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assessment include characterizing cumulative risk and revising the Guidelines for the Health Risk Assessment of Chemical Mixtures.

In addition, neurotoxic effects may result from short-term (acute), highconcentration exposures as well as from longer term (subchronic), lower level exposures. Neurotoxic effects may occur after a period of time following initial exposure or be obfuscated by repair mechanisms or apparent tolerance. The type and severity of effect may depend significantly on the pattern of exposure rather than on the average dose over a long period of time. For this reason, exposure assessments for neurotoxicants may be much more complicated than those for long-latency effects such as carcinogenicity. It is rare for sufficient data to be available to construct such patterns of exposure or dose, and professional judgment may be necessary to evaluate exposure to neurotoxic agents.

VI. Risk Characterization

A. Overview

Risk characterization, the culmination of the risk assessment process, consists of an integrative analysis and a risk characterization summary. The integrative analysis (a) involves integration of the toxicity information from the hazard characterization and dose-response analysis with the human exposure estimates, (b) provides an evaluation of the overall quality of the assessment and the degree of confidence in the estimates of risk and conclusions drawn, and (c) describes risk in terms of the nature and extent of harm. The risk characterization summary communicates the results of the risk assessment to the risk manager.

This summary should include but is not limited to a discussion of the following elements:

a. Quality of and confidence in the available data;

b. Uncertainty analysis;

c. Justification of defaults or assumptions;

d. Related research recommendations;
e. Contentious issues and extent of scientific consensus:

f. Effect of reasonable alternative assumptions on conclusions and estimates;

g. Highlight reasonable plausible ranges;

h. Reasonable alternative models; and i. Perspective through analogy.

The risk manager can then use the

risk assessment, along with other risk management elements, to make public health decisions.

An effective risk characterization must fully, openly, and clearly

characterize risks and disclose the scientific analyses, uncertainties, assumptions, and science policies that underlie decisions throughout the risk assessment and risk management processes. The risk characterization must feature values such as transparency in the decision-making process; clarity in communicating with each other and the public regarding environmental risk and the uncertainties associated with assessments of environmental risk; and consistency across program offices in core assumptions and science policies, which are well grounded in science and reasonable.

The following sections describe these four aspects of the risk characterization in more detail.

B. Integration of Hazard Characterization, Dose-Response Analysis and Exposure Assessment

In developing the hazard characterization, dose-response analysis and exposure portions of the risk assessment, the assessor must take into account many judgments concerning human relevance of the toxicity data, including the appropriateness of the various animal models for which data are available and the route, timing, and duration of exposure relative to expected human exposure. These judgments should be summarized at each stage of the risk assessment process (e.g., the biological relevance of anatomical variations may be established in the hazard characterization process, or the influence of species differences in metabolic patterns in the dose-response analysis). In integrating the information from the assessment, the risk assessor must determine if some of these judgments have implications for other portions of the assessment and whether the various components of the assessment are compatible.

The risk characterization should not only examine the judgments but also explain the constraints of available data and the state of knowledge about the phenomena studied in making them, including (1) the qualitative conclusions about the likelihood that the chemical may pose a specific hazard to human health, the nature of the observed effects, under what conditions (route, dose levels, time, and duration) of exposure these effects occur, and whether the health-related data are sufficient to use in a risk assessment; (2) a discussion of the dose-response characteristics of the critical effects(s), data such as the shapes and slopes of the dose-response curves for the various end points, the rationale behind the

determination of the NOAEL and LOAEL and calculation of the benchmark dose, and the assumptions underlying the estimation of the RfD or RfC; and (3) the estimates of the magnitude of human exposure; the route, duration, and pattern of the exposure; relevant pharmacokinetics; and the number and characteristics of the population(s) exposed.

If data to be used in a risk characterization are from a route of exposure other than the expected human exposure, then pharmacokinetic data should be used, if available, to make extrapolations across routes of exposure. If such data are not available, the Agency makes certain assumptions concerning the amount of absorption likely or the applicability of the data from one route to another (U.S. EPA, 1992).

The level of confidence in the hazard characterization should be stated to the extent possible, including the appropriate category regarding sufficiency of the health-related data. A comprehensive risk assessment ideally includes information on a variety of end points that provide insight into the full spectrum of potential neurotoxicological responses. A profile that integrates both human and test species data and incorporates a broad range of potential adverse neurotoxic effects provides more confidence in a risk assessment for a given agent.

The ability to describe the nature of the potential human exposure is important to predict when certain outcomes can be anticipated and the likelihood of permanence or reversibility of the effect. An important part of this effort is a description of the nature of the exposed population and the potential for sensitive, highly susceptible, or highly exposed populations. For example, the consequences of exposure to the developing individual versus the adult can differ markedly and can influence whether the effects are transient or permanent. Other considerations relative to human exposures might include the likelihood of exposures to other agents, concurrent disease, and nutritional status.

The presentation of the integrated results of the assessment should draw from and highlight key points of the individual characterizations of component analyses performed under these Guidelines. The overall risk characterization represents the integration of these component characterizations. If relevant risk assessments on the agent or an analogous agent have been done by EPA or other Federal agencies, these should