

SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety



**The Role of Mode of Action
in Dose-Response
Assessments:**

**Recommendations from
2009 NRC “Science and
Decisions”**

January 25, 2016





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The Role of Mode of Action in Dose-Response Assessments:

Recommendations from National Research Council's 2009 Report "Science and Decisions"

Lauren Zeise, Member, "Science and Decisions"
NRC Committee

Conflict of Interest Statement

- I declare that neither I nor my family members have any financial interest with a commercial organization that has a direct or indirect interest in the subject matter of my presentation
- I am employed by the California Environmental Protection Agency Office of Environmental Health Hazard Assessment (CalEPA OEHHA)
- The opinions stated are mine and do not necessarily reflect those of CalEPA, OEHHA, or the NRC



Outline



Key considerations for dose-response assessment



Framework for dose response assessment



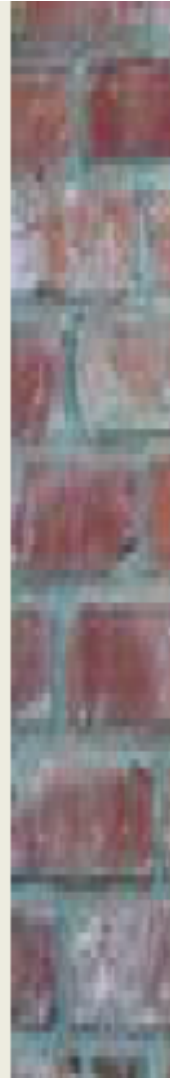
Constructing dose-response relationships



NRC Committee Observations on the Practice of Dose Response

Non-Cancer

- No risk measure produced
 - HI, RfD, MOE limited for risk/benefit assessment
- Possible low dose linearity not assessed
- Uncertainty not distinguished from variability or other adjustments



Cancer

- Inter-human variability
 - Not addressed (animal data based) or
 - Incomplete (epidemiologic data based)
- “Low dose nonlinear” carcinogens
 - No risk measure
- Uncertainty not characterized

Chemical Stressor

Background Exposure
(Endogenous and
Exogenous)

Health & Disease Status,
Genetics, Age, Sex

An
Individual's
Response

Chemical Dose

Heterogeneity in
Background Exposure
and Susceptibility

Population Dose
Response

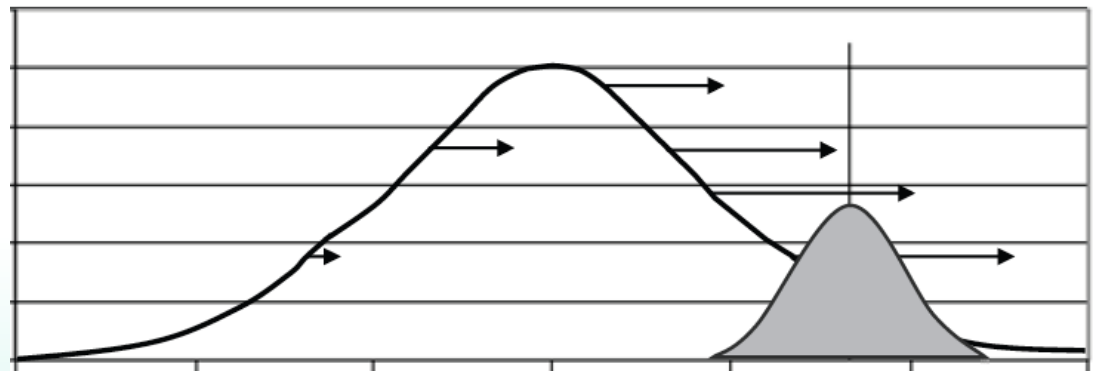
Chemical Dose

Key Considerations for Dose-Response Assessment

- Background
- Variability
- Mode of Action

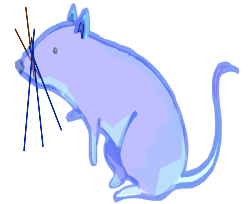
Background

the context for considering MOA



Background Dependent Dose-Response

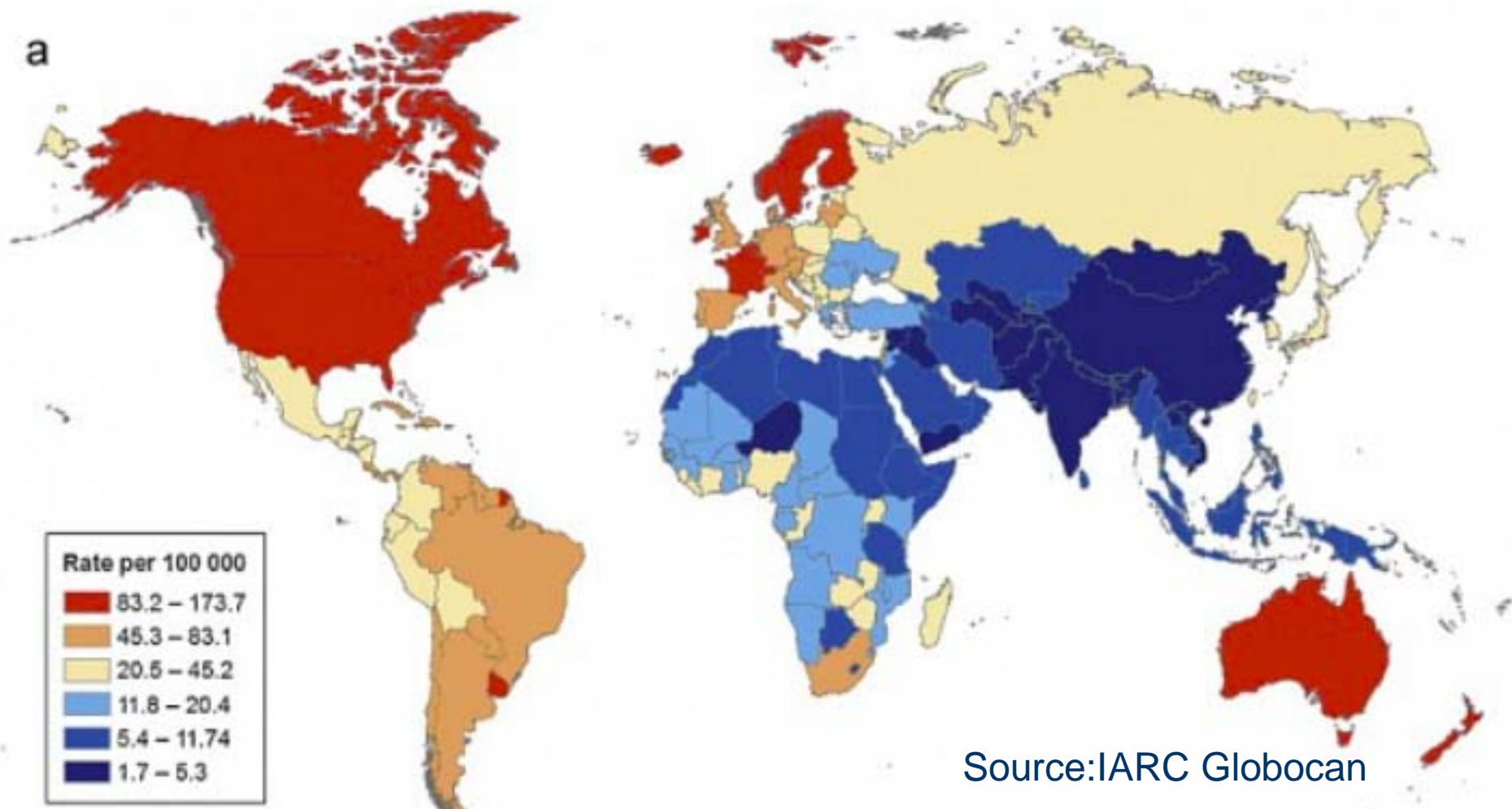
Diet and BPA effects on



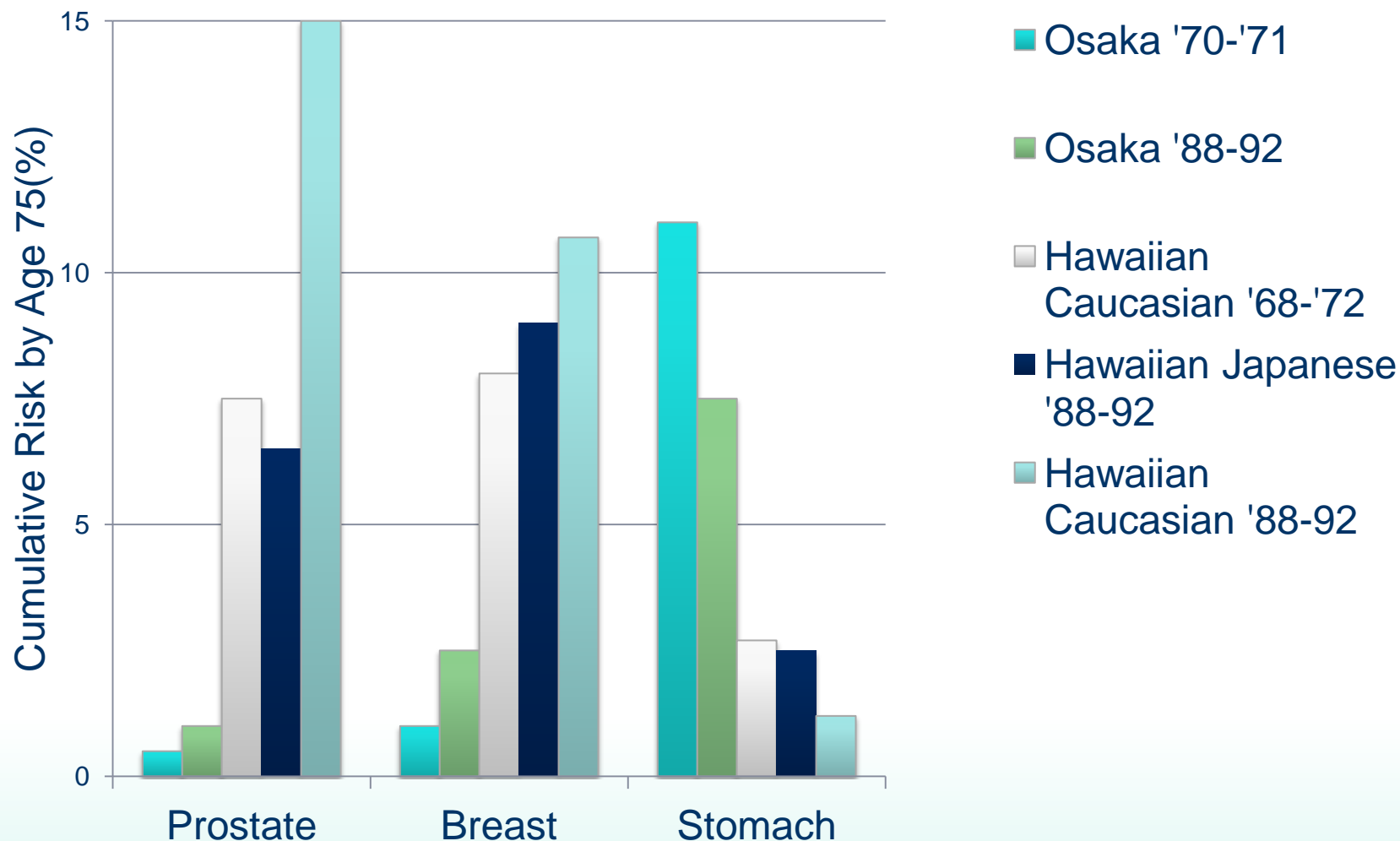
, bedding materials, water, and caging materials, controlling for their presence is a daunting task.” Muhlhauser et al. Biol Reprod 2009.

Kim Boekelheide slide, NRC Emerging Sciences Workshop, June 2012

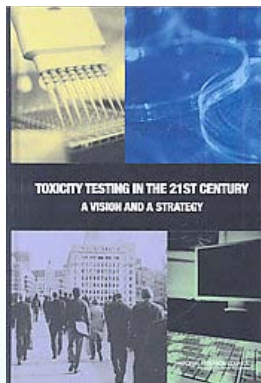
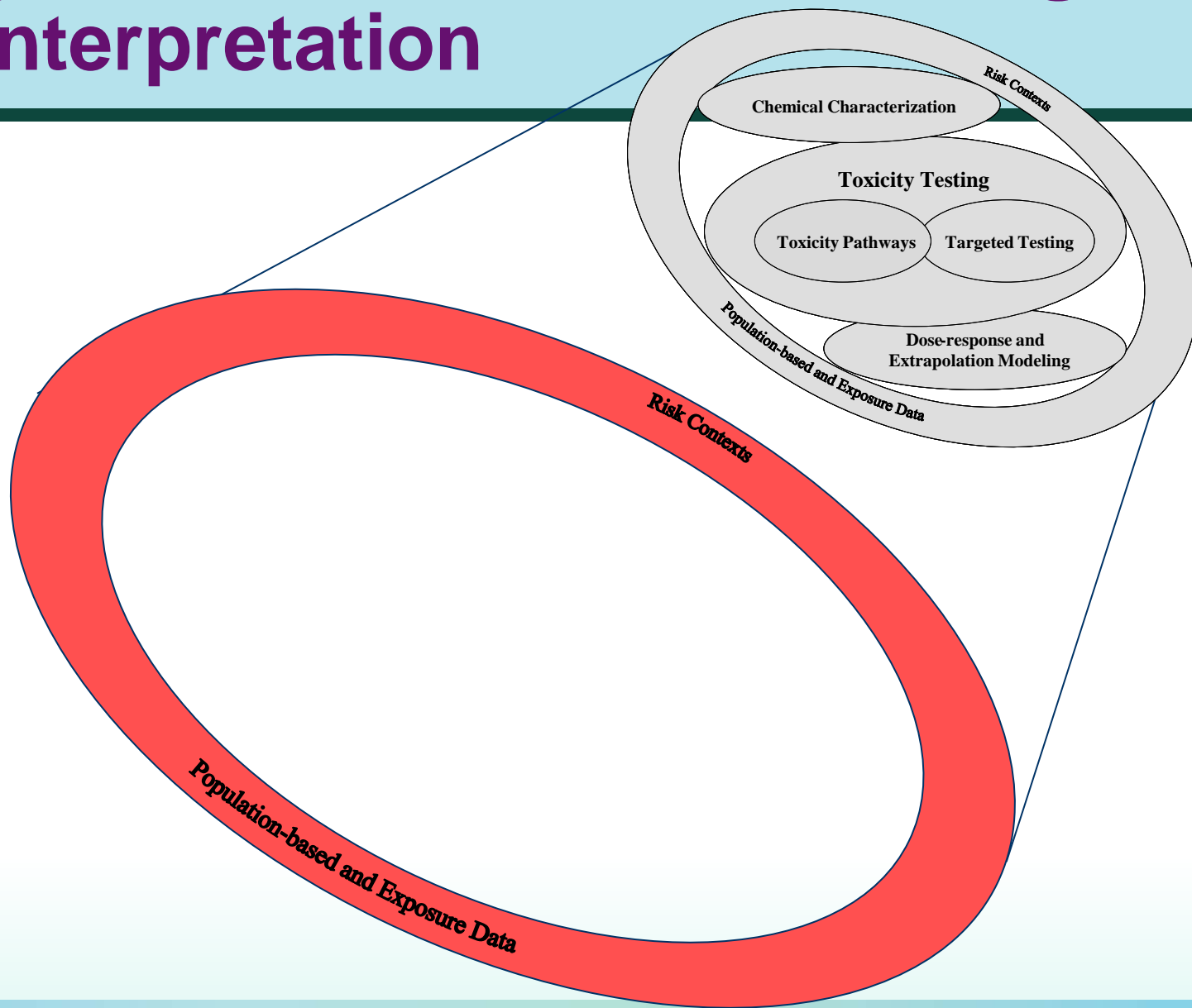
Background: Prostate Cancer Incidence



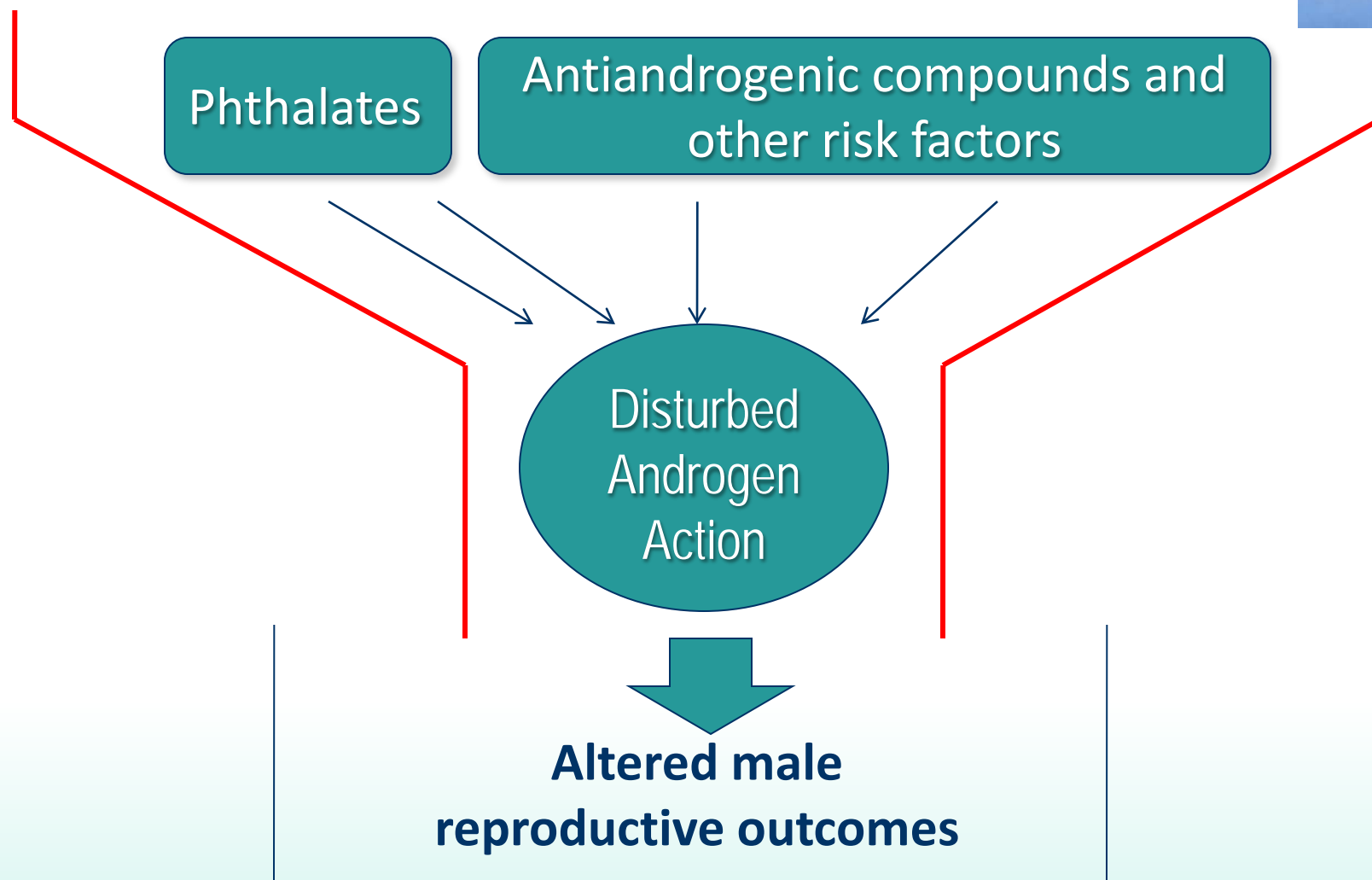
Background: Immigration Changes in Cancer Incidence

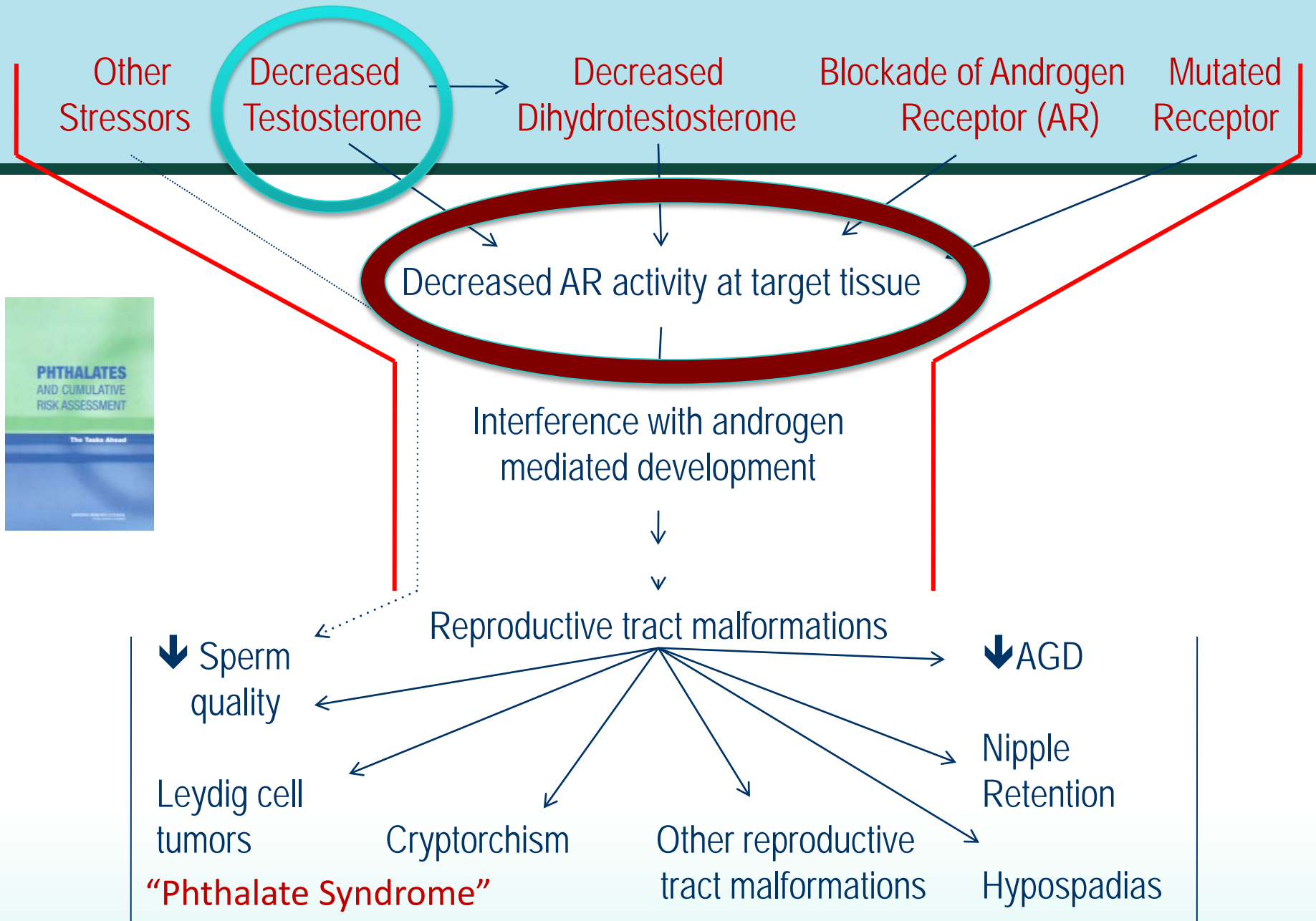


Background Context for Toxicological Data Interpretation

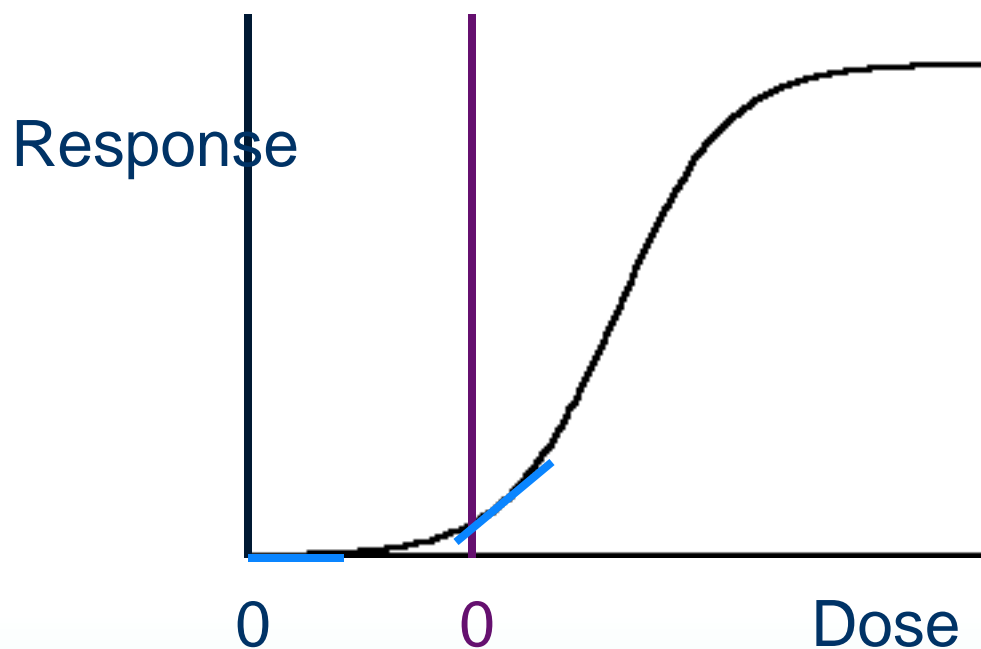


Multiple Exposures Leading to Common Adverse Outcomes





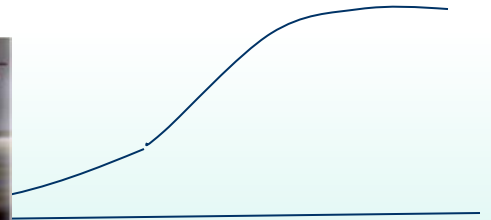
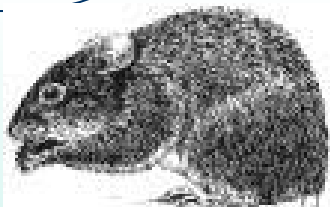
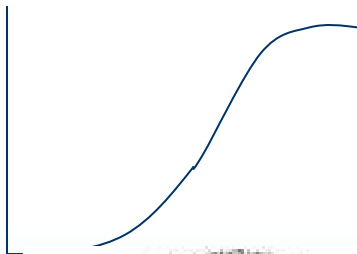
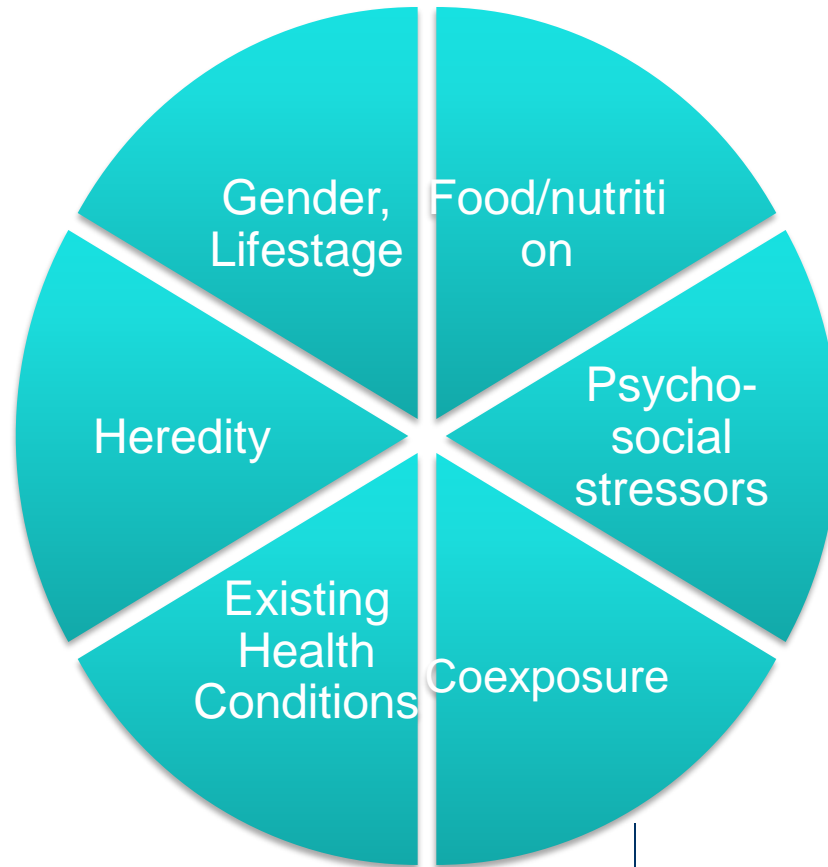
Background: Implications for Dose-Response



Variability

the context for considering MOA

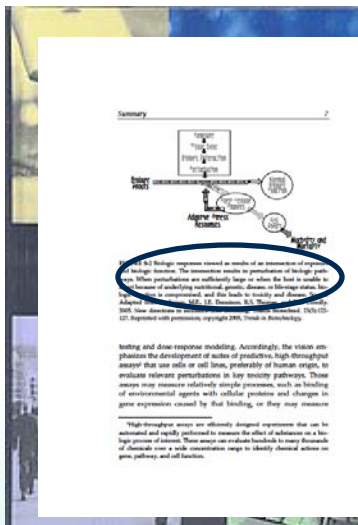
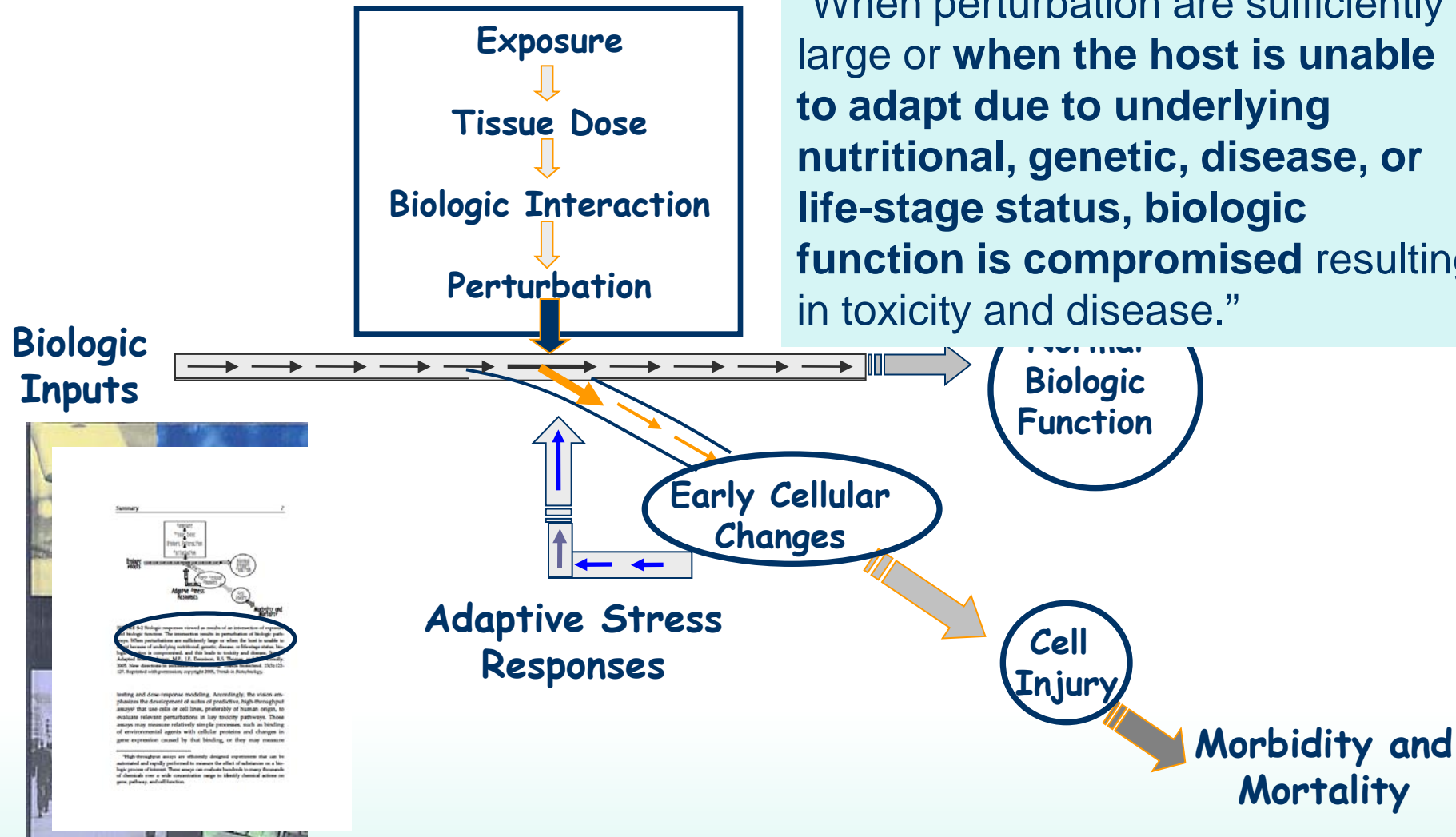
Sources of Differences in Response Among People



Consideration of Variability in the Context of the MOA

Figure Caption

“When perturbations are sufficiently large or when the host is unable to adapt due to underlying nutritional, genetic, disease, or life-stage status, biologic function is compromised resulting in toxicity and disease.”



Many new tools to interrogate the exposure to outcome continuum

in vitro
methods

In vivo
methods
animals

in vivo
methods
human

Genetic
heredity

Epigenetic
heredity

Lifestage

Existing health
conditions

Co-exposures

Food and
nutrition

Psychosocial
stressors

External exposure

Metabolism and Pharmacokinetics

Internal exposure

Biological molecule interactions

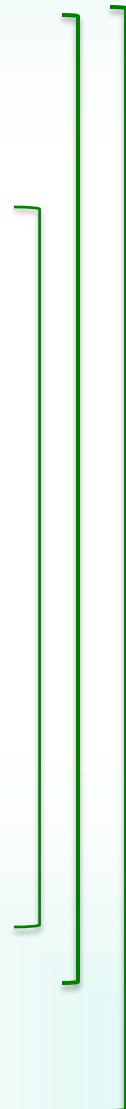
Cell responses

Tissue responses

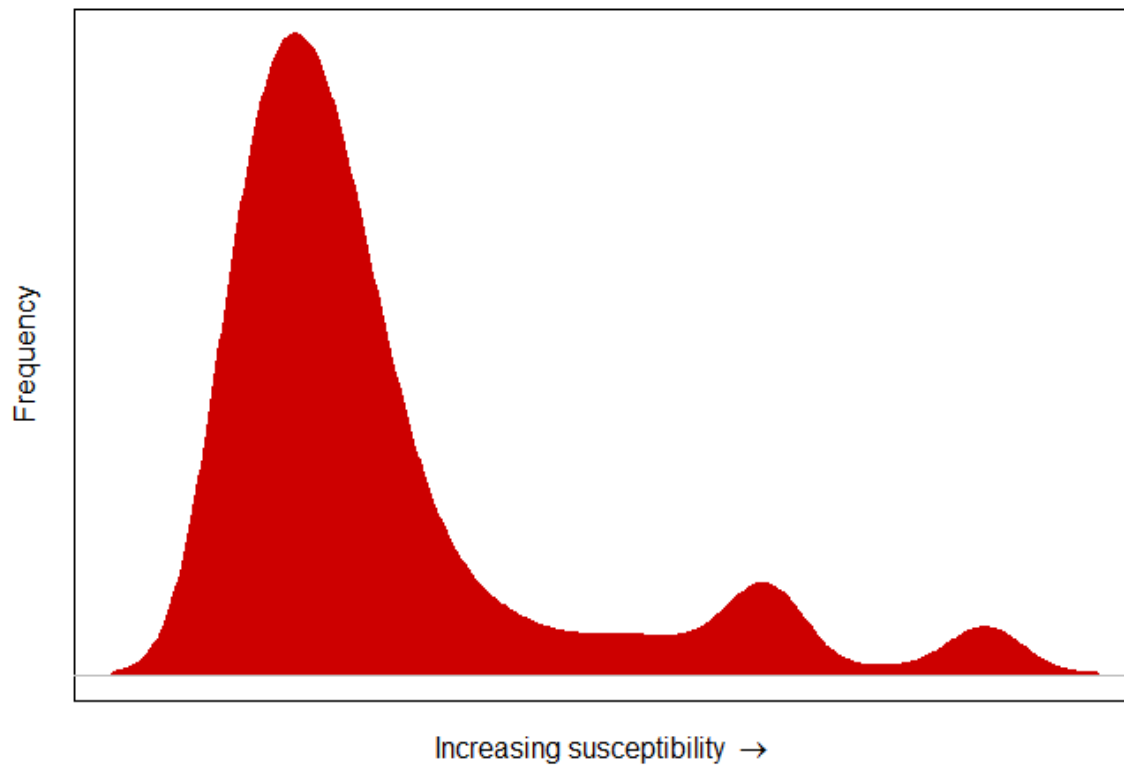
Organ responses

Individual responses

Population responses

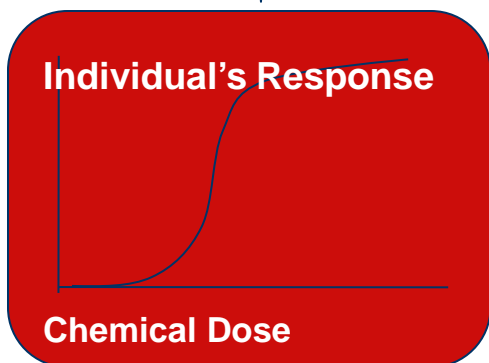
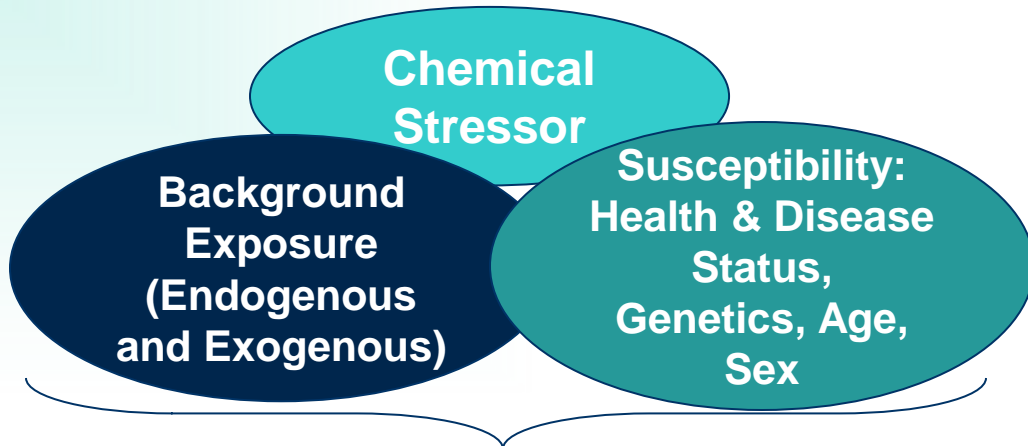


Implications for Dose Response

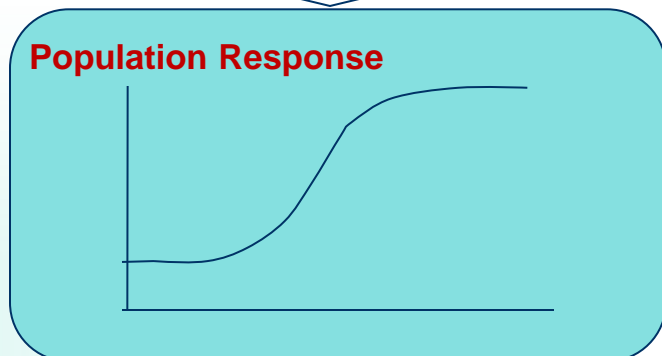


NRC 2009 Dose-Response Framework

Integrates concepts of background, inter-individual variability and MOA



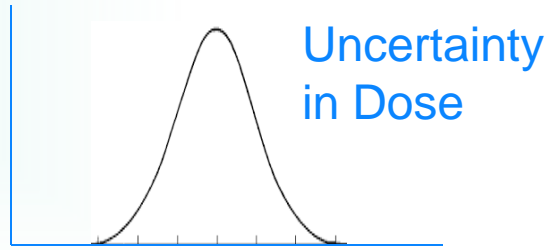
Heterogeneity in Background Exposure and Susceptibility



Conceptual Framework for Dose Response

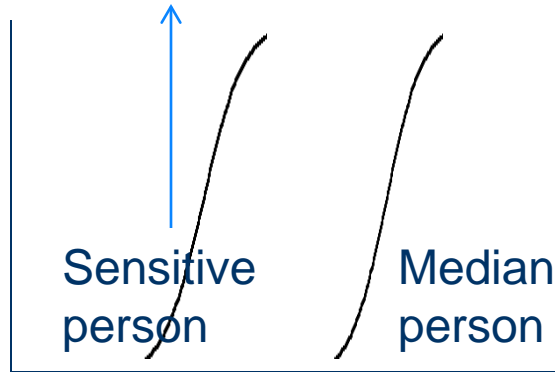
- Risk determined by individual's biologic make-up, health status, endogenous and exogenous exposures that affect toxic chemical process
- Differences among people in these factors affect the shape of the dose response

Frequency

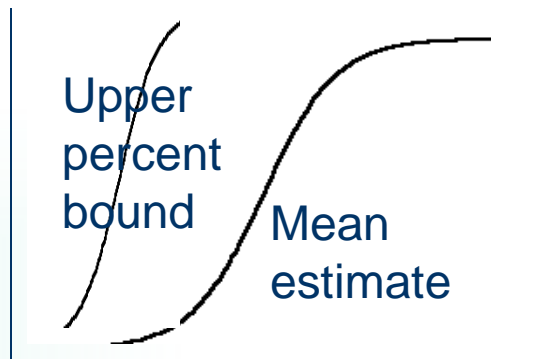


Dose posing 10^{-5} risk

Individual Risk
from Chemical



Fraction of
Population
Responding

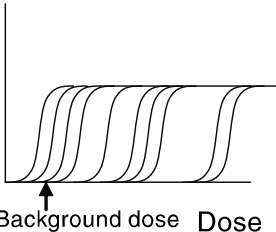
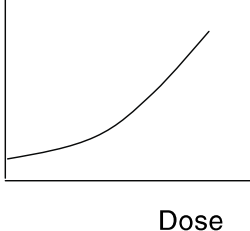
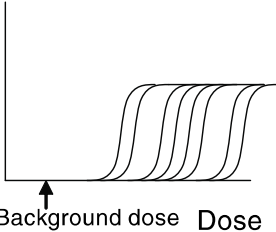
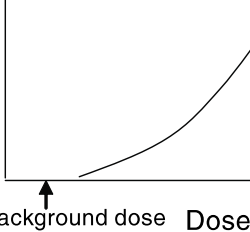
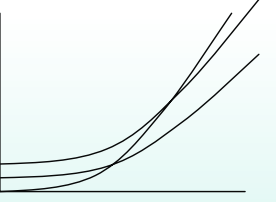
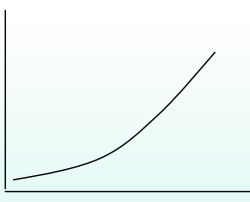


Chemical Dose

Risk depiction: Based on data, defaults and other inferences

- Risk estimated from
 - human, animal, MOA and other data
 - understanding background exposures, variability
- Risk depicted for
 - Population
 - Sensitive individuals
- Uncertainty also depicted

Examples of Conceptual Models

Conceptual Models for Low-Dose-Response	Individual Dose-Response	Population Dose-Response
<p>1. An individual's: Nonlinear The population: Linear</p>	<p>Probability of Effect</p>  <p>Background dose Dose</p>	<p>Fraction of Population Affected</p>  <p>Dose</p>
<p>2. An individual's: Nonlinear The population: Nonlinear</p>	<p>Probability of Effect</p>  <p>Background dose Dose</p>	<p>Fraction of Population Affected</p>  <p>Background dose Dose</p>
<p>3. An individual's: Linear The population: Linear</p>	<p>Probability of Effect</p>  <p>Dose</p>	<p>Fraction of Population Affected</p>  <p>Dose</p>

Dose-Response Recommendations in Science and Decisions



Formal, systematic assessment of human status

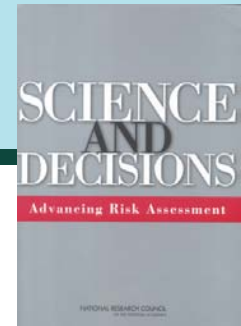
- background disease processes and exposures
- vulnerable populations
- use of modes of action in the assessment to identify modeling approach

Probabilistic risk estimation for “threshold” (nonlinear) endpoints

- Redefine the reference dose (RfD) as a risk-specific dose
- Characterize fraction of the population affected vs dose
- Describe uncertainty in that characterization
- Formal introduction of variability into cancer dose-response modeling

For implementation

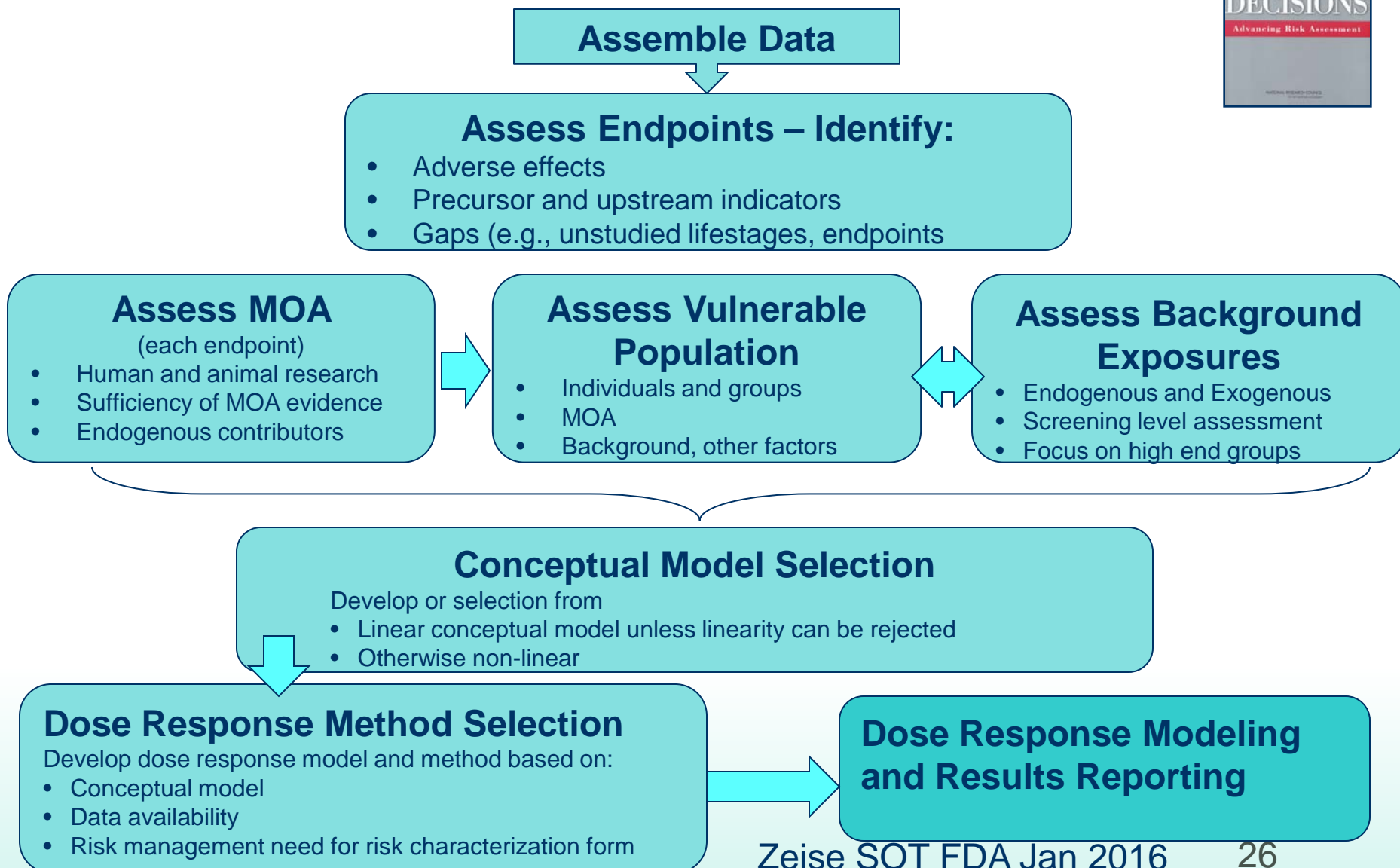
- Develop default distributions
- Quantitatively characterize adjustments and key uncertainties
- Develop Test cases to explore new framework



Constructing the Dose-Response Relationship

Unified approach to cancer and non-cancer dose response

Unified Approach to Dose-Response Assessment



Example Questions Identifying Conceptual Model



- What is the suspected or known MOA?
- What underlying disease processes might the chemical interact with?
 - What is the background incidence?
 - Have they been characterized in humans with markers of susceptibility and precursor effects?
- What environmental or endogenous chemicals are similar biologically to the chemical in question?
 - Could they operate by a similar MOA?
 - Can subgroups with high exposures be identified? Do some have pre-existing health conditions
- What other chemicals have the potential to affect the toxicological process?

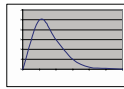
Which Conceptual Model?



- Example 1: Low Dose Linear - High background, heterogeneous individual thresholds
 - Particulate matter and cardiovascular mortality
 - Numerous genetic, environmental, disease state, behavioral factors contribute to distribution of thresholds
 - Ample epidemiological data to support derivation
 - Asthma exacerbating chemicals
 - High incidence of asthma
 - Existence of asymptomatic “hyperresponders”
 - Numerous genetic predisposing factors identified
 - “Bottom up” approach to modeling based on rates of airway hyper-responsiveness markers provided in “Science and Decisions”

Example 2: Low Dose Non-Linear, Low Background--Deriving a Risk Specific RfD

1: Determine adjustment needed to Animal POD



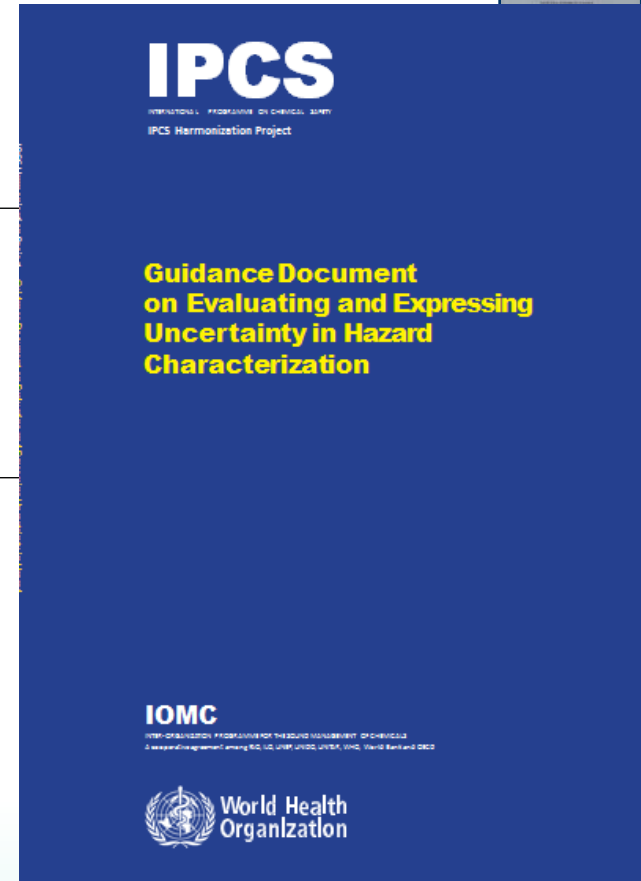
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2: Derive human POD

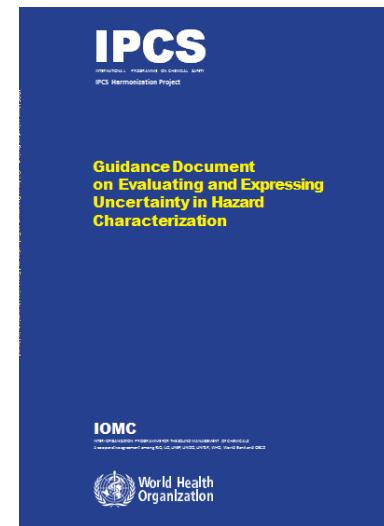
3: Extrapolate from human POD to low dose



Unified Dose Response Elements in Recent IPCS Report

- Low-dose non-linear assessments
 - Quantitative risk estimates (e.g., incidence)
 - Distinction between uncertainty from variability
- Cancer assessments
 - Explicit accounting of human variability
 - Incorporation of interspecies (or other) uncertainties

Harmonization Project
Document No. 11



Slide adapted from Weihsueh Chiu July 2015 presentation

 SOT FDA Colloquia on Emerging Toxicological Science
Challenges in Food and Ingredient Safety

Harmonizing Dose-Response
Assessment for Cancer and Non-
Cancer Endpoints in Human Health
Assessments

Weihsueh. A. Chiu, PhD

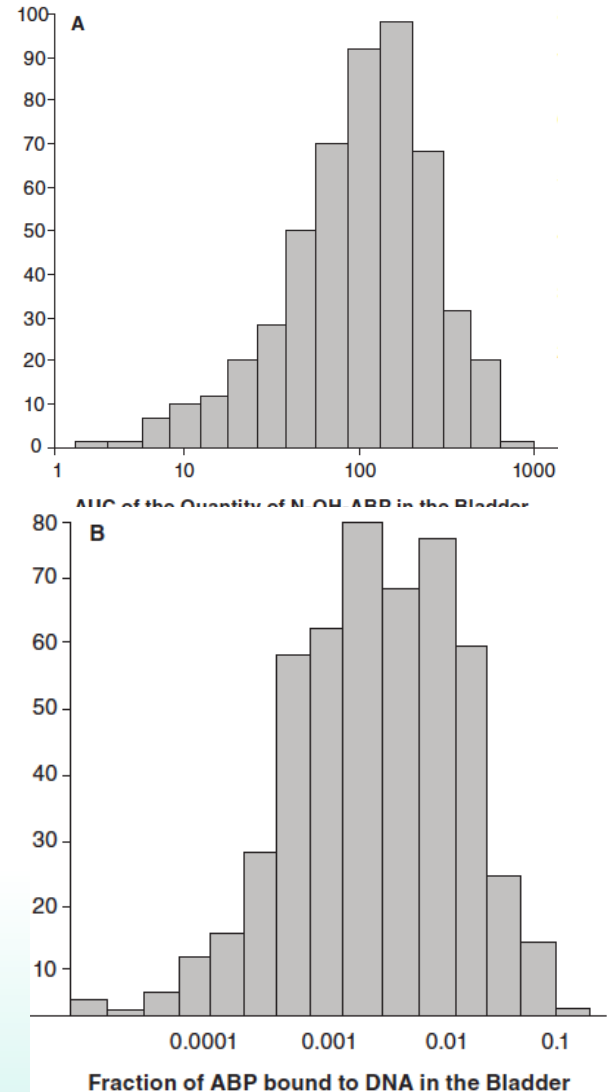
Example 3: Low-Dose Linear - 4-Aminobiphenyl

4-Aminobiphenyl

- Binds to bladder DNA, and is mutagenic in various test systems, including human cell culture
- Implicated as a cause of bladder cancer in smokers

Cancer response modeling coupled with physiologically based pharmacokinetic models

- Marked variation in activation and detoxification can be characterized
- Frequency of voiding by bladder and liquid consumption simulated



Concluding Remarks

- MOA data are a critical element in the NRC's 2009 vision for a unified approach to dose response analysis
 - For conceptual model selection
 - For specific approaches to dose response analysis
- More case examples of chemical-specific work explicitly accounting for background processes and human variability for in model selection would be helpful
- Progress has been made in the development of default approaches for establishing a probabilistic RfD

Zeise Jan 2016



Acknowledgements

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