EPA’s Advances in Human Health Assessment Research

Joint Meeting of
The Environmental Health Committee and
The Integrated Human Exposure Committee
U.S. EPA Science Advisory Board

Peter W. Preuss, Ph.D., Director
National Center for Environmental Assessment
Office of Research and Development
September 6, 2006

Topics for Discussion

1. Introduction: Risk Assessment at EPA
2. Mode of Action
3. Uncertainty Analyses
4. High to Low Dose Extrapolation
5. PBPK Modeling
6. Conclusions
Basic Principles of Risk Assessment

1. The starting point for risk assessment is a critical analysis of available scientific information.*
2. Quantitative estimates of risk are, to the extent possible,
   - Biologically-motivated
   - Data-driven.
3. When there is insufficient data, default methods are used that**
   - Protect public health
   - Ensure scientific validity (i.e., scientifically plausible and extensively peer reviewed)
   - Create an orderly and predictable process
4. Implementation of these principles involves...extensive peer review.**

*U.S. EPA 2005, Cancer Guidelines
**NRC 1994, “Science and Judgment in Risk Assessment”
NHEERL: Human Health Risk Assessment

- Mechanistic Data in Risk Assessment
  - Mechanistic work in response to NAS recommendations (e.g., arsenic, PM)
  - Mechanistic work to support regulatory decisions
- Fundamental research on models
  - Route to Route extrapolation models (e.g., 1,1,2-trichloroethane, methanol, ethanol, 1,2-dichloroethane)
  - Pharmacokinetic models for risk assessments (e.g., 1,1,2-trichloroethane, perfluorooctanoic acid [PFOA])
- Emerging technologies
  - Nanomaterials and health effects
  - Genomics technologies for computational toxicology
- Aggregate/Cumulative Risk
  - Organophosphate cumulative risk - data to support additivity model
  - Carbamate cumulative risk - PBPK model for cumulative risk
- Susceptible Subpopulations
  - Asthma Research - research related to the Asthma Research Strategy
  - Research in support of Cancer Guidelines for children
  - Research to support OPPTS testing guidelines - developmental neurotoxicology

NCEA: Human Health Assessment

- Conducting human health risk assessments and management of the Agency’s Integrated Risk Information System (IRIS) (e.g., tetrachloroethylene, methyl tertiary butyl ether, ethylene oxide, trichloroethylene, acrylamide, and 72 others)
- Producing Air Quality Criteria Documents
  - Ozone – completed February 2006
  - Lead – will be completed September 2006
  - Particulate Matter – completed October 2004
  - Nitrogen Oxides -- underway
  - Sulfur dioxide -- underway
  - Carbon Monoxide – completed June 2000
- Providing risk assessment research, methods, guidelines, training materials, and technical and regulatory support to EPA’s Program Offices and Regional Offices and the public
  - Uncertainty analysis
  - Identification of possible modes of action
  - Physiologically based Pharmacokinetics (PBPK) Modeling
  - Approaches to quantification
  - Approaches for Assessing Risk of Environmental Exposures to Age-Susceptible Populations (children, elderly)
  - Less than Lifetime Assessments
Major Recurring Issues

- Use of data from human studies in health assessments
- Accounting for less-than-lifetime exposure durations
- Qualitative and quantitative use of mode of action data in noncancer and cancer assessments
- Benchmark dose modeling and selection of the benchmark response
- Evaluation and use of PBPK models
- Accounting for life-stage and subpopulation susceptibility in uncertainty factors
- Use of data-derived uncertainty factors
- Characterization of uncertainty in noncancer and cancer analysis
- Use of time-to-tumor modeling for cancer assessments

Mode of Action: Key Events

Figure: A representative example of mode of action with key events
**Mode-of-Action Activities**

- **Purpose:** Promote a consistent approach to analyses of chemical MOAs
- **Issues:**
  - Identification of key events and testable hypotheses
  - Consideration of diverse data (across endpoints, chemicals)
  - Evidence necessary to draw conclusions and/or rule out alternatives
- **Impacts on uncertainty analyses**
  - Choice of internal dose metric(s) when using PBPK models
  - Choice of study(ies)/endpoint(s) for use in quantification
  - Choice of dose-response model(s)
  - Choice of low-dose extrapolation approach
Exploratory Review of the Scientific Foundation for Estimating Uncertainty in EPA Reference Values

- Continuing scientific and methodological advances have raised questions about whether current procedures could be improved
- Advances have included:
  - increased chemical specific data and the willingness of stakeholders/agencies to provide these data
  - improved methodologies such as benchmark dose modeling
  - development of physiologically-based pharmacokinetic (PBPK) models
  - development of biologically-based dose-response models (BBDR)
  - increased computing power to facilitate probabilistic assessment to convey the uncertainties in different parameters and results
- As the data have improved, the possible limitations of current methodologies have become more apparent
Moving Beyond the RfD/RfC

- Risk Assessment Forum (RAF) review of RfD and RfC processes (Dec 2002)
- RAF projects on chemical-specific adjustment factors (ongoing)
- NCEA workgroup review of the scientific foundations of “Uncertainty Factors” (UFs) (2004)
  - Data cited as basis for UFs and/or developing UF distributions
  - Probabilistic methods proposed for combining UFs
- Need for a common conceptual framework
  - Current RfD/RfC paradigm does not accommodate chemical-specific data in a biologically and statistically rigorous manner
  - Project being planned to examine alternative conceptual (probabilistic) frameworks, their underlying assumptions, and available data.

Practical Questions for Broad Application of a Risk-based Alternative to the RfD/RfC

- Are there “defaults” that can be developed for extrapolation (i.e., beyond the range of observation) of --
  - individual dose-response to low doses?
  - population variability to the tail of the distribution?
  - which are
  - science-informed?
  - public health protective?
- What are the “minimal” data requirements to develop such “defaults?”
- Is there a “smooth” transition from data-poor to data-rich situations?
- Should we still use an RfD/RfC if we fall below the minimal requirements?
Joint Meeting of
The Environmental Health Committee and
The Integrated Human Exposure Committee
U.S. EPA Science Advisory Board
September 6, 2006

Longer-Term Direction

Comprehensive probabilistic approach to risk assessment for both carcinogens and noncarcinogens:

...achieving \( x \) level of risk (probability of effect) for an individual at the \( y \)th percentile of the variable human population with \( z \) degree of confidence.

\[
P(\text{effect}|\text{dose}, \theta, \text{model}) P(\theta|\mu, \Sigma, \text{model}) P(\mu, \Sigma, \text{model})
\]

Organ-Specific RfDs
Central Estimates and Uncertainty Bounds in Dose-Response Models

- **Purpose:** Evaluate and support available methods to develop robust central tendency and statistical bounds on risk estimates.

- **Issues:**
  - Statistical instability of maximum likelihood estimations (MLE)
  - Bayesian estimation methods
  - Subjective versus non-informative priors

- **Impacts on uncertainty analyses**
  - Robust central tendency estimates
  - Statistically rigorous characterization of uncertainty
  - Potential applicability to decision-theoretic applications

---

Example of MLE stability -- Naphthalene

<table>
<thead>
<tr>
<th>Dose</th>
<th>Original data</th>
<th>One tumor moved</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0/49</td>
<td>0/49</td>
</tr>
<tr>
<td>10</td>
<td>6/49</td>
<td>7/49</td>
</tr>
<tr>
<td>30</td>
<td>8/48</td>
<td>8/48</td>
</tr>
<tr>
<td>60</td>
<td>15/48</td>
<td>14/48</td>
</tr>
</tbody>
</table>

**MLE risk**
- 3.5E-6
- 3.5E-6

**95th risk**
- 5.6E-6
- 5.7E-6

In this example, the MLE is stable and doesn’t change much when data on number of tumors is somewhat changed. The estimate of upper 95th percentile is also quite stable and close to the MLE.

In all examples, the number of stages in the multistage model equal number of doses minus one.

Risk at .0005ppm

Naphthalene: respiratory epithelial adenoma (REA) in male rats (Abdo et al., 2001)
Example of MLE Instability -- Formaldehyde

<table>
<thead>
<tr>
<th>Dose</th>
<th>Original data</th>
<th>One tumor moved</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0/341</td>
<td>0/341</td>
</tr>
<tr>
<td>0.07</td>
<td>0/107</td>
<td>0/107</td>
</tr>
<tr>
<td>2</td>
<td>0/353</td>
<td>1/353</td>
</tr>
<tr>
<td>6.01</td>
<td>3/343</td>
<td>3/343</td>
</tr>
<tr>
<td>9.93</td>
<td>22/103</td>
<td>22/103</td>
</tr>
<tr>
<td>15</td>
<td>162/386</td>
<td>161/386</td>
</tr>
<tr>
<td>MLE risk</td>
<td>4.5E-14</td>
<td>4.5E-7</td>
</tr>
<tr>
<td>95th risk</td>
<td>4.1E-6</td>
<td>9.4E-6</td>
</tr>
</tbody>
</table>

The MLE risk is not stable in the example from the actual animal experiment (formaldehyde). It changes 5 orders of magnitude when just one animal is moved between tumor groups.

Even when MLE is not near zero (last column), we cannot be sure that it is stable.

Formaldehyde: Squamous cell carcinoma (SCC) in rats (Kerns et al. (1983), Monticello et al. (1996))

Proposed Estimates of Risk

- **Bayesian estimate**
  At low doses:
  \[
  \text{Ave}(\text{ExcessRisk}(d)) = \text{Ave}(q_1) * d = \left( \int \ldots \int q_1 L(q_0, q_1, \ldots q_k) dq_0 \ldots dq_k \right) * d
  \]
  \[
  \text{Where } L(q_0, q_1, \ldots q_k) \text{ is the likelihood function for the parameters, } q_0, q_1, \ldots q_k, \text{ in the multistage model}
  \]
  We use Markov Chains Monte Carlo software to simulate posterior distribution of the risk.

- **Bootstrap based estimate**
  The two-step procedure is proposed. In the first step, Bayesian estimates of probabilities of tumor are obtained from the observed data. Then, obtained probabilities are used for parametric bootstrap of the dose-response curve. For each simulation, the MLE of risk is generated and distribution of the risk is obtained.
Purposes of Uncertainty Analyses (NRC 1994)

- Communicate the range of risk values consistent with our current knowledge and lack thereof
- Determine the degree (or lack) of conservatism in an estimate.
- Make clear to decision-makers and the public the ramifications of risk assessment
- Allow society to evaluate judgments made by experts when they disagree

NRC (1994) Taxonomy of Uncertainty

- Model uncertainty sources
  - Incorrectly specified relationships among variables
  - Simplification of complex systems
  - Incompleteness
  - Insufficient data to choose among models

- Parameter uncertainty sources
  - Measurement errors (random or systematic)
  - Use of generic or surrogate data
  - Misclassification
  - Sampling limitations
  - Representativeness of data
Uncertainty Analysis

- Low-Dose Extrapolation has both biological and statistical components.
- Population dose-response (thick blue lines) combines individual/biological dose-response and inter-individual variability.

Conceptual Model

What is the variability (in the tail)?
What are the relationships (at low dose)?
What is "adverse"?

What is the uncertainty?
## Approaches to Extrapolation Below the Range of Observation

- **Model-independent**
  - Linear from Point-of-Departure (POD)
  - RfD/RfC from POD using uncertainty factors (UFs)

- **Model-dependent**
  - Empirical models (e.g., multistage model)
  - Biologically-based models

- **Combination of approaches**
  - Linear from POD for target dose metric, pharmacokinetic model for exposure dose metric
  - RfD/RfC from POD with data-/model-based UFs

## Low Dose Linearity/Non-Linearity

- **Purpose:** Clarify basis and applicability of low dose linear extrapolation by updating, summarizing, and evaluating key data supporting or challenging its basis.

- **Issues:**
  - Background additivity
  - Population variability
  - Homeostasis/functional reserve

- **Impacts on uncertainty analyses:**
  - Choice of dose-response model
  - Choice of low-dose extrapolation approach
FORMALDEHYDE: Cancer Risk Assessment – Rat Data

CIIT Centers for Health Research (1999):
• Two linked parts to CIIT work developed over last decade; Dosimetry Model and Clonal Growth Model
  - Dosimetry Model
    - State of the art approach
    - Estimates dose to respiratory tissue
    - Input to Clonal Growth Model or dose estimate for benchmark model
  - Clonal Growth Model
    - Based on well-recognized biologically based tumor development model
    - Estimates tumor response for various activity patterns and exposures
• Alternatively, the benchmark model produces point of departure for extrapolation per draft cancer guidelines
• In the development and use of any model, assumptions due to information gaps are required
• The CIIT work to support these approaches provides important inputs for risk assessment.
• EPA is evaluating the CIIT model for possible use in its IRIS risk assessment.

Current Assessments
Exposure to Target Dose

Relationships between exposure and dose are complex
• Formaldehyde dosimetry in the respiratory tract:
  - Tissue dose is highly regional and localized
  - Rodent tumors in the nose are very site-specific
• Advances in dosimetry and pharmacokinetics are improving the estimates of target tissue dose for risk assessments
• Improved estimates of tissue dose reduce uncertainties and improves extrapolation

From Kimbell, JS; Subramaniam, RP; Gross, EA; et al. (2001)
Formaldehyde: Two-Stage (MVK) Carcinogenesis Model

- **Formaldehyde model (Conolly et al 2003, 2004)**
  - CFD dosimetry model
  - Hybrid PBPK-CFD model (and data) for DPX
  - Two-stage clonal growth model for nasal cancer
  - Parameter sources:
    - *in vitro* measurements (e.g., cell labeling)
    - Fitting to time-to-tumor data

Clonal Growth Models Exhibit Strong Parameter Sensitivity

- **Low dose extrapolation can be extremely sensitive to initiated cell birth and death rates**
- **Scaling to humans:**
  - Assumes use of parameters estimated for rodents
  - Other uncertainties due to lack of human data
- **More generally, low-dose extrapolation thus needs:**
  - Reliable information on biological parameters and/or their relationships at (low) dose.
  - Understanding of the sensitivity of low-dose extrapolation to parameter uncertainty and variability
  - Characterization of the range of risk estimates from different plausible model structures.
Joint Meeting of
The Environmental Health Committee and
The Integrated Human Exposure Committee
*U.S. EPA Science Advisory Board*
September 6, 2006

### Issues for Implementation of Model-Dependent Approaches

- Characterization of both qualitative and quantitative uncertainty/variability.
  - Model structure uncertainty, including dose-response of model parameters
  - Parameter uncertainty, and variability
  - Data reliability/relevance
  - Ultimate impact on quantitative risk estimate
- Given such a characterization, what level of confidence is necessary to replace estimates based on model-independent approaches?

### Conclusions and Continuing Questions

- Extensive amount of data is available from rodent studies on formaldehyde *(Two chronic bioassays, DPX data, labeling index studies, airflow simulations)*
- The CIIT model provides a conceptual framework to incorporate this data in risk assessment and to evaluate uncertainty
- Various uncertainties in this data and model specification need to be incorporated, so as to be able to calculate a plausible upper bound on risk and evaluate model inference on the role of formaldehyde-induced mutation
- EPA is carrying out various sensitivity analyses pertinent to key biological issues in the model
- Question: Should we give preference to empirical models using human epidemiology or mechanistic rodent-based risk assessment?
EPA Re-Implementation of CIIT Model

• A key inference of the optimal CIIT model is that formaldehyde-induced mutation is not needed to explaining its tumorgenicity.
  ➢ EPA’s results indicate that the role of formaldehyde-induced direct mutation could compare significantly with that of spontaneous mutation
  ➢ Such a model inference and key parameter estimates are very sensitive to choice of control data, i.e., determining whether, and which, historical controls may be lumped with concurrent controls

• Uncertainties in the human model are being investigated. A very limited sensitivity analysis of the CIIT scale-up to humans indicates that biologically plausible variations of their model can give added human risk estimates (at 0.1 ppm) that are two orders of magnitude higher than the CIIT upper bound. This analysis retains key assumptions used in the CIIT model.

Conclusions

• Risk assessment approaches are evolving in the presence of better understanding of biological mechanisms.
• Significant uncertainties remain and are being addressed
• Questions about the direction of risk assessment are being discussed:
  ➢ Focus on disease endpoints?
  ➢ Focus on cumulative risks?
  ➢ Focus on integrated environmental assessment?
• Each paradigm contributes a necessary component to understanding.
• Consideration of multiple scales is necessary for appropriate decision-making.
• Challenges for risk assessors:
  ➢ to evaluate when additional data are important for decision-making
  ➢ to collect, integrate, and make use of information on a variety of scales.
• Our concepts of risk are changing, and will need to continue to evolve.