INTEGRATING OCCUPATIONAL AND NON-OCCUPATIONAL EXPOSURES TO MULTIPLE AGENTS

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2011

Objectives

- The presentation will showcase drivers for taking a broad view of the impacts of combined exposure sources to worker health;
- Describe the existing tools and techniques for assessing cumulative risk for mixtures; and,
- Demonstrate the applications and impacts of current tools in the context of traditional industrial hygiene practice

Changes in Occupational Risk Assessment Practice

- We are clearly moving to more systematic evaluation of "actual" exposures including the complexities:
  - Multiple routes of exposure
  - Occupational and non-occupational (total exposure)
  - Mixtures of chemicals
  - Effects of chemicals plus non-chemical stressors

Impact on the IH Sphere of Practice

- Assess impacts of "total" exposure for local employees – increasing IH role in community health
- Mandate to "protect all or nearly all workers" needs to include view of human variability in sensitivity – including background exposure
- Best Management Practices
  - Increasing overall worker health improves organizational performance
  - Increasing emphasis on the exposome concept

Exposome

"… the measure of all the exposures of an individual in a lifetime and how those exposures relate to disease."

Source: http://www.cdc.gov/niosh/topics/exposome/

OELs for Total Exposure

- Traditional hazard index approach based on measure of external exposure has limitations for "total" or multiple exposure concerns

$$\text{Hazard Quotient} = \text{Exposure} / \text{OEL}$$

  - Why? Because metrics for exposure *level* and exposure *limit* vary for different types of exposures
- Total exposure should consider:
  - **Aggregate exposure** integrates across multiple routes
  - Cumulative exposure considers risk based on mixed chemical and non-chemical stressors (early effect marker-based OELs as first integration point)

Aggregate Exposure Approaches

- **Integration at "Dose"**
  - Internal Dose

    (e.g., biomarkers)
  - External Exposure
- **Integration at Risk**
  - Qualitative

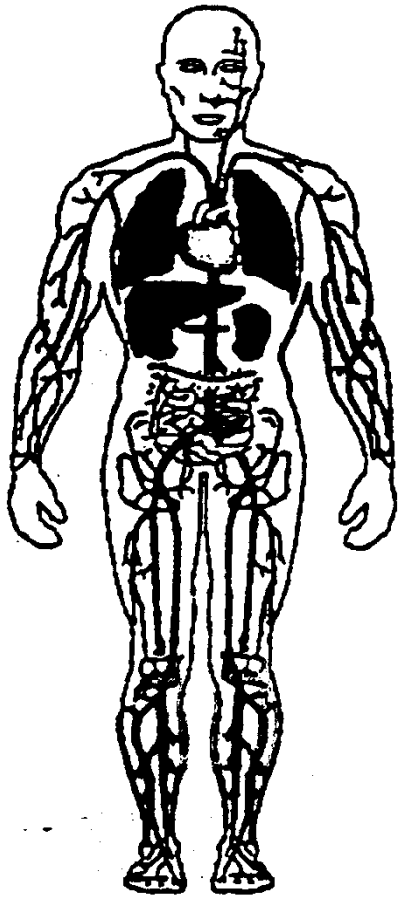
    (e.g., skin notations)
  - Quantitative

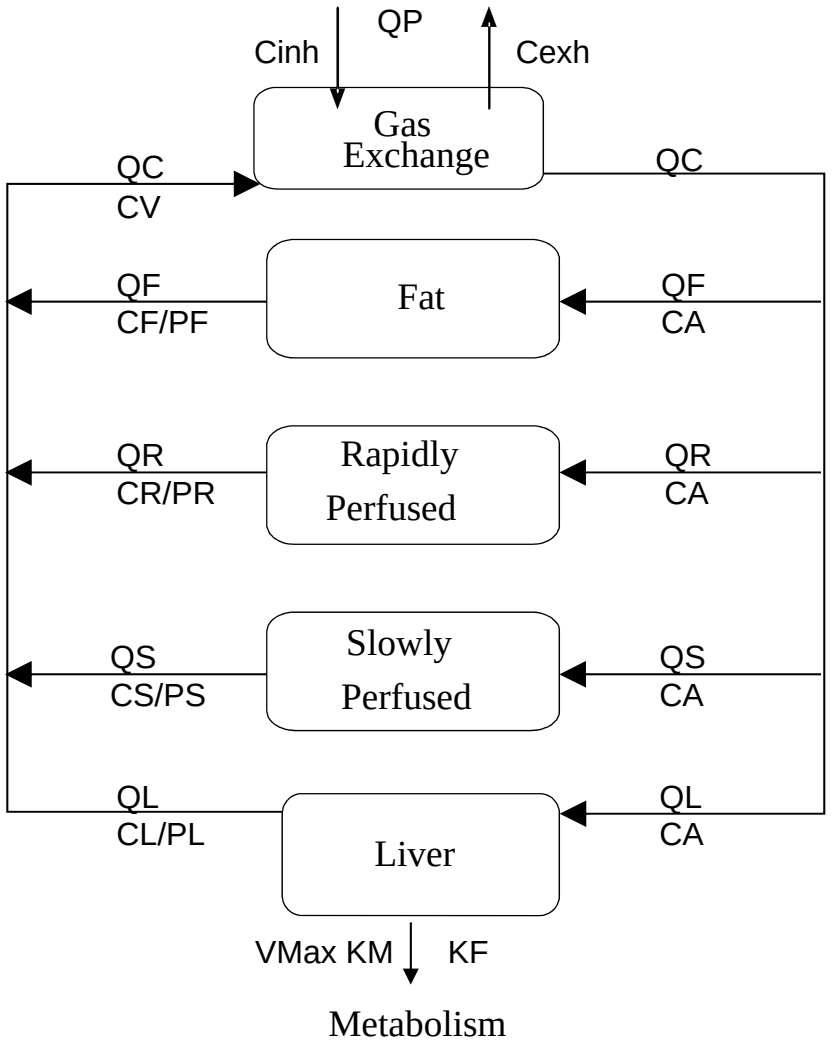
    (e.g., DNEL)

Dose Integration

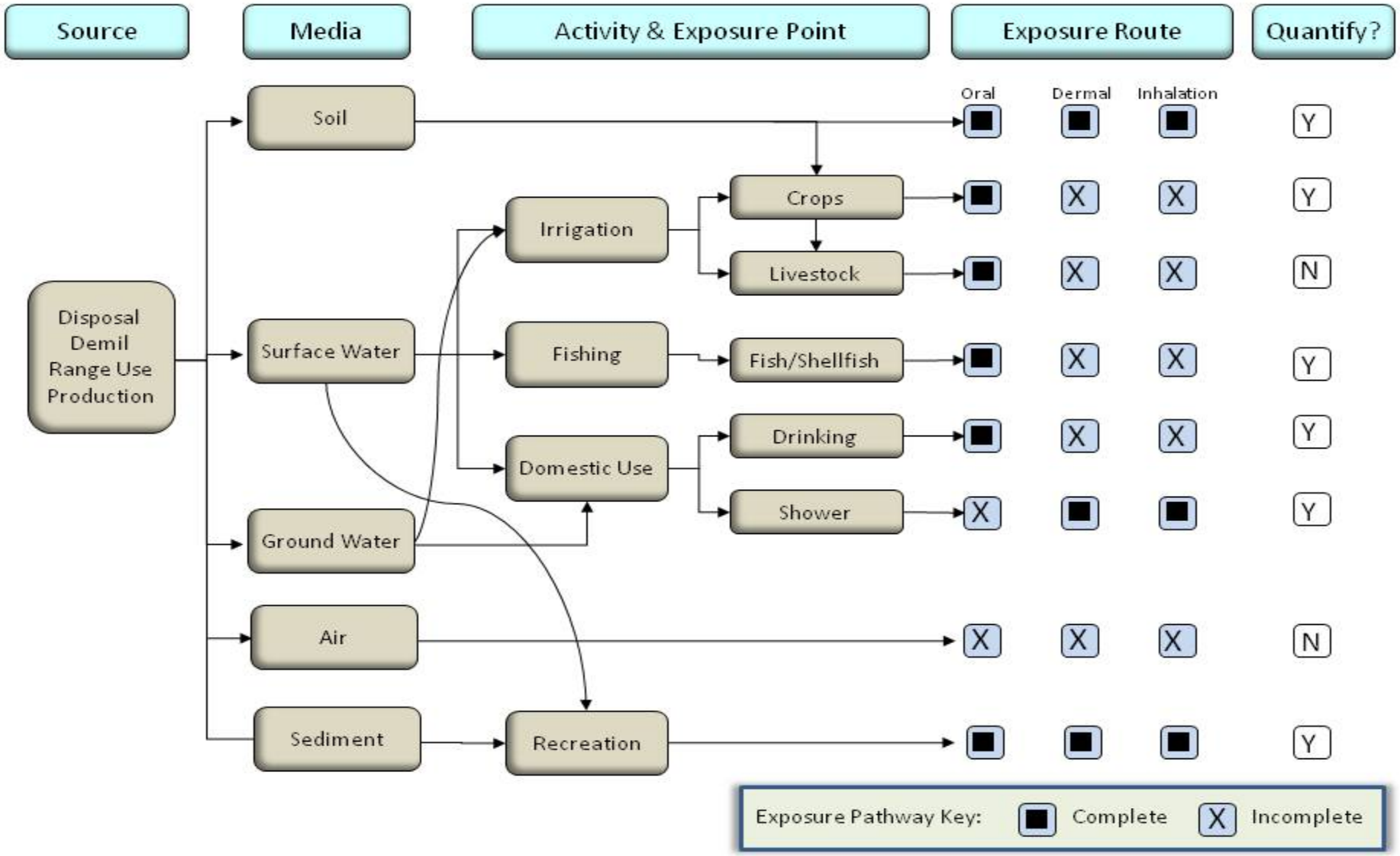
- Integration of doses across routes to identify the total systemic dose can be done with:
  - Measures of internal dose such as biological monitoring
  - Internal dose modeling such as physiologically-based pharmacokinetic (PBPK) models
- Advantages and disadvantages well characterized
- For some chemicals has been well validated and incorporated into routine risk assessment
- Significant research activity to increase use of internal dose metrics

PBPK Model Schematic





Exposure Pathways: A hypothetical conceptual exposure model



Risk Integration

- EPA Pathways Approach for Site Risk Assessment
- Calculates exposure from multiple pathway

Model Equation for Developing Acceptable Risk-Based Concentrations in Soil.
Acceptable Soil Cleanup Target Levels for Non-Carcinogens

$$SCTL = \frac{THI \times BW \times AT \times RBA}{EF \times ED \times FC \times \left[\left(\frac{1}{RfD_o} \times IR_o \times 10^{-6}\,kg/mg\right) + \left(\frac{1}{RfD_d} \times SA \times AF \times DA \times 10^{-6}\,kg/mg\right) + \left(\frac{1}{RfD_i} \times IR_i \times \left(\frac{1}{VF} + \frac{1}{PEF}\right)\right)\right]}$$

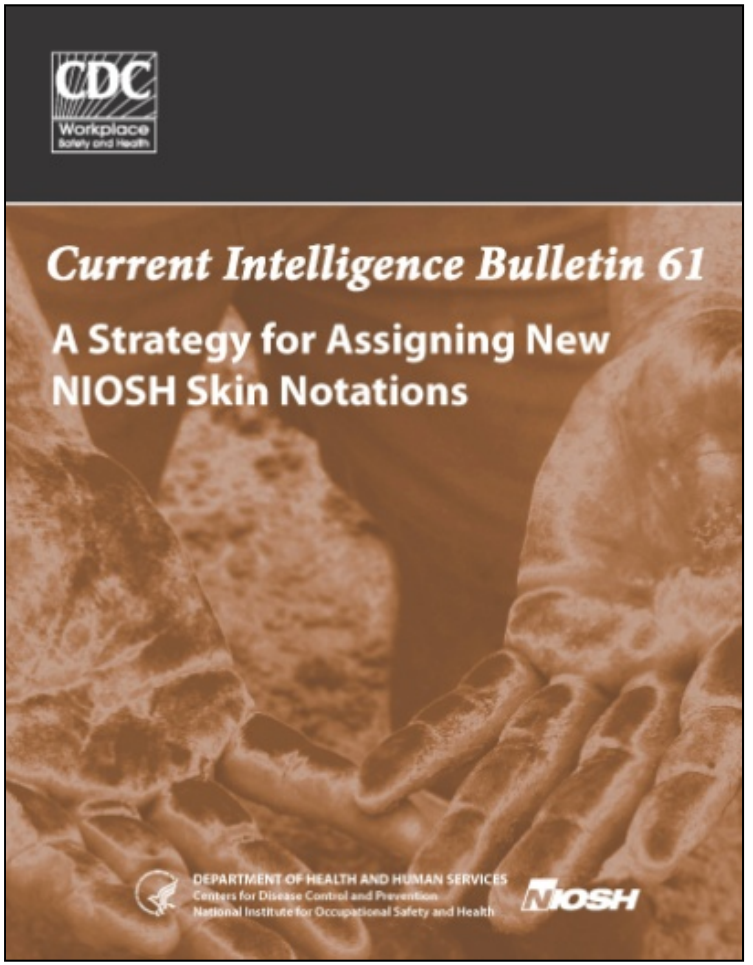
SCTL = Soil Cleanup Target Level
THI = target hazard index (unitless)
BW = body weight (kg)
AT = averaging time (days)
EF = exposure frequency (days/yr)
ED = exposure duration (years)
RBA = relative bioavailability factor (unitless)

FC = fraction from contaminated source (unitless)
IR_O = ingestion rate, oral (mg/day)
SA = surface area of skin exposed (cm^2/day)
AF = adherence factor (mg/cm^2)
DA = dermal absorption (unitless)
IR_i = inhalation rate (m^3/day)
VF = volatilization factor (m^3/kg)

PEF = particulate emission factor (m^3/kg)
RfD = reference dose (mg/kg-day)
RfD_O = oral
RfD_d = dermal
RfD_i = inhalation

Risk Integration

- Skin notations are an example of qualitative consideration for aggregate exposure.
- This notation coupled with workplace dermal exposures suggests caution in applying the inhalation-based OEL.
- Total systemic exposure may be increased by the aggregate exposure.



Risk Integration

- Relative Source Contribution (RSC)
  - is used to ensure that the concentration of a chemical when combined with other identified sources of exposure will not result in unacceptable exposures.
    - Apportions the chemical's allowable dose such as reference dose (RfD) or *OEL* for various environmental media, such as water, food, and soil
  - U.S. EPA RSC Guidance
    - Use values between 0.2 and 0.8
    - Total exposure should not exceed RfD
    - Allocation to water should not be unreasonably small

Relative Source Contribution

- Use of RSC in Calculations for Water Criteria and OEL
  - Maximum Contaminant Level Goal (MCLG)

$$MCLG = \frac{(RfD\ x\ BW\ x\ RSC)}{(water\ intake\ )}$$

  - RSC adjusted OEL

$$OEL = \frac{(NOAEL\ x\ RSC)}{(UF\ )}$$

BW = body weight; NOAEL = no observed adverse effect level; UF = uncertainty factor

Risk Integration

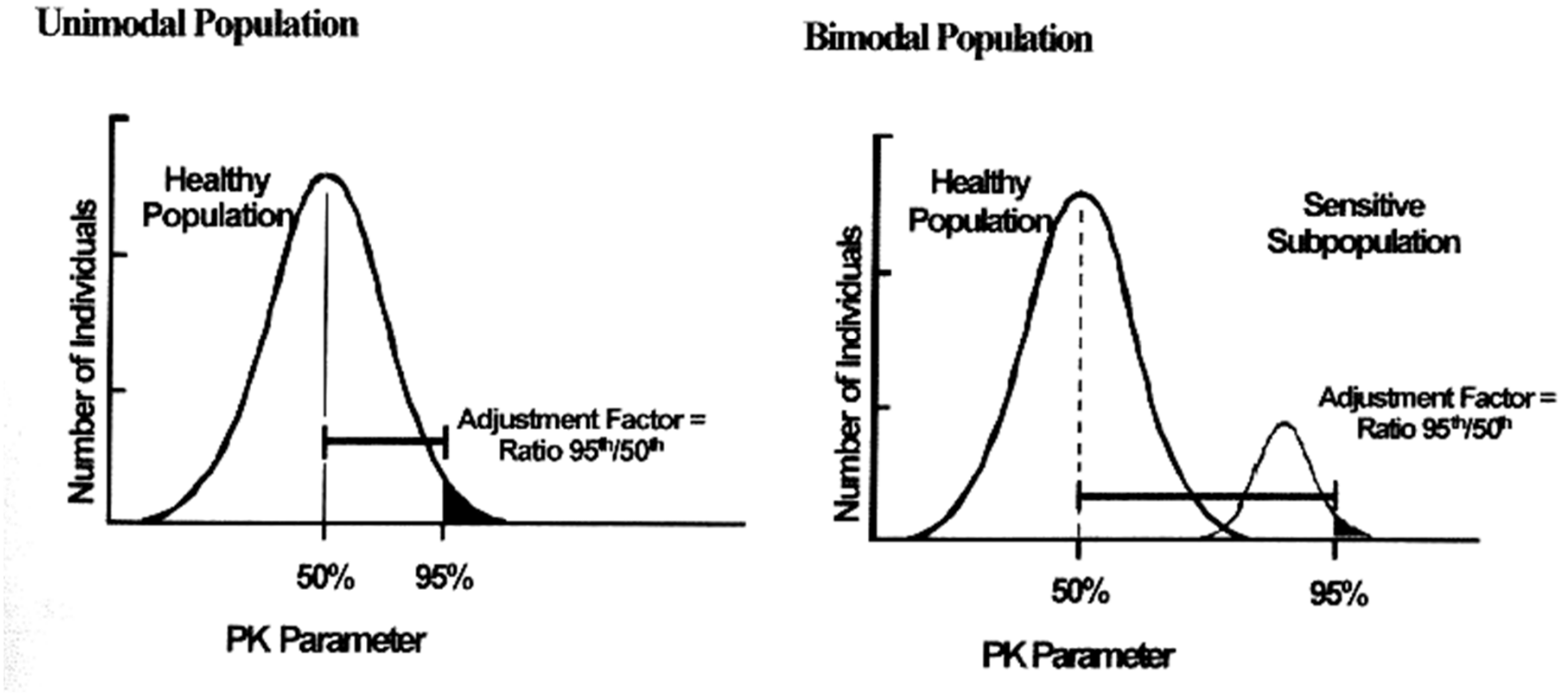
- Uncertainty and Modify Factors in OEL development can be used to address the impacts of multiple sources of exposure.

- Basic Approach

$$OEL = \frac{(Toxic\ Effect\ Level)}{(UF)}$$

- One UF considered is "human variability in susceptibility".
  - Thus, if some portion of the worker population is at risk due to significant background exposure then can increase the UF or apply a modifying factor to account for this variability.
  - Concept used by EPA in Children's Risk Assessment under the Food Quality Protection Act (FQPA)

Worker Population Variability



DNEL Risk Characterization Step

$$\text{Endpoint-specific DNEL} = \frac{NOAEL_{corr}}{AF_1 \times AF_2 \times \ldots \times AF_n} = \frac{NOAEL_{corr}}{\text{Overall AF}}$$

$$RCR = \frac{\text{Exposure}}{\text{DNEL}}$$

RCR (for simulatanous exposure via three routes) = RCR (oral) + RCR (dermal) + RCR (inhalation)

DNEL = derived no effect level; $NOAEL_{corr}$ = no observed adverse effect level corrected ; AF = assessment factors; RCR = risk characterization ratio

OELs for Total Exposure

- Traditional Hazard Index approach based on measure of external exposure
  - Has limitations for "total" exposure concerns

- Total exposure should consider:
  - Aggregate exposure integrates across multiple routes
  - **Cumulative exposure** considers risk based on mixed chemical and non-chemical stressors (early effect marker-based OELs as first integration point)

Cumulative Risk

- The approaches for chemical mixtures risk assessment are evolving
  - Tiered assessments
  - Better use of toxicological mode of action (MOA)
  - Incorporation of aggregate plus chemical mixtures
  - New challenge integration of chemical and non-chemical stressors

Mixtures Assessment

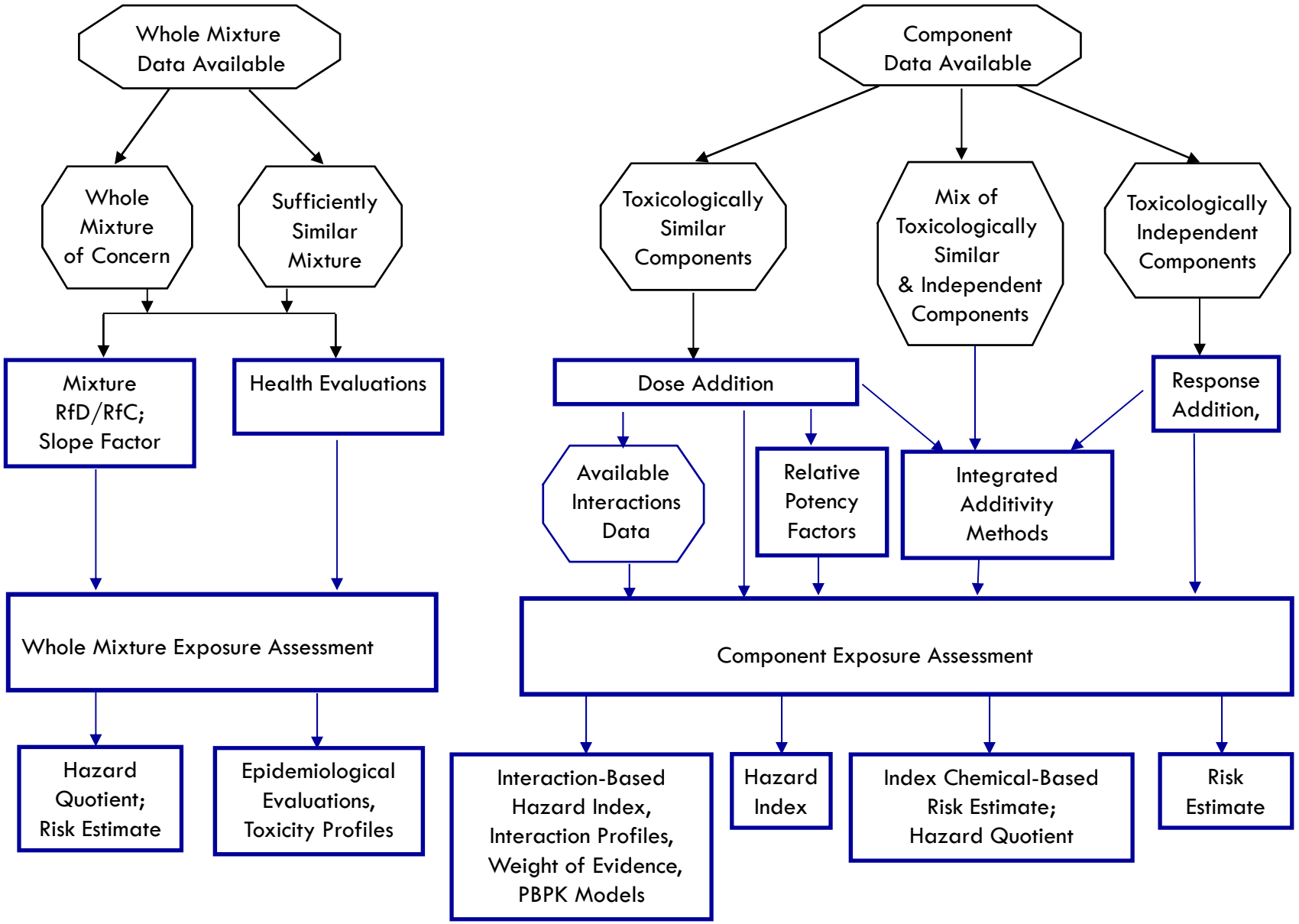
- Most common approach is the Hazard Index (HI)
- Hazard quotients (HQ) for all chemicals present are added together to give a total estimate of non-cancer risk. This sum is the HI:

$$HI = \left(\frac{C1}{T1}\right) + \left(\frac{C2}{T2}\right) + \left(\frac{C3}{T3}\right)$$

C = chemical concentration; T = OEL

  - As values reach and exceed 1 increases the level of concern for heath risk.

Flow Charts for Evaluating Chemical Mixtures



U.S. EPA. (United States Environmental Protection Agency) 2007. Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document. ORD, NCEA, Cincinnati, OH. EPA/600/R-06/013F

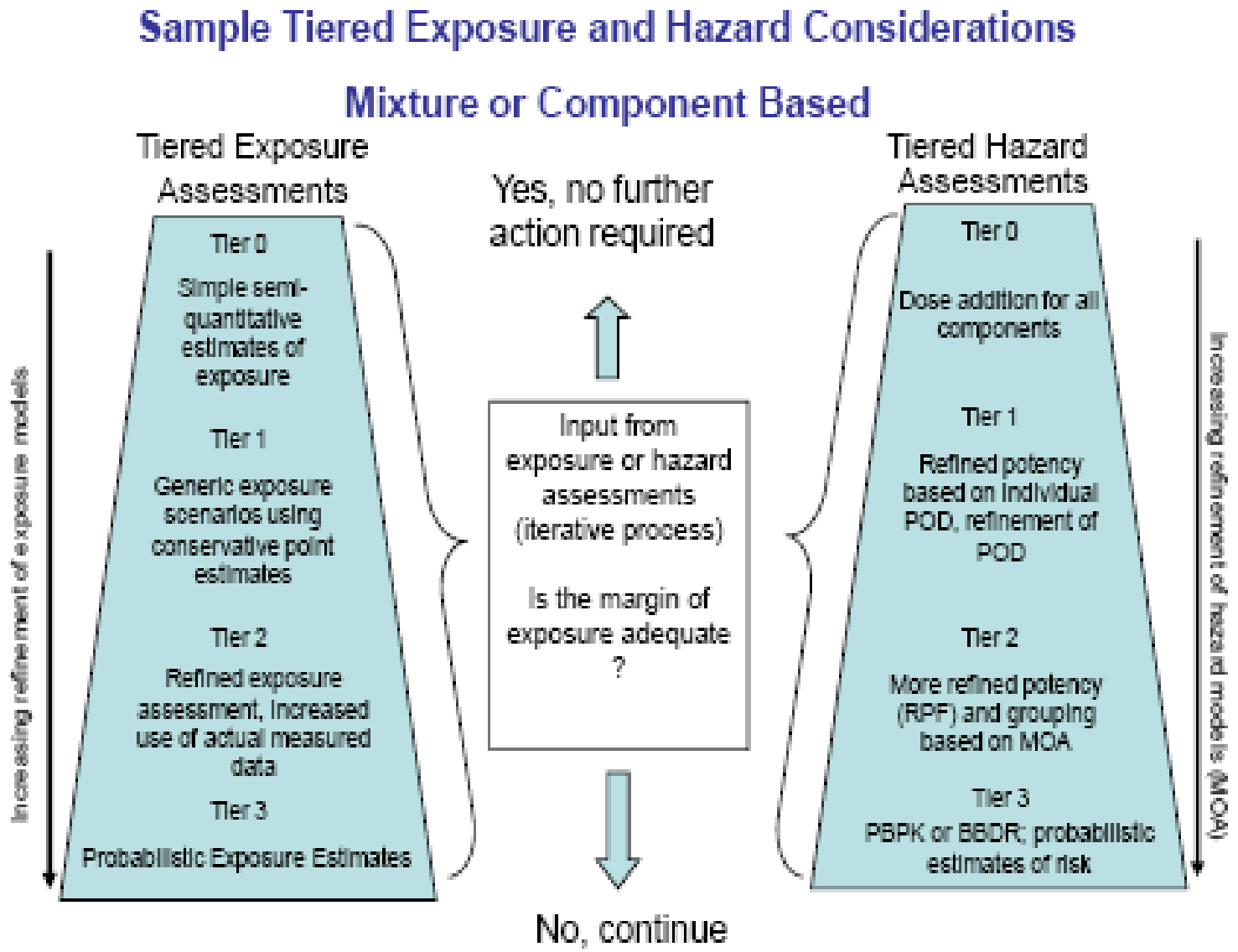


Figure 1: A conceptual representation of the framework (see text for details).

WHO/IPCS Draft Guidelines, 2009

WHO (2009) Assessment of combined exposures to multiple chemicals: Report of a WHO/IPCS international workshop on aggregate/cumulative risk assessment. Geneva, World Health Organization.

EPA Pesticides Approach

(1) Identify Common Mechanism Group (CMG);

(2) Identify Potential Exposures;

(3) Characterize and Select Common Mechanism Endpoint(s);

(4) Determine The Need For a Dosimetry-Based Cumulative Risk Assessment;

(5) Determine Candidate Cumulative Assessment Group

(6) Conduct Dose- Response Analyses and Determine Relative Potency and Points of Departure;

(7) Develop Detailed Exposure Scenarios All Routes and Durations;

(8) Establish Exposure Input Parameters;

(9) Conduct Final Cumulative Risk Assessment;

(10) Conduct Characterization of Cumulative Risk

Take Home Points

- Consideration of combined effects of exposure from all routes and sources is consistent with current principles of IH practice
- Many tools and approaches are available to achieve this goal some of which are routinely applied in related risk assessment fields
- We highlighted here techniques to use either exposure or risk as the point of integration

Questions?