Human Health Criteria and Standards
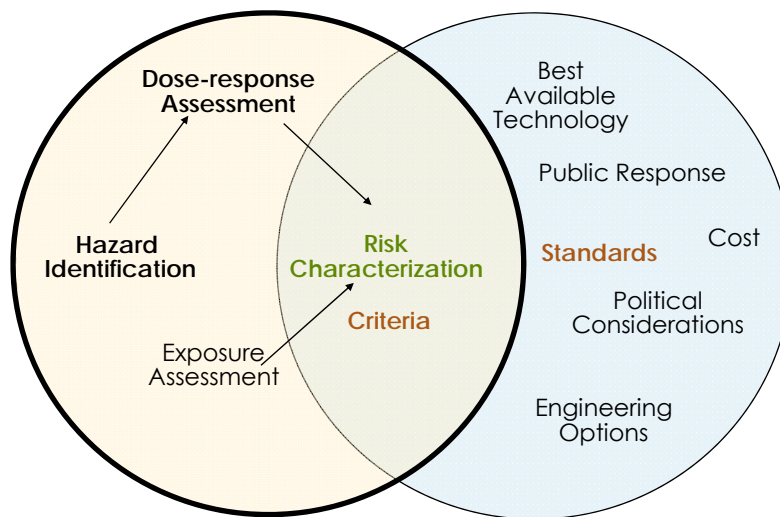
Submitted by: University of Cincinnati

Workshop on Metals Risk Assessment
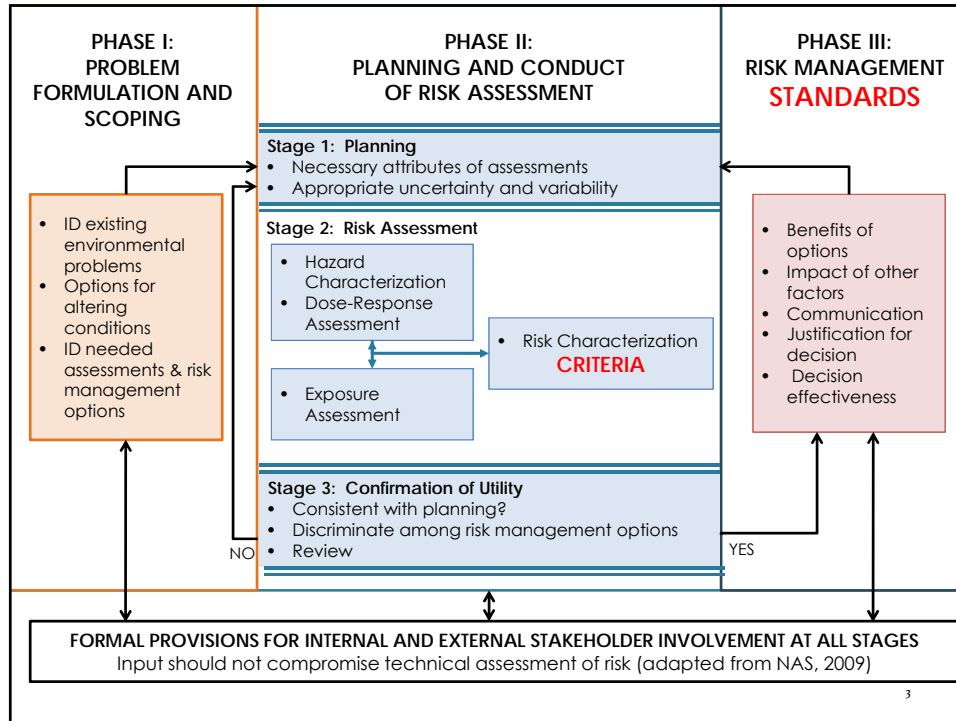**Cebu, Philippines**
28-29 August 2015

Human Health Criteria and Standards

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Risk Assessment/Management

Dose-response Assessment

Hazard Identification

Exposure Assessment

Risk Characterization

Criteria

Best Available Technology

Public Response

Standards

Cost

Political Considerations

Engineering Options

Source: NAS (1983).

PHASE I: PROBLEM FORMULATION AND SCOPING	PHASE II: PLANNING AND CONDUCT OF RISK ASSESSMENT	PHASE III: RISK MANAGEMENT STANDARDS

Stage 1: Planning
- Necessary attributes of assessments
- Appropriate uncertainty and variability

- ID existing environmental problems
- Options for altering conditions
- ID needed assessments & risk management options

Stage 2: Risk Assessment
- Hazard Characterization
- Dose-Response Assessment
- Exposure Assessment

- Risk Characterization **CRITERIA**

- Benefits of options
- Impact of other factors
- Communication
- Justification for decision
- Decision effectiveness

Stage 3: Confirmation of Utility
- Consistent with planning?
- Discriminate among risk management options
- Review

NO   YES

FORMAL PROVISIONS FOR INTERNAL AND EXTERNAL STAKEHOLDER INVOLVEMENT AT ALL STAGES
Input should not compromise technical assessment of risk (adapted from NAS, 2009)

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Risk Characterization

- **Integrates exposure data and dose-response (informed by hazard characterization) to obtain risk estimates**

- **Provides risk managers with information regarding the probable nature and distribution of health risks**

- **Has both quantitative and qualitative components**

- **Clearly delineates uncertainty and data gaps**

Key Components of Risk Characterization

- **Transparency: Is the rationale for all judgments clear?**
  - Logical steps, key assumptions
- **Clarity: Easy to understand**
- **Consistency…**
  - With guidelines and precedent; comparison with other assessments (e.g., RfDs of perchlorate and methyl mercury)
- **Reasonableness**
  - In context of state-of-science, default assumptions, science policy decisions

U.S. EPA. 2000. Science Policy Council Handbook: Risk Characterization. Offices of Science Policy & Research and Development, Washington, DC. EPA 100-B-00-002.

Expressions of Risk

- **Deterministic:**
  - Criteria & Health Advisories: Safe (e.g., RfD) or virtually safe dose (VSD) ÷ exposure assumptions
  - Margin of Safety: RfD or VSD ÷ actual exposures
  - Hazard Quotient (HQ): Exposure ÷ RfD or VSD
  - Hazard Index (HI): ∑ Exposure(s) ÷ RfD(s) per target organ
  - Margin of Exposure (MOE): NOAEL ÷ Exposure

  Disadvantages: No estimates of risks at or above the threshold or virtual threshold

Expressions of Risk

- **Probabilistic:**
  - Slope of cancer dose response curve (i.e., risk/dose)
  - Unit cancer risk (e.g., risk per µg/L in drinking water)
  - Risk per unit of the population (e.g., 1 in 100,000)
  - Risk above RfD using categorical regression or BMD model

  Disadvantages: Imply greater accuracy than is generally warranted

Considerations

- **How does the exposure scenario of interest compare to that for which the risk value is developed**
  - Separate risk values may be developed for acute or short-term exposure
- **Does the chemical form for the risk value apply to the exposure scenario?**
  - Solubility, aerosol particle size, metal form
- **How does the exposed population compare with that for the critical effect?**

Risk Characterization – Quantification

Deterministic:
Health Advisories and Criteria

These deterministic tools take the general form:
Advisory or Criterion = RfD or VSD ÷ exposure assumptions

- Advisories and criteria are then compared to actual exposures
- If they are exceeded then a remedial action might be indicated, as shown on the next slide
- These tools are not as flexible as the MOE (discussed next), since use requires the determination of a RfD or VSD
- These tools are useful when explaining whether a given concentration of a chemical found in particular environmental media (e.g., soil) is safe to the public
- In particular, these tools have been used for assessing exposures of different durations

Deterministic: Margin of Safety

- MOS = RfD or VSD ÷ exposure
- A MOS of 1 or more is acceptable
- This concept is not as flexible as the MOE (discussed later), since its use requires the determination of a RfD or VSD
- This concept is the inverse of the hazard quotient (discussed next)
- MOS is useful when explaining safe regions of dose or concentration to the public
- In particular, it has been used for assessing exposure scenarios of different durations

Deterministic: Hazard Quotient

- An alternative metric to the MOE is the hazard quotient

- Individual risk is estimated by comparing the daily exposure with the RfD for each chemical of concern as expressed by the following equation:
  - Hazard Quotient = Exposure ÷ RfD

Example of Hazard Quotient

- Daily exposure to chemical XYZ is 0.04 mg/kg-day

- RfD for this chemical is 0.02 mg/kg-day

  HQ = 0.04 mg/kg-day ÷ 0.02 mg/kg-day = 2.0

Where exposure is the total exposure to a single chemical from all sources in units of mg/kg-day and RfD is the reference dose

Hazard Quotient

HQ is << 1	HQ >> 1

Interpreting the Hazard Quotient

- When the hazard quotient is greater than 1, exposure exceeds the RfD and the exposed populations might be at risk

- The actual risk is related to the degree to which exposure exceeds the RfD as well as characteristics of the exposed population

- Therefore, using an RfD aims to describe a protective exposure limit rather than predicting risk for a given level of chemical exposure

Mixtures Assessment – Dose Addition – Hazard Index

- Therefore, the hazard quotients for all chemicals present are added together to give a total estimate of noncancer risk. This sum is called the Hazard Index

  - HI = HQ1 + HQ2 + HQ3….

  - e.g., HI = 0.3 + 0.08 +0.9 = ~1.28

    Which would round to a value of 1, since the underlying risk values are given as only 1 digit

U.S. EPA. 1986. Guidelines for the health risk assessment of chemical mixtures. Federal Register 51(185):34014-34025.
U.S. EPA. 2000. Supplementary Guidance for ConductingHealth Risk Assessment of Chemical Mixtures. EPA/630/R-00/002, August 2000.

Deterministic: Margin of Exposure

- MOE = effect level of concern (NOAEL, BMDL, etc.) ÷ exposure

- A large MOE means lower potential risk, usually…

- For the scenario of interest an acceptable margin between the critical effect NOAEL and the exposure is determined

- This concept is more flexible than the hazard quotient (discussed later), since it's applied to various exposure scenarios
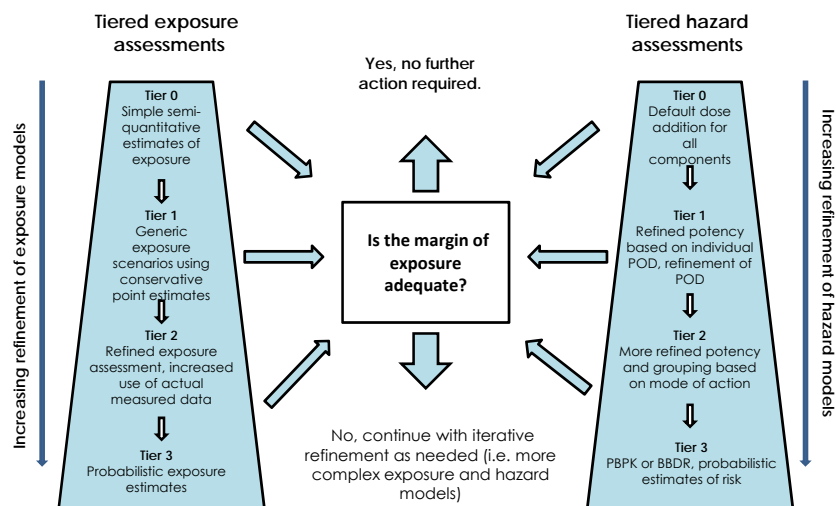
Deterministic: Margin of Exposure
(continued)

- MOE is useful when different exposure scenarios call for alternative critical effects and uncertainty considerations that were not used for the RfD

- In particular, it has been used for assessing short-term exposure scenarios or to assess risks for specific endpoints

Tiers for Addressing Uncertainty Using MOE (WHO)

- **Tier 0**: Default assumptions; deterministic (single value) output

- **Tier 1**: Qualitative—systematic identification and characterization of uncertainties

- **Tier 2**: Quantitative—bounding values, interval analysis, sensitivity analysis

- **Tier 3**: Probabilistic output

Example Tiered Exposure and Hazard Considerations: Mixture or Component Based

Source: WHO/IPCS Draft Guidelines, 2009; Figure 1: Conceptual representation of the framework.

Probabilistic: Linear Extrapolation

- For linear dose response assessment extrapolation, risk for each chemical is estimated by multiplying the estimated daily dose of the chemical by the potency value for the chemical

- For example:
  - Cancer risk = exposure x cancer potency
    - = mg/kg-day x risk (mg/kg-day)$^{-1}$
    - = mg/L x risk (mg/L)$^{-1}$

Cancer Risk Example

- A superfund site has 1,2-dichlorobadstuff as the predominant chemical of concern. 1,2-dichlorobadstuff has an upper bound cancer potency value of 1 x 10^{-4} per (mg/kg-day).

- The total estimated daily dose to 1,2-dichlorobadstuff for all exposure pathways is 0.04 mg/kg-day

- Therefore:
  - Risk = dose x cancer potency
  - Risk = 0.04 mg/kg-day x 10^{-4} per (mg/kg-day)
  - Risk = 4 x 10^{-6} or 4 per 1,000,000 (but, risk could be zero)
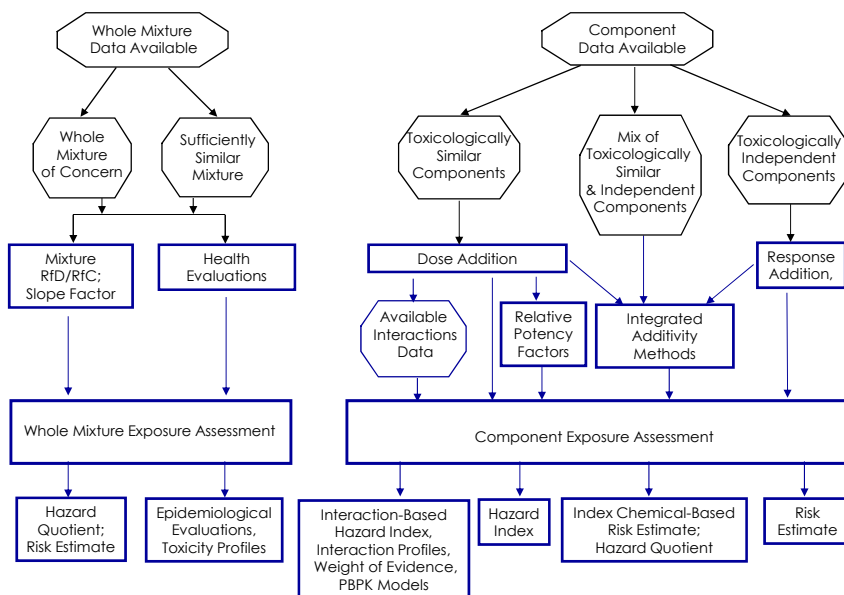
Mixtures Assessment

"What'll it be—one large risk or several small ones?"

Definitions

- **Aggregate exposure** =
  1 chemical, multiple routes

- **Mixture** =
  exposure to more than one chemical

- **Cumulative risk** =
  exposure to single or multiple chemicals and nonchemical stressors

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Flow Charts for Evaluating Chemical Mixtures

Source: Adapted from U.S. EPA 2007.

Mixtures Assessment: Dose Addition

- When the exposed population is exposed to multiple chemicals that act through the same mode of action or affect the same target tissue, the default assumption is that the toxicity and risk posed by these chemicals is additive

- Assumes scaled doses are additive, not risk or toxicity

- Assumes similarly shaped dose-response curves across components

- Use is appropriate at low doses where interaction effects less likely

Dose Addition: Toxicity Equivalence Factors

- Few chemical groups qualify (e.g., dioxins)
- Characteristics:
  - One relative potency value per congener
  - Mixture dose as equivalent dose of key congener
- Requires:
  - Similar chemical structure and toxicologic mechanism
  - Data for several toxicity measures
  - Relative potency is constant across all effect, organs, routes

Dose Addition: Relative Potency Factors

- **More chemical classes may qualify**

- **RPF may be specific for each organ, or route or efect**

- **Requirements:**
  - Similar structure or expression of toxicity
  - Empirical similarity – common MOA, not mechanism
  - Uncertainty description

More on Relative Potency Factors

- **RPF expresses toxicity relative to index compound**

- **Need to compare similar study design**
  - Same endpoint, route, duration, response level – e.g., ED_{10}, LC_{50}

- **Examples: OPP assessments for organophosphates; N-methyl carbamates; chloracetanilides; triazines**

Response Additivity: Toxicologically Independent

- **Used for cancer assessment or for noncancer toxicologically independent**

- **Calculate cancer risk for each exposure and sum**

  – Total risk = sum of risks

  – e.g., $1 \times 10^{-5} + 5 \times 10^{-5} + 1 \times 10^{-6} = 6.1 \times 10^{-5}$

  Which would round to a value of 6×10^{-5}, since the underlying risk values are given as only 1 digit

Practical Approaches for Combined Exposures

- **For a site assessment with multiple chemicals:**

  – As an initial screening approach, add the HQs for all the chemicals regardless of MOA or target tissue. If the HI is < 1, then low concern for risk

  – If the HI is >1, then group chemicals by MOA or target tissue and estimate separate HIs for each group (can also re-evaluate the exposure data in more detail)

  – EPA guidance provides more complex approaches for chemicals with known interactions (e.g., synergistic effects)

WHO/IPCS Framework
(Similar Application by OPP)

- **Group chemicals into Common Assessment Group (CAG) by MOA and purpose of assessment (prioritization, screening, quantitative RA) – multiple chemicals, multiple routes**

- **Iterative process – tiered approach based on exposure and hazard – separate tiers for exposure and hazard**

  - Aim is to evaluate potential for coexposure, provide rationale for considering chemicals as a CAG

What Is Cumulative Risk?

- **Cumulative risk is the combined risk from joint exposures to multiple stressors – chemical, physical, and/or biological agents**

  - Analysis, characterization, and if possible quantification

  - Human health and/or environment

  - Full assessment considers risk over time, across locations

  - Elements difficult to assess/quantify: Social, economic, behavioral, psychological factors that may contribute to adverse effects

More than Mixtures: Cumulative Risk Assessment

- Multiple chemical, physical, and/or biological stressors

- Complex, multiple-route exposures

- Stakeholder emphasis, population focus

- Considers vulnerabilities of population subgroups

- Extends beyond standard endpoints: Combined human health/welfare and ecology

Trends in Risk Characterization

- Provision to risk managers of a range of options with predicted risks, wherever possible, and clear delineation of associated uncertainties as a basis for decision-making

- The challenge:
  - Requires transparent delineation of decision-making criteria on science policy and other factors beyond risk assessment