Role of Risk Assessment in Regulatory Decision Making

Annie M. Jarabek
Acting Deputy Director
Human Health Risk Assessment (HHRA) national program
Senior Toxicologist
National Center for Environmental Assessment
Office of Research and Development

Standards Alliance Training on Analytical Tools for Regulatory Decision Making
Lima, Peru
October 30, 2014
Overview

- **Definition of risk assessment**
  - Risk assessment paradigm: History and evolution
  - Role in regulatory decision making
- **Critical components and terminology**
- **Fit-for-purpose concept**
- **Example applications**
- **Emerging challenges**
- **Resources**
  - Training and tools
  - Collaboration and contacts

**Disclaimer:** These views are those of the author and do not represent US EPA policy.
Definition of Risk Assessment is Contextual

Engineering/Structural

Environmental

Financial/Business

Security: Vulnerability and Threat

Human Health
US EPA Definition

- Qualitative and quantitative evaluation of the risk posed to human health and/or the environment by the actual or potential presence and/or use of specific pollutants

*From EPA’s “Terms of Environment” Glossary*
History and Evolution at EPA

- 1970: EPA established
- 1975: First EPA chemical assessment (vinyl chloride)
- National Research Council (NRC) publications on risk assessment
  - 1983: Managing the Process – the “Red Book”
  - 1989: Improving Risk Communication
  - 1994: Science and Judgment – the “Blue Book”
  - 1996: Understanding Risk
  - 2008: Phthalates and Cumulative Risk Assessment
  - 2009: Science and Decisions – the “Silver Book”
Risk Assessment Paradigm: Role in Regulatory Decision Making

Information

RESEARCH
- Epidemiology
- Clinical studies
- Animal studies
- In vitro & in silico studies
- Modeling

RISK ASSESSMENT
- Hazard Identification
- Dose-Response Assessment
- Exposure Assessment
- Risk Characterization

RISK MANAGEMENT
- Social
- Economic
- Legal
- Ban
- More research
- Standards: air, water, food
- Priorities: research, regulation

Research Needs

Assessment Needs
Why Do Risk Assessment?

- “...risk assessment should be viewed as a method for evaluating the relative merits of various options for managing risk ...” (Science and Decisions, 2009)

- To provide support for decisions to protect public health and the environment.
  - Complex and controversial
  - Risk assessment summarizes the science

- Risk assessment should continue to capture and accurately describe what various research findings do and do not tell us about threats to human health and to the environment, but only after the risk-management questions that risk assessment should address have been clearly posed, through careful evaluation of the options available to manage the environmental problems at hand.
Framework for Human Health Risk Assessment to Inform Decision Making


The Red Book Risk Assessment Paradigm shown by the red dashed lines.

Framework for Human Health Risk Assessment to Inform Decision Making
EPA/100/R-14/001  April 2014
www.epa.gov/raf/frameworkhhra.htm
Planning and Scoping to Target Assessment

Key Considerations for Planning and Scoping

- What decision is to be informed by risk assessment, when is the decision anticipated, and what are the risk management options?
- What legal/statutory requirements affect risk management options and level/type of analysis?
- What other considerations (e.g., environmental justice, life stage, cumulative risk, sustainability) or countervailing risks may influence risk management options and analyses?
- What assessments (e.g., risk, economic) are needed to address decision-making needs?
- What expertise, resources and timelines are available to conduct the assessments(s)?
Risk assessors and risk managers need to have a good sense of when a decision is *scientific judgment* versus when it is a *policy decision* informed by science.

Opinions vary on how *separated* risk assessment and risk management should be.

The most current frameworks recommend an *iterative process*.

*Transparency* is key.
Evolution will Continue…

- Presidential Commission on Risk Assessment and Risk Management (CRARM)
  - Addressed residual risks from HAPs
  - Developed an integrated risk management approach

- Continued evolution at EPA
  - Integrate multiple chemical (cumulative) and aggregate (all routes) risk
    - Ecological endpoints
    - Wellness
    - Resiliency
  - Community-scale and national-scale assessments
Risk assessment is the evaluation of scientific information on:

- the hazardous properties of environmental agents,
- the extent of human exposure to those agents, and
- the dose-response relationship of their toxicity.

The product of the risk assessment is a statement regarding the probability that populations or individuals so exposed will be harmed and to what degree.

From EPA’s Glossary of IRIS Terms
Hazard

- The inherent toxicity of a compound.
- Hazard identification of a given substance is an informed judgment based on verifiable toxicity data from animal models or human studies.

(EPA’s Glossary of Terms of the Environment)
Key Considerations in Determining Toxicity

- **Effects** – What effects are observed from the data collected?
- **Toxicokinetics** – What does the body do to the chemical?
- **Toxicodynamics** – What does the chemical do to the body?
- **Mode of action** – How does the chemical act to produce an effect?
- **Weight of evidence** – How likely is this chemical to cause non-cancer effects or cancer and under what conditions?
- **Causality Framework** – A way to organize and evaluate toxicity information to assess causality given those data.
Exposure

- Quantified as the amount of an agent available at the exchange boundaries or portal-of-entries of the organism (e.g., skin, respiratory tract, and GI tract).

Exposure or Applied Dose
Ingested ($\mu g / kg$)
Inhaled ($\mu g / m^3$), or applied to skin

Internal dose ($\mu g / kg$)
or dose rate ($\mu g / kg$-day)
Amount absorbed and available for interaction
Exposure Assessment

• Identifying the **pathways** by which toxicants may reach individuals, estimating how much of a chemical an individual is likely to be exposed to, and estimating the number likely to be exposed (EPA’s Terms of Environment).

• The determination or estimation (qualitative or quantitative) of the **magnitude, frequency, or duration, and route of exposure** (EPA’s Exposure Factors Handbook).
Exposure Specifications

Exposure Medium and Route
- Inhalation – air
- Oral – water, soil, food
- Dermal – soil, water, food, air

Exposure Duration
- Acute
- Short-term
- Longer-term
- Chronic (continuous)

Potentially Exposed Population
- Workers
- Emergency responders or victims
- Pregnant women
- Children or the elderly
Dose-response Assessment

- Evaluating the quantitative relationship between dose and toxicological responses.
- A determination of the relationship between the magnitude of an administered, applied, or internal dose and a specific biological response.
- Response can be expressed as:
  - Measured or observed incidence or change in severity level of response
  - Percent response in a group of subjects (or populations)
  - Probability of occurrence or change in severity level of response within a population
Risk Characterization

• The last phase of the risk assessment process that estimates the potential for adverse health or ecological effects to occur from exposure to a stressor and evaluates the uncertainty involved.
  • (EPA’s Terms of Environment)

• The integration of information on hazard, exposure, and dose-response to provide an estimate of the likelihood that any of the identified adverse effects will occur in exposed people.
  (EPA’s IRIS Glossary)
U.S. Regulatory Acts

Air
- Clean Air Act
- CAA Amendments of 1990

Water
- Safe Drinking Water Act
- Clean Water Act
- Oil Pollution Act

Hazardous Waste
- Resource Conservation and Recovery Act
- Comprehensive, Environmental Response, Recovery, and Liability Act
- Toxic Substances Control Act
- Superfund Amendments Reauthorization Act

Toxics & Pesticides
- Federal Insecticide, Fungicide, and Rodenticide Act
- Food Quality Protection Act
- Toxic Substances Control Act
- Pesticide Registration Improvement Act
EPA Role in U.S. Environmental Regulation

**EPA**
- Conduct research
- Perform risk assessments
- Set national standards
- Monitor compliance
- Enforce national standards

**States**
- Develop state-level standards
- Monitor compliance
- Enforce state and national standards
- Issue permits
• **Exposure Type:** Ambient
• **Duration:** Generally long-term
• **Medium:** Developed for air, water, and food
• **Enforceability:** Some are legally enforceable
• **Applicability:** Prevent harm from chemical exposures over the course of a lifetime; must protect sensitive subgroups
• **Adaptability:** Frequently developed for protection of human health and the environment
### Reference Values: Levels of Enforceability

<table>
<thead>
<tr>
<th>Exposure Standards</th>
<th>Exposure Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relatively few</td>
<td>Numerous</td>
</tr>
<tr>
<td>Mandated by statute and legally enforceable</td>
<td>Not legally enforceable</td>
</tr>
<tr>
<td>Rigid development process</td>
<td>Flexible development process</td>
</tr>
<tr>
<td>Developed by government agencies specified in statutes</td>
<td>Developed by many types of entity</td>
</tr>
<tr>
<td>Intended to protect health and the environment, but</td>
<td>Intended to protect human health and the environment</td>
</tr>
<tr>
<td>balances other considerations</td>
<td></td>
</tr>
</tbody>
</table>

25
Continuum of Confidence in Data and Concept of Fit-for-Purpose

**Robust Databases**
- Toxicokinetics
- ADME
- Characterization
- Cancer and noncancer endpoints
- Sensitive populations
- Biomarkers
- Mode of Action
- Developmental studies

**Preferred Values**
- Multiple durations
- Oral, inhalation, dermal, injection exposures
- Epidemiological data

**Limited Databases**
- Acute duration
- Partial characterization
- Only inhalation
- Frank effects
- Non-GLP
- Limited endpoints

**Less-Preferred Values**
## Exposure Standards

<table>
<thead>
<tr>
<th>Medium</th>
<th>Standard</th>
<th>Regulated Contaminants</th>
<th>Regulatory Authority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>National Ambient Air Quality Standards (NAAQS)</td>
<td>6 Criteria Pollutants in ambient air</td>
<td>EPA, as mandated by the Clean Air Act</td>
</tr>
<tr>
<td></td>
<td>Permissible Exposure Limits (PELs)</td>
<td>~500 contaminants in workplace air</td>
<td>OSHA, as mandated by the Occupational Safety and Health Act</td>
</tr>
<tr>
<td>Water</td>
<td>Maximum Contaminant Levels (MCLs)</td>
<td>90 chemical, microbiological, radiological, and physical contaminants in drinking water</td>
<td>EPA, as mandated by the Safe Drinking Water Act</td>
</tr>
<tr>
<td>Food</td>
<td>Maximum Residue Limits (MRLs)</td>
<td>Hundreds of pesticide chemicals in food and feed commodities</td>
<td>EPA, as mandated by the Federal Food, Drug, and Cosmetics Act, as amended by the Food Quality Protection Act</td>
</tr>
</tbody>
</table>
"Numerous and diverse mobile and stationary sources"

Widespread exposure: millions of people, ecosystems

Typically non-cancer health endpoints

Typically human health data available

Some produce ecological effects

Different considerations apply to setting NAAQS versus to achieving them

- Setting NAAQS: Health and environmental effects
- Achieving NAAQS: Account for cost, technical feasibility, time needed to attain
6 criteria pollutants (EPA can modify list):
- Ground-level (tropospheric ozone \(O_3\))
- Particulate matter (PM\(_{2.5}\) and PM\(_{10}\))
- Carbon monoxide (CO)
- Sulfur dioxide (SO\(_2\))
- Nitrogen
Framework for Air Quality Management

- **Goal: Air Quality Standards**
- **Environmental Condition:** Monitoring/Modeling, Emissions Inventory
- **Effects/Exposure Research**
- **Atmos Sciences/Engineering Research**
- **Enforcement/Compliance**
- **State Planning (SIP): Stationary and Mobile Sources**

Track Progress
Provide a concise review, synthesis, and evaluation of the most policy-relevant science to serve as the scientific foundation for review of the National Ambient Air Quality Standards (NAAQS) for criteria pollutants

Prepared in close coordination with EPA office of air quality planning and standards
ISA for Ozone

• Most recently released February 2013
  – 4,000+ studies considered; 2,270 studies cited
  – 1,038 new since 2006 Ozone Air Quality Criteria Document (AQCD)

• Implemented new weight of evidence framework for at-risk factors
  – Which individual- and pollutant-level factors result in increased (decreased) risk of an air pollutant induced health effect?
  – Four level classification of evidence for potential at-risk factors

• Multiple associated peer-reviewed journals
EPA’s Integrated Risk Information System (IRIS)

- Supports EPA’s programmatic actions and other entities.
- Intended to be the highest-quality, science-based toxicity reference values.
- Contains peer-reviewed, Agency-derived values.
- Derived for specific chemical substances.
- Based on review of all relevant toxicity, toxicokinetic, and mode of action (MOA) information.
### General Public Reference Values: IRIS

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Organization and Context</th>
</tr>
</thead>
<tbody>
<tr>
<td>RfD</td>
<td>Reference dose for noncancer endpoints (ingestion)</td>
</tr>
<tr>
<td>RfC</td>
<td>Reference concentration for noncancer endpoints (inhalation)</td>
</tr>
<tr>
<td>OSF</td>
<td>Oral slope factor of cancer risk</td>
</tr>
<tr>
<td>IUR</td>
<td>Inhalation unit risk for cancer</td>
</tr>
</tbody>
</table>

Integrated Risk information System (IRIS) values are:

- Developed to support hazard identification and dose-response assessment.
- Used to characterize public health risks of a given substance in a given situation.
- Used to form the basis for risk-based decision-making, regulatory activities, and other risk management decisions.
Review of the Integrated Risk Information System (IRIS) Process (NRC, May 2014): “EPA has made substantial improvements to the IRIS Program in a short amount of time”
IRIS Enhancements

• Development process  
  – Planning and scoping
  – Public meetings on released literature search and strategy, evidence tables, and exposure-response figures

• Improving the science
  – Systematic review
  – Concise, compact and clear document structure
  – SAB Chemical Assessment Advisory Committee (CAAC)

• Improving productivity and transparency
  – Workforce planning
  – Agency needs assessment
  – Stopping rules  

Example Application: IRIS Reference Value Used to Establish Fish Advisory

- IRIS includes an oral RfD for methylmercury
- RfD combined with exposure factors for ingestion and contaminant concentrations
- Result is general advice about fish consumption and location-specific advisories
**Example Application: IRIS Reference Value Used at Superfund Sites**

**Casmalia Resources in Santa Barbara County, CA**

- Former hazardous waste management facility
- Chemicals of concern include pesticides, solvents, acids (including hydrogen sulfide), PCBs, and heavy metals
- IRIS values support decisions about remedial actions including landfill covers, groundwater monitoring, and site improvements
Emergency Response Values: Characteristics

- **Exposure Type:** Workplace or general public
- **Duration:** Generally acute
- **Medium:** Generally concentrations in air or water
- **Enforceability:** Not legally enforceable
- **Applicability:** Inform emergency response and public health planning (e.g., determine egress and re-entry)
- **Adaptability:** Often specify levels of harm (e.g., mild or severe)
Provisional Peer-reviewed Toxicity Values (PPRTV)

- Limited data sets
- Peer-reviewed with legal standing
  - Determine cleanup levels
  - Establish monitoring
- Superfund Technical Support Center
  - Human health
  - Ecological

Provisional Peer-Reviewed Toxicity Values for Styrene-Acrylonitrile (SAN) Trimer (Various CASRNs)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268
New Data: New Opportunities

<table>
<thead>
<tr>
<th>Human Relevance/ Cost/Complexity</th>
<th>Throughput/ Simplicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTS 10s-100s/yr</td>
<td>10,000s- 100,000s/day</td>
</tr>
<tr>
<td>MTS Gene-expression 1000s/day</td>
<td></td>
</tr>
<tr>
<td>HTS</td>
<td></td>
</tr>
<tr>
<td>uHTS</td>
<td></td>
</tr>
</tbody>
</table>
Emerging Challenges: New Data

- Current characterization context: Comprehensive scope of disease pathogenesis
- Increased sophistication of measurements
- Growing understanding of mechanisms at molecular level (e.g., QSAR, HT and HTC assays)
- Animal models of susceptibility
- Enhanced computational capacity (in silico models) to describe processes quantitatively
Emerging Challenges: Sensor Data and Citizen Science

- Factors influencing measurement
  - Detection limits
  - Location
  - Collection conditions
- Representativeness, relevance, utility
- Curation and data management
- Interpretation
• Advance biotechnology and systems understanding → Pathway-based assessment to predict adversity
  – Protecting the public health and environment requires analysis, translation, and integration of data along source to effect pathways
  – Optimization of economic, environmental and societal concerns to support sustainability
• Requires transparent and tractable integration of diverse data types across scales
  • Spatial
  • Temporal
  • Biological
• Characterize dose-response using new endpoints with linkage to traditional outcome measures such as morbidity, mortality, histopathology and tumors

• Requires integration of diverse data sets across different domains (e.g., genomic versus population), methods (e.g., measurements / mining / models) and observational contexts
  – in vivo / ex vivo
  – Laboratory animal or other test species
  – Human and ecological

• Repurposing of data is typical problem area: Provide explicit evaluation of data quality, utility, and relevance to facilitate formal inferences

• Highlight how individual judgments concerning data on parameters for causality of specific steps influence the confidence in ultimate decision; emphasize accuracy and predictive power to establish confidence
Multi-scale Data Integration

- Disease-based context for other critical endpoints of interest
  - Respiratory, liver, cardiovascular, …
- Data from diverse sources and approaches
  - High Throughput/Content Screening
  - Adverse outcome Pathway/Mode of Action
  - Biomonitoring
  - Laboratory animal (ex vivo, in vivo)
  - Human (clinical, epidemiological)
  - Clinical chemistry
  - Virtual tissues

AOP and biomarkers serve to link elements and describe disease pathogenesis
Multi-criteria Decision Analysis (MCDA)

- System construct to evaluate impacts of modifying factors, including data gaps, on resultant decision
- Flexible – clearly defines parameters included (or not) in process and aids transferability
- Transparent valuation of choices
- Stakeholder engagement

Cultural and Operational Needs

• Access to discover, collect, and integrate data in a coordinated fashion
  – Encourage data repositories with maintenance and management
  – Enhance open access and change publication practice
• Mitigating uninformed use of models
  – Making application limitations known
  – Documentation of parameter values
• Facilitating collaboration and accommodating confidentiality
• Repurposing of data for new analysis requires context for data (metadata) including annotation and curation history; also requires dedicated data management
• Peer review: Transparency of assumptions and uncertainty propagation
• Visualization
• Simplicity of interfaces
Resources: ORD

**Mission statement**

- Perform research and development
- Provide technical support
- Integrate the work of ORD’s scientific partners
- Provide leadership in addressing emerging issues and in advancing the science of risk assessment
ORD Research Aligned with EPA Strategic Goals

Cross-Agency Strategies
- Sustainable Future
- Visible Difference in Communities
- New Era of Partnerships
- High-Performing Organization

EPA Goals 2014-2018
- Addressing Climate Change and Improving Air Quality
- Protecting America’s Waters
- Cleaning Up Communities and Advancing Sustainable Development
- Ensuring the Safety of Chemicals and Preventing Pollution
- Enforcing Laws, Ensuring Compliance

Research Programs
- Air, Climate & Energy
- Safe and Sustainable Water Resources
- Sustainable and Healthy Communities
- Chemical Safety for Sustainability
- Human Health Risk Assessment
- Homeland Security
Resources: Databases

HERONet Home

What is HERO?
The Health and Environmental Research Online is a database of scientific studies and other references used to develop EPA’s risk assessments aimed at understanding the health and environmental effects of pollutants and chemicals. It is developed and managed in EPA’s Office of Research and Development (ORD) by the National Center for Environmental Assessment (NCEA).

What data does HERO provide?
For each reference, HERO contains:
- Reference type
- Citation elements: authors, title, year of publication, journal, volume, issue, page numbers
- Abstract or brief description
- Topic areas that describe the reference (e.g., exposure, inhalation, etc.)
- Assessment(s) in which the reference was used

LitSearch

Journal Finder  Citation Linker

Select databases by category | Select databases individually

Basic Search  Advanced Search  Search tips

And
And
And
And
And

Year: [Format: yyyy]

Search

Select All
- AGRICOLA - indexes literature from agriculture, ecology, and related disciplines
- American Association for Cancer Research - content from the AACR
Risk Assessment Training and Education (RATE)

- Approximately 30 modules
  - General to detailed instruction on concepts and approaches
- *Can be tailored to user needs*
- Multiple international training events to date
  - Chile
  - Egypt
  - Europe
  - Saudi Arabia
  - New Zealand
- Exploring possibilities for web-based training in future
Resources: Research and Tools to Advance Applications

- Exposure science and support
  - EPA ExpoBox enhancements: New tools
  - Updating of specific exposure factors
- Scientific workshops
  - IRIS process: NRC review
  - Specific assessment issues: Inorganic arsenic
  - Critical challenges: MOA for mouse lung tumors
- Reports
  - NexGen Report: Sets stage for new applications
    http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=286690
- Interoperability and access:
  - IRIS web access, IRIS calendar, analysis tools,…
  - HERO support
- Publications (Available on Request)
Resources: Bulletins, Blogs and Listservs

• Opportunities for public comment and peer review
  - IRIS Bi-monthly meetings
• Listservs
  - HHRA Bulletin (5,986 recipients)
  - BMDS-News (4,839 recipients)
  - IRIS Updates (1,608 recipients)
  - ExpoBox Bulletin (559 recipients)
This site provides basic information about environmental risk assessments for the public. Additionally, the site offers a comprehensive set of links to key EPA tools, guidance and guidelines.
Acknowledgments and Contact Information

John V. Vandenberg, National Program Director
Human Health Risk Assessment

Abdel Kadry
Senior Advisor for Scientific Organizational Development and International Activities

Annie M. Jarabek
Mobile (best): 919-637-6016
Office: 919-541-4847
Email: Jarabek.Annie@epa.gov