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

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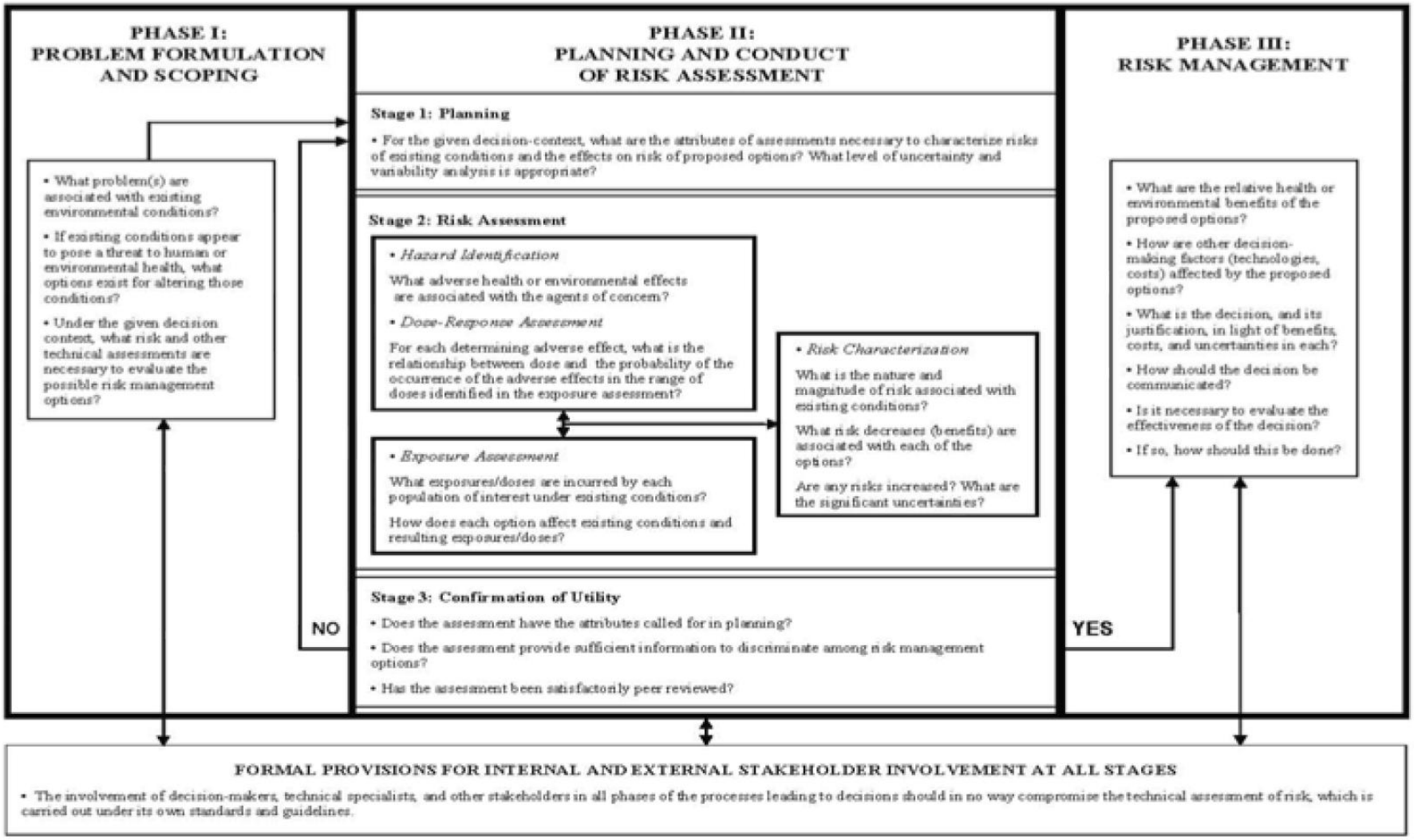


FIGURE S-1 A framework for risk-based decision-making that maximizes the utility of risk assessment.

Phase I

Problem Formulation

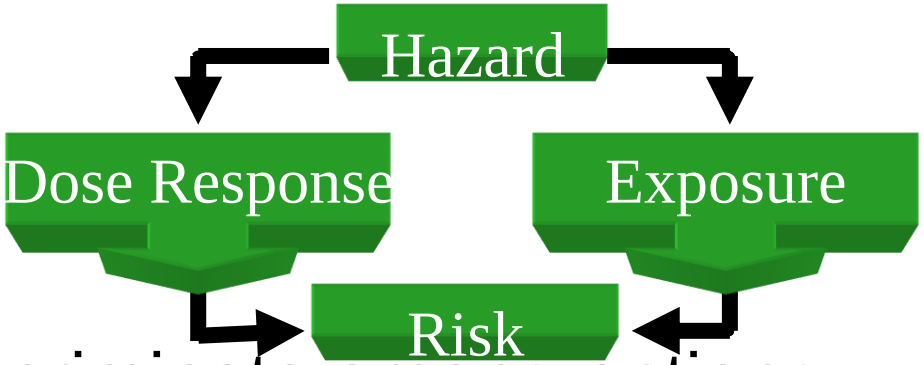
- Begins with a “signal” of potential harm
  - Positive bioassay or epidemiological study; industrial contamination
- What options are there to reduce the hazards or exposures?
- How can risk assessment be used to evaluate the merits of the various options?

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)

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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

= 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

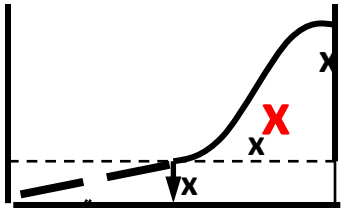
Reconciling Recommendations on Problem Formulation & Dose-Response

- 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
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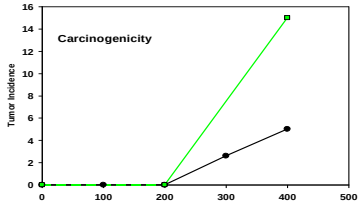
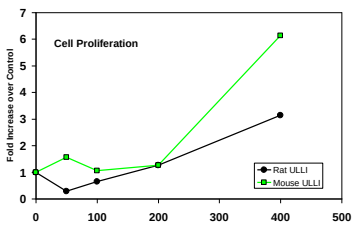
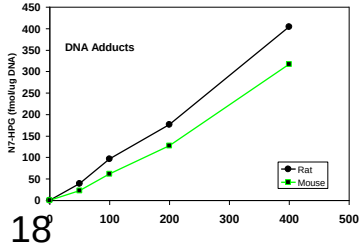
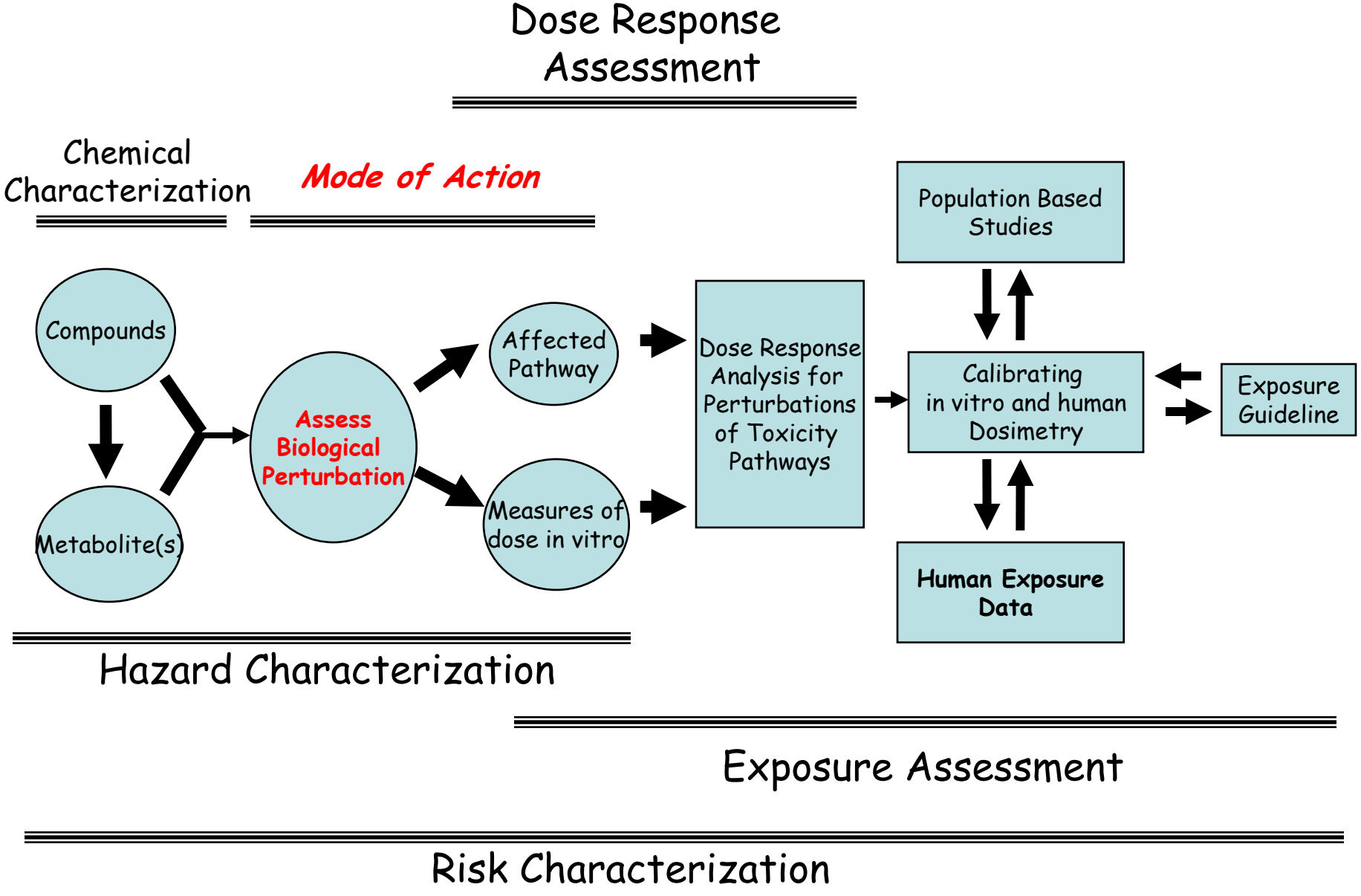






U.S. NRC Toxicity Testing in the 21st Century



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***
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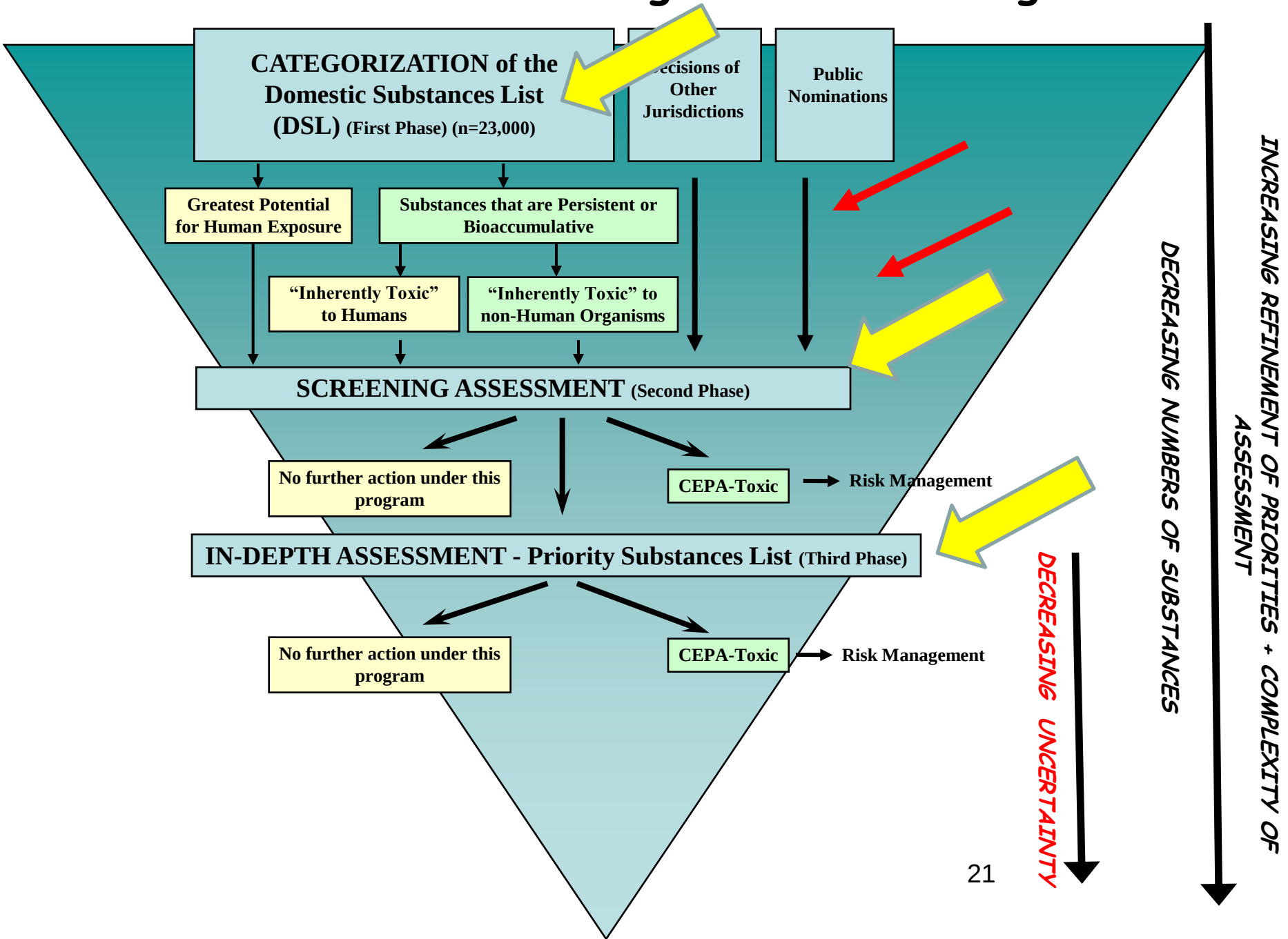
- IPCS Tiered Uncertainty Analysis (2007)

CEPA 1999 Existing Substances Program



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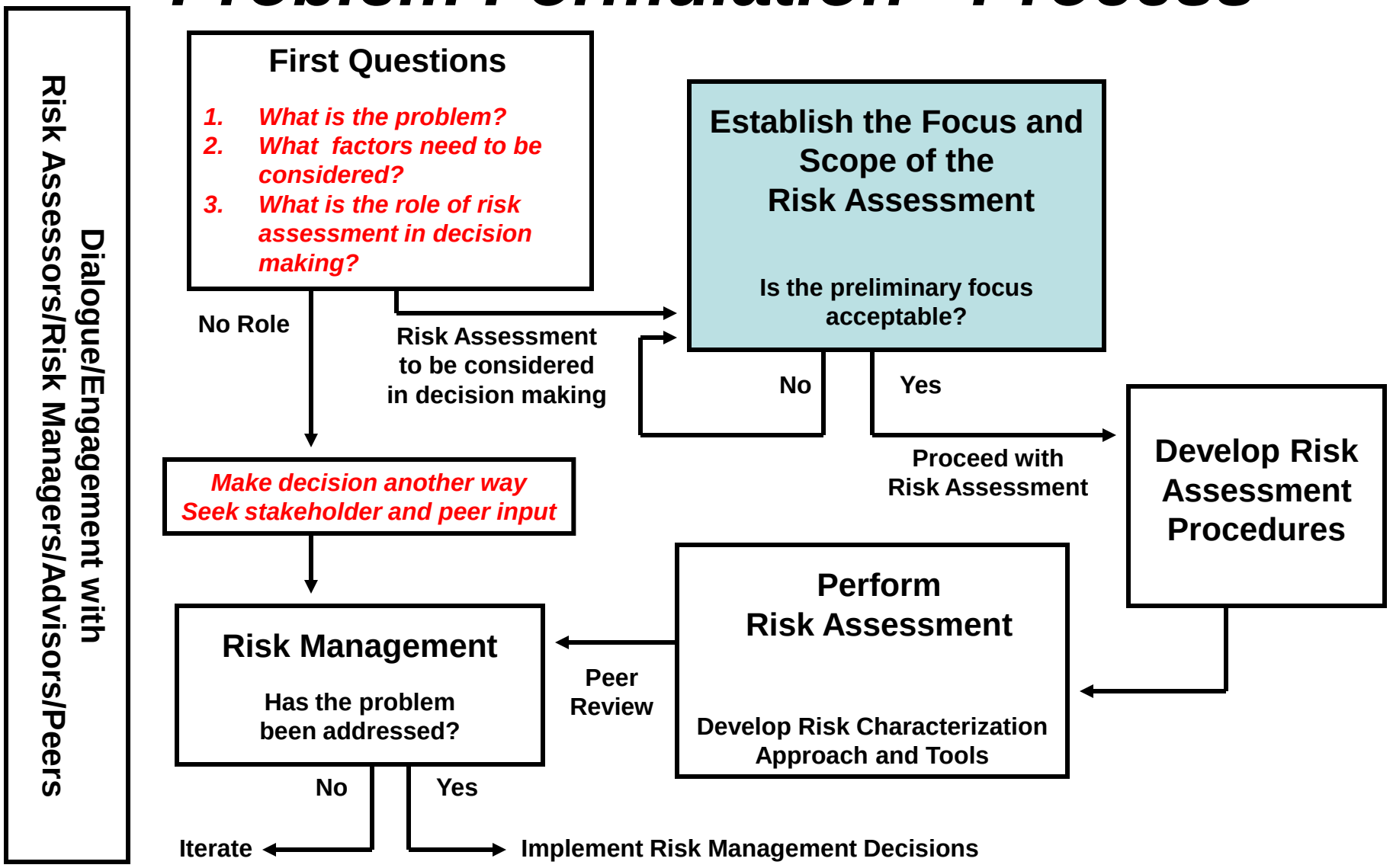
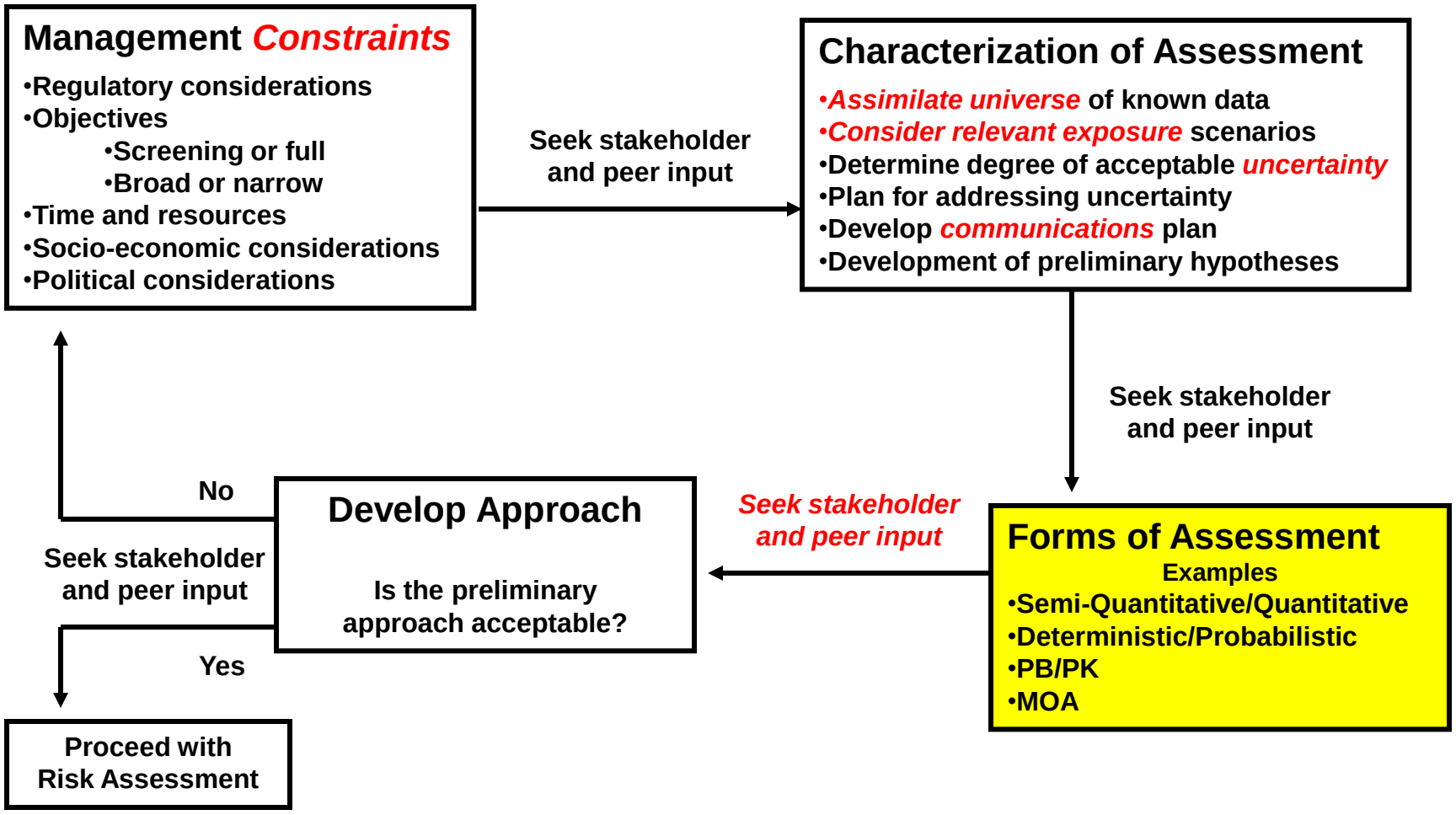
HC/ILSI
The Role of Formal Issue Identification
More than a Statement of the Issue; A Process

- ***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



Establish the Focus and Scope of the Risk Assessment



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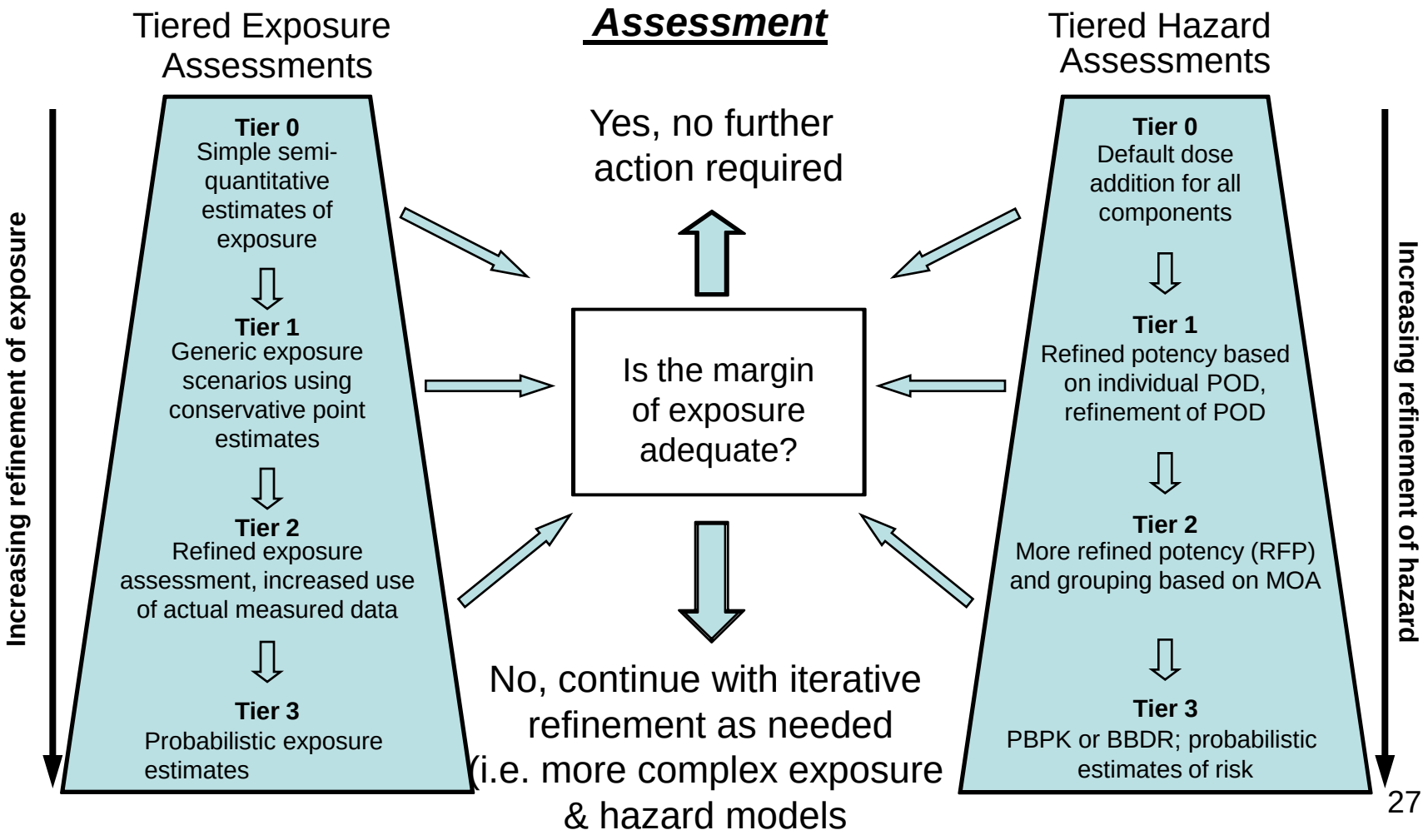
Problem Formulation

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



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?

Problem Formulation

More Information?

WHO/IPCS Harmonization Initiative

- http://www.who.int/ipcs/methods/harmonization/index.html

Categorization/Screening under CEPA

- Meek & Armstrong, in: ***Risk Assessment of Chemicals, Kluwer Academic Publishers, Dordrecht, 2007 (eds. Van Leeuwen, Vermeire)***
- Hughes et al., ***Reg. Toxicol. Pharm. 55:382-393, 2009***
- Existing Substances Division Website – http://www.hc-sc.gc.ca/exsd-dse