EPA United States

9/19/00

Environmental Protection Agency
Risk Assessment Forum

# Colloquium on Approaches to Quantifying Health Risks for Threshold or Nonlinear Effects at Low Dose

Omni Shoreham Hotel
2500 Calvert Street N.W.
Washington D.C. 20004

September 28, 2000

## Draft Agenda

**Colloquium Co-Chairs: Al McGartland and Vanessa Vu**

9:00AM **Welcome**
*Bill Wood, EPA Risk Assessment Forum*

9:05AM **Perspectives: A Risk Assessor's Point of View**
*Vanessa Vu*, National Center for Environmental Assessment

9:25AM **Perspectives: An Economist's Point of View**
*Al* McGartland, National Center for Environmental Economics

9:45AM **Dose-Response Based Distributional Analysis of Threshold Effects**
*Lorenz Rhomberg, Gradient Corporation*
*Sandra Baird, The Baird Group*

10:15AM **Characterizing Interspecies Uncertainty Using Data from Studies of Anti-neoplastic Agents in Animals and Humans**
*Paul Price, Ogden Environmental and Energy Services*

10:35AM **Expected Values of Population Dose Response Relationships Inferred from Data on Human Interindividual Variability in PK and PD Parameters**
*Dale Hattis, Clark University*

10:55AM BREAK

11:10AM **Interindividual Sensitivity**
*Dave Gaylor, Sciences International*

11:30AM **Use of the Categorical Regression Methodology to Characterize the Risk Above the RfD**
*Lynne Haber, Toxicology Excellence for Risk Assessment (TERA)*

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| 11:50AM | **Risks Between the LOAEL and the RfD/RfC: A Minimalist's Approach**<br>*Resha Putzrath*, Georgetown Risk Group |
| 12:10PM | LUNCH (on your own) |
| 1:15PM | **Facilitated Roundtable Discussion**<br>*Moderator: Bill Wood* |
| | ( BREAK 3:00 - 3:15PM ) |
| 4:30PM | **Concluding Comments and Next Steps**<br>*Vanessa Vu and Al McGartland* |
| 5:00PM | ADJOURN |

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# Colloquium on Approaches to Quantifying Health Risks for Threshold or Nonlinear Effects at Low Dose

NCEA Conference Room
Suite 400
808 17th Street N.W.
Washington D.C.

Friday, September 29, 2000

## Draft Agenda

Colloquium Co-Chairs: **Al McGartland and Vanessa Vu**

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| 8:30AM | **Welcome and Objectives**<br>*Vanessa Vu,* National Center for Environmental Assessment<br>Al McGartland, National Center for Environmental Economics |
| 8:50AM | **Facilitated Roundtable Discussion**<br>Moderator: Bill Wood |
| | (BREAK 10:15 - 10:30) |
| 11:45AM | **Concluding Comments and Next Steps**<br>Vanessa Vu and Al McGartland |
| 12:00PM | ADJOURN |

# Dose-Response Based Distributional Analysis of Threshold Effects

Lorenz Rhomberg, Sandra Baird, John Evans, Paige Williams, and Andrew Wilson

We propose an analytical approach for risk analysis of toxic effects that are expected to have individual exposure thresholds. Our approach is rooted in the familiar structure of existing non-cancer risk assessment methodology. However, we extend the methodology by using data-based statistical distributions to represent extrapolation factors. This provides a framework for a comprehensive description and analysis of the uncertainty involved when projecting observations of toxic effects in experimental animal bioassays to characterize risks at different levels of human exposure. This enables the analysis to move beyond a simple "safety" assessment to one based on identifying a projected human dose-response relationship (with full characterization of the uncertainty in the projection), allowing better separation of risk assessment and risk management concerns, and permitting a quantitative analysis of the likelihoods of different fractions of an exposed human population having toxic responses at doses above or below a traditional RfD/RfC.

Our approach is based on cataloguing the sources of uncertainty and variability in extrapolating animal bioassay toxicity observations to humans, with each component characterized by a statistical distribution based on empirical observations about case-to-case variation in that extrapolation element as observed for other toxic compounds. In particular: (1) the uncertainty in fitting an empirical dose-response model to the animal data is captured; (2) the case-by-case variation in toxicological equivalence of animal and human doses is based on empirically supported distributions and such variation is separated from the issue of optimal dose metrics for interspecies comparison; and (3) variation among humans is characterized by distributions of epidemiologically observed interindividual variation in responsiveness to toxic substances. This variation is used to define a human dose-response relationship based on the idea of tolerance distributions, which we propose to characterize in the human population rather than from data on specified and artificially uniform populations of experimental animals. A Monte Carlo simulation approach propagates these various sources of uncertainty into an overall characterization of human variability as a dose-response curve, with a full description of uncertainty in percentiles of that curve that arises from its origin in extrapolation from animal experiments.

In sum, we propose an extension of familiar methods using statistical distributions of the extrapolation factors based on observations regarding how these factors actually vary among real cases. We then use error propagation to fully characterize the uncertainty in projections to humans. Aside from our particular implementation, we provide a comprehensive framework for characterizing sources of uncertainty and for understanding their relative contributions to the uncertainty in human risk estimates. We believe the method has great utility for applications of involving comparative risk, analysis of costs and benefits, and harmonization with methods used for assessment of carcinogens.

Lynne Haber and Michael Dourson, TERA

Categorical regression has been proposed as a means of determining the risk above the RfD, with the dose-response curve in the range of the data assumed to extend down to the range of the RfD. This approach has been described as being of particular utility as a screening tool, allowing risk managers to compare the consequence of exposure to different chemicals exceeding the respective RfDs. Issues and interpretations of this approach will be discussed. For example, extrapolating to low doses is not recommended for benchmark dose (BMD) modeling, because such extrapolation increases the model-dependency of the results;a similar argument might be expected to apply to categorical regression. On the other hand, categorical regression uses more of the overall database, and so might be expected to better predict the actual human risk, as opposed to modeling based on the most sensitive species/sex/endpoint. Another issue that requires further research is how the use of uncertainty factors should be taken into account in the low-dose extrapolation. These issues will be addressed through case examples. Similarly assumptions regarding choice of uncertainty factors need to be considered for any approach for calculating the risk above the RfD or probabilistic RfDs.

Recommended reading: TEUSCHLER, L.K., M.L. DOURSON, W.M. STITELER, P. McCLURE. and H. TULLY. 1999. Health risk above the reference dose for multiple chemicals. Reg. Toxicol. and Pharmacol., 30: S19-S26.

Dale Hattis

"Expected Values of Population Dose Response Relationships Inferred from Data on Human Interindividual Variability in Pharmacokinetic and Pharmacodynamic Parameters--Update of Prior Work"

In previous work (Ref. 1) we have assembled a substantial database of information on human interindividual variability in parameters likely to affect susceptibility to various biological responses--mostly from the pharmaceutical literature. These data were then analyzed (Ref. 2) to (A) gauge the frequency with which the traditional 10-fold factor for interindividual variability, acting by itself, is likely to meet specific criteria for the incidence of adverse effects, and (B) assess the arithmetic mean "expected value" of specific incidences of adverse effects as a function of dose below an ED05 starting level, assuming that individual human susceptibilities are continuous unlimited lognormal distributions.

For this presentation, the "expected value" calculations will be revisited using our current larger database (over 420 datasets compared to the 218 used in the prior analysis) and some additional subcategorizations of the data by organ system affected and a crude measure of the severity of response.

I would recommend that people read reference 2 below as a good background for my talk. (Reference 2 is unfortunately a rather long and involved paper--the conclusions relevant to your workshop can be found toward the end on pp. 311-312.)

References:

1. Hattis, D. Banati, P., Goble, R., and Burmaster, D. "Human Interindividual Variability in Parameters Related to Health Risks, Risk Analysis, Vol. 19, No. 4, pp. 711-726, 1999.

2. Hattis, D., Banati, P., and Goble, R. "Distributions of Individual Susceptibility Among Humans for Toxic Effects--For What Fraction of Which Kinds of Chemicals and Effects Does the Traditional 10-Fold Factor Provide How Much Protection?" Annals of the New York Academy of Sciences, Volume 895, pp. 286-316, December, 1999.

**Characterizing Inter-species Uncertainty Using Data from Studies of Anti-neoplastic Agents in Animals and Humans** Paul S. Price, Ogden Environmental and Energy Services Inc.

Traditionally, non-cancer risk assessments has focused only on the determination of a "safe dose" that will be protective of both the general population and the "sensitive individual" (e.g., Dourson and Stara, 1983; Lewis et al. 1990; Dourson et al., 1996). This is in contrast to the characterization of carcinogenic risk where risks are expressed in terms of a predicted rate of response associated with a specified dose.

This talk will present a framework for defining a compound's RfD in terms of the compound's dose response curve in humans. Specifically, the RfD is defined as the lower confidence limit of the highest point on a compounds's dose response curve that causes a zero response (e.g., the population threshold). Using this definition, a method is presented for evaluating risks above the RfD (Price et al. 1997). The method produces predictions of a response rates for doses above the RfD and confidence limits for those rates This approach uses information on variability (as measured by difference between the $ED_{50}$ and the NOAEL) and distributions that characterize the uncertainty in the interspecies, intraspecies, and other uncertainty factors. The approach has a number of advantages in that it does not require large amounts of additional toxicological data nor does it require detailed information in the shape of the dose response curve for specific chemicals.

Price, P.S., R.E. Keenan, J.C. Swartout, C.A. Gillis, H. Carlson-Lynch and M.L. Dourson. 1997. An approach for modeling noncancer dose responses with emphasis on uncertainty. Risk Anal. Vol 17, No. 4. 427-437

Other relevant papers include:

Price, P.S., R.E. Keenan, B Schwab. 1999. Defining the Interindividual (Intraspecies) Uncertainty Factor. HERA. October. 5(5): 1023-1033.

Carlson-Lynch, H., P.S. Price, J.C. Swartout, M.L. Dourson and R.E. Keenan. 1999. Application of quantitative information on the uncertainty in the RfD to noncarcinogenic risk assessments. HERA. June. 5(3): 527-547.

Dourson, M.L. and J. Stara. 1983. Regulatory history and experimental support of uncertainty (safety) factors. Regulatory Toxicology and Pharmacology 3: 224-238.

Dourson, M.L., S.P. Felter and D. Robinson. 1996. Evolution of science-based Uncertainty factors in noncancer risk assessment. Regulatory Toxicology and Pharmacology 24: 108-120.

Lewis, S.C., J.R. Lynch and A.I. Nikiforov. 1990. A new approach to deriving community exposure guidelines from no-observed-adverse-effect levels. Regulatory Toxicology and

Pharmacology 11: 314-330.

Swartout, J.C., P.S. Price, M.L. Dourson, H. Carlson-Lynch and R.E. Keenan. 1998. A probabilistic framework for the reference dose. Risk Anal. (18)3, 271-282.

Risks between the LOAEL and the RfD/RfC: A Minimalist?s Approach. Resha M. Putzrath; Georgetown Risk Group; 3223 N Street, N.W.; Washington, D.C.

Evaluating risks between the LOAEL and the RfD/RfC requires estimation of dose-response curves for the region of interest. Before using generic assumptions, all of the chemical-specific data should be used to: (1) approximate the dose-response curve and (2) determine to what extent a more accurate risk assessment is required. Even if only an RfD/RfC, NOAEL, and LOAEL are available, these can provide sufficient information to characterize the dose-response curve (including an approximation of the likely threshold) which will often be sufficient to determine if a more accurate risk estimate is likely to affect the risk management decision. If a more accurate risk estimates is required, the exposure(s) of interest must be considered. For example, if the exposure is between the LOAEL and the NOAEL, the uncertainty in the estimation of the NOAEL is one significant factor. If the exposure is below the NOAEL, the distance between the NOAEL and the RfD/RfC (i.e., the magnitude of the combined uncertainty and modifying factors) should be considered, as well as whether the exposure is closer to the NOAEL or the RfD/RfC. Furthermore, the implications of using the LOAEL or NOAEL as the starting point for further analyses must be evaluated; use of the RfD/RfC is not recommend. For cancer, the default assumption is that, at low doses, the dose-response curve is a straight line. Thus, if the dose-response curve has been determined to be curvilinear, i.e., the default assumption is rejected, a reasonable amount of data must be available regarding the shape of the dose-response curve. These data should also be sufficient to estimate the dose-response curve (and its upper bound) at the exposure of interest.