USACHPPM
Readiness thru Health

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Just the Facts...

Reference Concentration

Reference Concentration (RfC). The inhalation RfC (earlier terminology was "inhalation reference dose" or "RfD_i") is an estimate, with an uncertainty possibly spanning an order of magnitude or greater, of a continuous inhalation exposure to the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of harmful noncancer health effects during a lifetime.[1] RfCs are also derived for the noncancer effects of chemicals that are carcinogenic. The RfC for inhalation exposure is generally reported as a concentration in ambient air in mg/m^3 for continuous, 24-hour/day exposures. RfCs 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).[3,4]

Dose-Response Assessments. This is the process of quantitatively evaluating the relationship between the amount of exposure to a substance (i.e., dose) and the incidence of adverse health effects in the exposed population. From a quantitative dose-response relationship, toxicity values are derived for use in the risk characterization step of risk assessments to estimate the likelihood of adverse effects occurring in humans at different exposure levels.[2] In the case of noncancer critical effects through inhalation, the USEPA terms this toxicity value the RfC.

NOAEL. The No-Observed-Adverse Effect Level (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) between the exposed group and its appropriate control group.[1] Some effects may be produced at this level, but they are not considered adverse nor immediate 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. The Lowest-Observed-Adverse Effect Level (LOAEL) is the lowest experimental dose of a chemical 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.[1] In some studies, only a LOAEL rather than a NOAEL is available.

References.

1. U.S. Environmental Protection Agency, EPA/600/8-90/066F, *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry,* Office of Research and Development, Washington, DC 20460, October 1994.

2. U.S. Environmental Protection Agency, EPA/540/1-89/002, *Risk Assessment Guidance for Superfund Volume 1 Human Health Evaluation Manual (Part A), Interim Final,* Office of Emergency and Remedial Response, Washington, DC 20460, December 1989.

3. U.S. Environmental Protection Agency, EPA/540/R-95/036, *Health Effects Assessment Summary Tables,* Office of Research and Development, Washington, DC 20460, May 1995.

4. U.S. Environmental Protection Agency, *Integrated Risk Information System (IRIS),* www.epa.gov, February 1998.

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Human Equivalent Concentration (HEC). In inhalation exposures, differences in respiratory anatomy and physiology may affect deposition, absorption, distribution, clearance, and redistribution of the contaminant. Differences in the size and shape of a particle or whether the contaminant is an aerosol or a gas can also affect the effective dose delivered to the target organ. The HEC is the exposure concentration for humans that has been adjusted for dosimetric differences between experimental animal species and humans to be equivalent to the exposure concentration associated with observed effects in the experimental animal species. If occupational human exposures are used for extrapolation (e.g., 8 hours/day and 5 days/week occupational exposure to a continuous chronic exposure), the HEC represents the equivalent human exposure concentration adjusted to 24 hours/day and 7 days/week.[1]

Selection of UFs and MFs. Uncertainty Factors (UF)s are adjustments, generally 1- to 10-fold factors, used in deriving the RfC to account for uncertainties in extrapolating from experimental data to an appropriate human scenario. Standard UFs are applied to extrapolate from: (1) average healthy humans to sensitive humans (UF_H); (2) animal data to humans (UF_A); (3) subchronic data to chronic (UF_S); (4) a $LOAEL_{[HEC]}$ to a $NOAEL_{[HEC]}$ (UF_L); and (5) incomplete to a complete database (UF_D). The composite UF when four factors are used generally is reduced from 10,000 to 3,000 in recognition of the lack of independence of these factors.[1]

A modifying factor (MF), greater than zero but ≤ 10 is applied to account for additional uncertainties not specifically addressed in the above UFs. The magnitude depends on professional judgment regarding uncertainties such as completeness of the overall database, critical study design anomalies, and chemical specific issues. The default value for the MF is 1.

Selection of the Critical Data. Estimating toxicity values for noncancer endpoints for inhaled chemicals requires consideration of subchronic or chronic toxicity data, identification of a critical effect, identification of a NOAEL or LOAEL and converting to HECs, and use of the UF and MF protocol. Although all relevant human and laboratory animal data of various study types are considered, data from animal studies are often selected because available human data are usually insufficient. In evaluating animal data, a series of professional judgments are made which include assessing relevance to humans and scientific quality of the studies.[2] In the absence of a species that is clearly the most relevant, the USEPA assumes the humans are at least as sensitive to the substance as the most sensitive animal species tested. Therefore, as a matter of scientific policy, the study on the most sensitive species is selected as the critical study for the basis of the RfC.

Derivation of Reference Concentration. The RfC is derived from the $NOAEL_{[HEC]}$ for the critical effect by consistent application of standard UFs. The RfC is determined by the following equation:[1,2]

$$RfC = \frac{NOAEL_{[HEC]} \text{ or } LOAEL_{[HEC]}}{UF_H \times UF_A \times UF_S \times UF_L \times UF_D \times MF}$$

The USEPA does not endorse the use of occupational exposure limits such as the Occupational Safety and Health Administration Permissible Exposure Limits or American Conference of Governmental Industrial Hygienists threshold limit values in deriving RfCs because of the different assumptions and intended application (i.e., healthy worker, intermittent exposure periods at the workplace, risk management values).[2]

Application. The RfC can be used to calculate "safe" media-specific concentrations where people may be at risk by inhalation of contaminated portions of that media. The RfC is translated into these safe media concentrations levels by incorporating site-specific information called exposure factors. These factors include information such as exposure time, exposure frequency, exposure duration, inhalation rate, and vapor-phase and particulate-phase inhalation. These site-specific variables and the RfC are incorporated into a health risk assessment according to USEPA-approved methodologies and calculations.[2] Thus, "safe" environmental standards are back calculated from the toxicological reference point (i.e., the RfC). The RfC is specifically developed to be protective for long-term exposure to a compound (as a Superfund program guideline, seven years to a lifetime).[2] The RfC methodology is not applied to the National Ambient Air Quality Standards criteria air pollutants (e.g., carbon monoxide, ozone, etc.) due to legislative requirements in the Clean Air Act as well as differences in the health databases of these pollutants.[1]