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The Inexact Science of Risk Assessment (and Implications for Risk Management)

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TBE NATURE OF RISK ASSESSMEENT

Human health risk estimates are calculated for use in setting standards, cleanup levels for hazardous wastes, or otherwise expressing an exposure level that is believed to be safe or associated with some risk. Most risk estimates are calculated to be protective of human health, rather than predictive of actual toxicity. For example, cancer potency factors calculated by the U.S. EPA are presented as the 95% upper confidence limit on the dose-response curve, rather than the maximum likelihood estimate. EPA goes on to say that risk assessors believe the actual cancer risk to be somewhere below this upper confidence limit, and that it could be as low as zero. This is an acknowledgm ment of the uncertainty inherent in the process of cancer risk assessment, which is a function of both cross-species and high-to-low dose extrapolation. Similarly, for noncancer risk assessments, U.S. EPA (1995) calculates Reference Doses (RfDs) and Reference Concentrations (RfCs) , which are defined as: *"...an estimate (with uncertainty spanningperhaps an order ofmagnitude) ofa daily or continuous exposure..."* The values generated by the process of risk assessment are imprecise; such imprecision is clearly articulated by the definitions provided.

Somewhere between the steps of risk assessment and risk management, however, the concept of risk estimates as inherently imprecise has been lost. This is probably due to a number of reasons, one of which is likely because the risk manager has to communicate with a public that wants to know with some certainty and precision what the risks from exposure to hazardous substances actually are (and in rather succinct terms), rather than hearing the risks described more appropriately as scientific judgments that are, by their very

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nature, imprecise. Or, perhaps this is because risk assessors themselves become so accustomed to using default positions/models to extrapolate risk (e.g., across species; to sensitive subgroups; from shorter to longer durations of exposure; from exposures that cause toxicity to those that do not) that they lose sight of the degree of uncertainty that is introduced with each extrapolated area.

In order to more clearly delineate the roles and responsibilities of risk assessors and risk managers, EPA has issued guidance on the functions of each. In the risk characterization guidance (EPA, 1995), it was emphasized that risk assessors and risk managers should be sensitive to these distinctions:

> For the *generators of the assessmmt,* distinguishing between risk assessment and risk management means that scientific information is selected, evaluated, and presented without considering issues such as cost, feasibility, or how the scientific analysis might influence the regulatory or site-specific decision....
> For *users of the assessment* and for decision-makers who integrate these assessments into regulatory or site-specific decisions, the distinction between risk assessment and risk management means refraining from influencing the risk description through consideration of other factors - e.g., the regulatory outcome - and from attempting to shape the risk assessment to avoid statutory constraints, meet regulatory objectives, or serve political purposes. Such management considerations are often legitimate considerations for the overall regulatory decision.... but they have no role in estimating or describing risk.... Matters such as risk assessment priorities, degree of conservatism, and acceptability of particular risk levels are reserved for decision-makers who are charged with making decisions regarding protection of human health.

INHERENT IMPRECISION IN RISK ESTBUTES

Despite the fact that the stated definition of EPA's Rfl) and RfC includes a statement that the risk value has "uncertainty spanning perhaps an order of magnitude," or that cancer potency factors are 95% upper confidence limits based on one statistical model, risk management decisions are often made as if these risk estimates are precise point estimates. The latitude provided for risk managers to make decisions based on multiple factors other than those in the risk characterization is rarely exercised. To a large extent, this may be because risk managers are often provided with only single numbers (e.g., an Rfl), RfC, or cancer potency factor) upon which to base their decisions. A full discussion of uncertainties is frequently lacking, so that the risk manager may not understand the limitations of the risk estimates that are provided.

The risk manager, faced with the prospect of presenting this information to the public, may indeed wish that these were precise numbers reflective of a high degree of scientific certainty and precision. This is perhaps the message the public would like to receive. Faced with potential exposures to chemicals

of varying degrees of hazard, one wants to know what level is safe. At the same time, excessive or unnecessarily conservative regulations that stifle industry and the economy are not desirable. The job of the risk manager, then, is to balance the knowns and unknowns provided in the risk characterization with societal values, analytical and technical feasibility, and economic and political factors.

To the credit of those who generate RfDs and RfCs for the EPA, these numbers are accompanied by a confidence statement which describes the risk assessors' degree of confidence in the principal study used to calculate the risk estimate, the database as a whole, and the resulting risk estimate itself. This information, while quite meaningful to the risk assessor, does not tend to influence risk management decisions. This may be because a risk manager, faced with an Rfl) that has "low confidence" or one with "high confidence," cannot use this information in decision-making without more explicit guidance on what these confidence statements mean in a quantitative sense.

Even when the full range of the Rfl) is contemplated, however, several interpretations of the "order of magnitude" range are possible, and in fact, are used within EPA:

1. *range = x to* 10x. (where point estimate of Rfl) = x). This view is supported by those who believe that the risk assessment process is so inherently conservative that the RfD should be considered to be the lowest estimate, with the range of imprecision all resting *above* this point estimate.

2. *range = 0.3x to 3x.* This is the view held by many EPA's RfD/RfC Work Group members, wherein the Rfl) is associated with uncertainty on either side. The order of magnitude is divided into half-logs.

3. *range = 0. Ix to x.* This is the view held by many risk managers. That is, regulatory decisions *(e.g.,* setting of standards or clean-up levels) are made based on the assumption that we are "OK" as long as we do not exceed the level of the Rfl).

4. *range= O.1x to* 10x. This range could be envisioned if one were to assume that the order of magnitude range could be on *either* side of the point estimate x

Finally, even if there were agreement among risk assessors as to how this "order of magnitude" uncertainty should be interpreted, it is questionable as to whether this interpretation should be applied to all RfDs/RfCs equally. As described more fully below, the degree of precision associated with an RfD or RfC is a function of the database used to calculate this number and also of chemical specific factors *(e.g.,* the slope of the dose-response function).

Similarly, while EPA states that cancer potency factors are a 95% upper confidence limit, and that the true risk is likely below this level and may even be zero, these sorts of statements are of limited use to the risk manager. Without more explicit information on the range associated with these risk

numbers, the risk manager has little choice other than to treat them as point estimates.

THE WAY IT SHOULD BE: RISK ASSESSMENT AS AN INEXACT SCIENCE

Each risk estimate (e.g., RfD, RfC, cancer potency factor) is determined from an assessment of a distinct data base for each individual chemical. just as all risk estimates are not created equal in terms of knowledge bases, neither is the precision, or range of uncertainty, associated with each. The determination of an appropriate range must be handled on a chemical-specific basis. In this way, more meaningful information will be provided to the risk manager and the public for use in making and understanding risk management decisions.

Several factors will affect the precision of the range associated with any risk estimate as illustrated in Figure 1. These include: the amount and type of data available (including toxicological, mechanistic, pharmacokinetic, etc.; the number and magnitude of uncertainty factors used; if applicable, the mathematical model used in the dose-response assessment (e.g., cancer low-dose extrapolations, benchmark dose methodology); the subjective confidence level in the risk estimate; the dose spacing used in the critical study; the severity of the critical effect; the slope of the dose-response curve (and whether it changes); the degree of concordance between studies.

Using the types of information listed above and other appropriate data, guidance can be developed for how to best express the inherent imprecision and the corresponding appropriate range for a risk estimate on a chemicalspecific basis.

Advantages

There are clear advantages to more clearly articulating the imprecision of risk estimates in a formal manner. Most significantly, the expression of a range is more appropriate than a single point estimate in almost all cases, because sufficient data are not available to be able to precisely determine a lifetime threshold in humans for noncancer effects or a *"de* minimis" level of risk for cancer. Even where data are plentiful, the variability within humans still argues for the expression of risk estimates as a range, although perhaps smaller. As those involved in the risk assessment process strive to be more scientifically credible, it will do them well to remember this quote of Aristotle:

> 'It is the mark of an instructed mind to rest satisfied with the degree of precision which the nature of the subject permits and not to seek an exactness where only an approximation of the truth is possible."

Risk assessors should not infer levels of precision that clearly are not appropriate for quantitative risk assessments. Also, for risk managers, a range of values may help in the prioritization of contamination problems. For

Factors Affecting the Precision in the RfD							
Critical Effect (NOAEL/LOAEL)				Size of UF	Confidence In RfD/C	Other Areas	**Precision In RfD**
Dose Spacing	Severity of Effect	Slope of Dose-Response	Species/Strain Concordance				
Small	Minor	Steep	Good	Small	Higher		**Tight**
↕	↕	↕	↕	↕	↕	?	↕
Large	Severe	Shallow	Poor	Big	Lower		**Broad**

example, levels of two contaminants may be above the level of concern indicated by the point estimate RfD. But given a range, it can be more easily determined *which of* the two *is of* more *of* an immediate concern to human health.

Another advantage to expressing risk numbers as a range is embodied in the principles of harmonization of risk assessment methodologies. International agencies engaged in risk assessment practices often derive different values for a given chemical, even though the supporting database is the same (cf. Dourson and Lu, 1995; ITER, 1998). This is often because of the use of different assumptions or the application of different uncertainty factors. Given that these are a matter of professional judgment, it is clear that one answer is not necessarily "right", while another is "wrong." Rather, these differences might reflect the imprecision of the risk assessment numbers. If risk estimates were more often expressed as ranges, which incorporate the use of a number of different models or default assumptions, the risk assessment community may begin to see more similarities than differences in risk assessment outcomes. The information embodied in any group's risk characterization, then, could be used and modified as appropriate by the risk managers.

Potential Problems

Although there are clear benefits to expressing the precision of risk estimates as a range, potential problems exist as well. Concerns have been voiced that insufficient information will be provided to risk managers who will have to use values within this range (or the range itself) in establishing criteria, clean up levels, etc. It may be more difficult for risk managers to defend their decisions (particularly in the legal arena) if other risk managers make different decisions based on the same risk assessment. There may be a tendency for risk managers to simply default to using the top or bottom *of* a stated range to help prevent charges of inconsistency. Clearly, the decision to consider values within a range will necessitate the concurrent development *of* guidance for interpreting and using these ranges.

SUMMARY

In summary, risk assessment is an inexact science. It would be fortunate if clear and easy answers existed to complicated questions of risk to human health following exposure to potentially harmful chemicals. Indeed, risk assessors often present their risk values as if they were precise and reflective of actual risk. The underlying data seldom support such precision.

Risk assessors need to better characterize risk, complete with a discussion of assumptions made and remaining uncertainties, in a meaningful way that is transparent to the user. likewise, the risk manager needs to acknowledge that risk assessment often cannot provide clear cut answers, and that theirjob does in fact involve making trade-offs and decisions in which risk characterizations play only one part of the answer to risk management problems.

REFERENCES

Dourson, M.L. and F.C. Lu. 1995. Safety/Risk assessment of chemicals compared for different expert groups. Biomed. *Environ. Sci., 8, 1-13*.

ITER (International Toxicity Estimates for Risk). 1998. Online. Accessible through the internet at the HomePage of Toxicology Excellence for Risk Assessment at http:// www.tera.org.

USEPA (Environmental Protection Agency). 1995. Guidance for risk characterization. Science Policy Council. Washington, D.C. February.