

Ohio EPA
Division of Environmental Response and Revitalization
Assessment, Cleanup & Reuse Section, Remedial Response Program

TECHNICAL DECISION COMPENDIUM

Title: Application of Bioavailability in the Assessment of Human Health Hazards and Cancer Risk

Date: 26 March 2002; Updated: August 14 2009

Key Words: Bioavailability, bioaccessibility, fractional relative absorption factor, absorption efficiency, internal dose, biologically effective dose.

Purpose: The purpose of this document is to provide guidance on the application of bioavailability in human health risk assessment, to define relevant terms, and to determine if and when bioavailability may be used as a factor modifying the concentration term.

Background: In a site-specific risk assessment, the chemical form of a contaminant, the exposure medium in which the contaminant is found, and the route of exposure are critical factors determining the potential site-related risk. If one or more of these factors differ from those applied in the derivation of the toxicity criterion by the regulatory agency (e.g., U.S. EPA¹), then adjustment of the concentration term for absorption may be appropriate. Since the U.S. EPA neither prohibits nor requires such adjustments, the burden of proof for supporting any proposed site-specific adjustment falls on the risk assessors who are evaluating the site in question.² In addition, U.S. EPA Risk Assessment Guidance for Superfund outlines the use of adjustments for absorption efficiency, but does not give specific guidance on the development of site-specific bioavailability factors.³ An adjustment factor, broadly described as a fraction of the chemical present in the medium that can be absorbed by and interact with the human body, is referred to as *bioavailability*.^{4,5}

Bioavailability (*F*) has been defined in a variety of ways, but for application in human health risk assessment, it refers to the fraction of the total amount of chemical in contact with a body portal-of-entry (lung, skin, gut) that enters systemic circulation and may interact with the target tissue (internal dose). Bioavailability reflects the degree to which a chemical, drug or other substance becomes available to the target tissue after exposure or deliberate administration and subsequent absorption.

Bioavailability is typically a function of the chemical properties and the physical state of the material (medium and matrix) to which an organism is

exposed, and the ability of the individual organism to absorb the chemical. Thus, in most cases bioavailability should be determined *in vivo*. For most materials (media), dissolution or volatilization is a prerequisite of absorption, although a certain amount of a chemical in particulate or suspended/ emulsified form may be absorbed by pinocytosis. The term *bioaccessibility* is used to describe the ability of a chemical to be dispersed in such a way that it can be absorbed by an organism.

Bioaccessibility generally refers to the fraction of an administered substance that may become available for absorption (e.g., solubilized in the gastrointestinal fluid, volatilized into inhaled air, released from the matrix in a topically absorbable form). For ionizable compounds, bioaccessibility depends strongly on pH. Upon certain conditions bioaccessibility may be estimated *in vitro*.

Absolute Bioavailability (F_A) is a ratio of the amount of a substance entering the blood *via* a particular route of exposure (e.g., ingestion) to the total amount administered by this route (e.g., amount of lead ingested with soil). Absorption of a chemical into the blood may be expressed quantitatively as the area under the curve (AUC) representing a function of concentration in plasma *versus* time. In experimental animals, the absolute bioavailability is defined as the ratio of AUC resulting from the external administration of the chemical (AUC_{route}) to the AUC resulting from the intravenous injection of the same dose of the chemical (AUC_{IV}). In most cases, the toxicological databases do not include the results from detailed testing of chemicals administered in the same form (valency, cationic and anionic composition) and the same vehicle (matrix) through all possible routes. Therefore, even significant differences in absolute bioavailability, and sometimes in mechanism-of-action, across different media and different routes of exposure may remain unaccounted for. In general, U.S. EPA's position is that the **potential** for toxicity manifested *via* one route of exposure is relevant to any other route of exposure⁽¹⁾, unless convincing evidence exists to the contrary.

Relative Bioavailability (F_R) refers to the ratio of two absolute bioavailability values. Relative bioavailability represents a comparison of the absorption of a chemical in two different forms (e.g., availability of a contaminant relative to purified reference) or under two sets of circumstances (e.g., availability of a chemical from soil relative to its availability from water).

Relative bioavailability is an appropriate factor for the adjustment of the concentration term in an intake equation to account for differences between the conditions under which the toxicity criterion was derived and those conditions being quantified in the site-specific risk assessment. For application in human health risk assessment, relative bioavailability may

be measured experimentally and expressed as a fractional relative absorption factor that describes the absorbed fraction of a chemical from particular exposure medium relative to the fraction absorbed from the dosing vehicle used in the toxicity study for that compound.

Although the U.S. EPA recognized the need to consider bioavailability adjustments in risk assessments, and in many cases applies a factor modifying the concentration term,^{2,3,5} it also cautioned stakeholders that the mutual agreement on the value of the bioavailability factor may not be reached. In such cases, the U.S. EPA has reserved the right to use its expertise to develop appropriate site-specific factors, criteria and terminology¹. In any case, while the site-specific studies of relative bioavailability **are encouraged**, the research findings from any such study must be appropriately validated. Thus, any research finding may or may not be acceptable to the U.S. EPA.⁹

Decision: If a toxicity criterion for a given chemical was developed by the regulatory agency using data based on a different chemical form, different exposure medium, or different route of exposure than the site-specific conditions, then, it may be appropriate to incorporate *bioavailability* into the risk assessment process. When calculating chemical intake, the **Relative Bioavailability** (F_R) may be applied as a factor modifying the concentration term, provided that: (1) the values are validated and scientifically justifiable; (2) the data source(s) are clearly stated; and (3) the values are approved either by the U.S. EPA or Ohio EPA. Alternatively, bioavailability determined experimentally is acceptable if conducted *in vivo* in accordance with the good laboratory practice (GLP) methodology, e.g., as described in the U.S. FDA guidance⁶.

Where available, site- and substance- specific data for bioavailability (including dermal absorption factor, bioconcentration factor, *etc.*) should be used. Where bioavailability data for ingested, inhaled or topically applied contaminants are of poor quality or unknown, the value of 1.0 (signifying a 100% absorption) should be used as a default.

Rationale: Under certain site- and chemical-specific circumstances, bioavailability data may help to determine how much of a chemical contaminant present in the environment is actually absorbed into the body from ingestion or other routes of exposure. When the available toxicity values do not reflect these data for a specific chemical form or specific medium, a relative bioavailability variable may be used as a modifying factor to adjust the concentration term. This decision is applicable only to chemicals whose availability from the medium (matrix) will not increase with time.

Attachment: Appropriate equations and references.

Contact Person: Janusz Z. Byczkowski, Tel. 614-644-3070;
e-mail: janusz.byczkowski@epa.state.oh.us

ATTACHMENT:

Bioavailability quantitatively governs several parameters which are used to calculate intake, including *dermal absorption factor* (**ABS_d**) and *oral absorption factor* (**ABS_{GI}**).

As a pharmacokinetic parameter, *absolute bioavailability* (**F_A**) is quantitatively defined as a product of the ratio of the area under the curve obtained by a specific route of administration of the chemical (AUC_{route}) to an area under the curve obtained by intravenous injection (AUC_{IV}) and the ratio of intravenous dose of the chemical (D_{IV}) to dose administered by the specific route (D_{route}):

$$F_A = AUC_{route}/AUC_{IV} \times D_{IV}/D_{route}$$

Relative Bioavailability (**F_R**) is indexed by measuring the bioavailability of a particular substance in an environmental medium (e.g., lead in soil), relative to the bioavailability of a standardized soluble reference material. The reference should be of the same chemical form (salt of the same cation and anion and at the same valency), in the same matrix, and/or dissolved in the same exposure medium as the experimental chemical substance that was used in the critical toxicity study (e.g., such as lead acetate in water). If there is no difference between the chemical form, matrix and exposure medium used in the toxicity study and those conditions being quantified in the site-specific risk assessment, then there is no need to determine bioavailability.

Relative Bioavailability, expressed as a fraction of chemical absorbed from environmental medium (matrix) by the specific route (**F_R**), may be applied as a factor modifying the concentration term (e.g., C_s) in equations used to calculate intake. For example, residential exposure to a chemical in soil *via* ingestion, inhalation, or dermal contact may be calculated using the following equations:

a. By ingestion:

$$\text{Intake (mg/kg/day)} = \frac{C_s \times \mathbf{F}_{R-Ing} \times IR \times CF \times EF \times ED}{BW \times AT}$$

b. By inhalation:

$$\text{Inhaled dose (mg/kg/day)} = \frac{C_s \times \mathbf{F}_{R-Ing} \times InhR \times EF \times ED \times \left(\frac{1}{PEF} + \frac{1}{VF} \right)}{BW \times AT}$$

c. By dermal contact:

$$\text{Absorbed dose (mg/kg/day)} = \frac{C_S \times \mathbf{ABS} \times SA \times CF \times AF \times EF \times ED}{BW \times AT}$$

where:

C_S = Chemical concentration in soil (mg/kg).

F_{R-Ing} = Bioavailability, *i.e.*, absorbed fraction of the ingested substance.

IR = Ingestion rate (mg soil/day).

CF = Conversion factor (10 E-6 kg/mg).

EF = Exposure frequency (days/year).

ED = Exposure duration (years).

BW = Body weight (kg).

AT = Averaging time (days).

F_{R-Inh} = Bioavailability of substance *via* inhalation.

InhR = Inhalation rate (m³/day).

PEF = Particulate emission factor (m³/kg)⁷.

VF = Volatilization factor (m³/kg).

ABS = Dermal bioavailability - absorption factor for substance when on skin*.

SA = Skin surface area available for contact (cm²/event).

AF = Soil to skin adherence factor (mg/cm²).

If necessary, a fraction of contaminated source (unitless) ingested, inhaled, or contacted dermally may be added to the numerator in these equations.

* When site-specific value for dermal ABS from soil cannot be determined, for the purpose of screening evaluations, the U.S. EPA⁸ generic defaults may be used, for example:
(for screening evaluations only)

for PAH assume ABS = 0.13

for Semi volatile organic compounds assume ABS = 0.1

for Inorganic chemicals assume ABS = 0.1

for Arsenic assume ABS = 0.03

for Cadmium assume ABS = 0.001

References:

1. Reference Dose (RfD): Description and Use in Health Risk Assessments Background Document 1A (March 15, 1993) <http://www.epa.gov/iris/rfd.htm>

2. Rembish, S.J., Duffy, J., Maull, E.A.: Development of Bioavailability Adjustment Factors: a Feasibility Study. U.S. Air Force IERA, IERA-RS-BR-TR-2001-0001. Brooks Air Force Base, TX, December 2000

3. U.S. EPA Risk Assessment Guidance for Superfund, Volume 1, Human Health Evaluation Manual (Part A), Appendix A, EPA/540/1-89/002
<http://www.epa.gov/oswer/riskassessment/raqsa/index.htm>

4. National Environmental Policy Institute (NEPI). Assessing the bioavailability of organic chemicals in soil for use in human health risk assessments. Washington, DC: NEPI 2000a.

5. National Environmental Policy Institute (NEPI). Assessing the bioavailability of metals in soil for use in human health risk assessments. Washington, DC: NEPI 2000b..

6. Code of Federal Regulations, Title 21, Volume 5, Part 320, .23 - .29 (Revised as of April 1, 1998). http://www.access.gpo.gov/nara/cfr/waisidx_98/21cfr320_98.html

7. U.S. EPA Soil Screening Guidance: Technical Background Document (TBD). EPA Document Number: EPA/540/R-95/128, July 1996.

<http://www.epa.gov/oerrpage/superfund/health/conmedia/soil/toc.htm>

8. U.S. EPA. Supplemental Guidance for Developing Soil Screening Levels for Superfund Sites. Document Number: OSWER 9355.4-24, March 2001.

http://www.epa.gov/superfund/health/conmedia/soil/pdfs/ssg_main.pdf

9. U.S. EPA. Assessing Relative Bioavailability in Soil at Superfund Sites: Guidance and Technical Reports, 2009. <http://www.epa.gov/superfund/bioavailability/guidance.htm>