

# Science and Decisions: An Overview

Presentation to the Chronic Hazard Advisory Panel on  
Phthalates

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# SCIENCE AND DECISIONS: ADVANCING RISK ASSESSMENT

National Research Council  
Committee on Improving Risk Analysis Approaches Used by EPA  
Board on Environmental Studies and Toxicology



# COMMITTEE

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John M. Balbus, Environmental Defense

Joshua T. Cohen, Tufts New England Medical Center

Adam M. Finkel, University of Medicine and Dentistry of New Jersey

Gary Ginsberg, Connecticut Department of Public Health

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Joseph V. Rodricks, ENVIRON International Corporation

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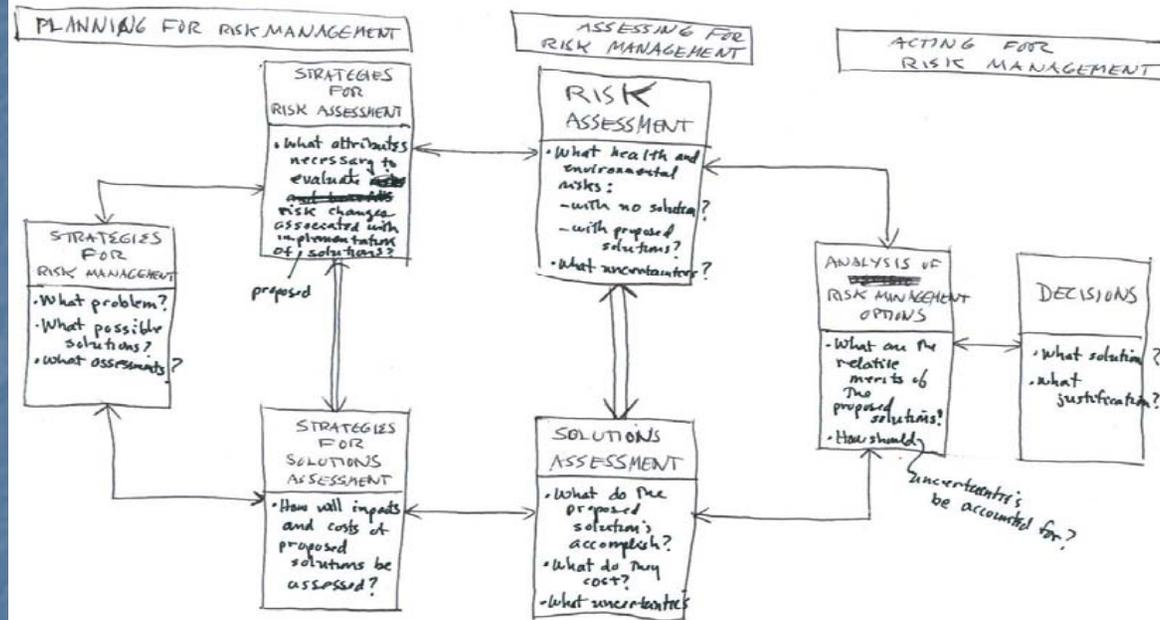
Lauren Zeise, California Environmental Protection Agency

## COMMITTEE'S CHARGE

- Develop scientific and technical recommendations for improving risk analysis approaches used by EPA, including practical improvements that EPA could make in the near term (2-5 years) and in the longer term (10-20 years).
- Focus primarily on human health risk assessment, but also consider implications of findings and recommendations for ecologic risk analysis.

# No easy task.....

FIG. 1 A SOLUTIONS-BASED FRAMEWORK FOR IMPROVED RISK MANAGEMENT  
 Improving RISK ASSESSMENT Requires Embedding it in a Problem-Solving Framework  
 (See TEXT for discussion of steps in the Framework)



• FORMAL PROVISIONS FOR STAKEHOLDER INVOLVEMENT AT ALL STAGES •

The involvement of decision-makers, technical specialists, and other stakeholders in all phases of the processes leading to decisions should in no way compromise the technical assessment of risk, which is carried out under its

# EVALUATION

Two broad elements:

- Improving *technical analysis* entails the development and use of scientific knowledge and information to promote more accurate characterizations of risk.
- Improving *utility* entails making risk assessment more relevant to and useful for risk-management decisions.

# CONCLUSIONS AND RECOMMENDATIONS

- Design of risk assessment
- Uncertainty and variability
- Selection and use of defaults
- A unified approach to dose-response assessment
- Cumulative risk assessment
- Improving the utility of risk assessment
- Stakeholder involvement
- Capacity-building

# On Design

- Are our current risk assessments effectively designed to meet the needs of the programs and decision makers?

# DESIGN OF RISK ASSESSMENT

- “Design” - The process of planning a risk assessment and ensuring that its level and complexity are consistent with the needs to inform decision-making.

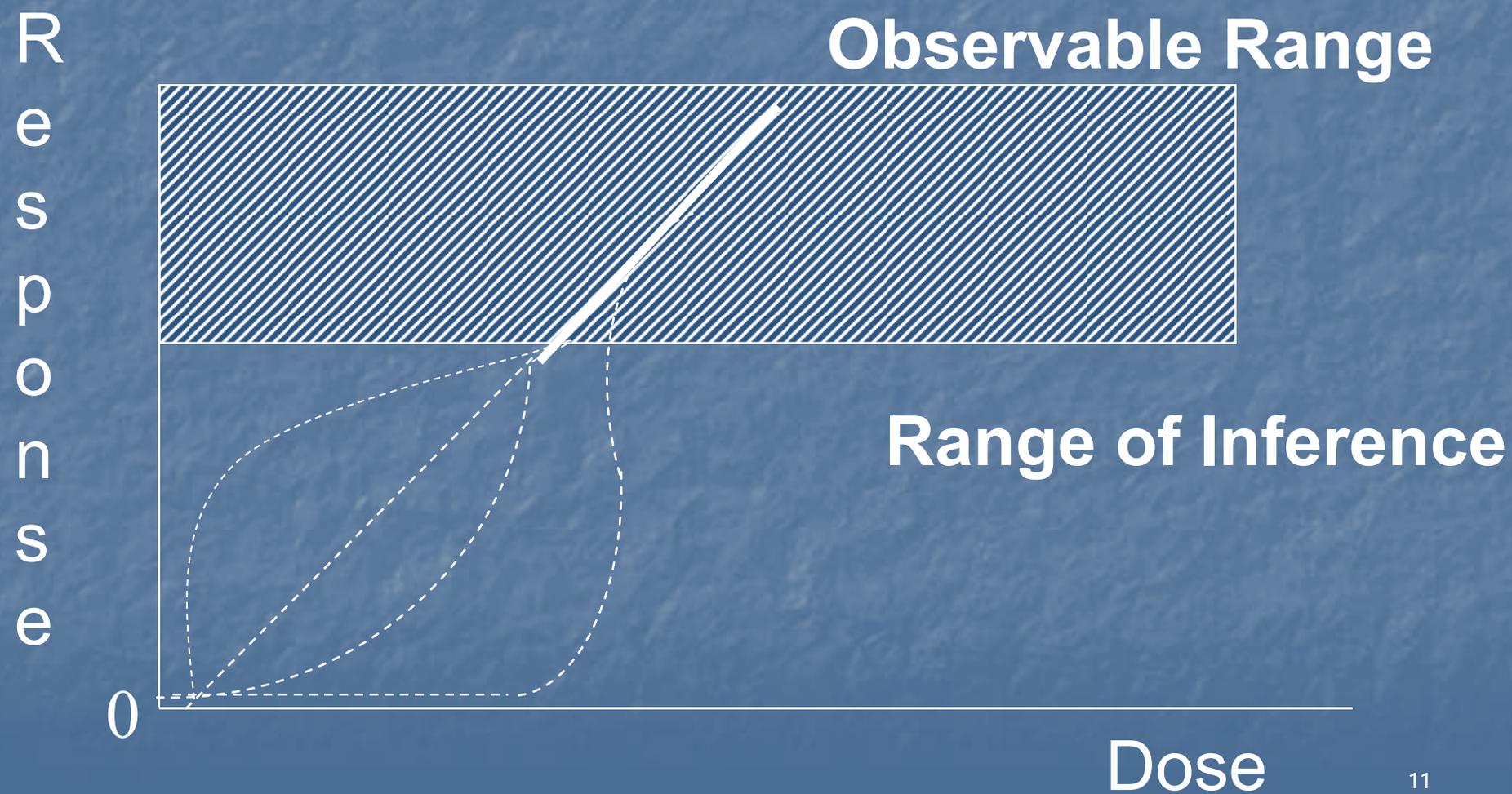
**Recommendation:** Increased attention to the design of risk assessment in its formative stages is needed. The committee recommends that planning and scoping and problem formulation, as articulated in EPA guidance documents (EPA 1998, 2003), should be formalized and implemented in EPA risk assessments.

# UNCERTAINTY AND VARIABILITY

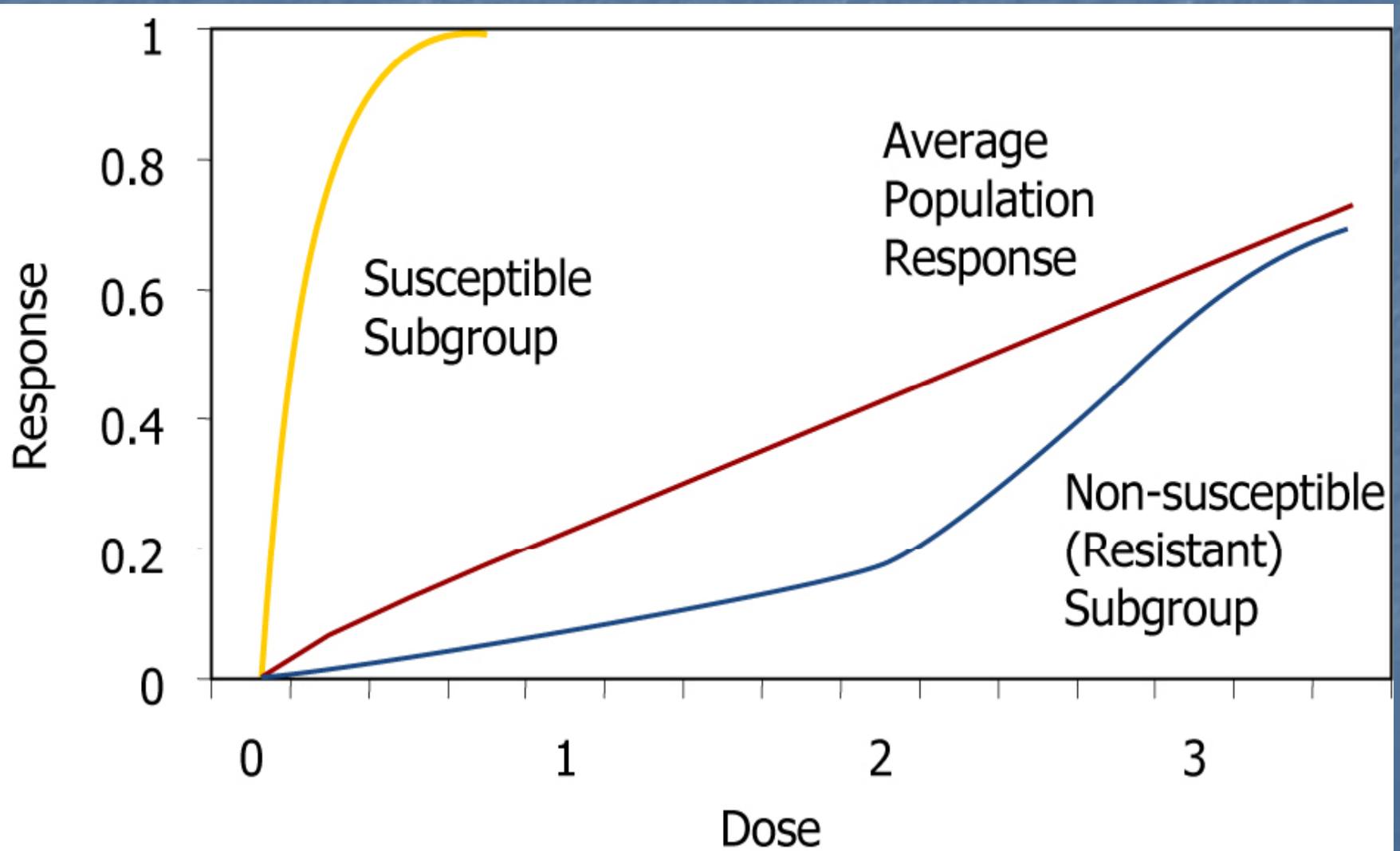
- Uncertainty stems from lack of knowledge, so it can be characterized and managed but not eliminated. Uncertainty can be reduced by the use of more or better data.
- Variability is an inherent characteristic of a population, inasmuch as people vary substantially in their exposures and their susceptibility to potentially harmful effects of the exposures. Variability cannot be reduced, but it can be better characterized with improved information.

# The Big Uncertainty: Low Doses

## *Dose-Response Curve*

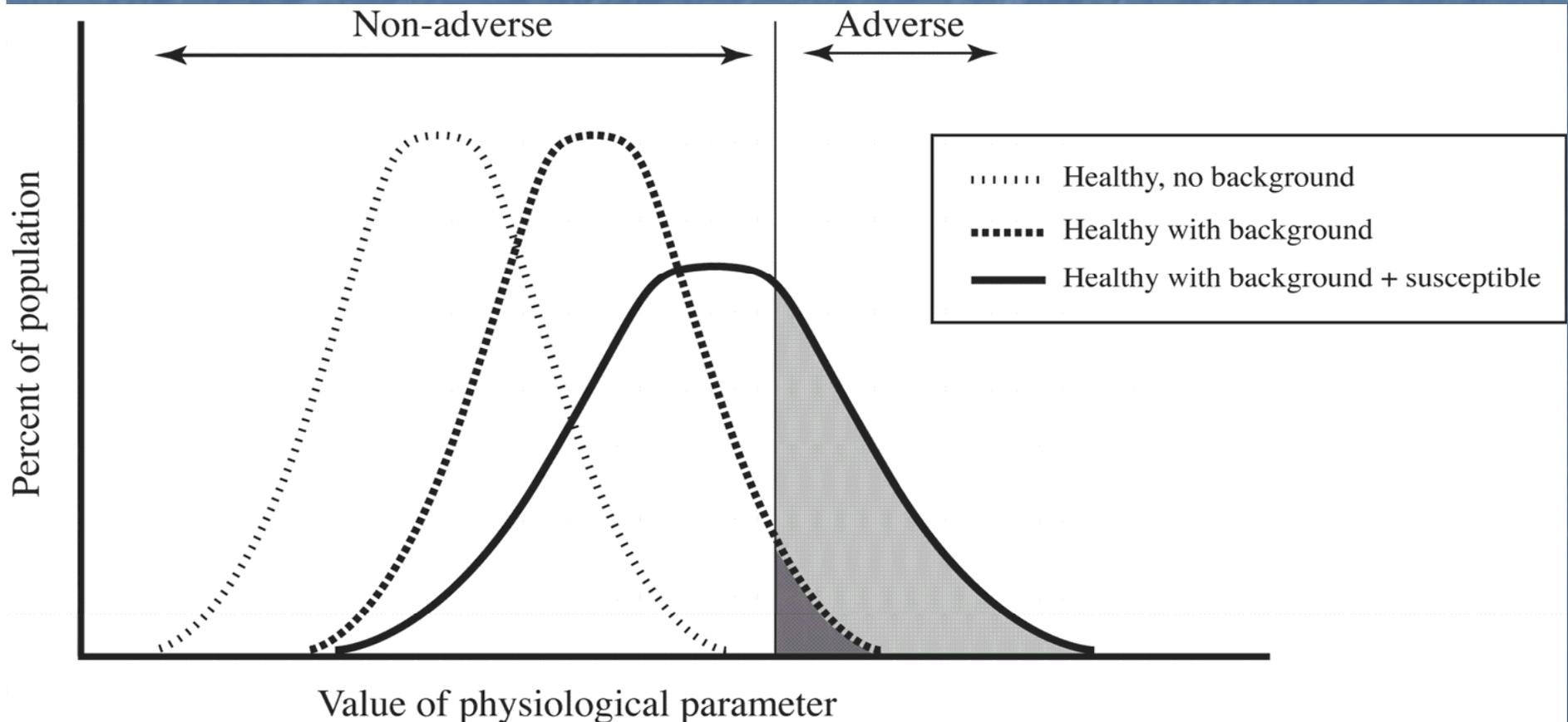


# Susceptible Subgroups in the Population



# Factors that influence risk of adverse of health effects

- Background
  - Biological
  - Exposure
- Vulnerability, e.g., from
  - Life stage
  - Genetics
  - Health disease status



# UNCERTAINTY

- The level of detail for characterizing uncertainty is appropriate only to the extent that it is needed to inform specific risk-management decisions appropriately.
- Inconsistency in the treatment of uncertainty among components of a risk assessment can make the communication of uncertainty difficult and sometimes misleading.

# UNCERTAINTY AND VARIABILITY

## Recommendation:

- EPA should encourage risk assessments to characterize and communicate uncertainty and variability in all key computational steps—for example, exposure assessment and dose-response assessment.
- Uncertainty and variability analysis should be planned and managed to reflect the needs for comparative evaluation of the risk management options.
- In the short term, EPA should adopt a “tiered” approach for selecting the level of detail to be used in the uncertainty and variability assessments, and this should be made explicit in the planning stage.
- EPA should develop guidance to determine the appropriate level of detail needed in uncertainty and variability analyses to support decision-making and should provide clear definitions and methods for identifying and addressing different sources of uncertainty and variability.

# SELECTION AND USE OF DEFAULTS

- Uncertainty is inherent in all stages of risk assessment, and EPA typically relies on assumptions when chemical-specific data are not available.
- Much of the scientific controversy and delay in completion of some risk assessments has stemmed from the long debates regarding the adequacy of the data to support the use of a default or an alternative approach.
- The 1983 Red Book recommended the development of guidelines to justify and select from among the available defaults to ensure consistency and to avoid manipulations in the risk-assessment process.
- The committee acknowledges EPA's efforts to examine scientific data related to defaults, but recognizes that changes are needed to improve the agency's use of them.

# SELECTION AND USE OF DEFAULTS

- Established defaults need to be maintained for the steps in risk assessment that require inferences and that clear criteria should be available for judging whether, in specific cases, data are adequate for direct use or to support an inference in place of a default.
- EPA, for the most part, has not yet published clear, general guidance on what level of evidence is needed to justify use of agent-specific data and not resort to a default.
- There are also a number of defaults (missing or implicit defaults) that are engrained in EPA risk-assessment practice but are absent from its risk-assessment guidelines.

# SELECTION AND USE OF DEFAULTS

## Recommendation:

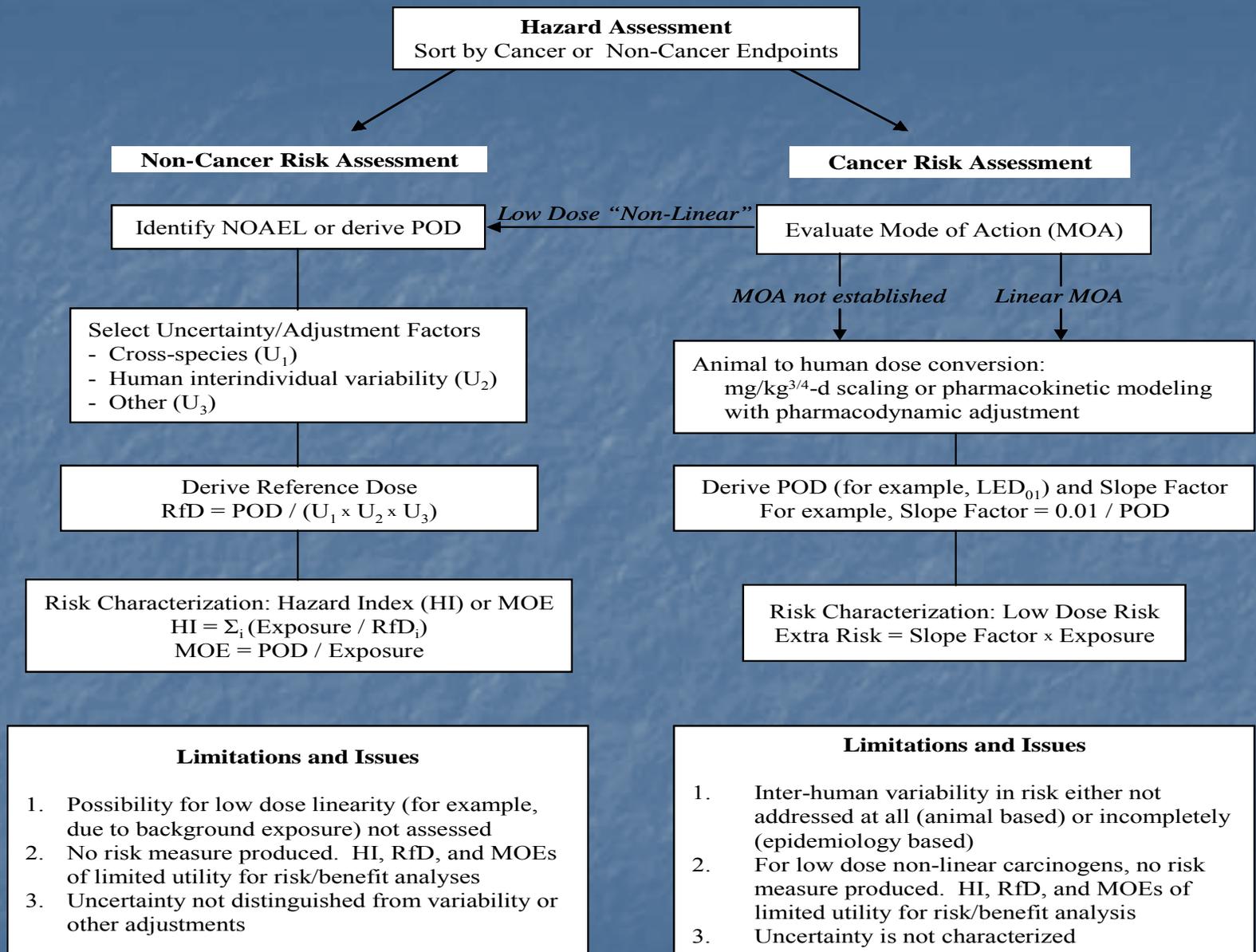
- EPA should continue and expand use of the best, most current science to support and revise default assumptions.
- EPA should develop clear, general standards for the level of evidence needed to justify the use of alternative assumptions in place of defaults.
- EPA should work toward the development of explicitly stated defaults to take the place of implicit defaults.

# UNIFICATION APPROACH TO DOSE-RESPONSE ASSESSMENT

- Historically, dose-response assessments at EPA have been conducted differently for cancer and noncancer effects, and the methods have been criticized for not providing the most useful results. Consequently, noncancer effects have been underemphasized, especially in benefit-cost analyses.
- A consistent approach to risk assessment for cancer and noncancer effects is scientifically feasible and needs to be implemented.

# Current EPA Dose-Response Approach

- EPA has taken important steps to harmonize cancer and noncancer approaches, but with many scientific and operational limitations:
  - Noncancer effects do not necessarily have threshold or low-dose nonlinearity
  - The mode of action of carcinogens varies.
  - Background exposures and underlying disease processes contribute to population background risk
    - can lead to linearity at the population doses of concern.
  - RfDs and RfCs do not quantify risk for different magnitudes of exposure but rather provide a bright line
    - Their use in risk-management decision-making is limited.
  - Cancer risk assessments usually do not account for human differences in cancer susceptibility (other than possible differences in early-life).



**Hazard Assessment**  
Sort by Cancer or Non-Cancer Endpoints

**Non-Cancer Risk Assessment**

**Cancer Risk Assessment**

Identify NOAEL or derive POD

Evaluate Mode of Action (MOA)

*Low Dose "Non-Linear"*

*MOA not established*

*Linear MOA*

Select Uncertainty/Adjustment Factors  
- Cross-species (U<sub>1</sub>)  
- Human interindividual variability (U<sub>2</sub>)  
- Other (U<sub>3</sub>)

Animal to human dose conversion:  
mg/kg<sup>3/4</sup>-d scaling or pharmacokinetic modeling  
with pharmacodynamic adjustment

Derive Reference Dose  
RfD = POD / (U<sub>1</sub> x U<sub>2</sub> x U<sub>3</sub>)

Derive POD (for example, LED<sub>01</sub>) and Slope Factor  
For example, Slope Factor = 0.01 / POD

Risk Characterization: Hazard Index (HI) or MOE  
HI = Σ<sub>i</sub> (Exposure / RfD<sub>i</sub>)  
MOE = POD / Exposure

Risk Characterization: Low Dose Risk  
Extra Risk = Slope Factor x Exposure

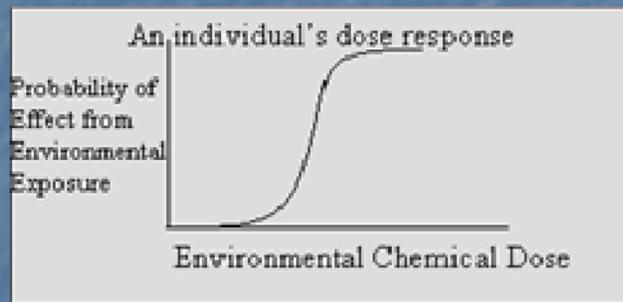
- Limitations and Issues**
1. Possibility for low dose linearity (for example, due to background exposure) not assessed
  2. No risk measure produced. HI, RfD, and MOEs of limited utility for risk/benefit analyses
  3. Uncertainty not distinguished from variability or other adjustments

- Limitations and Issues**
1. Inter-human variability in risk either not addressed at all (animal based) or incompletely (epidemiology based)
  2. For low dose non-linear carcinogens, no risk measure produced. HI, RfD, and MOEs of limited utility for risk/benefit analysis
  3. Uncertainty is not characterized

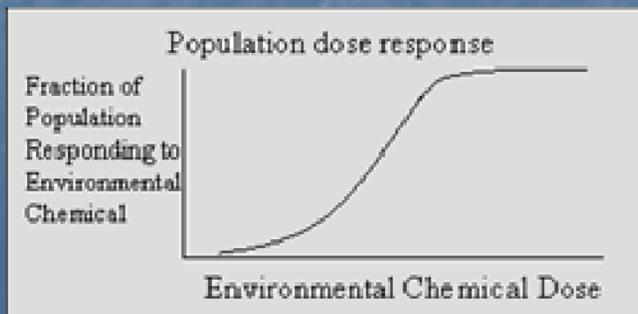
# UNIFICATION APPROACH TO DOSE-RESPONSE ASSESSMENT

- The committee recommends a consistent, unified approach for dose-response modeling that includes formal, systematic assessment of background disease processes and exposures, possible vulnerable populations, and modes of action that may affect a chemical's dose-response relationship in humans.
- Redefines the RfD or RfC as a risk-specific dose that provides information on the percentage of the population that can be expected to be above or below a defined acceptable risk with a specific degree of confidence.

## Risk Determinants



Heterogeneity in Background Exposure and Susceptibility



Dose-response relationship is dependent on heterogeneity in:

- Background exposure (endogenous and xenobiotic)
- Biological susceptibility

**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:

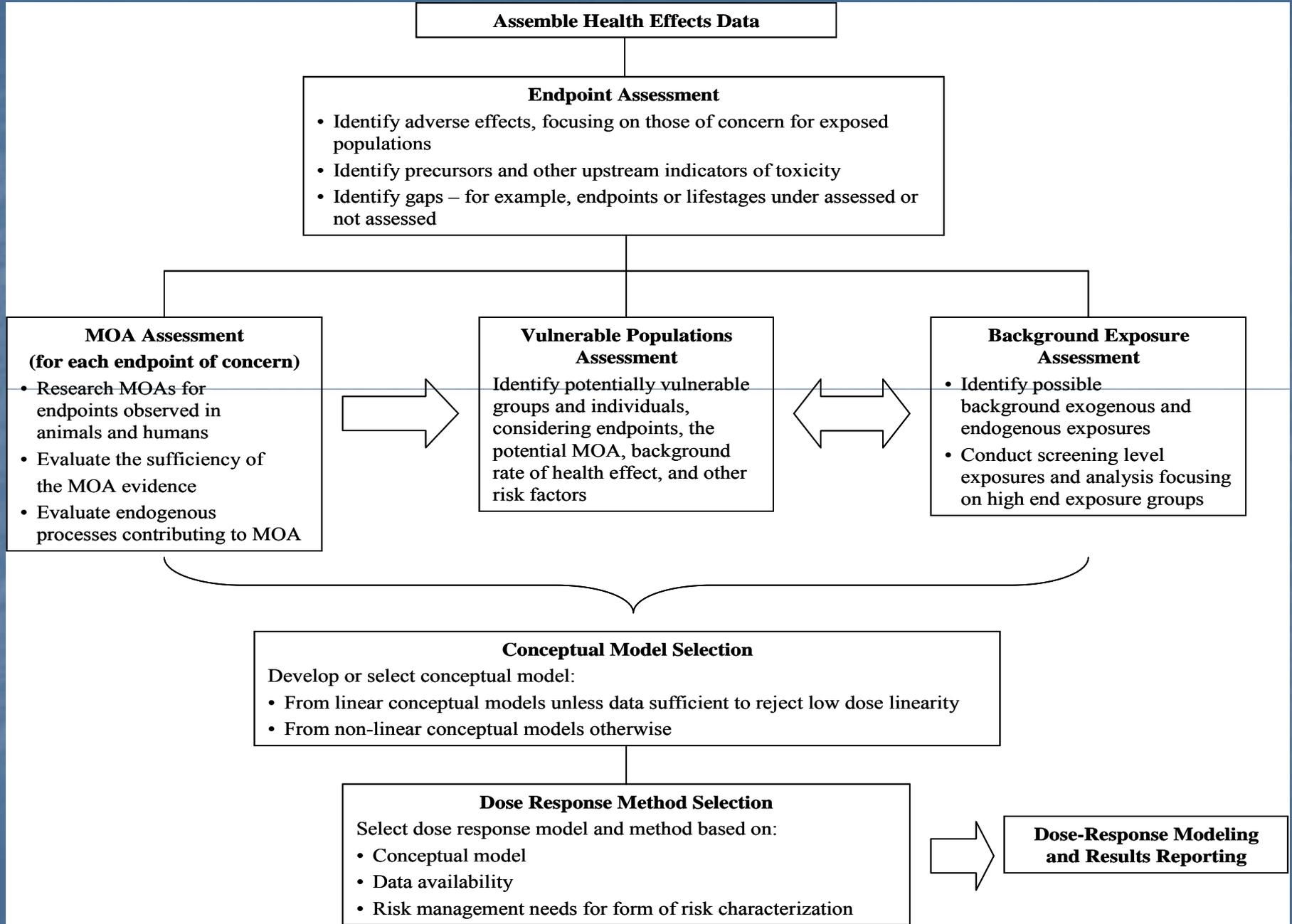
- From linear conceptual models unless data sufficient to reject low dose linearity
- From non-linear conceptual models otherwise

**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**



# CUMULATIVE RISK ASSESSMENT

- EPA is increasingly asked to address broad public-health and environmental-health issues that stakeholder groups often consider inadequately captured by current risk assessments
  - multiple exposures
  - complex mixtures
  - vulnerability of exposed populations
- There is a need for cumulative risk assessments as defined by EPA that include
  - combined risks posed by exposure to multiple agents or stressors
  - aggregate exposure to a given agent or stressor
    - all routes, pathways, and sources of exposure
  - Chemical, biologic, radiologic, physical, and psychologic stressors are considered.

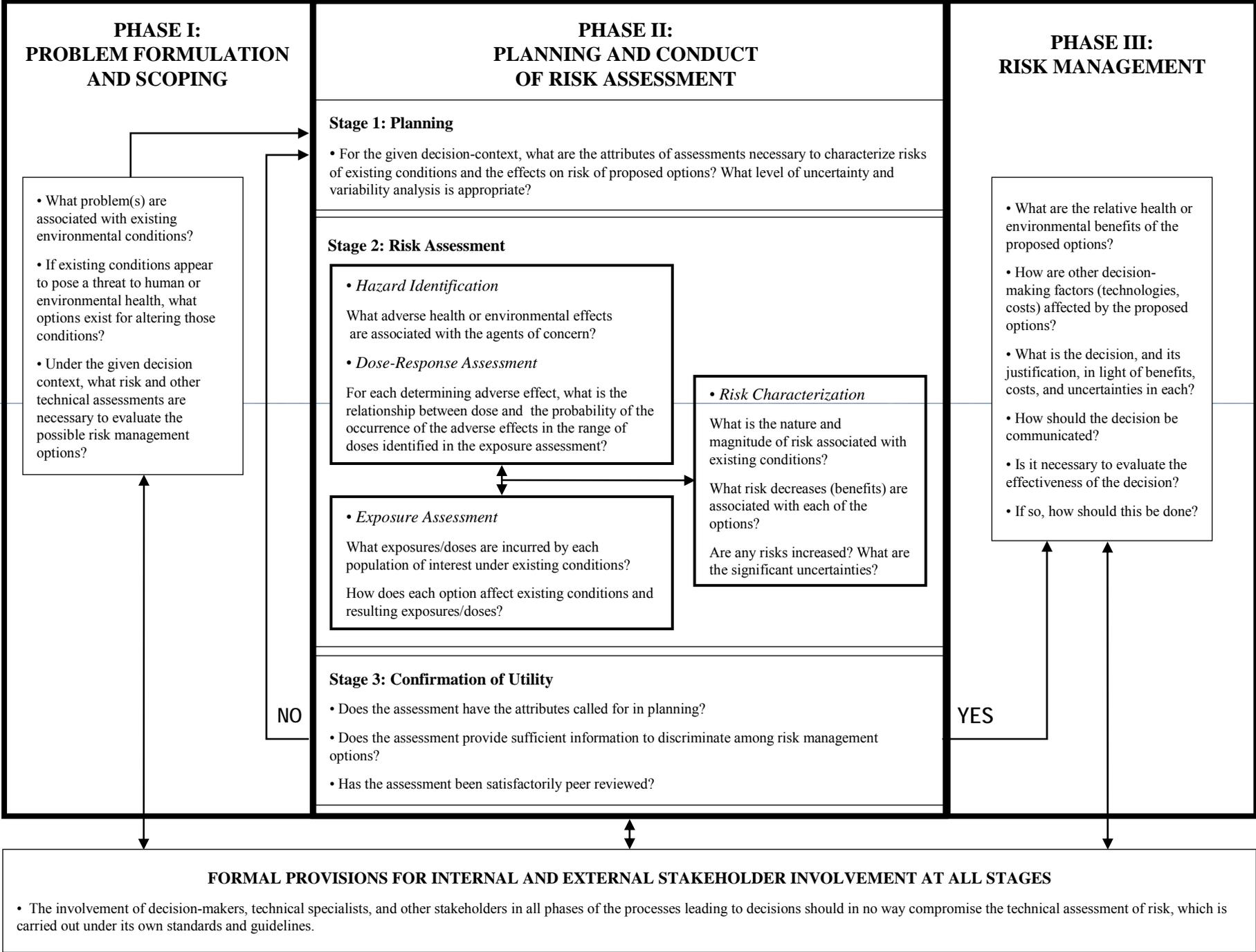
# CUMULATIVE RISK ASSESSMENT

## Recommendation:

- EPA should draw on other approaches, including those from ecologic risk assessment and social epidemiology, to incorporate interactions between chemical and non-chemical stressors in assessments;
- Develop guidelines and methods for simpler analytical tools to support cumulative risk assessment and to provide for greater involvement of stakeholders.
- In the short-term, EPA should develop databases and default approaches to allow for incorporation of key non-chemical stressors in cumulative risk assessments in the absence of population-specific data, considering exposure patterns, contributions to relevant background processes, and interactions with chemical stressors.
- In the long-term, EPA should invest in research programs related to interactions between chemical and non-chemical stressors, including epidemiologic investigations and physiologically-based pharmacokinetic modeling.

# IMPROVING THE UTILITY OF RISK ASSESSMENT

- Committee proposes a framework for risk-based decision-making.
  - At its core is the risk assessment paradigm
  - It differs primarily in its initial and final steps
- Framework asks implicitly: What *options* are there to reduce the *hazards* or *exposures* that have been identified, and how can risk assessment be used to evaluate the merits of the various options?



# IMPROVING THE UTILITY OF RISK ASSESSMENT

## Phase I: Problem Formulation and Scoping

- a. What is the problem to be investigated, and what is its source?
- b. What are the possible opportunities for managing risks associated with the problem? Has a full array of possible options been considered, including legislative requirements?
- c. What types of risk assessments and other technical and cost assessments are necessary to evaluate existing conditions and how the various risk-management options alter the conditions?
- d. What impacts other than health and ecosystem threats will be considered?
- e. How can the assessments be used to support decisions?
- f. What is the required timeframe for completion of assessments?
- g. What resources are needed to undertake the assessments?

## **Phase II**

# **Planning and Conduct of Risk Assessment**

### **Stage 1: Planning**

- For the given decision-context, what are the attributes of assessments necessary to characterize risks of existing conditions and the effects on risk of proposed options?
- What level of uncertainty and variability analysis is appropriate?

### **Stage 2: Risk Assessment**

### **Stage 3: Confirmation of the Utility**

- Does the assessment have the attributes called for in planning?
- Does the assessment provide sufficient information to discriminate among risk-management options?
- Has the assessment been satisfactorily peer reviewed?

## Phase III

# Risk Management

- What are the relevant health or environmental benefits of the proposed risk-management options?
- How are other decision-making factors (technologies, costs) affected by the proposed options?
- What is the decision, and its justification, in light of benefits, costs, and uncertainties in each?
- How should the decision be communicated?
- Is it necessary to evaluate the effectiveness of the decision? If so, how should this be done?

# IMPROVING THE UTILITY OF RISK ASSESSMENT

**Recommendation:** To make risk assessments most useful for risk management decisions, the committee recommends that EPA adopt a framework for risk-based decision-making that embeds the Red Book risk assessment paradigm into a process with initial problem formulation and scoping, upfront identification of risk-management options, and use of risk assessment to discriminate among these options.

# STAKEHOLDER INVOLVEMENT

**Recommendation:** EPA should establish a formal process for stakeholder involvement in the framework for risk-based decision-making with time limits to ensure that decision-making schedules are met and with incentives to allow for balanced participation of stakeholders, including impacted communities and less advantaged stakeholders.

# KEY MESSAGES

- Enhanced framework
- Formative focus
- Four steps still core
- Matching analysis to decisions
- Clearer estimates of population risk
- Advancing cumulative assessments
- People and capacity building

# TAKE HOME MESSAGE

## It's all about better decisions

- Committee recommends an important extension of the Red Book model—that risk assessment should be viewed as a method for evaluating the relative merits of various options for managing risk rather than as an end in itself.
- Risk assessment should continue to capture and accurately describe what various research findings do and do not tell us about threats to human health and to the environment, but only *after* the risk-management questions that risk assessment should address have been clearly posed, through careful evaluation of the options available to manage the environmental problems at hand.