Combining Multiple Studies When Information is Sparse

Disclaimer: These comments do not necessarily represent the views of the Office of Environmental Health Hazard Assessment, the California Environmental Protection Agency or the State of California

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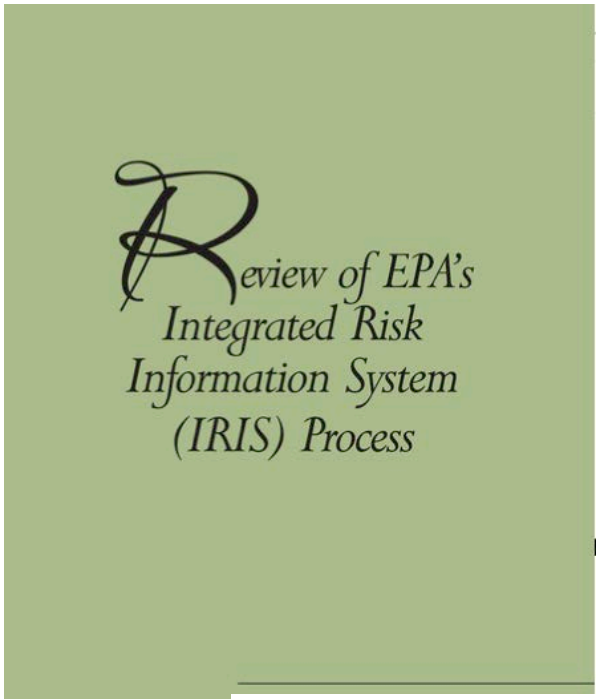
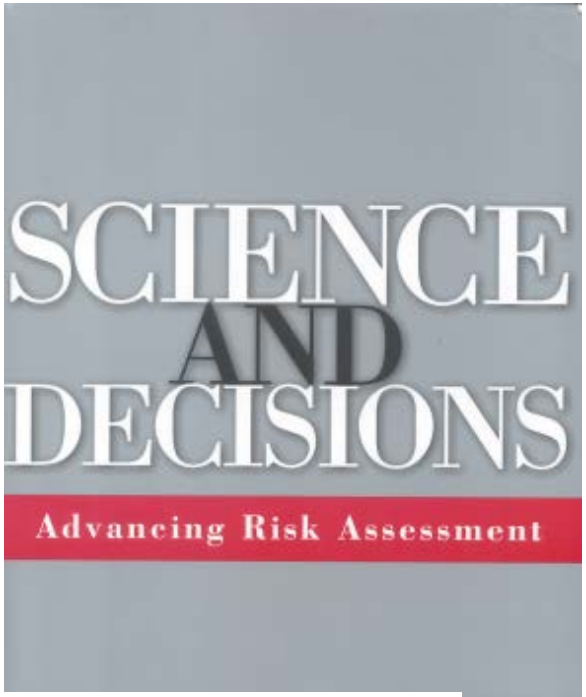
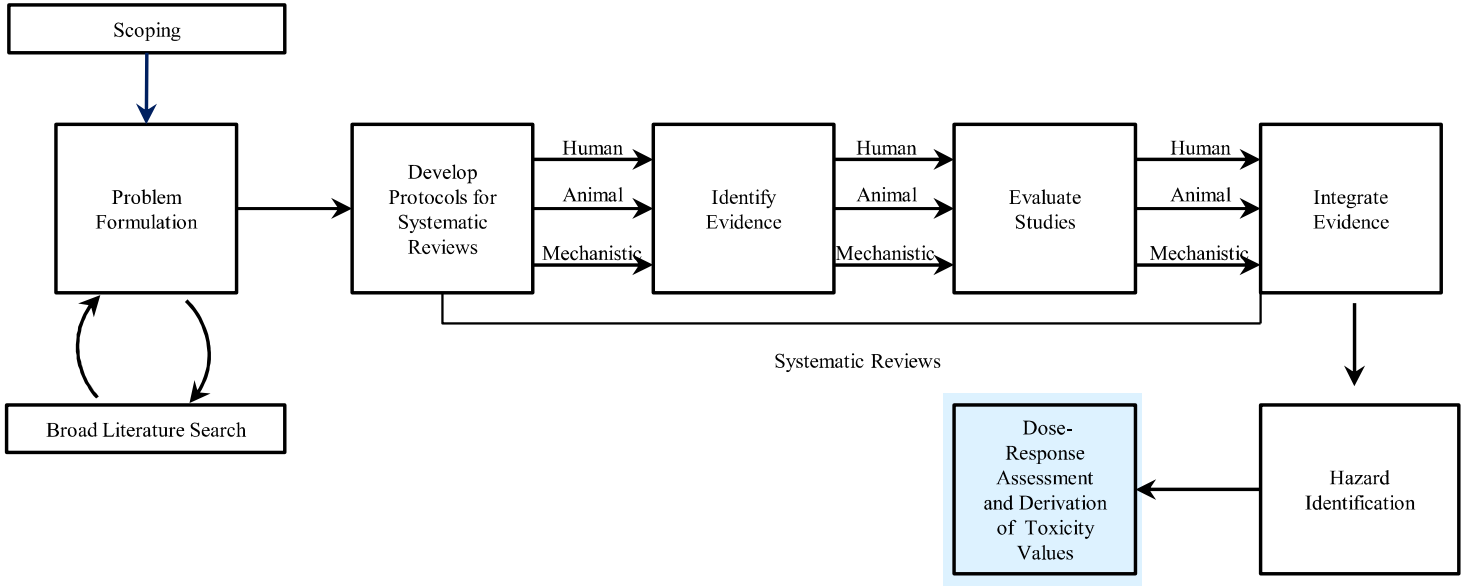
California Environmental Protection Agency

EPA IRIS Workshop on the NRC Recommendations

October 15-16, 2014
US EPA, One Potomac Yard
Arlington, VA


Review of EPA's
Integrated Risk
Information System
(IRIS) Process


SCIENCE
AND
DECISIONS
Advancing Risk Assessment


Scoping
Problem Formulation
Broad Literature Search
Develop Protocols for Systematic Reviews
Human
Animal
Mechanistic
Identify Evidence
Human
Animal
Mechanistic
Evaluate Studies
Human
Animal
Mechanistic
Integrate Evidence
Systematic Reviews
Hazard Identification
Dose-Response Assessment and Derivation of Toxicity Values

Main Goal of Dose Response Assessment: Develop Reference Value

RfD: “An estimate
(with uncertainty spanning perhaps an order of magnitude)
of a daily oral exposure to the human population
(including sensitive subgroups)
that is likely to be without an appreciable risk of deleterious effects during a lifetime”

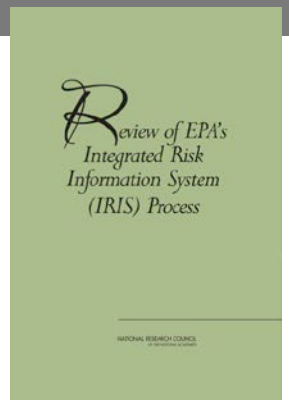
EPA 2013

Main Goal of Dose Response Assessment: Develop Reference Value

RfC: An estimate
(with uncertainty spanning perhaps an order of magnitude)
of a continuous inhalation exposure to the human population
(including sensitive subgroups)
that is likely to be without an appreciable risk of deleterious effects during a lifetime"

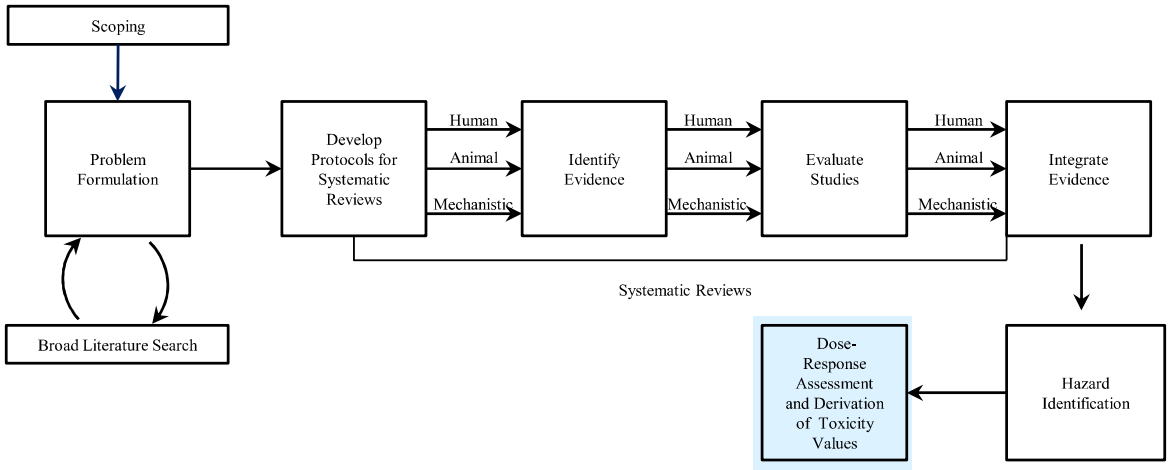
EPA 2013

NRC's Handoff of Evidence from Hazard Identification Step to Dose Response Step

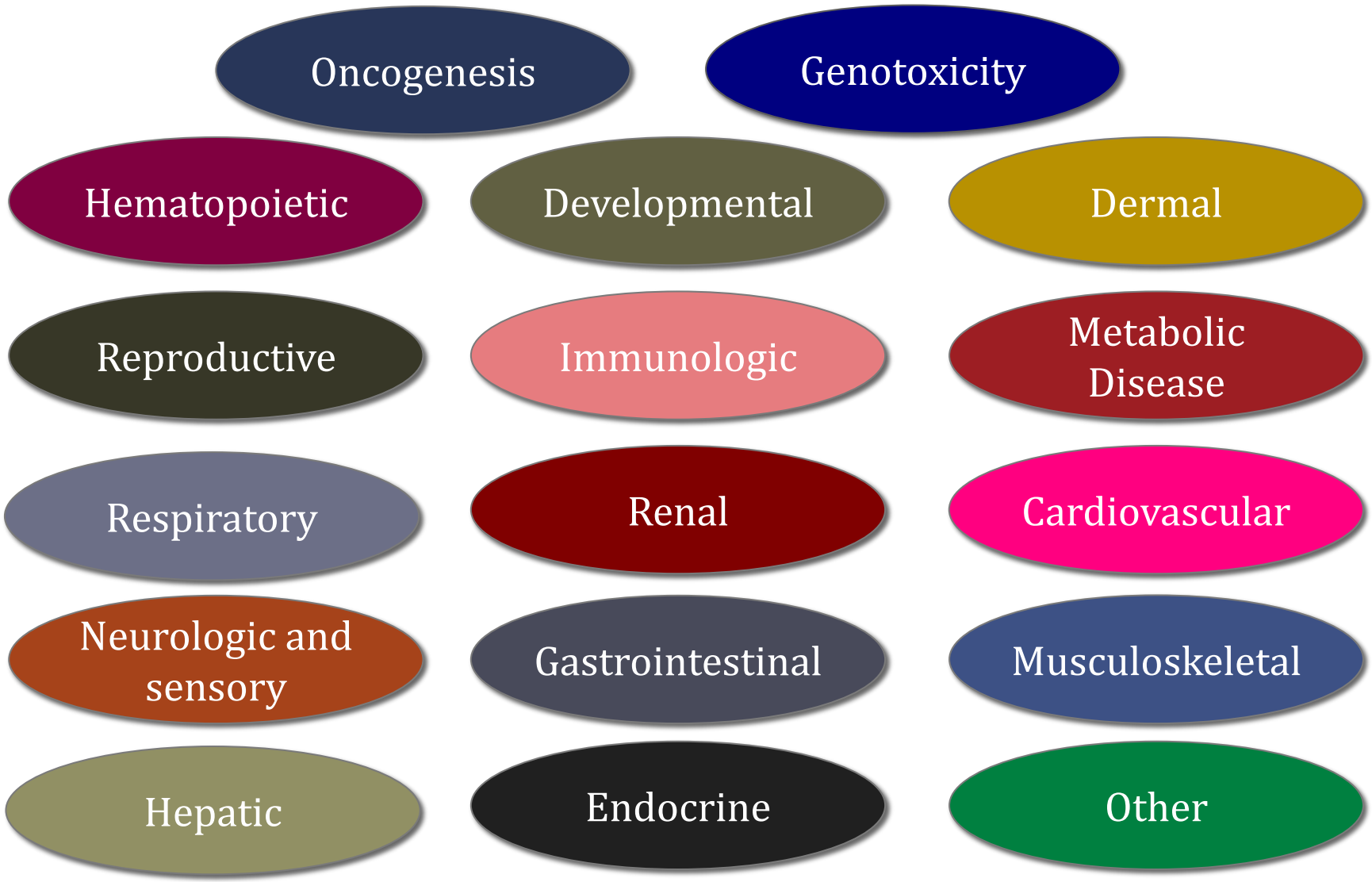


Systematic Review and Evidence Integration for Hazard

Evidence Integration for Dose Response

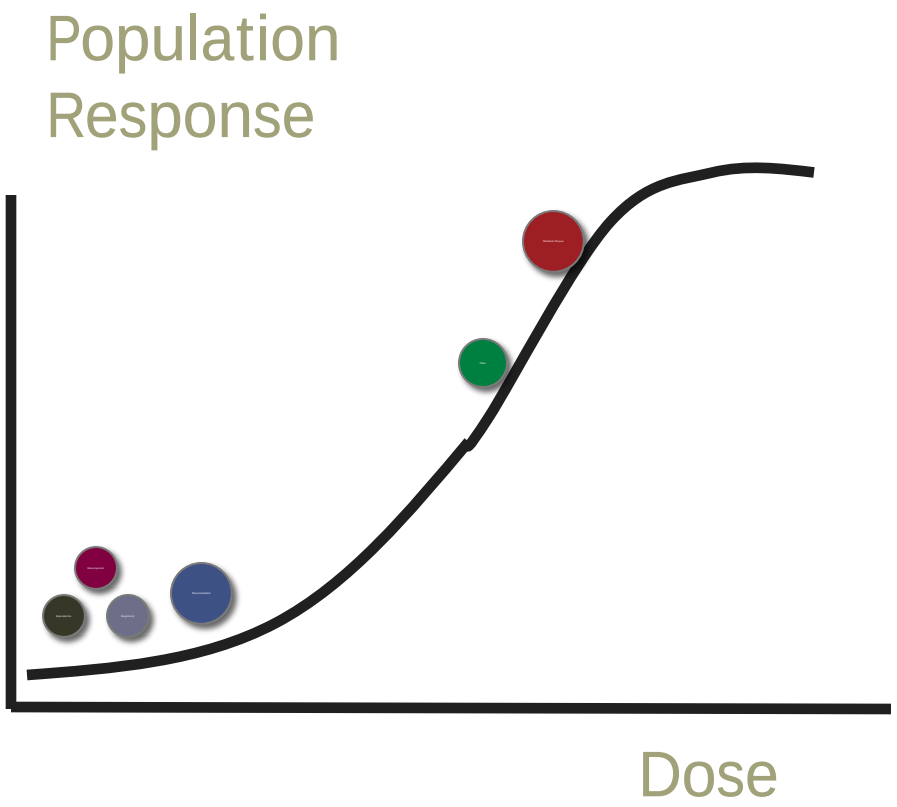


Example Hazard Traits Potentially Evaluated

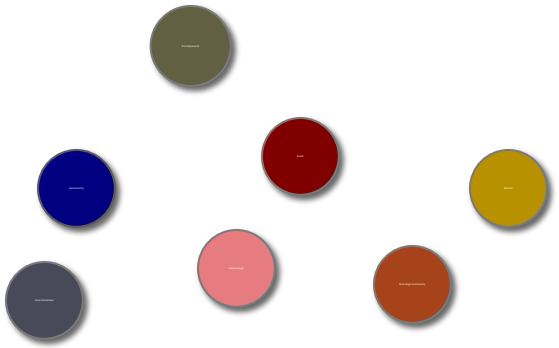


named in NRC 2014, p. 35

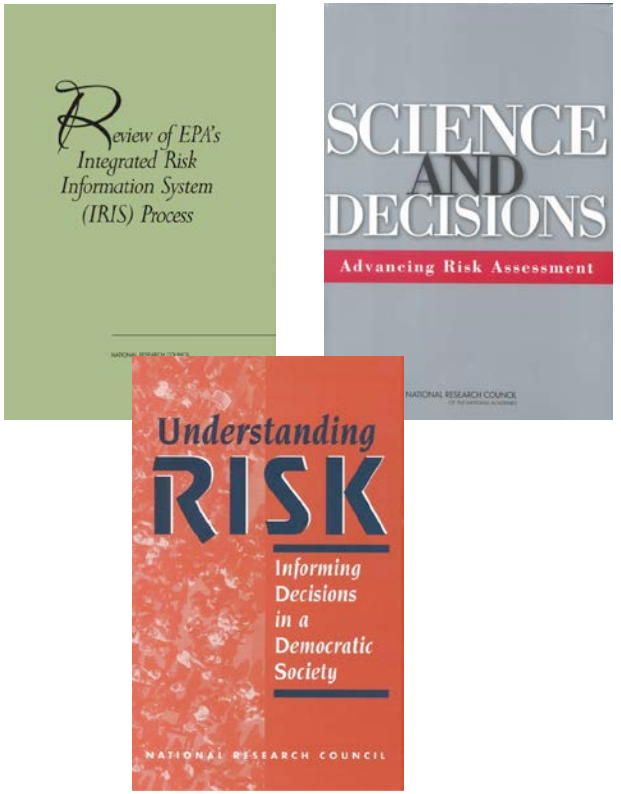
Target for Reference Dose: Most dose-sensitive adverse endpoints



Hazards without reliable data or suggestive evidence



Fit for purpose assessment



Scale, depth and nature match the need

Focus attention on potential sensitive endpoints

Dose Response Framework

for typical assessments

Evidence for current dose response assessments

Dose response

Less Direct Evidence

Mechanistic

Direct in vivo evidence

Endpoints

≈ 50 IRIS and IA chemicals

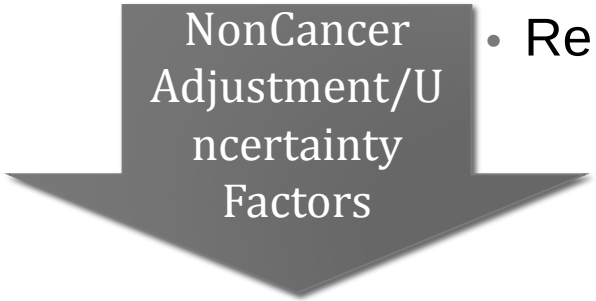
≈ 400 IRIS chemicals

≈ 375 PPRTV

- Perchlorate (CA)
- TEFs fir dioxin-like compounds and PAHs (provisional)

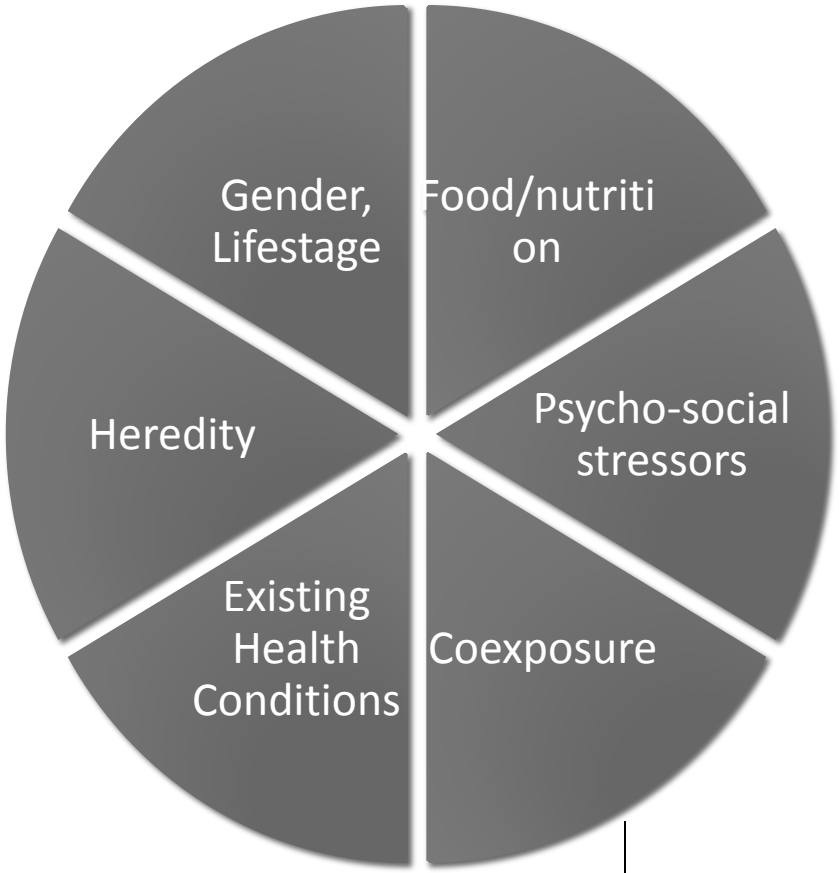
Typical Studies for Dose Response

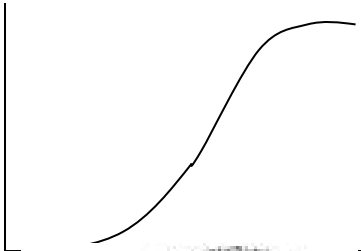
- Bioassay
  - Homogeneous animals
  - Limited age range and exposure duration
  - Controlled dose
  - Controlled environment
  - High Dose
  - Small numbers
- Workers or clinical group
  - Typically males from living in same community
  - Exposed as adults
  - Relatively high dose
  - “Healthy workers”
  - Relatively small number

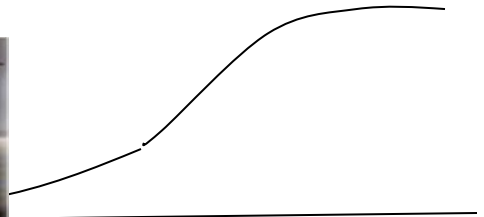


- General Population
  - All ages and fetus
  - Male and female
  - Heterogeneous Pharmacokinetics and Dynamics
  - Varied environments, health status, habits
  - Very big numbers

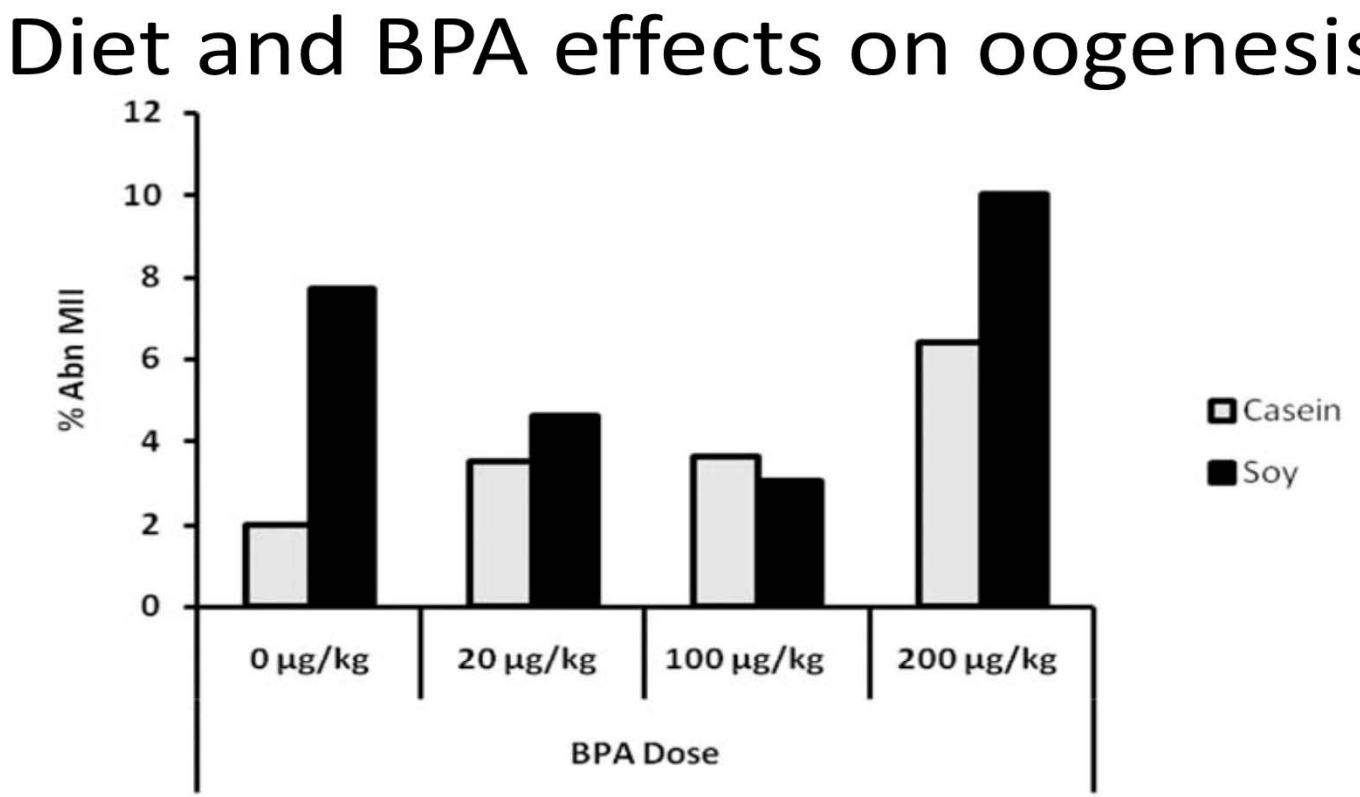
Sources of differences in response among people







Context dependent, low dose effects

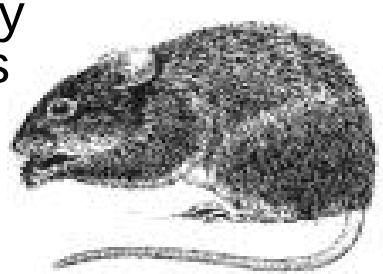


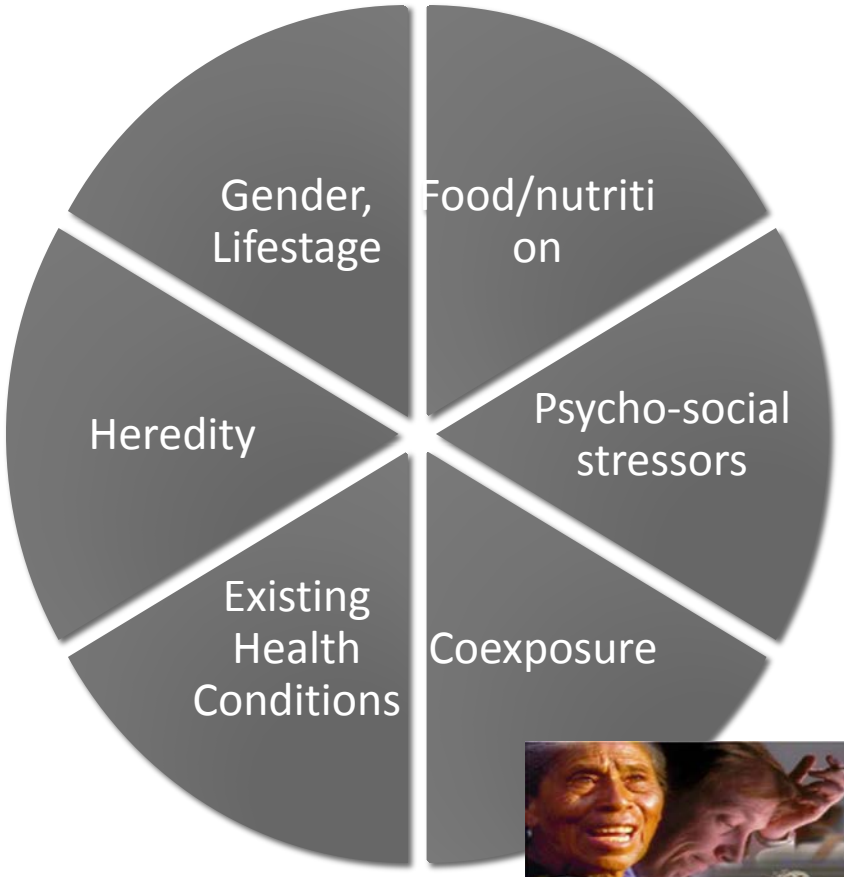
"Exogenous estrogens are a serious confounding variable in rodent studies designed to assess the effects of endocrine-disrupting chemicals, and, because estrogenic contaminants can be present in food, bedding materials, water, and caging materials, controlling for their presence is a daunting task." Muhlhauser et al. Biol Reprod 2009.

Kim Boekelheide slide, NRC Emerging Sciences Workshop, June 2012

Challenge: Addressing "discordance"

- Different experimental designs
- Differences in animal findings
  - Strain
  - Sex
  - Species
  - Comorbidities
  - Laboratory conditions
  - Feed

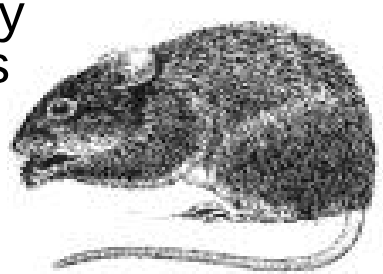




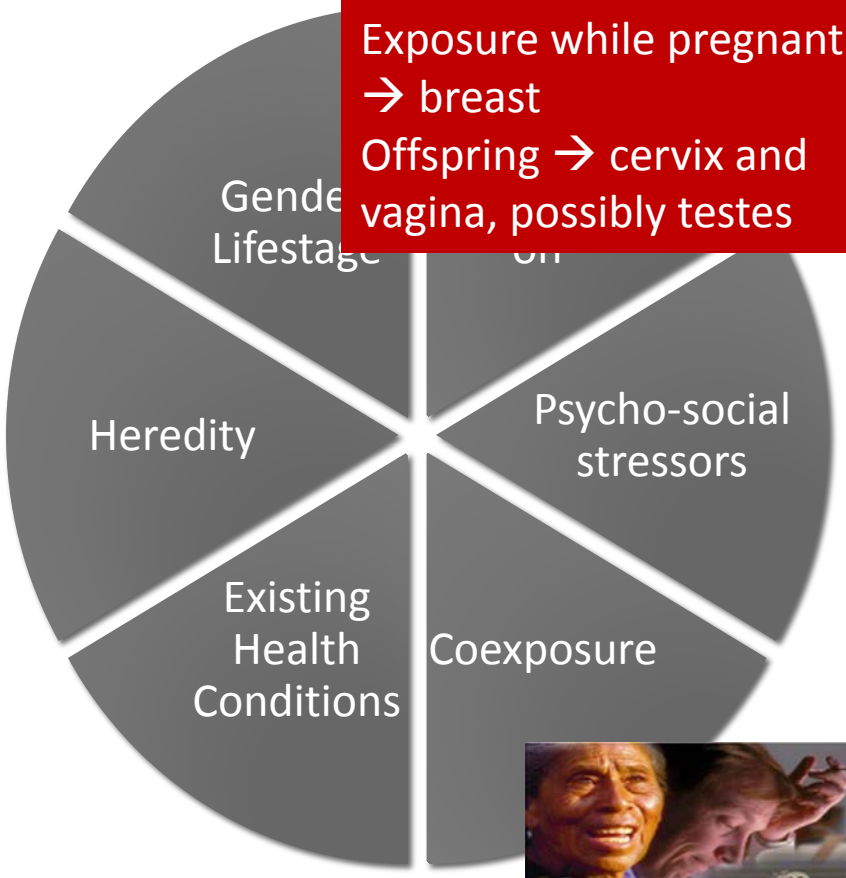
Challenge: Addressing "discordance"

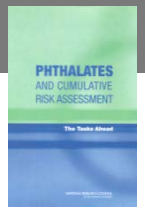
- Different experimental designs
- Different animal models
  - Strain
  - Sex
  - Species
  - Comorbidities
  - Laboratory conditions
  - Feed

DES cancer sites
Hamster→ kidney
Mouse → ovary, endometrium, cervix, mammary
Mouse perinatal → lymphomas, uterus, and pituitary, vagina, ovary



DES human cancer sites
Exposure while pregnant → breast
Offspring → cervix and vagina, possibly testes





Varied related outcomes – upstream endpoint

Other Stressors

Decreased Testosterone

Decreased Dihydrotestosterone

Blockade of Androgen Receptor (AR)

Mutated Receptor

Decreased AR activity at target tissue

Interference with androgen mediated development

Reproductive tract malformations

↓ Sperm quality

Leydig cell tumors

Cryptorchism

Other reproductive tract malformations

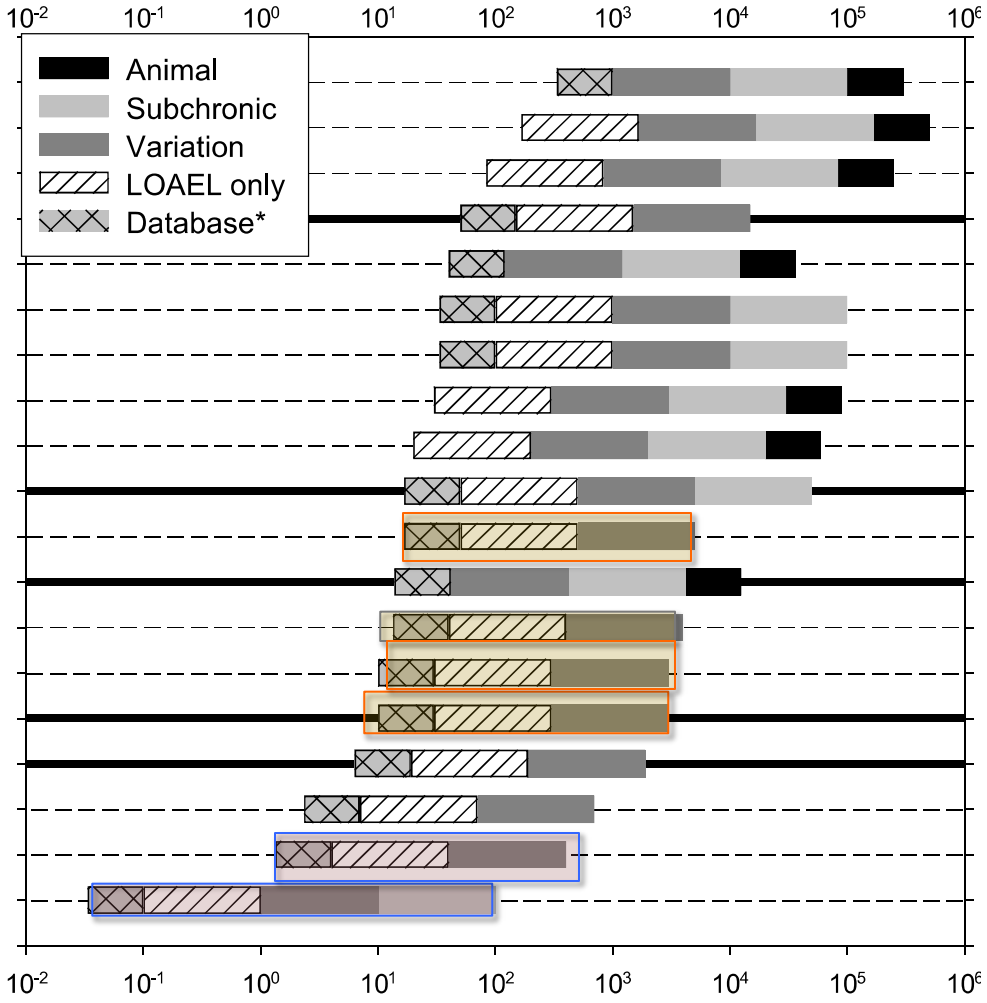
↓AGD

Nipple Retention

Hypospadias

"Phthalate Syndrome"

Arraying potential RfDs

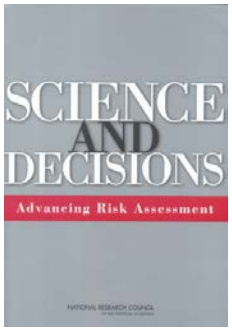


Same frank effect

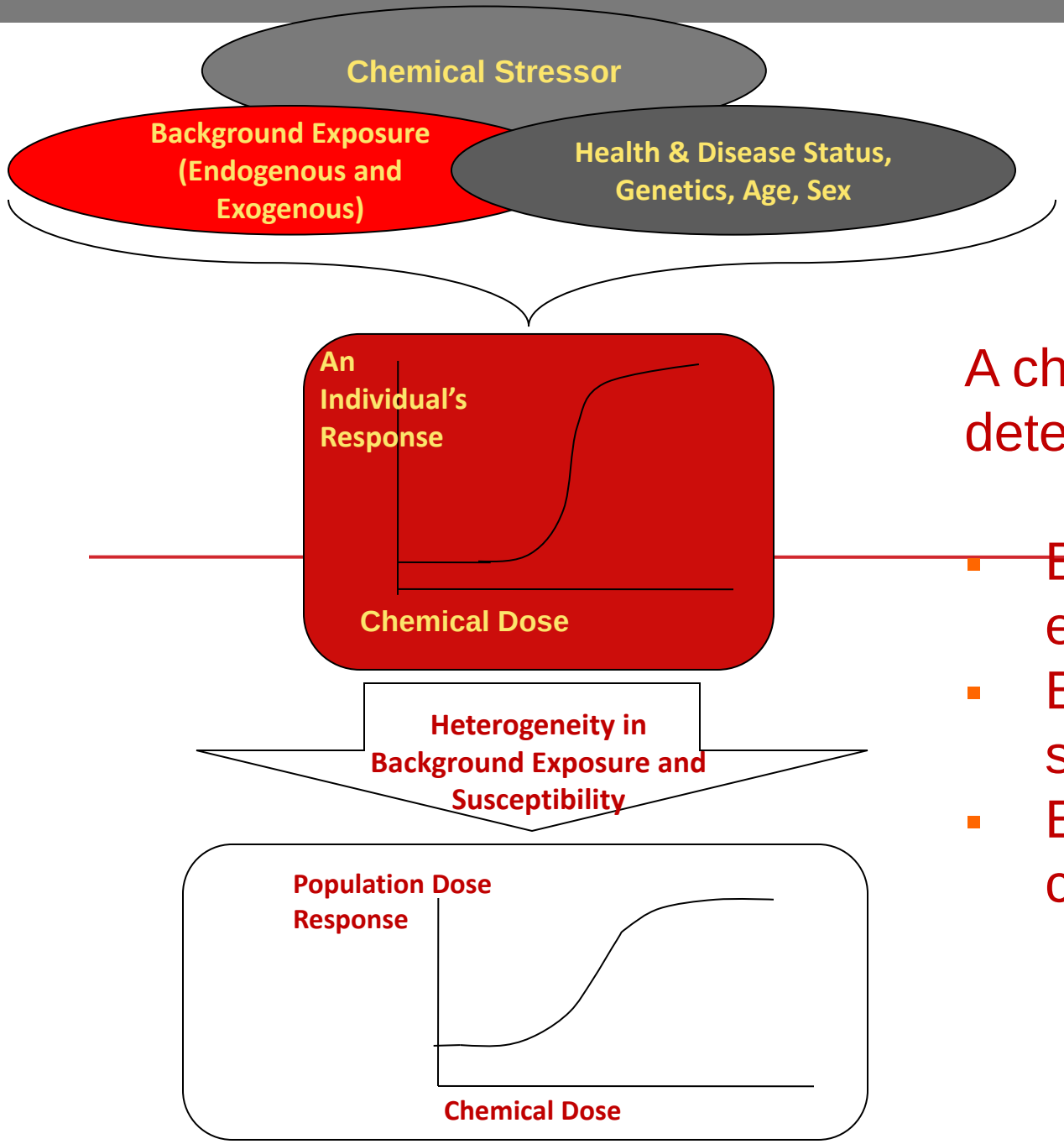
Upstream perturbation

Constructing the Dose Response Relationship

Unified approach to cancer and non-cancer dose response

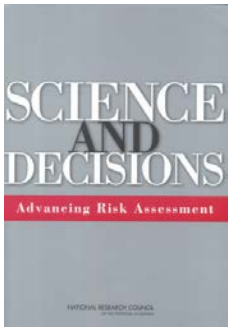


Complexity of Exposure and Multifactor Risk



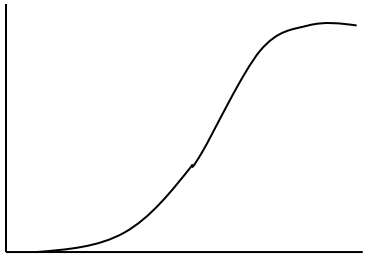
A chemical's risk is determined by:

- ~~Background~~ exposures
- Biological susceptibility
- Exposure level to the chemical

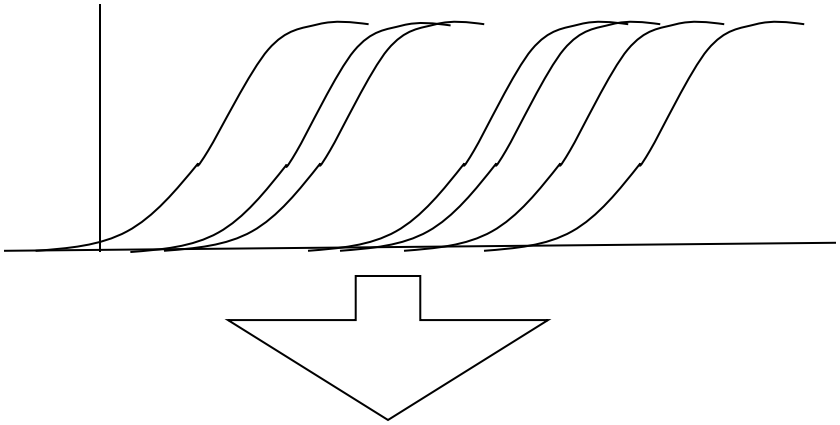


Implications for Risk

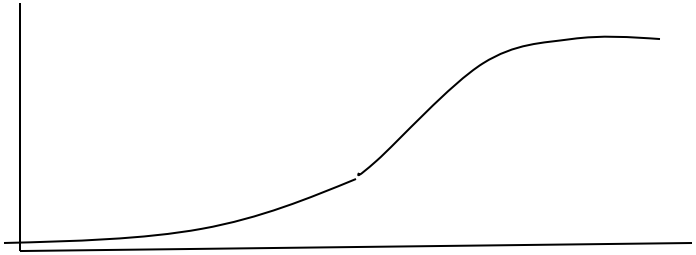
- Animal Study Group



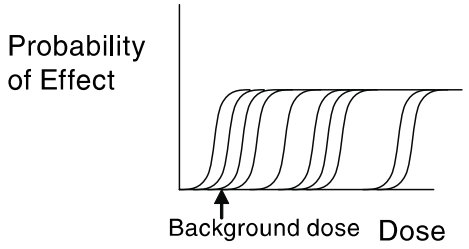
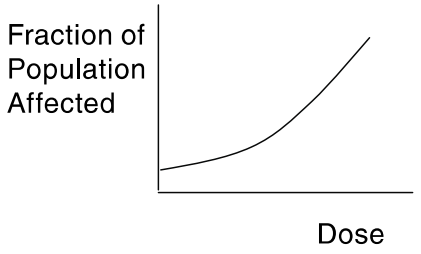
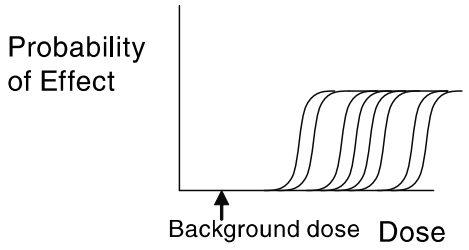
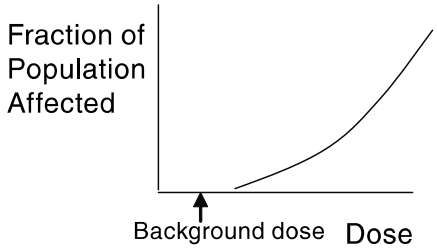
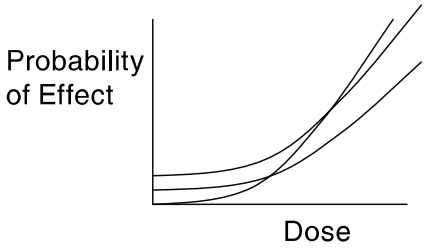
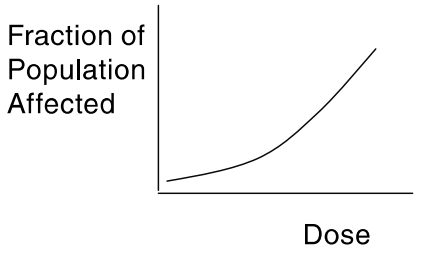
- Human Subpopulations



- Human Population



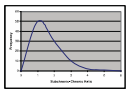
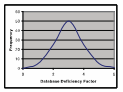
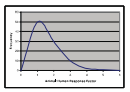
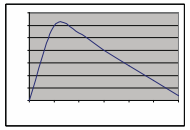
Examples of Conceptual Models

Conceptual Models for Low-Dose-Response	Individual Dose–Response	Population Dose–Response
1. An individual's: Nonlinear The population: Linear		
2. An individual's: Nonlinear The population: Nonlinear		
3. An individual's: Linear The population: Linear		

Deriving a Risk Specific RfD Based on Human Variability and Adjustments

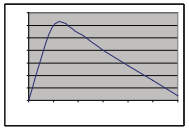
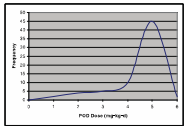
: Determine adjustment needed to Animal POD

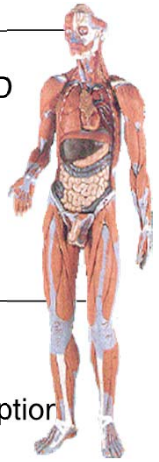
Subchronic/Chronic × Data Gaps × Animal-Human = Overall Adjustment Distribution

2: Derive human POD

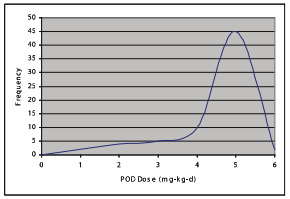
Animal POD
(derived by benchmark dose methods) ÷ Overall Adjustment Distribution = Human Adjusted POD Distribution

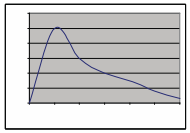


3: Extrapolate from human POD to low dose

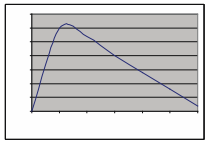
Human Adjusted POD Distribution



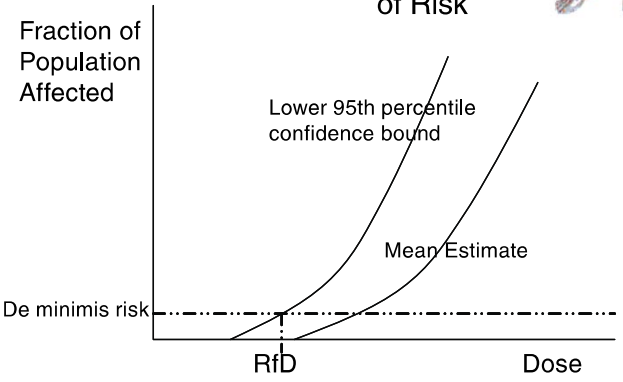
Inter-Human PK



Inter-Human PD



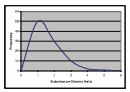
Probabilistic Description of Risk



Deriving a Risk Specific RfD Based on Human Variability and Adjustments

: Determine adju

Subchronic/Chron



2: Derive human

Animal
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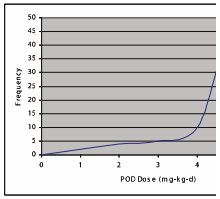
dose me

3: Extrapolate fro

Human Adjusted
Distribution



This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization, the International Labour Organization or the United Nations Environment Programme.

Harmonization Project Document 11

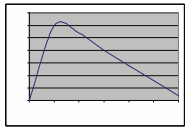
GUIDANCE DOCUMENT ON EVALUATING AND EXPRESSING UNCERTAINTY IN HAZARD CHARACTERIZATION

This project was conducted within the IPCS project on the Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals.

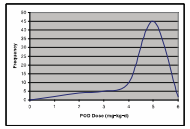
Published under the joint sponsorship of the World Health Organization, the International Labour Organization and the United Nations Environment Programme, and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals.

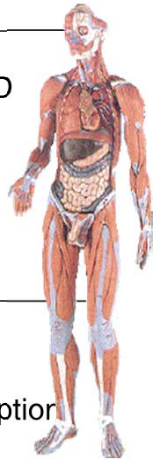
World Health Organization

Adjustment Distribution



nan Adjusted POD
Distribution





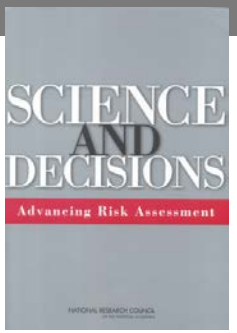
obabilistic Description
of Risk

wer 95th percentile
nfidence bound

Mean Estimate

RfD

Dose



Assemble Health Effects Data

End-point Assessment

- Identify adverse effects, focusing on those of concern for exposed populations
- Identify precursors and other upstream indicators of toxicity
- Identify gaps – for example, end points or lifestages under assessed or not assessed

MOA Assessment
(for each end point of concern)

- Research MOAs for end points observed in animals and humans
- Evaluate the sufficiency of the MOA evidence
- Evaluate endogenous processes contributing to MOA

Vulnerable Populations Assessment

Identify potentially vulnerable groups and individuals, considering end points, the potential MOA, background rate of health effect, and other risk factors

Background Exposure Assessment

- Identify possible background exogenous and endogenous exposures
- Conduct screening level exposures and analysis, focusing on high-end exposure groups

Conceptual Model Selection

Develop or select conceptual model:

- From linear conceptual models unless data sufficient to reject low-dose linearity
- From nonlinear conceptual models otherwise

Dose-Response Method Selection

Select dose-response model and method based on

- Conceptual model
- Data availability
- Risk-management needs for form of risk characterization

Dose-Response Modeling and Results Reporting