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Options for Dealing with Uncertainties in Developing Tolerable Upper Intake Levels

Methods for dealing with uncertainties in scientific data are generally understood by working scientists and require no special discussion here except to point out that such uncertainties should be explicitly acknowledged and taken into account whenever a risk assessment is undertaken. More subtle and difficult problems are created by uncertainties associated with some of the inferences that need to be made in the absence of directly applicable data; much confusion and inconsistency can result if they are not recognized and dealt with in advance of undertaking a risk assessment.

The most significant inference uncertainties arise in risk assessments whenever attempts are made to answer the following questions (NRC, 1994):

- What set or sets of hazard and dose-response data (for a given substance) should be used to characterize risk in the population of interest?
- If animal data are to be used for risk characterization, which endpoints for adverse effects should be considered?
- If animal data are to be used for risk characterization, what measure of dose (e.g., dose per unit body weight, body surface, or dietary intake) should be used for scaling between animals and humans?
- What is the expected variability in dose response between animals and humans?

- If human data are to be used for risk characterization, which adverse effects should be used?
- What is the expected variability in dose response among members of the human population?
- How should data from subchronic exposure studies be used to estimate chronic effects?
- How should problems of differences in route of exposure within and between species be dealt with?
- How should the threshold dose be estimated for the human population?
- If a threshold in the dose-response relationship seems unlikely, how should a low-dose risk be modeled?
- What model should be chosen to represent the distribution of exposures in the population of interest when data relating to exposures are limited?
- When interspecies extrapolations are required, what should be assumed about relative rates of absorption from the gastrointestinal tract of animals and of humans?
- For which percentiles on the distribution of population exposures should risks be characterized?

At least partial, empirically based answers to some of these questions may be available for some of the nutrients under review, but in no case is scientific information likely to be sufficient to provide a highly certain answer; in many cases there will be no relevant data for the nutrient in question.

It should be recognized that for several of these questions, certain inferences have been widespread for long periods of time and, thus, it may seem unnecessary to raise these uncertainties anew. When several sets of animal toxicology data are available, for example, and data are not sufficient for identifying the set (i.e., species, strain, and adverse effects endpoint) that *best* predicts human response, it has become traditional to select that set in which toxic responses occur at lowest dose (the *most sensitive* set). In the absence of definitive empirical data applicable to a specific case, it is generally assumed that there will not be more than a 10-fold variation in response among members of the human population. In the absence of absorption data, it is generally assumed that humans will absorb the chemical at the same rate as the animal species used to model human risk. In the absence of complete understanding of biological mechanisms, it is generally assumed that, except possibly for certain carcinogens, a threshold dose must be exceeded before toxicity is expressed. These types of long-standing assumptions, which

are necessary to complete a risk assessment, are recognized by risk assessors as attempts to deal with uncertainties in knowledge (NRC, 1994).

A past National Research Council (NRC) report (1983) recommended the adoption of the concepts and definitions that have been discussed in this report. The NRC committee recognized that throughout a risk assessment, data and basic knowledge will be lacking and that risk assessors will be faced with several scientifically plausible options (called *inference options* by the NRC) for dealing with questions such as those presented above. For example, several scientifically supportable options for dose scaling across species and for high-to-low dose extrapolation will exist, but there will be no ready means for identifying those that are clearly best supported. The NRC committee recommended that regulatory agencies in the United States identify the needed inference options in risk assessment and specify, through written risk assessment guidelines, the specific options that will be used for all assessments. Agencies in the United States have identified the specific models to be used to fill gaps in data and knowledge; these have come to be called *default options* (EPA, 1986).

The use of defaults to fill knowledge and data gaps in risk assessment has the advantage of ensuring consistency in approach (the same defaults are used for each assessment) and for minimizing or eliminating case-by-case manipulations of the conduct of risk assessment to meet predetermined risk management objectives. The major disadvantage of the use of defaults is the potential for displacement of scientific judgment by excessively rigid guidelines. A remedy for this disadvantage was also suggested by the NRC committee: risk assessors should be allowed to replace defaults with alternative factors in specific cases of chemicals for which relevant scientific data are available to support alternatives. The risk assessors' obligation in such cases is to provide explicit justification for any such departure. Guidelines for risk assessment issued by the U.S. Environmental Protection Agency, for example, specifically allow for such departures (EPA, 1986).

The use of preselected defaults is not the only way to deal with model uncertainties. Another option is to allow risk assessors complete freedom to pursue whatever approaches they judge applicable in specific cases. Because many of the uncertainties cannot be resolved scientifically, case-by-case judgments without some guidance on how to deal with them will lead to difficulties in achieving scientific consensus, and the results of the assessment may not be credible.

Another option for dealing with uncertainties is to allow risk assessors to develop a range of estimates based on application of both defaults and alternative inferences that, in specific cases, have some degree of scientific support. Indeed, appropriate analysis of uncertainties seem to require such a presentation of risk results. Although presenting a number of plausible risk estimates has the advantage that it would seem to more faithfully reflect the true state of scientific understanding, there are no well-established criteria for using such complex results in risk management.

The various approaches to dealing with uncertainties inherent to risk assessment are summarized in Table J-1.

As will be seen in the chapters on each nutrient, specific default assumptions for assessing nutrient risks have not been recommended. Rather, the approach calls for case-by-case judgments, with the recommendation that the basis for the choices made be explicitly

TABLE J-1 Approaches for Dealing with Uncertainties in a Risk Assessment Program

Program Model	Advantages	Disadvantages
Case-by-case judgments by experts	Flexibility; high potential to maximize use of most relevant scientific information bearing on specific issues	Potential for inconsistent treatment of different issues; difficulty in achieving consensus; need to agree on defaults
Written guidelines specifying defaults for data and model uncertainties (with allowance for departures in specific cases)	Consistent treatment of different issues; maximization of transparency of process; resolution of scientific disagreements possible by resort to defaults	Possibly difficult to justify departure or to achieve consensus among scientists that departures are justified in specific cases; danger that uncertainties will be overlooked
Presentation of full array of estimates from all scientifically plausible models by assessors	Maximization of use of scientific information; reasonably reliable portrayal of true state of scientific understanding	Highly complex characterization of risk, with no easy way to discriminate among estimates; size of required effort may not be commensurate with utility of the outcome

stated. Some general guidelines for making these choices will, however, be offered.

REFERENCES

- EPA (U.S. Environmental Protection Agency). 1986. Guidelines for carcinogen risk assessment. *Fed Regist* 51:33992–34003.
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