessments. RfDs are usually given in units of intake per day on a body weight basis (written as mg/kg-d).

^(a)The phrase "dose-response" is used generally here and elsewhere in the document. EPA's values for ingestion, however, are related to oral intake rather than dose. Consideration of the relationship between exposure concentration, dose, and dosimetry (what happens to a chemical in the body once it is ingested) may be considered, depending on data availability in the derivation of these values.

^aSee <http://www.epa.gov/ttn/atw/toxsource/summary.html> for an up-to-date list of dose-response values.

21.2 Hazard Identification

The hazard identification process for the ingestion pathway is identical to that for the inhalation pathway, although the specific toxic effects of concern and details of the toxicity studies are derived from feeding a chemical to animals (either in food or drinking water) rather than on having the animals inhale the chemical. As with inhalation, the hazard identification step includes consideration of various types of studies (e.g., feeding, in vitro, etc.) and the resulting weight of evidence with regard to potential for carcinogenicity and identification of critical effects. See Part II, Chapter 12, for information on the hazard identification step.

21.3 Predictive Approach for Cancer Effects

The approach to dose-response assessment for cancer effects is identical to that for the inhalation pathway discussed in Chapter 12, including:

- Determination of the **point of departure (POD)**;
- **Duration adjustment** of the POD to a continuous exposure;
- Extrapolation of an animal study POD into its corresponding **Human Equivalent Dose (POD_{HED})**; and
- **Low-dose extrapolation** from the POD_{HED} to lower doses for the purposes of deriving the oral cancer risk estimate.

As with inhalation, the first three steps are also performed in the derivation of reference values for ingestion, such as the oral RfD. In addition to the steps shown above, the derivation of RfDs are followed by the application of uncertainty factors (see Section 21.4). Additionally, the use of tools such as pharmacokinetic modeling, which go beyond these default approaches, may facilitate the accomplishment of several of these steps.

21.3.1 Determining the Point of Departure (POD)

The process for determining the POD for ingestion exposures is identical to that for inhalation exposures. The POD may be the no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL), or it may be a **benchmark dose (BMD)** for noncancer effects.^(b)

21.3.2 Deriving the Human Equivalent Dose

The optimal approach for extrapolating from an animal study to a human dose-response relationship is to use Physiologically Based Pharmacokinetic (PBPK)^(c) modeling. When such a model is used, the duration adjustment step is incorporated into that model. Otherwise, any duration adjustment, if necessary (e.g., when the exposure is not via daily feed), would be accomplished by deriving an average daily dose for the exposure period (e.g., two years in an animal cancer bioassay).

^bNote that the corresponding value for inhalation exposures is the benchmark concentration (BMC).

^cA model that estimates the dose to a target tissue or organ by taking into account the rate of absorption into the body, distribution among target organs and tissues, metabolism, and excretion.

For purposes of cancer assessment, an animal to human body weight-based scaling factor is applied to the oral study POD (duration-adjusted if applicable) to extrapolate to a human equivalent oral exposure.⁽²⁾ The default scaling factor is based on the body mass raised to the 3/4 power of the test animals relative to humans. This step stems from the consideration of various studies of the species differences in toxicity of certain compounds, including data collected on chemotherapeutic agents.⁽³⁾ These data served as the principal basis for the use of a body surface area or metabolic rate scaling as the default method in cancer risk assessments. Empirically, the best estimate of surface area scaling is $BW^{2/3}$ and for metabolic rate scaling is $BW^{3/4}$.⁽⁴⁾ These findings reflect general expectations of more rapid distribution, clearance, and metabolism by smaller animals.

In the case of the RfD, a scaling factor is not currently applied. Instead, the interspecies uncertainty factor is intended to account for potential differences in sensitivity of humans compared to the test animal, including this consideration.^(d)

A PBPK model can accommodate adjustments for metabolic rate as well as other species-related dosimetric variables such as liver perfusion rates. The model therefore provides a more accurate estimate of steady-state target site concentrations than use of default methods. EPA's preferred approach for calculating a HED for oral exposures is to use a chemical-specific PBPK model parameterized for the animal species and body regions (e.g., of the gastrointestinal tract) involved in the toxicity.

21.3.3 Extrapolating from POD to Derive the Oral Cancer Slope Factor

As with inhalation, extrapolation from the POD_{HED} to lower doses is usually necessary and, in the absence of a data set rich enough to support a biologically based model (e.g., a PBPK model), is conducted using linear extrapolation or a nonlinear extrapolation using a Reference Dose approach.

The **Cancer Slope Factor (CSF)** for oral exposures is derived in a similar way as the unit risk estimate for inhalation (URE) (see Chapter 12). The CSF is derived using the upper bound estimate of risk. In other words, the true risk to humans, while not identifiable, is not likely to exceed the upper-bound estimate (the CSF). The CSF is presented as the risk of cancer per mg of intake of the substance per kg body weight per day ($[mg/kg\text{-day}]^{(-1)}$).

21.4 Dose-response Assessment for Derivation of a Reference Dose

The oral **reference dose** is expressed as a chronic dietary intake level (in units of mg of the substance per kilogram body weight per day, or mg/kg-day) for the human population (including sensitive sub-populations) that is likely to be without an appreciable risk of deleterious effects during a lifetime. In other words, exposures at or below the RfD will probably not cause adverse health effects, even to sensitive sub-populations. While the RfD is routinely employed for

^dAt the time of publication, an Agency activity is underway to "harmonize" the cancer assessment and RfD development methods with regard to the method employed for interspecies scaling, which may result in the use of body weight scaling in the development of the RfD.

noncancer effects, it may be inclusive of cancer for those pollutants for which a nonlinear (e.g., threshold) mode of action has been demonstrated consistent with the Cancer Guidelines.

As with the derivation of an inhalation reference concentration, the reference dose is derived by dividing the POD by one or more **uncertainty factors (UFs)**. EPA includes with each RfD a statement of high, medium, or low confidence based on the completeness of the database for that substance. High confidence RfDs are considered less likely to change substantially with the collection of additional information, while low confidence RfDs may be especially vulnerable to change.⁽⁵⁾

The UFs are applied to account for recognized uncertainties in the extrapolations from the experimental data conditions to an estimate appropriate to the assumed human scenario. As with the derivation of RfCs, a UF of 10, 3, or 1 is applied for each of the following extrapolations:

- Animal to human;
- Human to exposed sensitive human populations;
- Subchronic to chronic;
- LOAEL to NOAEL; and
- Incomplete to complete database.

The UFs are generally an order of magnitude (10), although consideration of available information on the chemical may result in the use of reduced UFs for RfDs (3 or 1). It is noted that as there is currently no default dosimetric adjustment for the oral route. The uncertainty factor for extrapolation from animal to human data is usually the full 10, as compared to the reduced factor of 3, routinely used for RfCs which employs an interspecies dosimetric adjustment. Additional discussion on the application of uncertainty factors is provided in Section 12.4.3.

21.5 Sources of Human Health Reference Values for Risk Assessment

Appendix C provides a current listing of chronic oral dose-response values (i.e., RfDs and CSFs) for HAPs. Chapter 12 describes additional sources of human health reference values for risk assessment for the ingestion route.

References

1. U.S. Environmental Protection Agency. 2001. *Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment) Interim Review Draft - For Public Comment*, Office of Emergency and Remedial Response, Washington, D.C. EPA/540/R/99/005, available at: <http://www.epa.gov/superfund/programs/risk/ragse/index.htm>.

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