



Risk Assessment and Genomics – Science and Policy: EPA’s Evolving Policy on the Use of Genomic Data

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*Presentation to the American College of Toxicology
November 3, 2003*

U n i t e d S t a t e s E n v i r o n m e n t a l P r o t e c t i o n A g e n c y



Today's Presentation

- Risk Assessment at EPA
- Computational Toxicology, including emphasis on EPA Genomics Initiatives
- Human Health Research Strategy



EPA Mission

- The mission of the EPA is to protect human health and to safeguard the natural environment — air, water, and land — upon which life depends.
- Determining environmental standards, policies, guidelines, regulations, and actions requires making decisions. Environmental decision making is often a complex process involving the interplay among many forces: science, social and economic factors, political considerations, technological feasibility, and statutory requirements.

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Risk Assessment at EPA

- EPA conducts risk assessment in order to provide the best possible scientific characterization of the risk in question, based on a scientifically sound, rigorous analysis of available information and knowledge.
- Risk assessment informs decision makers about the science implications of the risk in question.



Risk Assessment

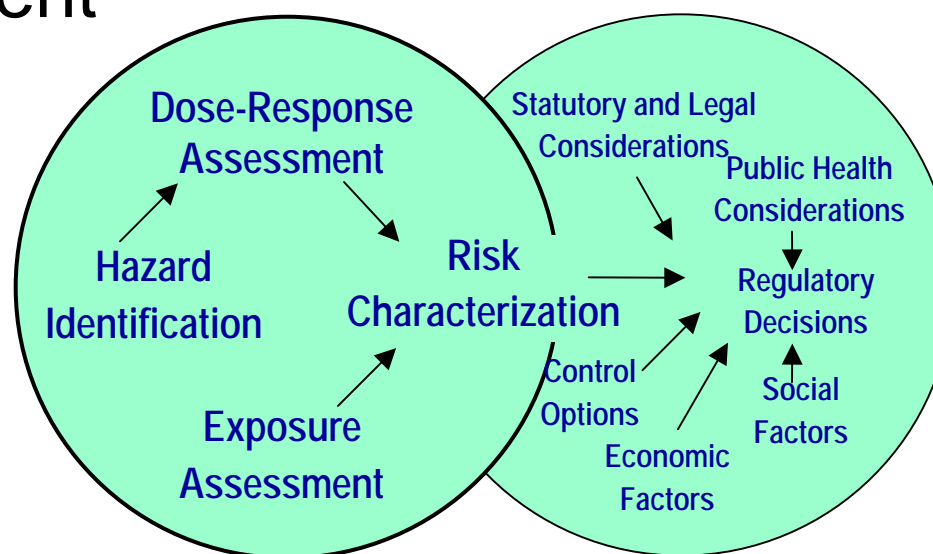
Risk assessment is a process where information is analyzed to determine if an environmental hazard might cause harm to exposed persons and ecosystems.

Paraphrased from “**Risk Assessment in the Federal Government**” (National Research Council, 1983)



NRC Risk Assessment Paradigm

Risk Assessment



Risk Management

National Research Council, 1983

United States Environmental Protection Agency



EPA Risk Assessment Efforts

- Since the NAS “Red Book” in 1983, EPA is constantly promoting and enhancing the consistency and quality of its risk assessments
- Published a series of Risk Assessment Guidelines
- Established policies to enhance risk assessments, e.g., Peer Review & Risk Characterization Policies
- Integrated the use of the Quality System at EPA
- Implemented application of the Information Quality Guidelines



EPA Risk Assessment Efforts

- The data and information we use in developing risk assessments has inherent uncertainty and variability.
- Due to the general uncertainty and variability of the data, information, and methodologies EPA assesses, we tend to take a more health and environmentally protective stance to ensure we do not underestimate risk.



Uncertainty

“The dominant analytic difficulty [in decision-making based on risk assessments] is pervasive uncertainty...There is often great uncertainty in estimates of the types, probability and magnitude of health effects associated with a chemical agent, of the economic impacts of a proposed regulatory action, and of the extent of current and possible human exposures.”

**“Risk Assessment in the Federal Government”
(National Research Council, 1983)**

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EPA Criticized

- Despite all these EPA efforts, EPA is criticized for its risk assessment practices
- Generally, the nature of these criticisms are:
 - EPA must not intermingle policy judgments within the scientific assessment of risk
 - Risk assessments should not rely on conservative (“worst case”) assumptions that distort outcomes and yield estimates that grossly overstate risk
 - Risk assessments should acknowledge the presence of considerable uncertainty



EPA Risk Assessment Approach

- Confidence in our risk assessments is critical.
- Approach is to use to fullest extent site- and chemical-specific data relevant to the decision needed.
- Without such information, we use defaults to ensure we cover the uncertainty of the remaining data or lack of data.



Current EPA Risk Assessment Themes

- Encourage the development of the specific data necessary to more accurately assess potential risks, including mode of action data.
- When we don't have the specific data, we must continually look for opportunities to increase our certainty and confidence in the defaults and assumptions we use, i.e., encourage the derivation of more data-derived defaults.



Current EPA Risk Assessment Themes

- Further, EPA needs to do a better job in explaining its risk assessment practices and choices as well as how it reaches a particular decision.
- Focus on better communication of the data, assumptions and defaults used in our risk assessments, including how we deal with uncertainty.



Computational Toxicology

- An exciting area where EPA can increase the use of relevant data is in Computational Toxicology.
- Computational Toxicology is the application of mathematical and computer models for prediction of effect and the understanding of mechanism.



Computational Toxicology Objectives

- Improve linkages in source-to-outcome paradigms
- Provide predictive models for hazard identification
- Enhance quantitative risk assessment



Computational Toxicology

Enhance the science underlying human health and environmental assessments

- Delineate mode(s) and mechanism(s) of action
- Identify biomarkers of exposure and effect
- Strengthen linkages between exposure, dose, and effect
- Characterize susceptible sub-populations
- Quantify inter-individual and population variability
- Detect potential risk from low level exposure
- Improve extrapolations (e.g., high to low dose, route to route, animal to human, use of uncertainty factors)



Computational Toxicology

Toxicity Testing

- Develop more **predictive test models and methods** to enhance effectiveness of screening and testing programs
- Further contribute to **refine, reduce, and replace** animal uses

Risk Management

- Provide **early indicators** of environmental stress that could lead to prevention and intervention before adverse outcomes are observed
- Target sensitive populations and possibly **redefine sensitive population** to the level of “individual”



Genomics & Computational Toxicology

- Utilize genomics approaches to provide data for the computational modeling of toxicological pathways for single chemicals or classes of chemicals.
- Define specific biologic markers for the various steps in the pathway to identify key events for chemicals that are tied to adverse outcomes.



Application of Genomics to Toxicology

- The study of how the genome is linked to responses to environmental stressors/toxicants
- Understanding gene-environment interactions in disease through integration of knowledge of:
 - Genetics
 - Genomic-scale mRNA expression
 - Cell- and tissue-wide protein expression
 - Toxicology
 - Bioinformatics



Application of Genomics to Risk Assessment

- Pattern Recognition for Exposure Assessment
- Cross-species Extrapolation
- Understanding Mechanisms of Toxic Action
- Input to Biologically-Based Toxicokinetic and Toxicodynamic Response Models
- Identification and Characterization of Sensitive Life Stages or Individuals



Science Policy for Genomics

In early 2002, the Science Policy Council (SPC) charged an Agency Work Group to:

- Develop an Interim Genomics Policy
- Develop an Action Plan to address technical and policy challenges for appropriate use of genomics technologies and data in EPA



Interim Policy on Genomics

- June 25, 2002, EPA issued its Interim Policy
- <http://www.epa.gov/osp/spc/genomics.htm>
- EPA encourages and supports continued genomics research as a powerful tool for understanding the molecular basis of toxicity and developing biomarkers of exposure, effects, and susceptibility.



Interim Policy on Genomics

- Genomics data alone are currently insufficient as a basis for risk assessment and management decisions.
- Limited use while Agency gain experience in assessing the quality, accuracy, and reproducibility and relevance of the data.
- May be useful in a weight-of-evidence approach for human health and ecological risk assessments.



Genomics Action Plan: Issues for EPA to Consider

- Scientific Research: Computational Toxicology
- Methods/Data Management: standardization of methods and databases, bioinformatics, QA
- Ethical, Legal, Social Implications: Ensuring privacy and fairness in the use and interpretation of genetic information including responsible use and integration of genetic technology in research



Genomics Action Plan: Issues for EPA to Consider

- Risk Assessment: Explore ways to incorporate genomic information into Agency risk assessments, refine risk assessment guidelines
- Training: Develop a coordinated genomics education agenda
- Communication: Effectively distribute genomic science and policy decisions internally and externally



Genomics Action Plan: Progress

- Two specific actions to mention:
 - Charged SAB to form Bioethics Panel to serve as Agency resource
 - Genomics
 - Human Subject Testing
 - Animal Welfare
 - Charged Agency staff to identify possible regulatory decisions where genomics information will have a likely impact



Possible Regulatory Scenarios

- Prioritization: for screening purposes, for testing purposes, for making a decision
 - Group a chemical with a class that may require testing or not
 - Improving predictive capability of traditional SAR approaches



Possible Regulatory Scenarios

- Monitoring: for determining the state of the environment, site-specific or media-specific data
 - Assessment and compliance purposes
 - Evaluate status and trends of various environmental indicators



Possible Regulatory Scenarios

- Health assessments: improve the quality of these assessments
 - Identify possible mode(s) of action
 - Identify possible LOAEL/NOAEL
 - Use in cumulative risk – determine common mode(s) of action
 - Identify possible sensitive populations



Possible Regulatory Scenarios

- Reporting: how genomics information may trigger reporting requirements, right-to-know provisions
 - Adverse effects by chemicals, stressors; e.g. TSCA 8(e), FIFRA 6(a)(2)
 - Toxics Release Inventory (TRI)



Human Health Research Strategy

- Genomics and many of our risk assessment activities have been built into a conceptual framework for human health research at EPA's Office of Research & Development for the next 5 to 10 years
- Release of EPA's Human Health Research Strategy today



Human Health Research Strategy

- Addresses EPA Program and Regional Office needs, recommendations by external advisory groups, and goals established in EPA's 2000 and 2003 Strategic Plans
- Reviewed by many groups inside and outside the Agency, e.g. EPA's Science Advisory Board



Human Health Research Strategy

Focuses research to improve scientific foundation of human health risk assessment by refining:

- Principles for use of mechanistic data to reduce uncertainty in risk assessment
- A scientific understanding of the biological basis for susceptible populations
- The science to improve aggregate and cumulative risk assessment



Human Health Research Strategy

Provides a strategic approach to address research needs in ORD initiatives:

- Computational Toxicology Initiative
- National Children's Study
- Aging Initiative
- Cumulative Risk Initiative
- Research in support of the Asthma Research Strategy



The End

Thank you very much

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