Increasing the Use of Mechanistic Data in Risk Assessment: The Perchlorate Example

Annie M. Jarabek
National Center for Environmental Assessment
U.S. Environmental Protection Agency

Partners in Environmental Toxicology
SERDP / ESTCP Symposium and Workshop
Arlington, VA
29 November 2000

Presentation Outline

- Motivation and historical context
- Framework for mode-of-action approach
- Perchlorate as an example
- Brief big picture on the problem
- Summary

Historical Perspective on Dose-Response Assessment

- **Limited Understanding of Mechanism of Action due to**
  - Experimental design
  - Measurement techniques
  - Animal models
- **Biological Motivation for Default Approaches Appropriate in this Historical Context**
  - Biological rationale for LMS model in 1970's
  - "Threshold" approach for noncancer toxicity

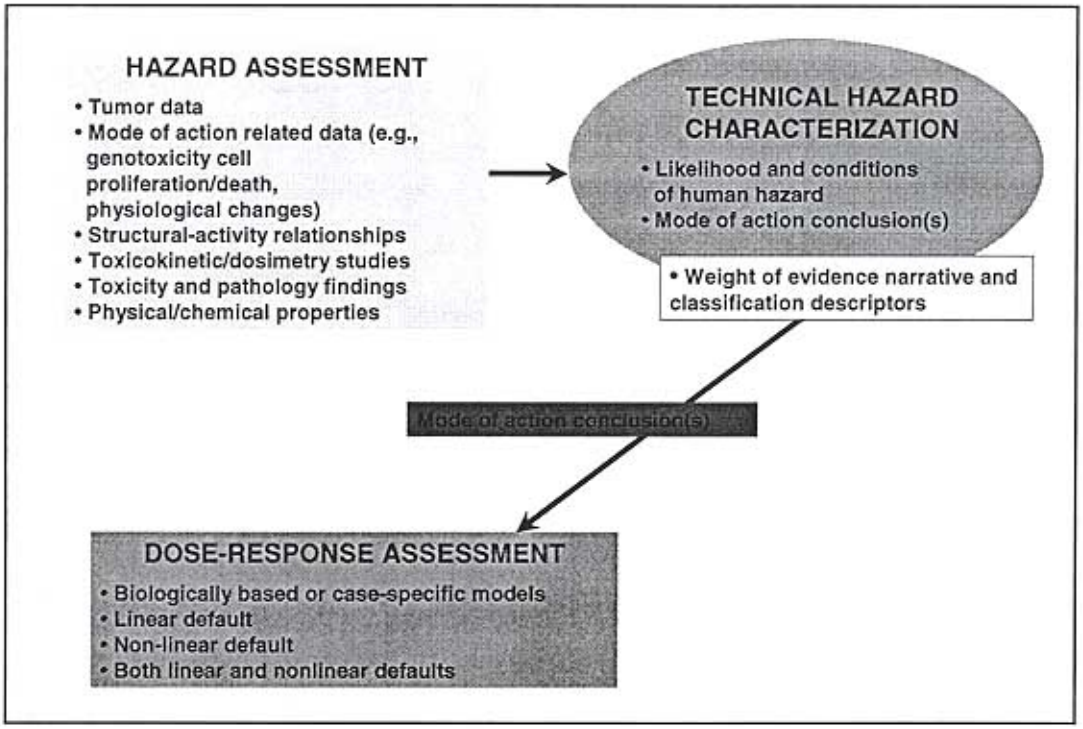
Contemporary Toxicology

- **Bioassays and Data Bases More Comprehensive in Scope**
- **Increased Sophistication of Measurements**
- **Growing Understanding of Mechanisms at Molecular Level**
- **Animal Models of Susceptibility**
- **Enhanced Computational Capacity to Describe Processes Quantitatively**

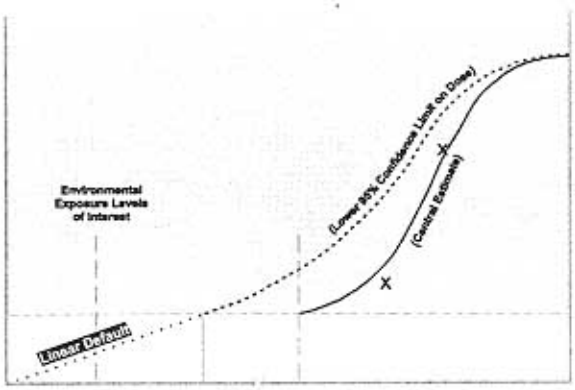
Recent Emphasis on the Use of Mechanistic Data

"The quality of risk analysis will improve as the quality of input improves. As we learn more about biology, chemistry, physics, and demography, we can make progressively better assessments of the risks involved. Risk assessment evolves continually, with re-evaluation as new models and data become available."

Science and Judgement in Risk Assessment
(National Research Council, 1994)



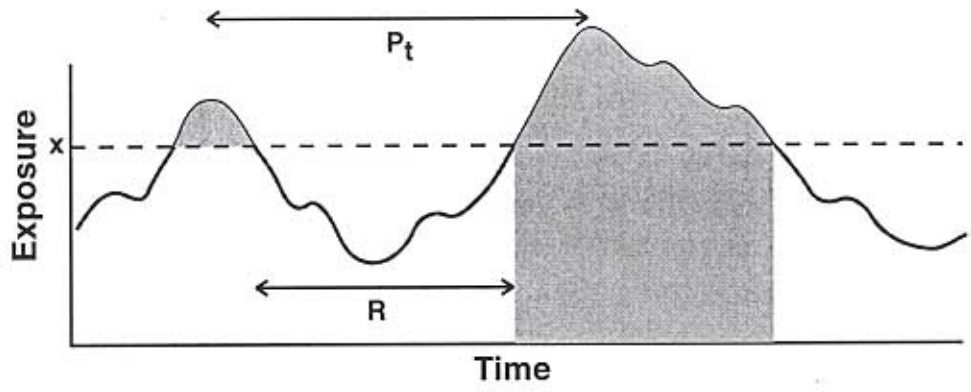
Proposed EPA Cancer Guidelines
Extrapolation Approaches Based on Mode of Action



Breaking Down the Dichotomy

Cancer	Non-Cancer
• Non-Threshold	• Threshold
• Irreversible	• Reversible
• Risk Estimate	• "Safety" Estimate
Slope factor	RfD / RfC
Unit Risk	ADI / TDI
Risk-specific dose	MRL

Potential Dose Profile Metrics



"Effective Exposure" depends on magnitude, duration, and frequency of exposure. Timing in turn can affect these parameters.

Hierarchy of Model Structures for Exposure-Dose-Response and Interspecies Extrapolation

"Optimal" model structure

- Structure describes all significant mechanistic determinants of chemical disposition, toxicant-target interaction, and tissue response
- Uses chemical-specific and species-specific parameters
- Dose metric(s) described at level of detail commensurate to toxicity data

Default model structure

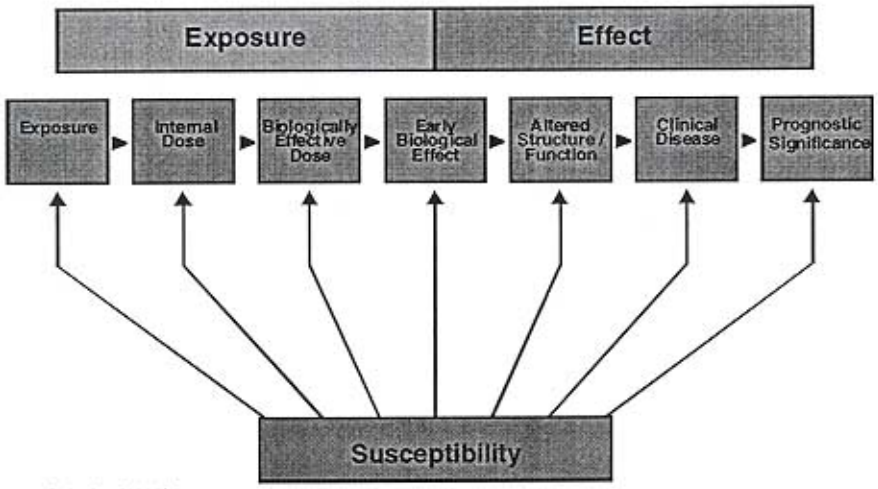
- Limited or default description of mechanistic determinants of chemical disposition, toxicant-target interaction, and tissue response
- Uses categorical or default values for chemical and species parameters
- Dose metric(s) at generic level of detail

U.S. EPA (1994)

Molecular Epidemiology Basic Biological Tenets

- Early biological effects are more prevalent in a population than the late effects (e.g., mortality and morbidity) that were historical outcome measures of interest to risk assessment
- Early event may be more specific to the exposure than the end disease outcome
- Technological advances allow xenobiotics to be directly or indirectly quantified by some identification of dose-related response

Biological Marker Components in Sequential Progression Between Exposure and Disease

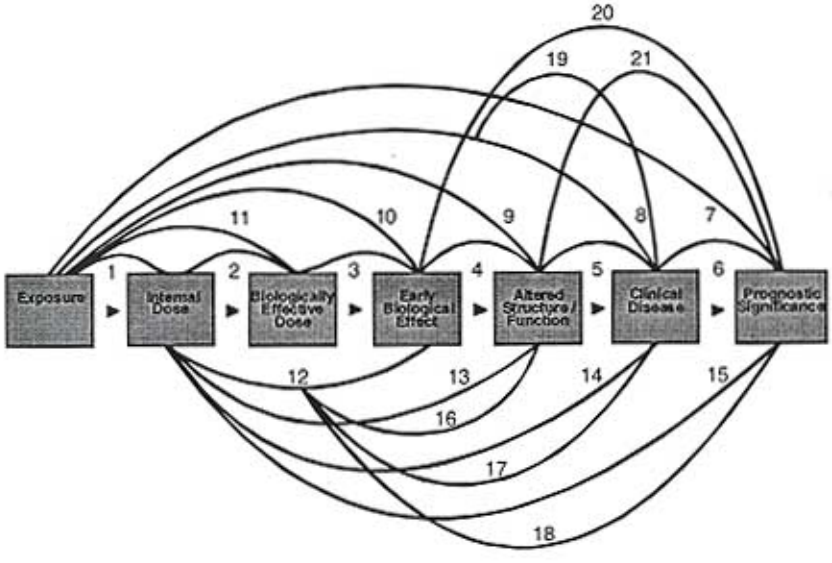


Source: Schulte (1989).

Key Event Examples

- Metabolism
- Receptor-ligand changes
- DNA or chromosome effects
- Increased cell growth and organ weight
- Hormone or other physiological perturbations
- Hyperplasia, cellular proliferation

Potential Research and Risk Assessment Correlations



Demonstrating a Mode of Action

To show that a postulated ***mode-of-action*** is operative, it is generally necessary to:

- **outline** the sequence of events leading to effects;
- **identify** key events that can be measured; and
- **weigh** information to determine whether there is a causal relationship between events and cancer formation.

Use of Mode-of-Action Data in Dose Response Assessment

- Construct a biologically-based or case-specific model
- Link dose-response curve for precursor effect to dose response for tumor effect
- Use dose-response for other effect in lieu of that for tumor effect if it is judged to be a better measure of potential risk
- Use to inform assessment of possible dose response in range of extrapolation

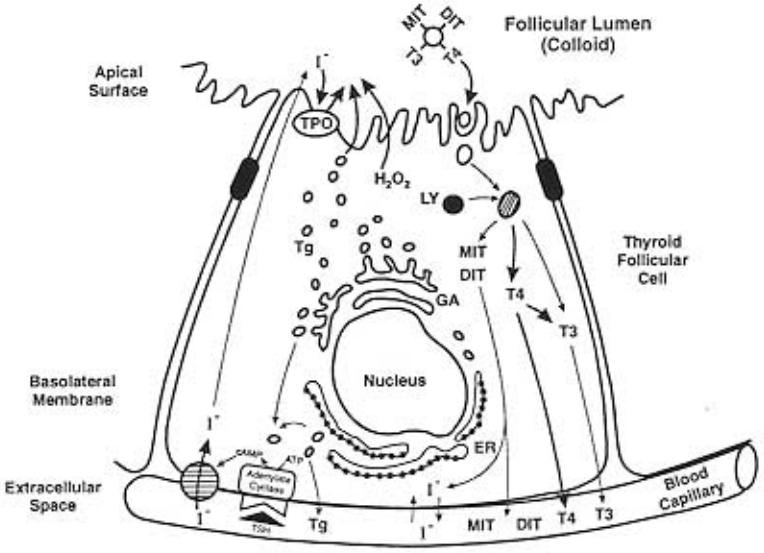
Dose-Response Assessment
Second Step: Range of Human Exposure

- **Use approach(es) indicated by mechanism of action**
  - Choose biologically-based model if possible
  - Second choices are:
    - Linear, or
    - Non-linear, or
    - Margin of Exposure (M-O-E) analysis: How far is observed range from human exposure range?
- **Characterize results, presenting alternative approaches when appropriate**

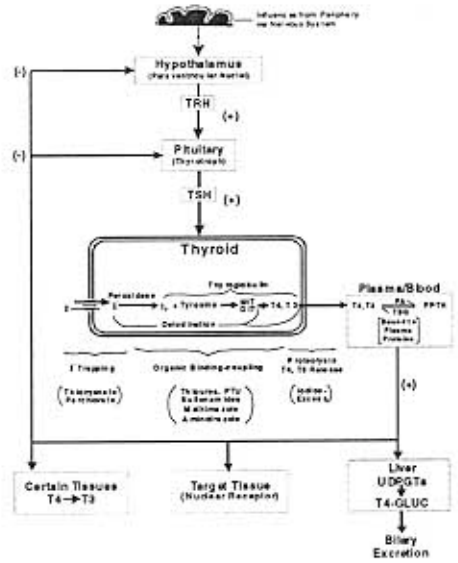
Decision Logic for Dose Response Assessment

- **Linear**
  - DNA reactive or other evidence supporting linearity
  - Not DNA reactive but insufficient data to characterize a non-linear mode of action
- **Non-linear**
  - Not DNA reactive or otherwise linear, and sufficient data to characterize a non-linear mode of action
- **Both**
  - Differing activity at different targets
  - Complex activity needing both approaches to describe

Thyroid Hormone Biosynthesis and Secretion



Hypothalamic-Pituitary-Thyroid Axis and Feedback Mechanisms



Mechanisms of Anti-Thyroid Mediated Neoplasia in Rodents

- DNA Directed:
  - X - rays
  - 131 I
  - Genotoxic chemicals
- Indirect
  - Partial thyroidectomy
  - Transplantation of TSH-secreting pituitary tumors
  - Iodide deficiency
  - Chemicals inhibiting iodide uptake
  - Chemicals inhibiting thyroid peroxidase
  - Chemicals inhibiting TH
  - Chemicals inhibiting conversion of T3 & T4
  - Chemical inhibiting hepatic thyroid hormone metabolism and excretion

Demonstrating Anti-thyroid Activity

Required Data	Desirable Data
1. Increases in cellular growth	6. Lesion progression
2. Hormone changes	7. Structure-activity relationships
3. Site of action	8. Other studies
4. Dose correlations	
5. Reversibility	

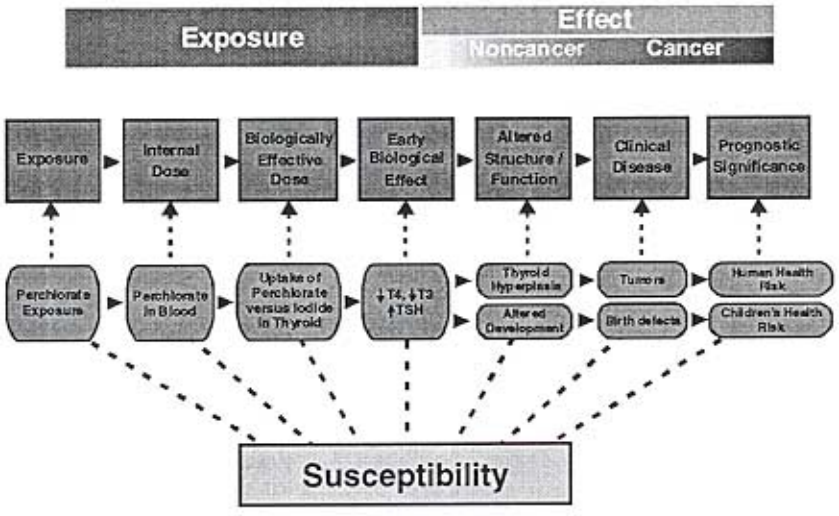
Source: U.S. Environmental Protection Agency (1998a).

Recommended Studies*

- 90-Day subchronic bioassay (rats)
- Developmental neurotoxicity study (rats)
- Genotoxicity assays (Salmonella, MN, lymphoma)
- Mechanistic studies
- ADME - Absorption, Distribution, Metabolism and Elimination
- Developmental study (rabbits)
- 2-Generation reproductive toxicity study (rats)
- Immunotoxicity (mice)

* Hormone analyses (T4, T3, and TSH), thyroid histopathology, and recovery satellites also added

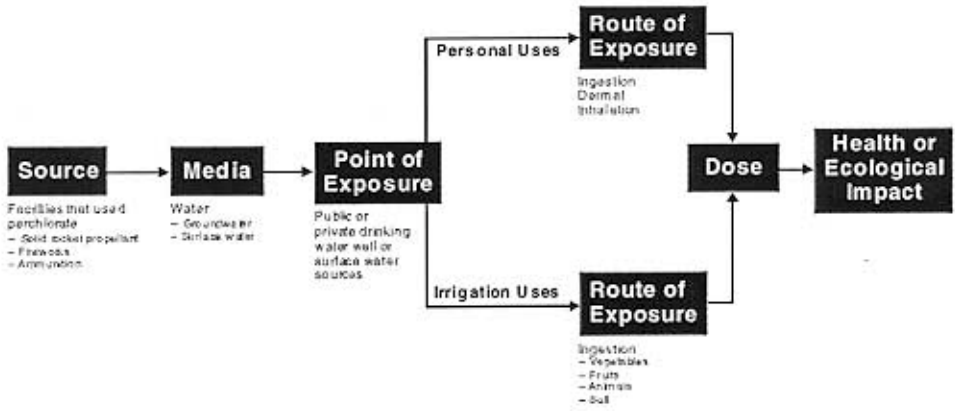
Mode-of-Action Model for Risk Assessment of Perchlorate



Summary: Role of Mode of Action and Dosimetry in Risk Assessment

- Evolution of science and methods
- Mode of action (when known) is important to defining the dose metric related to tissue response
  - Response related to appropriate metric
  - Extrapolations based on these metrics with an understanding of the relationship of these tissue dose metrics to response
- Improve hazard characterization through use of biomarkers of response with mechanistic linkage to endpoints of concern
- Strengthen inferences regarding the shape of dose-response curves outside the range of observation

Comprehensive Characterization of Perchlorate Contamination



Acknowledgments

US EPA Perchlorate Risk Assessment Team

InterAgency Perchlorate Steering Committee (IPSC)

US Air Force Research Laboratory

Perchlorate Study Group (PSG) and its contractors