Ensuring Efficiency in Assessment to Meet Identified Needs

Problem Formulation/Issue Identification

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Outline

• The NAS Report
  – Science & Decisions: Advancing Risk Assessment

• Coordinating & Extending Specific Recommendations
  – Potential Contribution of Other Initiatives
    • National & International

• Dose Response tailored to Need
  – Problem Formulation/Dose Response Analysis
Science and Decisions: Advancing Risk Assessment

Final Report Released, 2008
NAS Committee: Advancing Risk Assessment - Background

• “Chemical Risk assessment at a crossroads”
• Facing substantial challenges, e.g.,
  – long delays in completing complex risk assessments, some of which take decades
  – lack of data
  – the need to address the many unevaluated chemicals in the marketplace
• Recommendations for practical improvements to the U.S. Environmental Protection Agency (EPA)
  – Shorter (2-5 y) and
  – longer (10-20 y) term
NAS Committee: Advancing Risk Assessment

- **Design of risk assessment**
  - implementing scoping and problem formulation
- **Uncertainty and variability**
- **Selection and use of defaults**
- **A unified default approach to dose-response**
- **Combined Exposures risk assessment**
- **Improving the utility of risk assessment**
- **Stakeholder involvement**
- **Capacity building**
NAS Committee: Advancing Risk Assessment

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FIGURE S-1 A framework for risk-based decision-making that maximizes the utility of risk assessment.
Phase I

Problem Formulation

• Begins with a “signal” of potential harm
  – Positive bioassay or epidemiological study; industrial contamination

• What options are there to reduce the hazards or exposures?

• How can risk assessment be used to evaluate the merits of the various options?

*Purpose oriented risk assessment*
Phase II
Planning, Risk Assessment & Confirmation of Utility

- **Level & complexity consistent with the goals of decision-making**
  - Including uncertainty & variability analysis

- Assessment

- Meet the need, discriminate among options, adequate process?

  “Fit for Purpose” Risk Assessment
Phase III

Risk Management

• Based on consideration of a broader range of options and array of impacts, beyond individual effects to include individual health status and ecosystem protection

The entire process to protect against political interference, engage stakeholders and meet time constraints

(Details to follow)
NAS Committee: Advancing Risk Assessment

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Unified Approach to Default Dose Response Assessment

• “A consistent approach to risk assessment for cancer and non-cancer effects is scientifically feasible and needs to be implemented”

• “Because the RfD and RfC do not quantify risks for different magnitudes of exposure…their use in risk-risk and risk-benefit comparisons and risk management decision-making is limited”
  – This seemed to prevail over discussions related to modes of action, background exposures & susceptibility
Though it was additionally recommended that:

- EPA implement a phased-in approach to consider chemicals under a unified dose-response assessment framework that includes a systematic evaluation of background exposures and disease processes, possible vulnerable populations, and modes of action that may affect human dose-response relationships.

\[= \text{mode of action}\]
Assemble Health Effects Data

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

**MOA Assessment (for each endpoint of concern)**
- Research MOAs for endpoints 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 endpoints, 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 non-linear 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**

Figure 5.8 New unified process for selecting approach and methods for dose-response assessment for cancer and noncancer.
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Selection and Use of Defaults

• “EPA should develop clear, general standards for the level of evidence needed to justify the use of agent-specific data and not resort to default”

• This is helpful to increase transparency as a basis to separate science judgment from science policy

• However:

• It rather sets up “default” as representing something other than:
  – what we use when we don’t have predictive data about how chemicals induce their effects
  – Recognizing that the scientific basis of defaults is nebulous, at best
Reconciling Recommendations on Problem Formulation & Dose-Response

• The need for more efficient assessment as a basis to address the many unevaluated chemicals in the marketplace identified by the Committee as one of the more significant challenges requires:
  – Moving to more predictive, mode of action based approaches
    • Systems biology approaches considering toxicity as a function of a cascade of failures of control mechanisms
      – Toxicity testing in the 21st Century
  – Tailoring of dose-response analysis to meet the objectives of specific assessments, based on problem formulation
    • Necessitates a range of available options, depending on needs of risk managers & nature of assessment
Traditional (Default)

- Curve fitting at high dose for point of departure for late (apical) endpoints
- Linear extrapolation or N/LO(A)EL or BMC/D UF
- Interspecies differences/human variability (x10)

Biologically (MoA) Based

- Earlier endpoints in the most relevant species, considering kinetic and dynamic data, to address extrapolations

Graphs showing data for Carcinogenicity, Cell Proliferation, and DNA Adducts for Rat and Mouse.
U.S. NRC Toxicity Testing in the 21st Century

Dose Response Assessment

Chemical Characterization

Mode of Action

Compounds

Assess Biological Perturbation

Metabolite(s)

Affected Pathway

Dose Response Analysis for Perturbations of Toxicity Pathways

Measures of dose in vitro

Population Based Studies

Calibrating in vitro and human Dosimetry

Dose Response

Population Based Studies

Calibrating in vitro and human Dosimetry

Exposure Guideline

Human Exposure Data

Exposure Assessment

Risk Characterization
Relevant Initiatives

- **Existing Substances Program under Canadian Environmental Protection Act (CEPA)**

- Mode of Action/Predictive Tools
  - WHO/IPCS in collaboration with ILSI/OECD/others

- **ILSI/Health Canada initiative on Problem Formulation/Issue Identification (2007)**

- **IPCS Combined Exposures Framework**
  - In collaboration with OECD/others

- **IPCS Tiered Uncertainty Analysis (2007)**
CATEGORIZATION of the Domestic Substances List (DSL) (First Phase) (n=23,000)

Decisions of Other Jurisdictions

Public Nominations

Greatest Potential for Human Exposure
Substances that are Persistent or Bioaccumulative

“Inherently Toxic” to Humans
“Inherently Toxic” to non-Human Organisms

SCREENING ASSESSMENT (Second Phase)

No further action under this program
CEPA-Toxic

Risk Management

IN-DEPTH ASSESSMENT - Priority Substances List (Third Phase)

No further action under this program
CEPA-Toxic

Risk Management

CEPA 1999 Existing Substances Program

INCREASING REFINEMENT OF PRIORITIES + COMPLEXITY OF ASSESSMENT

DECREASING NUMBERS OF SUBSTANCES

DECREASING UNCERTAINTY
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The Role of Formal Issue Identification
More than a Statement of the Issue; A Process

• **Early Consideration** of All Relevant (assimilated) information/expertise
  – Relying as much as possible on existing assessments, “peers”
• Determining **need for risk assessment** based on consideration of factors such as nature and feasibility of risk management
• Determining **focus and scope** of risk assessment, based on potential options for management
• Ensuring that any assessment **meets the considered need**
• **Communication** and formal engagement
  – Stakeholders/risk managers/public
**Problem Formulation - Process**

1. **First Questions**
   1. What is the problem?
   2. What factors need to be considered?
   3. What is the role of risk assessment in decision making?

2. **Establish the Focus and Scope of the Risk Assessment**
   - Is the preliminary focus acceptable?
     - Yes
     - No

3. **Develop Risk Assessment Procedures**

4. **Risk Management**
   - Has the problem been addressed?
     - Yes
     - No

5. **Perform Risk Assessment**
   - Develop Risk Characterization Approach and Tools

6. **Dialogue/Engagement with Risk Assessors/Risk Managers/Advisors/Peers**

7. **Implement Risk Management Decisions**

8. **Make decision another way**
   - Seek stakeholder and peer input

9. **Peer Review**

10. **Iterate**

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*Risk Assessors/Risk Managers/Advisors/Peers*
Establish the Focus and Scope of the Risk Assessment

Management **Constraints**
- Regulatory considerations
- Objectives
  - Screening or full
  - Broad or narrow
- Time and resources
- Socio-economic considerations
- Political considerations

Characterization of Assessment
- *Assimilate universe* of known data
- *Consider relevant exposure* scenarios
- Determine degree of acceptable **uncertainty**
- Plan for addressing uncertainty
- Develop *communications* plan
- Development of preliminary hypotheses

Develop Approach
- Is the preliminary approach acceptable?
  - No
  - Seek stakeholder and peer input
  - Proceed with Risk Assessment
  - Yes

Forms of Assessment
- Examples
  - Semi-Quantitative/Quantitative
  - Deterministic/Probabilistic
  - PB/PK
  - MOA

Seek stakeholder and peer input
Relevant Initiatives

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**Problem Formulation**

Nature of exposure?
Is exposure likely?
Co-exposure within a relevant timeframe?
Rationale for considering compounds in an assessment group?

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**Tiered Exposure Assessments**

- **Tier 0**
  - Simple semi-quantitative estimates of exposure
- **Tier 1**
  - Generic exposure scenarios using conservative point estimates
- **Tier 2**
  - Refined exposure assessment, increased use of actual measured data
- **Tier 3**
  - Probabilistic exposure estimates

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**Assessment**

Yes, no further action required

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**Is the margin of exposure adequate?**

No, continue with iterative refinement as needed (i.e. more complex exposure & hazard models)

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**Tiered Hazard Assessments**

- **Tier 0**
  - Default dose addition for all components
- **Tier 1**
  - Refined potency based on individual POD, refinement of POD
- **Tier 2**
  - More refined potency (RFP) and grouping based on MOA
- **Tier 3**
  - PBPK or BBDK; probabilistic estimates of risk

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Nature of exposure?
Is exposure likely?
Co-exposure within a relevant timeframe?
Rationale for considering compounds in an assessment group?
Outstanding Areas for Consideration/Questions

- More robust integration of mode of action
- Importance of and approach for tiered, efficient assessment strategies
- Focus of the NAS panel deliberations?
More Information?

WHO/IPCS Harmonization Initiative

• [http://www.who.int/ipcs/methods/harmonization/index.html](http://www.who.int/ipcs/methods/harmonization/index.html)

Categorization/Screening under CEPA


• Hughes et al., *Reg. Toxicol. Pharm. 55:382-393, 2009*

• Existing Substances Division Website – [http://www.hc-sc.gc.ca/exsd-dse](http://www.hc-sc.gc.ca/exsd-dse)