

Reference dose of the United States Environmental Protection Agency^{1,2}

by Michael L Dourson, PhD³

Empirical data demonstrate that, as the administered dose of a chemical increases, the toxic responses generally increase. These increases occur in both the severity of the response (eg, with new and more severe effects being observed) and the intensity of the response (ie, magnification of an effect of given severity), and the percentage of the population affected increases as well. Such dose-response relationships are well founded in the theory and practice of toxicology and pharmacology.

Dose-response assessment follows hazard identification in the risk assessment process as defined by the United States National Academy of Sciences (NAS) (1). Dose-response assessment involves the quantitative evaluation of toxicity data to determine the likely incidence of the associated effects on humans. The information available for dose-response assessment ranges from well-conducted and controlled studies of human exposure and epidemiologic studies with large numbers of subjects, well-characterized exposures and supportive studies on several animal species to a lack of human and animal toxicity data with only structure-activity relationships to guide the evaluation. In any case, scientists should consider all pertinent studies in this process — even a single human case study can provide useful information. However, only data of sufficient quality, as judged by experts such as the EPA Reference Dose Reference Concentration Work Group, should be used in the dose-response assessment of a chemical.

With at least a moderate amount of toxicity data, one goal has been to determine a level of daily exposure that is likely to be without an appreciable risk of deleterious effects during a lifetime. The World

Health Organization and many other health agencies have used the concept of acceptable daily intake (ADI) in this regard. The Environmental Protection Agency (EPA) in the United States has also used the ADI in many of its evaluations. However, the EPA has also rethought this approach and developed new, clarifying terminology in congruence with that of the NAS risk assessment-risk management paradigm, which calls for a clear demarcation between scientific and nonscientific factors in regulatory decisions (1). The older ADI approach included both scientific and nonscientific considerations. By contrast, the oral reference dose (RfD) and the inhalation reference concentration (RfC) approaches of the EPA strive to include only scientific considerations. The history and rationale for the change in terminology and practice from ADI to RfD is described in detail in documentation supporting the Integrated Risk Information System (IRIS) of the EPA (2, 3). Descriptions of the development of the RfC concept are also available (4, 5).

EPA (2) defines the RfD as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is determined by use of the following equation: $RfD = NOAEL \text{ or } LOAEL / (UF \times MF)$ where:

NOAEL = an exposure level at which no statistically or biologically significant increases occur in the frequency or severity of adverse effects between the exposed population and its appropriate reference group. *Some effects may be produced at this level, but they are not considered to be adverse, nor to be precursors to specific adverse effects.* (In an experiment with several NOAEL values, the regulatory focus is primarily on the highest NOAEL observed. This practice leads to the common usage of the term NOAEL to mean the highest exposure without adverse effect.)

LOAEL = the lowest exposure level at which statistically and biologically significant increases occur in the frequency or severity of adverse effects between the exposed population and its appropriate reference group.

Extended abstract: full report to be published in Olin S, ed. *Risk Assessment of Essential Elements: Proceedings of a Conference on Risk Assessment of Essential Elements*. Herndon, Virginia. In press.

Disclaimer: The views expressed in this paper are those of the author and do not necessarily reflect the views and policies of the Environmental Protection Agency, Environmental Criteria & Assessment Office, United States Environmental Protection Agency, Cincinnati, Ohio, United States.

Address for correspondence: Dr ML Dourson, Environmental Criteria & Assessment Office, US Environmental Protection Agency, 26 W Martin Luther King Drive, Cincinnati, OH 45268, USA.

UF = one of several, generally 10-fold, default factors used in operationally deriving the RfD from experimental data. (Under special circumstances a factor of less than 10 can be employed.)

MF = an uncertainty factor greater than zero and less than or equal to 10, the default value for the MF being 1.

The oral RfD and inhalation RfC are useful reference points for gauging the potential effects of other doses. Doses at the RfD (or less) or concentrations at the RfC (or less) are not likely to be associated with any health risks, and they are, therefore, assumed likely to be protective and of little regulatory concern. In contrast, as the level and frequency of exposures exceeding the RfD or RfC increase, the probability of adverse effects being observed in a human population also increases. However, the conclusion that all doses below the RfD or RfC are acceptable and that all doses in excess of the RfD or RfC are unacceptable cannot be categorically stated. Moreover, the precision of the RfD or RfC depends in part on the overall magnitude of the composite uncertainty and modifying factors used in its calculation. The precision at best is probably one significant figure and more generally an order of magnitude, base 10. As the magnitude of this composite factor increases, the estimate becomes even less precise.

Determining an RfD or RfC requires scientific judgment as to the appropriate NOAEL of the critical effect and the appropriate uncertainty and modifying factors based on database limitations. (See the full report for the logic behind judgments on the selection of toxicity data, confidence in the RfD, the selection of uncertainty factors, the selection of modifying factors, and assumptions and limitations.)

References

1. United States National Academy of Sciences (NAS). Risk assessment in the Federal Government: managing the process. Washington, DC: National Academy Press, 1983.
2. United States Environmental Protection Agency (EPA). The integrated risk information system (IRIS). Online. Cincinnati, OH: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, 1992.
3. Barnes DG, Dourson ML. Reference dose (RfD): description and use in health risk assessments. *Reg Toxicol Pharmacol* 1988;8:471—86.
4. United States Environmental Protection Agency (EPA). Interim methods for development in inhalation reference doses. Washington, DC: Office of Health and Environmental Assessment, 1990. (EPA/600/8—90—066A, 1990.)
5. Jarabek AM, Menach MG, Overton JH, Dourson ML, Miller FJ. The US Environmental Protection Agency's inhalation RfD methodology: risk assessment for air toxics. *Toxicol Ind Health* 1990;6(5):279—301.

Appendix

Common definitions used in noncancer risk assessment

Below are some common definitions used in noncancer risk assessment. These definitions are for illustration only. Other terms are used by different organizations and countries.

Acceptable daily intake (ADI) — estimate of the daily exposure dose that is likely to be without deleterious effect even if continued exposure to a toxicant occurs over a lifetime.

Acute exposure — one-dose or multiple-dose exposure occurring within a short time (<24 h).

Adaptive effect — effect that enhances the performance of an organism as a whole or its ability to withstand a challenge (ie, homeostatic mechanism). An increase in hepatic smooth endoplasmic reticulum is an example of an adaptive effect if hepatic metabolism reduces the toxicity of the chemical.

Adverse effect — biochemical change, functional impairment, or pathological lesion that impairs performance and reduces the ability of the organism to respond to additional challenge.

Chronic exposure — multiple or continuous exposure occurring over an extended period or over a significant fraction of the lifetime of the animal or individual.

Compensatory effect — effect that maintains overall function without enhancement or significant cost. Increased respiration due to metabolic acidosis is an example of a compensatory effect.

Critical effect — first adverse effect, or its known precursor, that occurs as the dose rate increases. A critical effect can vary among toxicity studies of different durations, it can be influenced by the toxicity

in other organs, and it can differ depending on the availability of data on the shape of the dose-response curve.

Frank-effect level (FEL) — exposure level which produces unmistakable adverse effects, such as reversible or irreversible functional impairment or mortality, at a statistically or biologically significant increase in frequency or severity between an exposed population and its appropriate reference.

Health hazards (adapted in part from Klaasen CD, Amdur MO, Doull J. Casarett and Doull's toxicology: the basic science of poisons. 3rd ed. New York, NY: MacMillan Publishing Company, 1986):

1. *Acute toxicity* — another term used to describe immediate toxicity. Its use is associated with toxic effects that are severe (eg, mortality) in contrast to the term "subacute toxicity," which is associated with toxic effects that are less severe. The term "acute toxicity" is often confused with that of acute exposure.

2. *Allergic reaction* — adverse reaction resulting from previous sensitization to the chemical or to a structurally similar one.

3. *Chronic toxicity* — effects that persist over a long period whether or not they occur immediately or are delayed. The term "chronic toxicity" is often confused with that of chronic exposure and is often used to describe delayed toxicity.

4. *Idiosyncratic reaction* — a genetically determined abnormal reactivity to a chemical.

5. *Immediate versus delayed toxicity* — immediate effects occur or develop rapidly after a single administration of a substance, while delayed effects occur after the lapse of some time. These effects have also been referred to as acute and chronic, respectively.

6. *Reversible versus irreversible toxicity* — Reversible toxic effects can be repaired, usually by the ability of a specific tissue to regenerate or mend itself after chemical exposure, while irreversible toxic effects cannot be repaired.

7. *Local versus systemic toxicity* — local effects occur at the site of entry (eg, lungs, stomach) of a toxicant into the body; systemic effects are elicited after absorption and distribution of the toxicant from its entry point to a distant site.

Lowest-observed adverse-effect level (LOAEL) — lowest exposure level at which statistically or biologically significant increases occur in the frequency or severity of adverse effects between the exposed population and its appropriate reference.

Modifying factor (MF) — uncertainty factor that is greater than zero and less than or equal to 10; the magnitude of the modifying factor depends upon the professional assessment of scientific uncertainties of the study and data base not explicitly treated with the standard uncertainty factors (eg, the number of animals tested); the default value for the modifying factor is 1.

No-observed adverse-effect level (NOAEL) — exposure level at which no statistically or biologically significant increases occur in the frequency or severity of adverse effects between the exposed population and its appropriate reference; *some effects can be produced at this level, but they are not considered to be adverse, nor to be precursors to specific adverse effects.* In an experiment with several NOAEL values, the regulatory focus is primarily on the NOAEL seen at the highest dose. This practice leads to the common usage of the term NOAEL to mean the highest exposure without adverse effect.

No-observed effect level (NOEL) — exposure level at which no statistically or biologically significant increases occur in the frequency or severity of any effect between the exposed population and its appropriate reference.

Reference concentration (RfC) — estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime.

Reference dose (RfD) — estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime.

Subchronic exposure — multiple or continuous exposure occurring usually over three months.

Uncertainty factor (UF) — one of several, generally 10-fold, factors used in operationally deriving the reference dose from experimental data. Uncertainty factors are intended to account for (i) variation in sensitivity among the members of the human population, (ii) uncertainty in extrapolating animal data to the case of humans, (iii) uncertainty in extrapolating from data obtained in a study that is of less-than-lifetime exposure, (iv) uncertainty in using data on the lowest-observed adverse-effect level rather than data on the no-observed adverse-effect level, and (v) the inability of any single study to address all possible adverse outcomes in humans adequately.

Additional reading

1. Clegg DJ. Toxicological basis of the ADI — present and future considerations. In: Frehse H, Geissbuhler H, ed. Pesticide reviews. Oxford (England): Pergamon Press, 1978.
2. Cothorn CR, ed. Comparative environmental risk assessment. Boca Raton, FL, Lewis Publishing Co, 1992.
3. Cothorn CR, Mehlman M, Marcus W, ed. Risk assessment and risk management of industrial and environmental chemicals. Princeton, NJ: Princeton Scientific Publishing Co Inc, 1988.
4. Dourson ML, Knauf LA, Swartout JC. On reference dose (RfD) and its underlying toxicity data base. Toxicol Ind Health 1992;8(3):171—89.
5. Hallenbeck WH, Cunningham KM. Quantitative risk assessment for environmental and occupational health. Boca Raton, FL: Lewis Publishers, 1986.
6. Johannsen FR. Risk assessment of carcinogenic and noncarcinogenic chemicals. CRC Crit Rev Toxicol 1990;20(5):341—67.
7. Klaassen CD, Amdur MO, Doull J. Casarett and Doull's toxicology: the basic science of poisons. 3rd ed. New York, NY: MacMillan Publishing Company, 1986.
8. Lu F. Acceptable daily intake: inception, evolution and application. Reg Toxicol Pharmacol 1988;8(1):45—60.
9. Vettorazzi G. Pesticide residues in food in the context of the international activities of the Joint JAO/WHO Meeting on Pesticide Residues and the Codex Committee on Pesticide Residues: principles for the toxicological assessment of pesticide residues in food. Geneva: International Programme on Chemical Safety, World Health Organization, 1984. (Environmental health criteria; no 104.)