Where the rubber meets the road: A practical methods compendium for risk assessors

Lynne Haber, Oliver Kroner
Toxicology Excellence for Risk Assessment

Beyond Science and Decisions: From Problem Formulation to Dose-Response

Alliance for Risk Assessment

www.allianceforrisk.org

- A collaboration of organizations dedicated working together to solve public health issues
  - Improve communication among groups
  - Provide transparency in development of products
  - Foster harmonization and consistency in risk assessments
  - Share costs and human resources

Expert Panel

- **Michael Bolger**, U.S. Food and Drug Administration
- **James S. Bus**, The Dow Chemical Company
- **John Christopher**, CH2M/Hill
- **Rory Conolly**, U.S. Environmental Protection Agency
- **Michael Dourson**, Toxicology Excellence for Risk Assessment
- ***Adam M. Finkel**, UMDNJ School of Public Health
- **William Hayes**, Indiana Department of Environmental Management (Workshop II only)
- **R. Jeffrey Lewis**, ExxonMobil Biomedical Sciences, Inc.
- **Randy Manning**, Georgia Department of Natural Resources (Workshop III only)
- **Bette Meek**, University of Ottawa (Chairperson)
- **Paul Moyer,** Minnesota Department of Health (MDH) (Workshop II only)
- ***Greg Paoli**, Risk Sciences International
- **Rita Schoeny**, U.S. Environmental Protection Agency

- *On NAS Science and Decisions panel

Collaborators

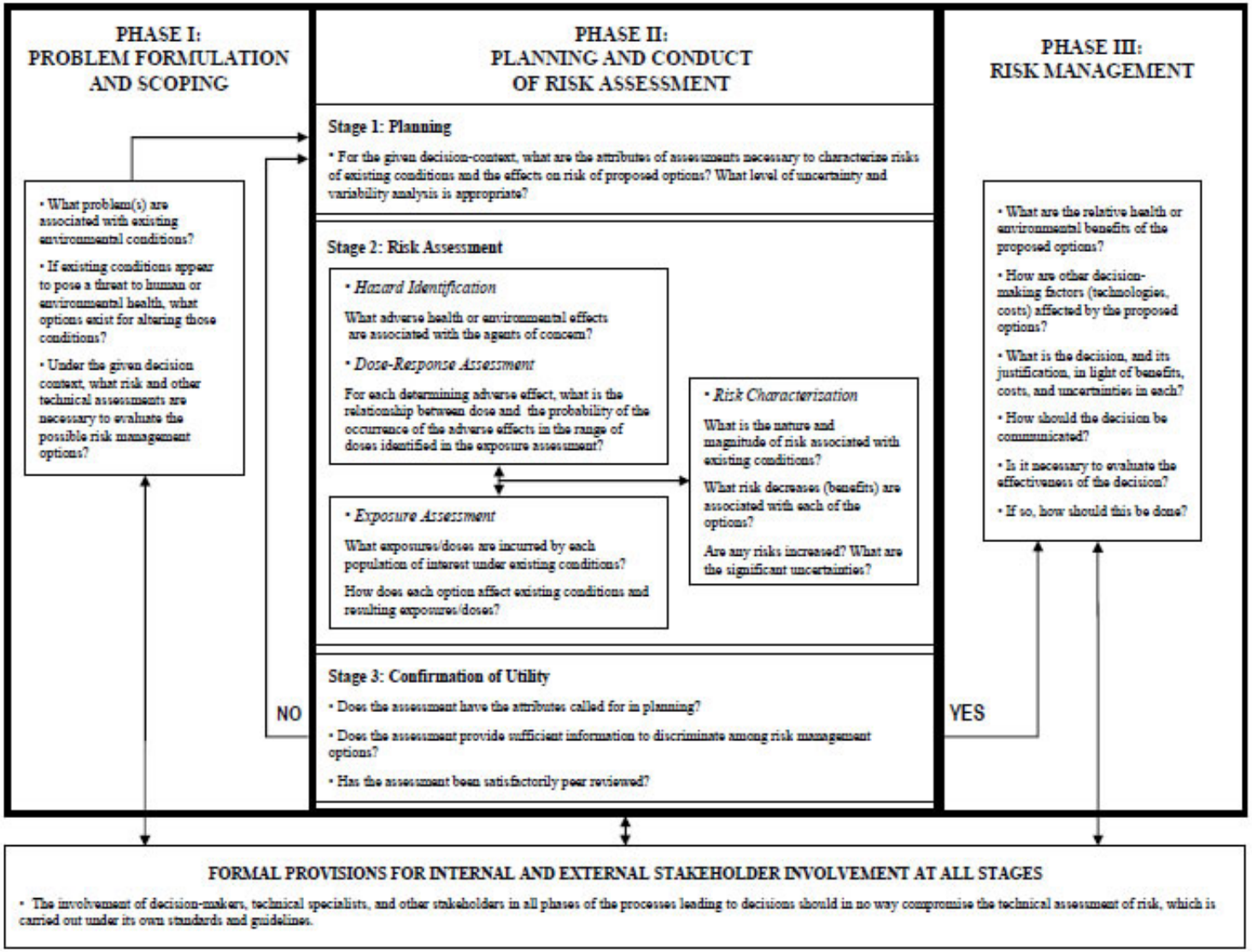
Case Study Process

- Process encouraged engagement from wide variety of stakeholders
- Proposed in brainstorming prior to first workshop
- Initial vetting and review in breakout groups at first workshop
- Presentations at second workshop
- Additional case studies and issues identified at second workshop
- 30+ case studies proposed
- 24 case studies presented and reviewed by panel

Case Study Process & Dose-Response Framework

- Need for systematic organization of methods and ability to identify gaps
- Need for framework as a resource for risk assessors
- An interactive tool – draft framework - was developed by panel members and interested workshop participants to aid in selecting dose-response methods based on:
  - Problem formulation; data availability; regulatory context
- The framework was used by the panel to prioritize new case studies for third workshop, focusing on 3 topic areas:
  - Problem formulation
  - Mode of action
  - Endogenous & background exposures

Figure S-1 from NAS (2009) *Science and Decisions: Advancing Risk Assessment*.



Dose-Response Framework

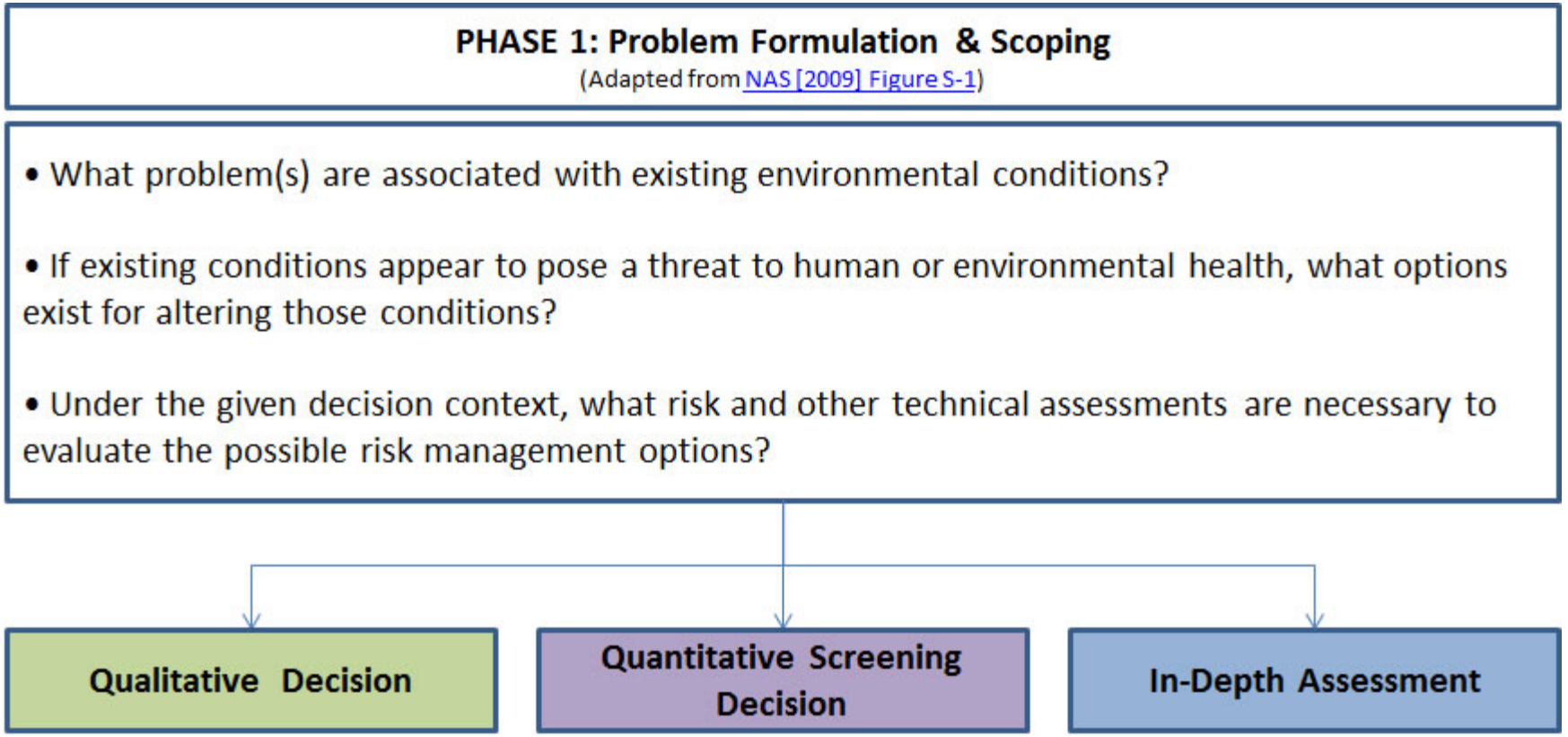
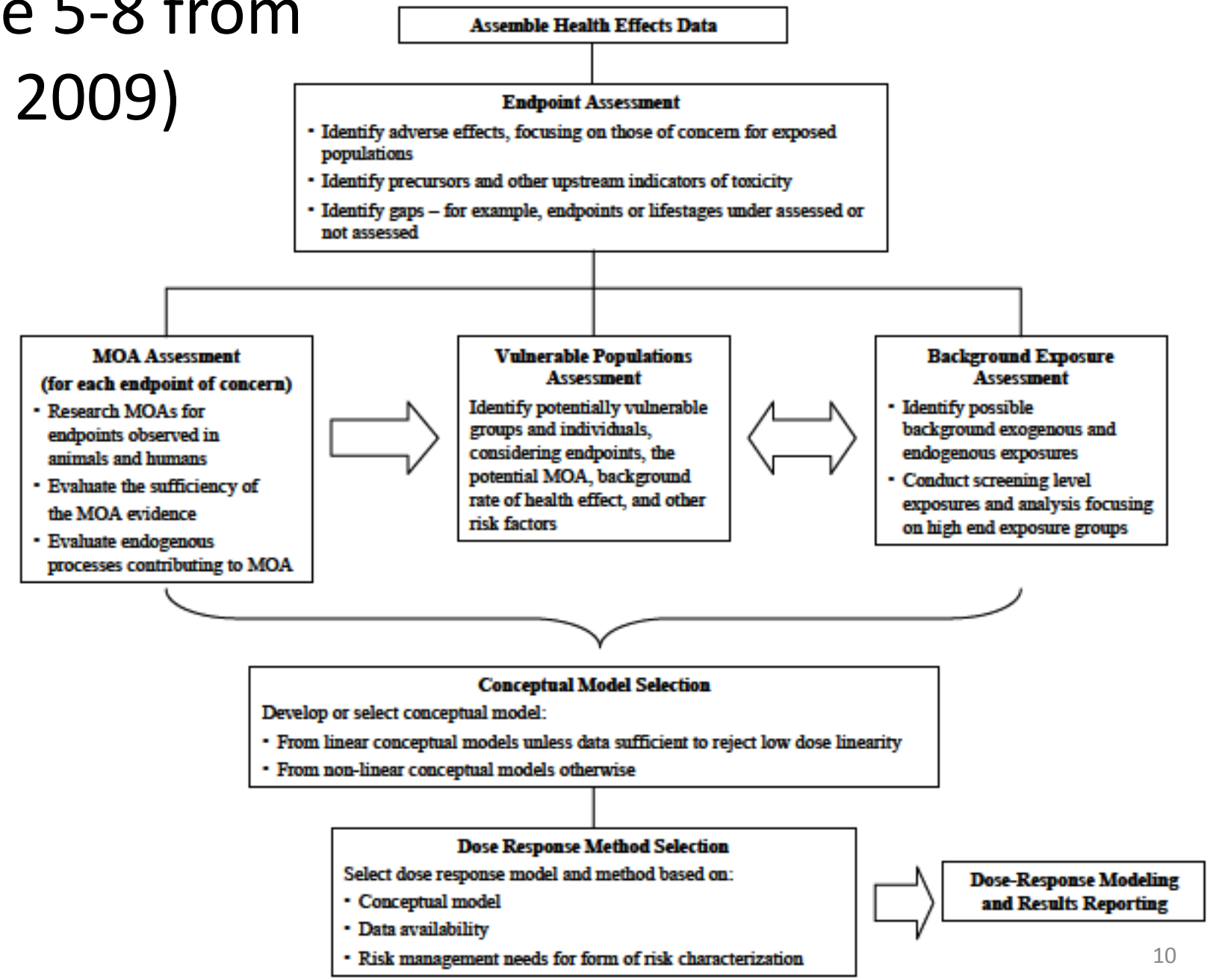
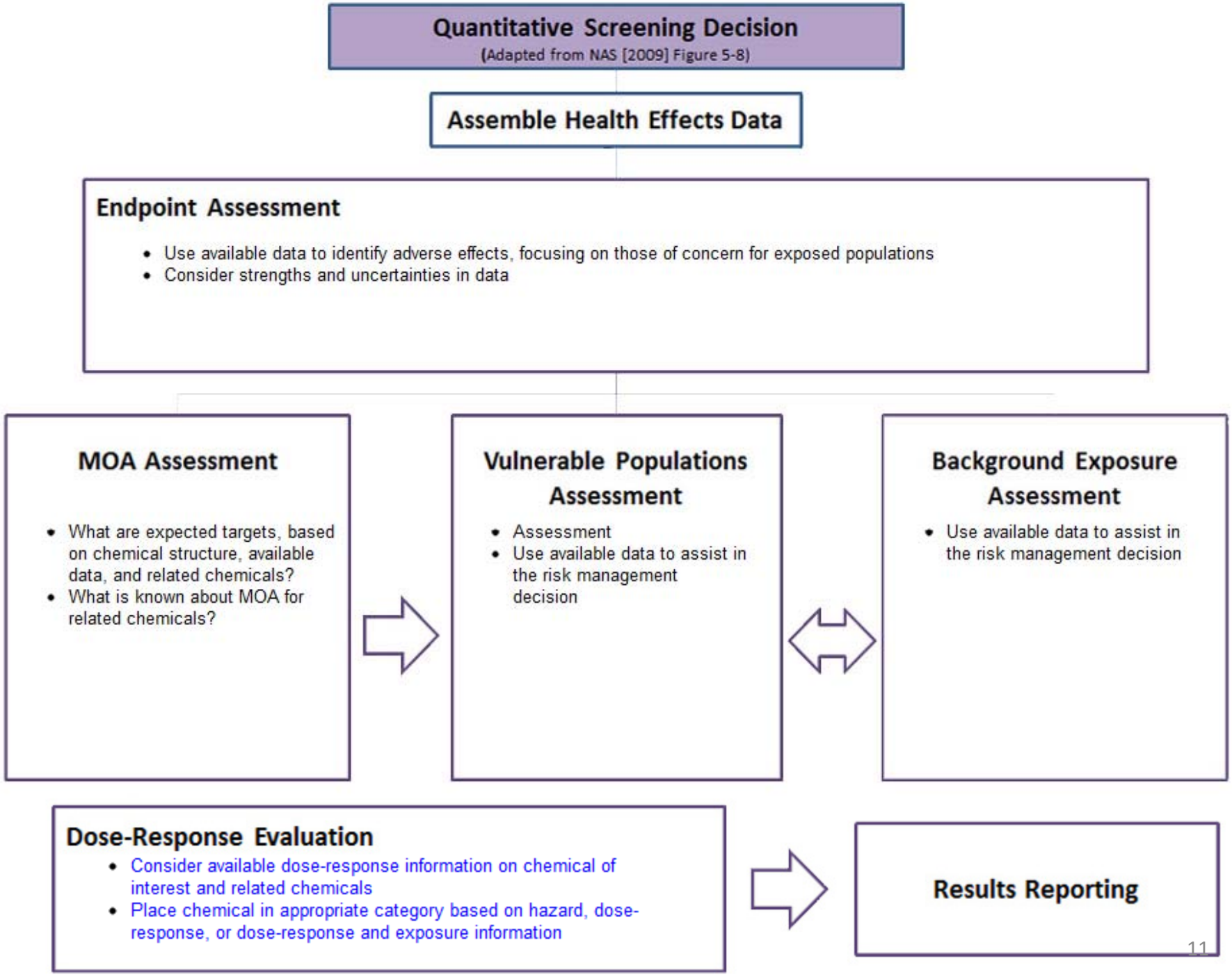


Figure 5-8 from (NAS 2009)




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 Framework

The risk assessor is guided to methods that address key issues, such as:

- Mode of action assessment
- Vulnerable population assessment
- Endogenous/background exposure
- Dose-response methods reflecting different
  - Conceptual models
  - Data availability
  - Risk management needs

Methods Presentation

Methods linked to case studies to illustrate real-world application

- Summaries that briefly describe method, provide key references, outline the minimum data requirements, describe strengths and weaknesses
  - Summary addresses the method's potential to address human variability, sensitive populations, and background exposures or responses.
- In depth full case study
- Workshop presentation slides

Quantitative Screening Methods

- Tiered approach case study (includes threshold of concern approach)
- Low-dose Extrapolation from BMD(L)
- Threshold of toxicological concern
- Threshold of regulation
- Screening-level safe dose
- Structure-activity relationships and read-across
- Quantitative SAR

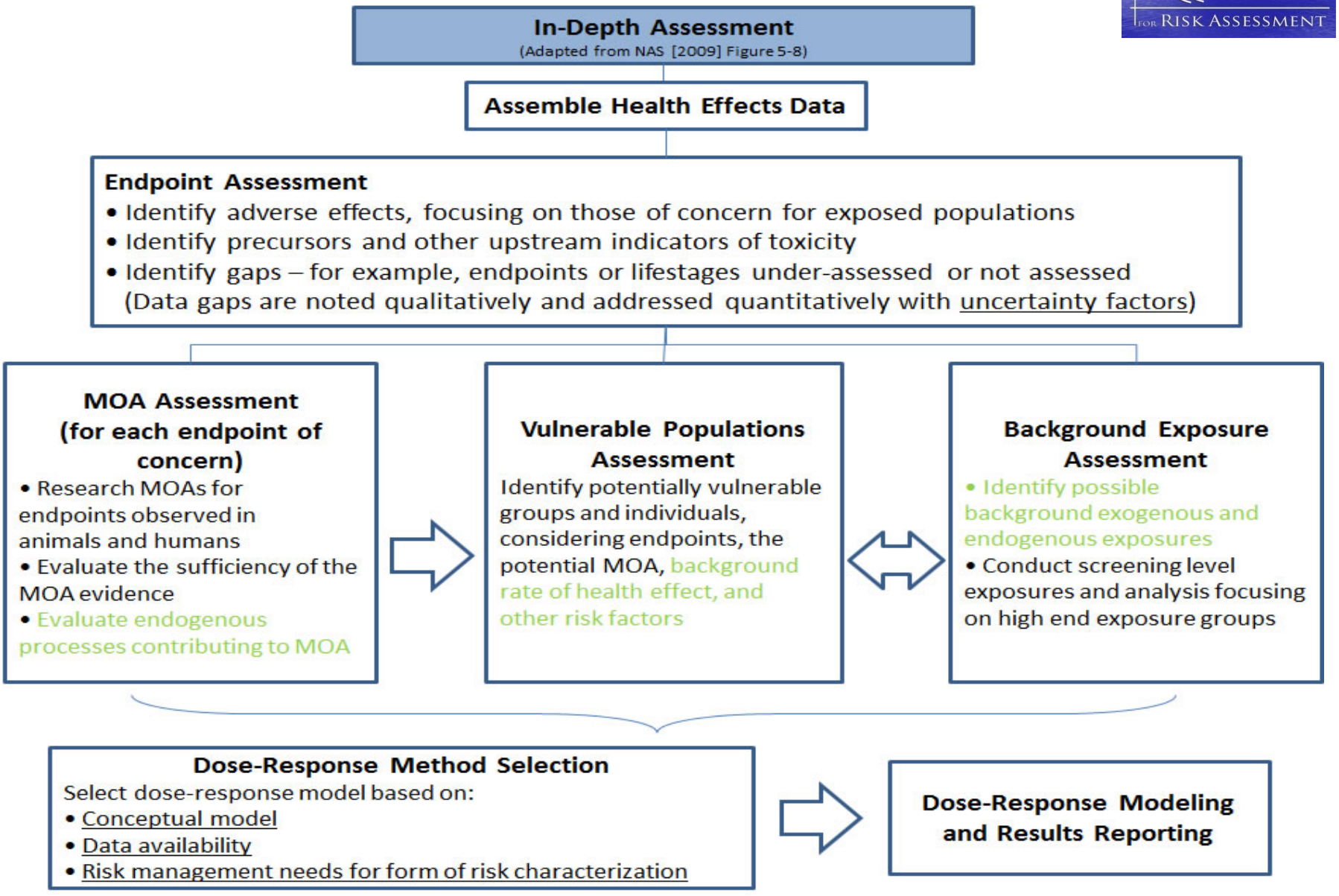
DOSE-RESPONSE EVALUATION

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 regulation
- ⊞ Class Based Exposure Level – (CBEL)
- ⊞ Screening-level safe dose
- ⊞ Structure-activity relationship (SAR) and read-across
- ⊞ Provisionally Peer Reviewed Toxicity Values (PPRTV)
- ⊞ Quantitative SAR

In-Depth Dose-Response Assessment



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

Method Case Studies

Sufficiency of MOA evidence/research MOAs - MOA/HRF/KEDRF Butadiene

- Butadiene Ovarian Case Study
- Butadiene Cancer Case Study
- Ethanol Case Study
- Low-Dose Evaluation for Genotoxicity
  - **Assessment of Low-Dose Dose-Response Relationships (Non-linear or Linear) for Genotoxicity, Focused on Induction of Mutations & Clastogenic Effects**
    Moore M., Pottenger L., Zeiger E., and Zhou T.
    - Case Study Summary
    - Addendum
    - Presentation
- Dioxin Case Study (Key Events Dose Response Framework)

Endogenous Processes Contributing to MOA

- Butadiene Ovarian Case Study
- Biologically Based Dose Response to Address Endogenous Exposure - Formaldehyde
- Endogenous/Background DNA Damage
- Kinetic Variability Based on PON1 Polymorphism (Integrated with PBPK)- Chlorpyrifos

Workshop Results

- **24 case studies** were developed by outside parties and reviewed by the expert panel.
  - Additionally evolved methodologies in specific areas
  - Explored crosscutting issues raised by NAS (2009), including---but not limited to---problem formulation, Mode of Action (MOA), background & endogenous exposures, & dose response methods
- Paper on workshop series and framework in preparation

Workshop Results

- The **expert panel determined** that:
  - A wide range of problem formulations or decision contexts exist for which different dose-response analysis techniques are needed.
  - It is important for risk assessors to explain criteria applied in the choice of a particular dose-response or risk assessment approach, and how the dose-response results will be used in a risk management decision.
  - Additional case studies would be useful on topics such as:
    - Combined exposures
    - Value of information
    - Illustrating an entire risk assessment, from problem formulation to conclusion
    - *In vitro* to *in vivo* extrapolation

Next Steps

- Framework will be “evergreen,” growing and evolving over time. It will be updated with additional methods and guidance documents, illustrated by case studies and with papers addressing and resolving cross-cutting issues.
- The National Library of Medicine has expressed interest in hosting the Framework. Some structural changes needed
- A standing panel will be created to meet twice a year to review additional case studies and issue/resolution papers.
  - Nominations and self-nominations welcome - Haber@tera.org
- Additional sponsors/participants will be invited to join in the overall effort.

Framework

- **ARA Dose Response Framework – (working beta)** http://www.allianceforrisk.org/workshop/framework/ problemformulation.html
- Part 2 of the symposium presents several sample methods and case studies