The Role of Mode of Action in Dose-Response Assessments: Recommendations from 2009 NRC “Science and Decisions”

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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”

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NRC Committee
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
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

Source: IARC Globocan
Background: Immigration Changes in Cancer Incidence

Cumulative Risk by Age 75(%)
Background Context for Toxicological Data Interpretation

- Chemical Characterization
- Toxicity Testing
  - Toxicity Pathways
  - Targeted Testing
- Dose-response and Extrapolation Modeling

Risk Contexts

Population-based and Exposure Data
Multiple Exposures Leading to Common Adverse Outcomes

Phthalates

Antiandrogenic compounds and other risk factors

Disturbed Androgen Action

Altered male reproductive outcomes
Decreased AR activity at target tissue

Interference with androgen mediated development

Decreased Sperm quality

Leydig cell tumors

“Phthalate Syndrome”

Cryptorchism

Other reproductive tract malformations

AGD

Nipple Retention

Hypospadias

Decreased Testosterone

Decreased Dihydrotestosterone

Blockade of Androgen Receptor (AR)

Mutated Receptor

Other Stressors

Stressors

Testosterone

Dihydrotestosterone

Receptor (AR)

Receptor
Background: Implications for Dose-Response

Response

Dose

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Variability

the context for considering MOA
Sources of Differences in Response Among People

- Gender, Lifestage
- Food/nutrition
- Heredity
- Psychosocial stressors
- Existing Health Conditions
- Coexposure

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Consideration of Variability in the Context of the MOA

Figure Caption
“When perturbation 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

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

in vitro methods
In vivo methods
animals
human
Implications for Dose Response

- Population
- Subpopulations

Frequency

Increasing susceptibility →
NRC 2009 Dose-Response Framework

Integrates concepts of background, inter-individual variability and MOA
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
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

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## Examples of Conceptual Models

<table>
<thead>
<tr>
<th>Conceptual Models for Low-Dose-Response</th>
<th>Individual Dose-Response</th>
<th>Population Dose-Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. An individual’s: Linear</td>
<td>Probability of Effect</td>
<td>Fraction of Population Affected</td>
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<td>The population: Linear</td>
<td>Background dose Dose</td>
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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

Assemble Data

AssessEndpoints – Identify:
- Adverse effects
- Precursor and upstream indicators
- Gaps (e.g., unstudied lifestages, endpoints)

Assess MOA (each endpoint)
- Human and animal research
- Sufficiency of MOA evidence
- Endogenous contributors

Assess Vulnerable Population
- Individuals and groups
- MOA
- Background, other factors

Assess Background Exposures
- Endogenous and Exogenous
- Screening level assessment
- Focus on high end groups

Conceptual Model Selection
Develop or selection from
- Linear conceptual model unless linearity can be rejected
- Otherwise non-linear

Dose Response Method Selection
Develop dose response model and method based on:
- Conceptual model
- Data availability
- Risk management need for risk characterization form

Dose Response Modeling and Results Reporting

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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”

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

1: Determine adjustment needed to Animal POD

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

Slide adapted from Weihsueh Chiu July 2015 presentation
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
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