Evolution of the ARA Framework on Problem Formulation to Dose-Response

Presented by:

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Alliance for Risk Assessment

www.allianceforrisk.org

- Organizations collaborating to address public health issues
  - Includes representatives of academic, federal & state Governments, NGOs & NPOs, to:
    - Improve communication among groups
    - Foster harmonization and consistency in risk assessments
    - Share costs and human resources

Objectives – ARA Project
Problem Formulation to Dose Response (2010 to present)

- ***Coordinating & Extending s***pecific recommendations in the NAS Report on Science & Decisions: Advancing Risk Assessment (2009)
- ***Sharing and additionally evolving*** "fit for purpose" risk assessment tools
  - Considering a broad range of (internationally available) tools & their potential evolution to address critical areas identified in the report
- ***Considering Dose Response tailored to Need***
  - Appropriate consideration of Mode Of Action (MOA) and Value of Information
  - Evolving consideration of human variability & biologically based methodology for determining probability of response
  - Tiered, "Purpose Oriented" Assessment, in appropriate context
    - Through consideration of case studies

Roles/Responsibilities

- ***The Alliance for Risk Assessment Steering Committee (ARA SC)***
  - representatives from state, tribal, and federal government, academia, and environmental NGOs
  - selected members of the Expert Panel after a review of publically solicited nominations
- ***Dose Response Advisory Committee (DRAC)***
  - sponsors including state, federal, industry, and NGO representatives
  - Developed workshop structure & charge questions, presenters, consulting with ARA Steering Committee
- ***Science Panel***
  - input on the utility of the case study methods to address specific problem formulations, and identify areas for additional development

Process/Output - Workshops

March 2010

Pre workshop: Broad solicitation and brainstorming regarding illustrative case studies

Initial vetting and review of proposals for case studies

October 2010

- Review of case studies
- Recommendation for draft methods framework for "fit for purpose" dose-response analysis, reflecting:
  - different conceptual models, data availability & risk management needs

May 2011, May & October, 2012

- Additional case studies and identified issues :
  - Problem formulation, Mode of action, Endogenous & background exposures, counterfactual evidence in MOA analysis, tiered interpretation of biomonitoring data

Process/Output/Learnings

Recommendations:

- Identified need to dissemination dose-response analysis techniques for a wide range of problem formulations or decision contexts
- Development of templates for transparency in selecting dose-response approaches, relevant to use in specified risk management
- Additional case studies on:
  - combined exposures,
  - value of information
  - *in vitro to in vivo* extrapolation
  - an entire purpose driven risk assessment, from problem formulation to conclusion

Process/Output *(Cont'd)*

Ongoing:

- manuscript submitted
- Framework to be ***"evergreen"*** with a Standing Panel to review case studies/issue papers
- Considering best framing/access to framework & case studies
  - As a basis to facilitate use
- Continuing evolution of tiered approaches

Learnings:

- Need to have assessors considering context to address appropriate focus & complexity (problem formulation for assessment)

Evolving Framework & 27 case studies

Engagement Model

"Fit for Purpose"

PHASE I: PROBLEM FORMULATION AND SCOPING

PHASE II: PLANNING AND CONDUCT OF RISK ASSESSMENT

PHASE III: RISK MANAGEMENT

Stage1: Planning
Risk attributes, uncertainty and variability

-Benefits
-Influence to other
-Uncertainties
-Decision communication
-Implementation methodologies

-Problems on existing environment
-Possible alternatives
-Issues for possible risk management measures

Stage 2: Risk assessment

Hazard identification
Dose response
Assessment

Risk characterization

Exposure Assessment

Broader range of options and array of impacts Individual, population

Purpose oriented

NO

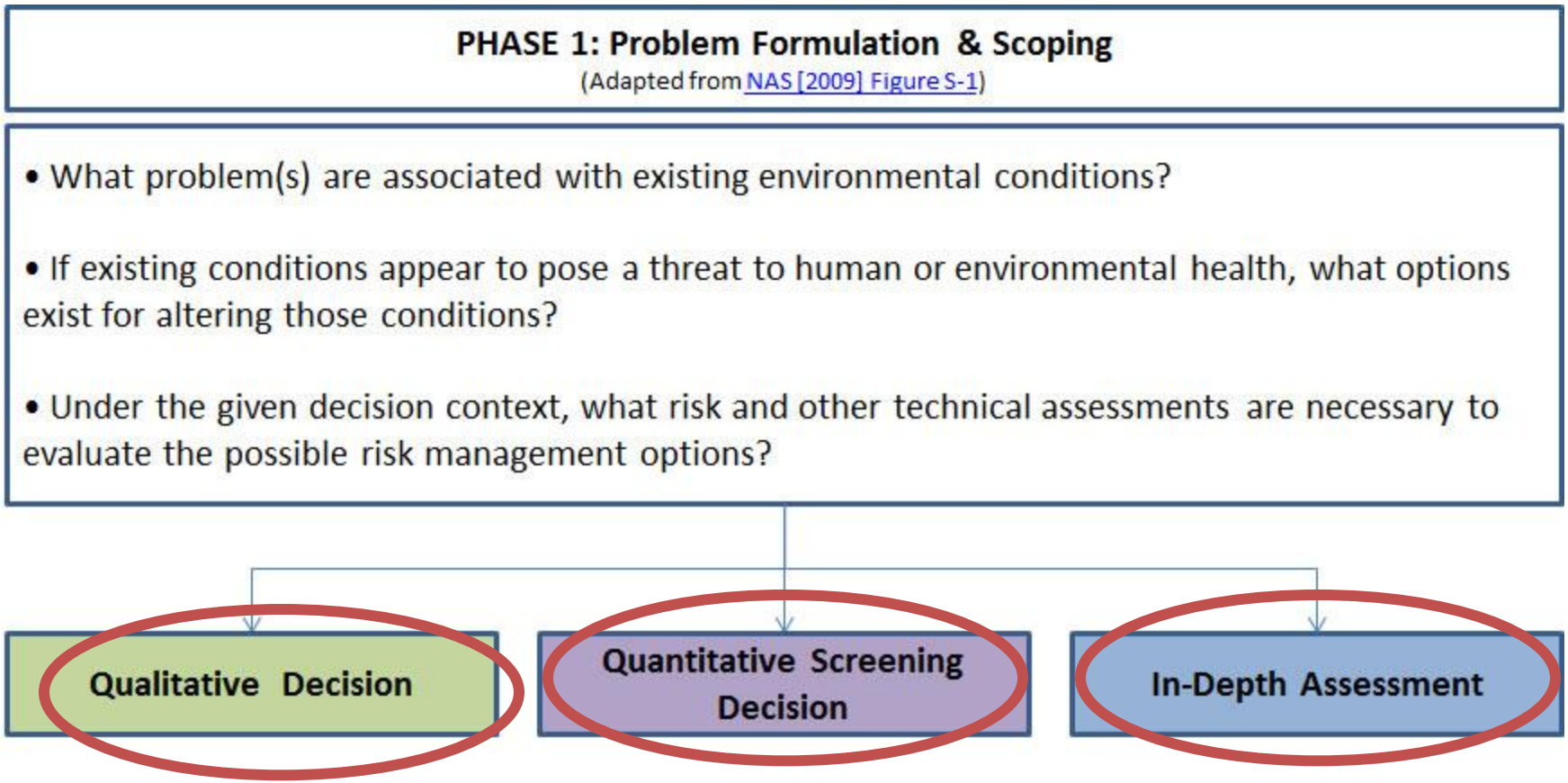
Stage 3: Confirmation of utility
-Planning
Sufficient information
-Review

YES

Formal provisions for internal and external stakeholder involvement at all stages
- Decision-makers, technical specialists, and other stakeholders

Figure S-1 A framework for risk based decision making that maximizes the utility of risk assessment

Organizational Framework



Unified Approach to "Default" Dose Response Assessment; Use of "Defaults"

- "A consistent approach to risk assessment for cancer and non-cancer effects is scientifically feasible and needs to be implemented"
  - Predicated principally on the basis of perceived need to quantify risks for risk-risk and risk-benefit comparisons

- "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"

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

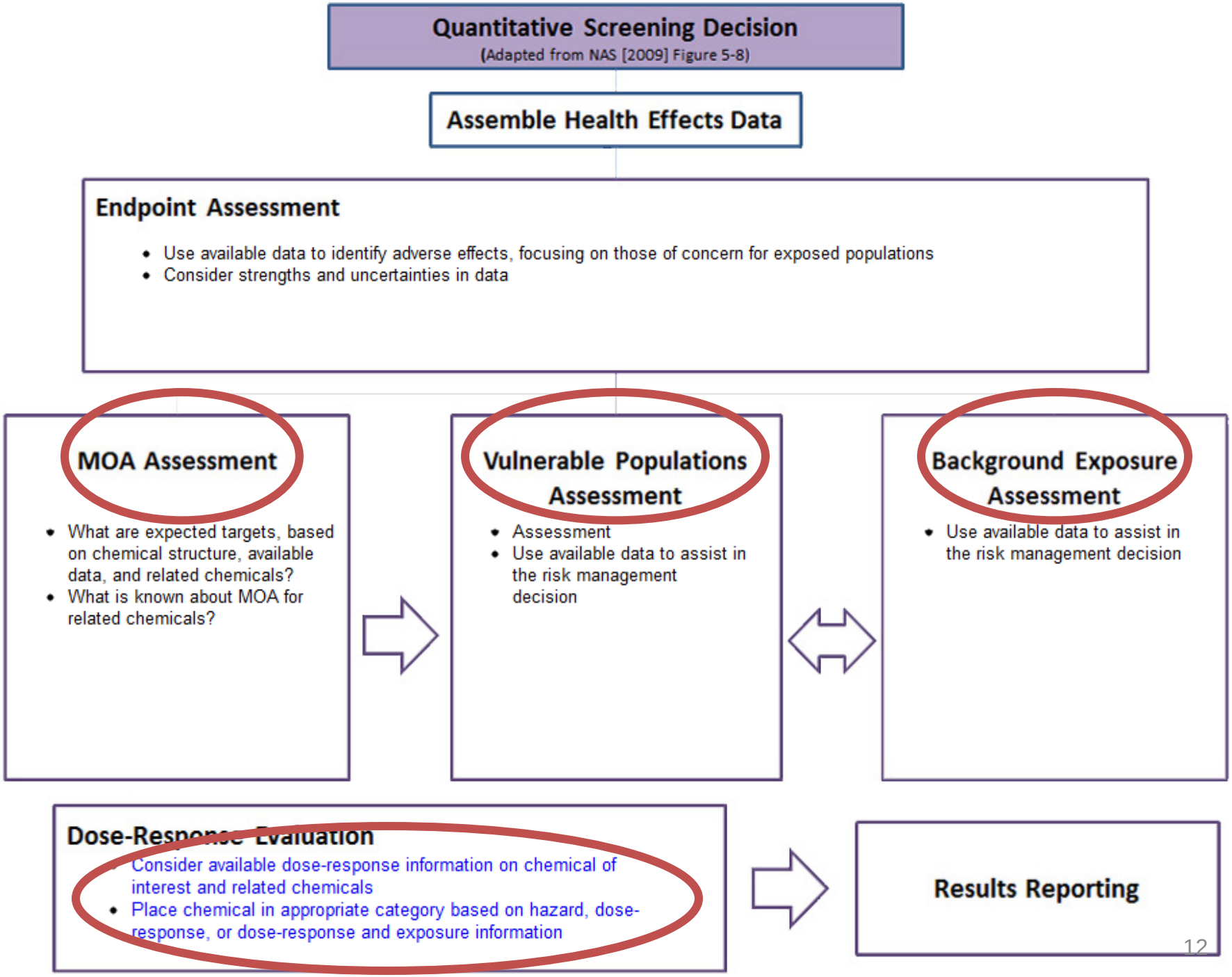
Dose Response Method Selection

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 .


Quantitative Screening Decision
(Adapted from NAS [2009] Figure 5-8)
Assemble Health Effects Data
Endpoint Assessment
Use available data to identify adverse effects, focusing on those of concern for exposed populations
Consider strengths and uncertainties in data
MOA Assessment
What are expected targets, based on chemical structure, available data, and related chemicals?
What is known about MOA for related chemicals?
Vulnerable Populations Assessment
Assessment
Use available data to assist in the risk management decision
Background Exposure Assessment
Use available data to assist in the risk management decision
Dose-Response Evaluation
Consider available dose-response information on chemical of interest and related chemicals
Place chemical in appropriate category based on hazard, dose-response, or dose-response and exposure information
Results Reporting

DOSE-RESPONSE EVALUATION

Note: In general, the methods used here apply substantially health-protective assumptions to avoid type II errors*

Method Case Studies

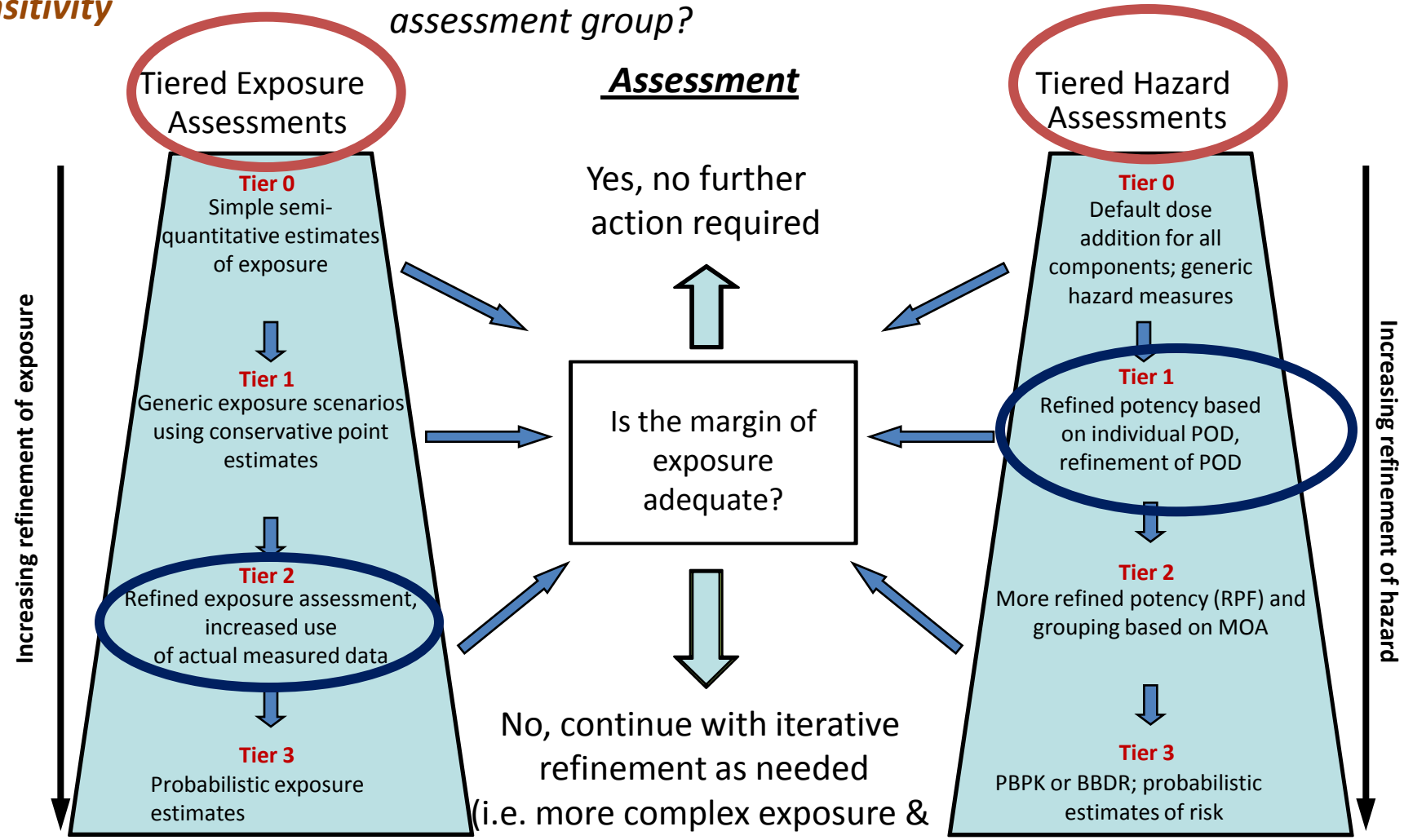
- Tiered Approach Case Study (includes threshold of concern approach)
- Low Dose Extrapolation from the BMD(L)
- Threshold of Toxicological Concern
  - **Deriving Health-Protective Values for Evaluation of Acute Inhalation Exposures for Chemicals with Limited Toxicity Data Using a Tiered Screening Approach**
    Grant R.L., Phillips T., Ethridge S.
    - Summary
    - Case Study
    - Presentation Slides
- Threshold of [illegible]
- Class Based Exposure Level – (CBEL)
- Screening-level safe dose
- Structure-activity relationship (SAR) and read-across
- Provisionally Peer Reviewed Toxicity Values (PPRTV)
- Quantitative SAR

Problem Formulation for Grouping

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

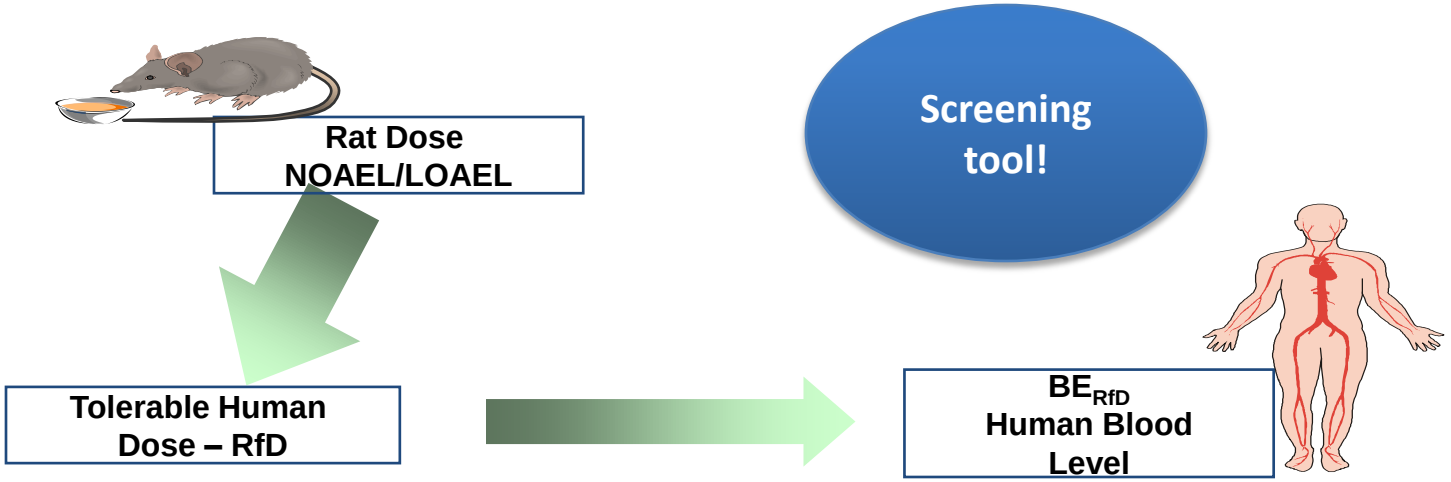
Uncertainty

Sensitivity



Case Study – Combined Exposures Screening Assessment for Noncancer Effects of THMs using Biomonitoring Data (Aylward et al.)

- Use of internal dose measures for both:
  - Exposure metrics – NHANES blood THM data
  - Dose-response – Biomonitoring Equivalents (BEs)



- Several approaches:
  - Hazard quotient/Hazard index
  - Low dose risk extrapolation (2 approaches)

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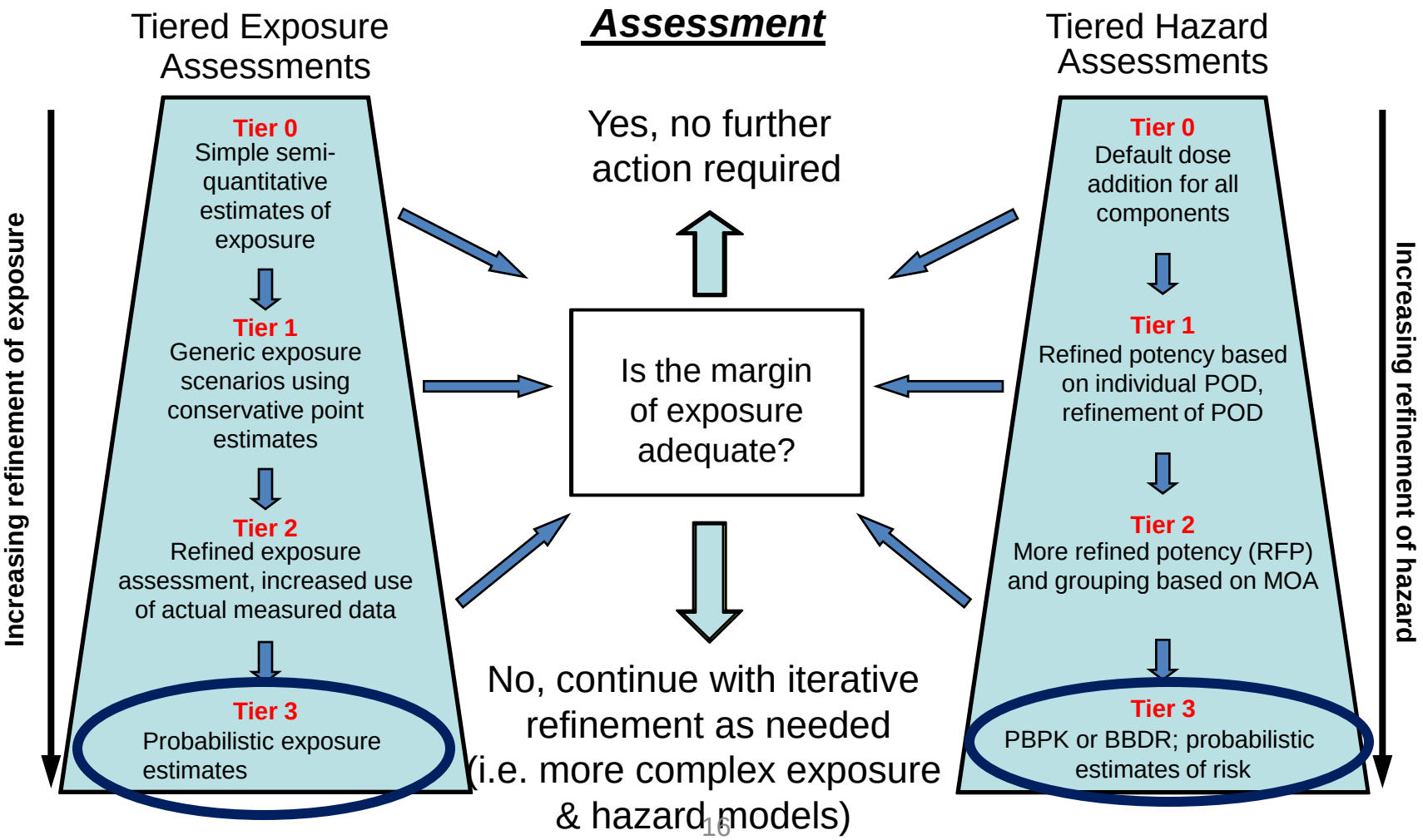


Application of a Source-to-Outcome Model to Quantitatively Assess Variability in Dose and Sensitivity in Humans (Chlorpyrifos; Price et al.)

- Tier 3 analysis (probabilistic exposure estimates, PBPK & reliance on MOA-related precursor)
  - reserved for cases where there is a small margin between exposure and effect; combined effects
- Relevant to substances that act by a similar mode of action (i.e., AChE inhibition)
- Addresses more generic issues raised by the NAS committee

Relevance to Advancements in Risk Assessment

MOA Based:

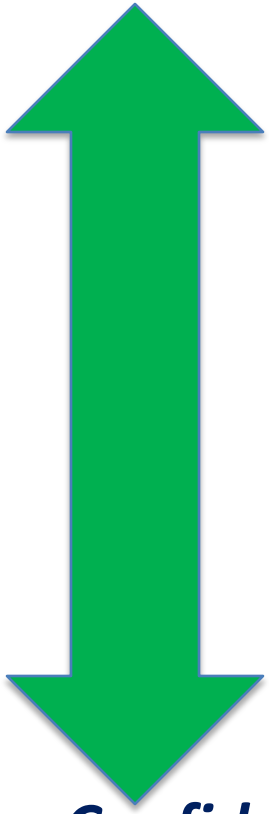
- Assessed variability in both
  - exposure (variation of residue levels across foods and variation in individual's dietary consumptions) and
  - response (variation in physiology and metabolism)
- Evaluated response to the range of actual human exposures
- Assessed human sensitivity in multiple age groups (infants, children, adults)
- Modeling was made more predictive by focusing on early "key event" - namely cholinesterase inhibition (ChEI)

Some Recent Case Studies

- Grant et al. – risk communication re inhalation effect levels
- Bogert et al. – “counterfactual” evidence in mode of action analysis
- Becker et al. – tiered approach to development of Biomonitoring Equivalents
- Gentry et al. – consideration of endogenous exposure in the BBDR for formaldehyde

Tiered Development of Guidance Values for Biomonitoring Data

Higher Confidence



Lower Confidence

- Classical BE
- Sufficient Tox Data
- Chem-Specific PK Data /Models Lacking
- Chem-Specific Tox and PK Data /Models Lacking But Robust Category / Class Data
- Threshold of Toxicological Concern (TTC)

Forward Looking Assessment

- Public problem formulation with proposal for “fit for purpose” assessment
  - Assimilated Overview of Data
  - Proposed Focus
  - Efficiency
  - Proposed Process
- Tiered assessment options drawing on predictive tools in early tiers
  - Importance of mechanistic underpinning
- What’s the engagement strategy?

55+ sponsors and collaborators:

- 12 government agencies
- 19 industry groups
- 7 scientific societies
- 9 non-profit orgs/consortia
- 8 consulting groups

ARA Steering Committee

- **Annette Dietz**, Oregon Department of Environmental Quality
- **William Hayes**, State of Indiana
- **Bette Meek**, University of Ottawa
- **Anita Meyer**, United States Army Corps of Engineers
- **Edward Ohanian**, U. S. Federal Government
- **Ralph Perona**, Neptune & Company, Inc.
- **Phil Wexler**, National Library of Medicine

-----recused-----

- **Michael Dourson**, Toxicology Excellence for Risk Assessment
- **Michael Honeycutt**, Texas Commission on Environmental Quality

Dose-Response Advisory Committee

- **Rick Becker**, ACC
- **Tiffany Bredfeldt**, TCEQ
- **Michael Dourson**, TERA
- **Julie Fitzpatrick,** EPA
- **Roberta Grant**, TCEQ
- **Lynne Haber**, TERA
- **Lynn H. Pottenger**, Dow Chemical
- **Jennifer Seed**, EPA

Expert Panel

- **Richard Beauchamp,** Texas Dept State Health Services
- **James S. Bus**, Dow Chemical
- **Rory Conolly**, U.S. EPA, NHEERL
- **Michael Dourson**, TERA
- **R. Jeffrey Lewis**, ExxonMobil Biomedical Sciences, Inc.
- **Bette Meek**, U of Ottawa (Chairperson)
- ***Greg Paoli**, Risk Sciences International
- **Rita Schoeny**, U.S. EPA (Co-chairperson)
- **Alan Stern,** New Jersey Dept of Environmental Protection

- *Ad hoc Workshop IV Panel member:* **Lorenz Rhomberg,** Gradient

*On NAS Science and Decisions panel

More Information?

ARA Dose Response Framework – (working beta)

http://www.allianceforrisk.org/workshop/framework/problemformulation.html

Evolution of the ILSI/IPCS Frameworks – Mode of Action

- Meek & Klaunig (2010) Chemico-Biological Interactions 184:279–285
- Carmichael et al. (2011) Crit Rev Toxicol. 41(3):175-86

Combined Exposures

- Meek et al. (2011) Reg Tox Pharm 60: S1-S14