U.S. Army Center for Health Promotion and Preventive Medicine

Just the Facts

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Reference Dose

Reference Dose (RfD). RfD is an estimate, with an uncertainty spanning perhaps an order of magnitude or greater, of a daily exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects during a lifetime.[2] RfD doses are expressed in units of milligram chemical per kilogram body weight per day (mg/kg/da). They are used in evaluating the potential noncarcinogenic effects associated with exposure periods of between 7 years (approximately 10 percent of a human lifetime) and a lifetime. RfDs are applicable to the oral exposure pathway, such as from ingestion of contaminated soil or water. RfDs for the majority of the contaminants of concern at Superfund Program cleanup sites are listed by the United States Environmental Protection Agency (USEPA) in its Integrated Risk Information System (IRIS), or Health Effects Assessment Summary Tables (HEAST).[3]

Dose-Response Assessments. This is the process of quantitatively evaluating toxicity information and characterizing the relationship between the dose of a contaminant administered or received and the incidence of adverse health effects in the exposed population. From a quantitative dose-response relationship, toxicity values are derived that are used in the risk characterization step to estimate the likelihood of adverse effects occurring in humans at different exposure levels[2]. In the case of noncancer critical effects, the USEPA terms this toxicity value the RfD.

Selection of the Critical Data. Estimating an RfD for a given compound requires consideration of subchronic or chronic toxicity data, identification of a critical effect, identification of a Lowest-Observed-Adverse Effect Level (LOAEL) or a No-Observed Adverse-Effect Level (NOAEL), and use of the uncertainty factor (UF) and modifying factor (MF) protocol.[2] All available studies examining the toxicity of a chemical following exposure by the oral route are to be gathered and judged for their scientific merit. Occasionally, studies based on other exposure routes are considered, and the data adjusted for application to the oral route by means of standard assumptions. Any differences between studies are to be reconciled and an overall evaluation reached. If adequate human data are available, these should be used as the

References.

1. Cicmanec, J.L., M.L. Dourson and R.C. Hertzberg, Noncancer Risk Assessment: Present and Emerging Issues," Chapter 17, in Fan, A. M. and L.W. Chang (eds), *Toxicology and Risk Assessment: Principles, Methods, and Applications,* Marcel Dekker, Inc., New York, NY, 1996.

2. U.S. Environmental Protection Agency, EPA/540/1-89/002, *Risk Assessment Guidance for Superfund Volume I Human Health Evaluation Manual (Part A), Interim Final,* Office of Emergency and Remedial Response, Washington, DC, December, 1989.

3. U.S. Environmental Protection Agency, *Integrated Risk Information System (IRIS), Online,* Environmental Criteria and Assessment Office, Cincinnati, OH, 1990.

Office of the Scientific Advisor
U.S. Army Center for Health Promotion and Preventive Medicine
Aberdeen Proving Ground, Maryland 21010-5422
Commercial (410) 671-2307, DSN: 584-2307
email: Stephen_Kistner@CHPPM-ccmail.apgea.army.mil

basis for an RfD. Otherwise, data from animal studies are to be used.[2] Scientific judgment must be exercised during the selection process. In the absence of a species that is clearly the most relevant, USEPA assumes that humans are at least as sensitive to the substance as the most sensitive animal species tested. Therefore, as a matter of science policy, the study on the most sensitive species is selected as the critical study for the basis of the RfD.

NOAEL. The NOAEL is the highest experimental dose of a chemical at which there is no statistically or biologically significant increase in frequency or severity of an adverse effect (including the critical toxic effect) in individuals in an exposed group when compared with individuals in an appropriate control group. Some effects may be produced at this level, but they are not considered to be adverse, nor precursors to specific adverse effects. The NOAEL is one of the most important data points obtained from the study of the dose-response relationships and is the primary measurement upon which the quantitative assessment of the human risk is based. The NOAEL selection is based in part on the assumption that, if the critical toxic effect is prevented, then all toxic effects are prevented.

LOAEL. In dose-response experiments, the LOAEL is defined as the lowest exposure level at which there are statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group.[2] The effect thus characterized, after adjustment for species differences, is referred to as the critical toxic effect. In some studies, only a LOAEL rather than a NOAEL is available.

Selection of UFs and MFs. UFs are adjustments in the NOAEL or LOAEL to accommodate areas of scientific uncertainty inherent in most toxicity data sets. Currently, UFs from 1 to 10 each are applied to extrapolate from animals to humans (UF_H), to provide protection for unusually sensitive individuals if the animal species in the critical study is more sensitive to a chemical than humans (UF_A), to expand from subchronic to chronic exposure (UF_S), to estimate a NOAEL from the LOAEL (UF_L) and to reflect deficiencies in the data base (UF_D). Lower UFs may be applied in instances where they can be justified. For example, a non-adverse critical effect which is symptomatic of more serious effects at higher levels (e.g., moderate changes in blood cholinesterase levels), requires a lower UF (e.g., UF=3) than adverse toxic effects (e.g., liver damage). In calculating the composite UF, the product should reflect the imprecision of the overall UF determination (e.g., 3 x 3 is 10). The maximum total UF applied in the derivation of an RfD is 10,000.[1]

There may be additional uncertainties in estimating an RfD such as scientific uncertainties in the key study, study design anomalies, or chemical specific issues. In these instances, an MF greater than zero but ≤ 10 is applied to account for these considerations. The default value for the MF is 1.

Derivation of Reference Dose. The RfD is derived from the NOAEL or LOAEL by consistent application of UFs that reflect various types of data sets used to estimate RfDs. The RfD is calculated as follows:

$$RfD = \frac{\text{NOAEL or LOAEL}}{UF_H \times UF_A \times UF_S \times UF_L \times UF_D \times MF}$$

Application. The RfD can be used to calculate safe drinking water levels, soil cleanup levels, safe food contaminant levels, and other "safe" media-specific concentrations where persons may be at risk by ingesting contaminated portions of that media. The RfD is translated into these safe media concentrations levels by incorporating site-specific information called exposure factors. These exposure factors include information such as exposure frequency, exposure duration, estimated amount of contaminated soil/water/specific food ingested, ingestion rate, and body weight. These site-specific variables and the RfD are incorporated into a health risk assessment according to USEPA-approved methodologies and calculations.[2] Thus "safe" environmental standards are backcalculated from the toxicological reference point (i.e., the RfD). The actual determination of whether a material is "safe" will be dependent on the situation.