

Advancing Human Health Risk Assessment: Integrating Recent **Advisory Committee Recommendations**

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Abstract

Over the last dozen years, many national and international expert groups have weighed specific improvements to risk assessment. Many of their stated recommendations are mutually supportive, but others appear conflicting, at least in an initial assessment. This review identifies areas of consensus and difference and recommends a practical, biological-centric course forward, which includes: (1) Incorporating a clear problem formulation at the outset of the assessment with a level of complexity that is appropriate for informing the relevant risk management decision; (2) Using mode of action (MOA) information and an understanding of the relevant biology as the key, central organizing principle for dose response assessment; (3) Integrating MOA information into dose-response assessments using existing guidelines for noncancer and cancer assessments, and applying this knowledge to enable interpretation of human biomonitoring data in a risk context; and (4) Using a tiered, iterative approach developed by the World Health Organization/International Programme on Chemical Safety (WHO/IPCS) as a scientifically robust, fit-for-purpose approach for risk assessment of combined exposures (chemical mixtures). While scientificallybased defaults will remain important and useful when data on MOA or other data to refine an assessment are absent or insufficient, assessments should always strive to use the available 21st century knowledge of biological processes, chemical interactions and dose response at the molecular, cellular, organ and organism levels. Achieving this ultimate use will minimize the need for extrapolation and reliance on default approaches.

Programme on Chemical Safety (2005).

Problem Formulation Linked To Risk Management Solution

- The concept of problem formulation as a prelude to a risk assessment work is generally, and should be uniformly, embraced globally by all health organizations
- Differences in risk management decisions, and in the products of individual components of hazard identification, dose-response assessment, exposure assessment, and risk characterizations, should be expected based on different problem formula-
- Risk management input on problem formulation is essential in order for risk assessment scientists to develop useful information. This upfront identification of risk management options should not be seen as changing or subverting the scientific process of risk assessment.

Adapted from Schulte (1989).

Evolution of The "Safe" Dose and Its Related Safety Factor(s)

- IPCS and EPA have guidelines for using chemicalspecific or chemical-related data to characterize interspecies difference and human variability and replace default UFs. Application of these guidelines should be a standard part of developing toxicity values, , as indeed they are already for
- Scientifically based defaults are important and useful when data are insufficient to develop an adequate CSAF.
- Additional factors may be utilized to account for database deficiencies such as insufficient study length (e.g., 90-day study only), absence of dose levels without adverse effects, available effects are clinically severe, or lack of data on key endpoints (e.g., developmental toxicity). Typically, these factors are applied during the derivation of a "safe dose" for data-poor chemicals.

Figure 2. Series of steps that occurs between exposure and the effect of clinical disease and prognostic significance.

VARIABILITY

SUSCEPTIBILITY

From Critical Effects To Mode Of Action (MOA)

- Focus must shift away from identification of only a toxicant-induced apical effect (critical effect) towards identification of a sequence of key events/MOA as the organizing principle for risk assessment.
- Development and acceptance of standardized definitions are essential for adverse effect, adaptive response, and MOA, and for how such data may be integrated with clinical knowledge in order to improve risk assessment.
- Identification of early, driving key events in toxicity/biological pathways will be necessary to apply MOA as the organizing principle. To effectively analyze such key events, a refined concept of the dose necessary to elicit them is needed in relation to doses actually experienced from real-world exposures

Transition From Linear Modeling To Dose-Dependent Transitions in Toxicology

- Harmonization of cancer and non-cancer dose-response assessments should be conducted on the basis of MOA understanding, using such frameworks as the MOA/Human Relevance Factor and Key Event Dose Re-
- Systems biology approaches will be useful in better characterizing the biology of low, environmentally relevant dose-responses and their relevance to clinical findings.
- Additional work is needed on dose-response methods and models that better capture the biology in the low dose region.

Biomonitoring

- Analytical methods in human biomonitoring now provide accurate quantification of many substances in biological samples; biomonitoring programs exist at the national, state, and international levels and provide a unique and valuable snapshot of population exposures to chemicals in our environment.
- Biomonitoring Equivalents and supporting methods for interpreting human biomonitoring data in a health risk context now exist and should be used. Case studies published in the open literature are available for further guidance.
- Interpreting human biomonitoring data in a public health risk context vastly increases the value of population-based biomonitoring programs by allowing risk managers to easily compare population risks from chemical exposures across a broad range of compounds.
- Epidemiological studies investigating potential associations of biomonitoring results with health status or health outcomes should include the development of communication materials in their protocols and subject to Internal Review Board review.
- Publications of cross sectional and case control studies should explicitly include a discussion of the effects of multiple comparisons and analysis of consistency of associations, temporality, specificity, biological plausibility, and dose-response.

Figure 4. Unifying integrating framework for evaluating the risk of combined exposure of

Cumulative Risks and

Mixtures

Approaches to the risk assessment of

chemical mixtures should be iterative.

A Hazard Index summation method based

on common adverse outcomes offers a

simplistic approach that will adequately

protect public health against adverse ef-

fects. However, this approach is not appli-

The tiered framework of IPCS (Meek et al.,

2011) integrates relevant and scientifically

appropriate prior information and should

iterative approach guides refinement of

the exposure assessment and/or use of

Different problem formulations allow dif-

common MOA to replace the screening HI

ferent uses of the iterative IPCS framework.

be used as a template for future work. This

cable beyond screening.

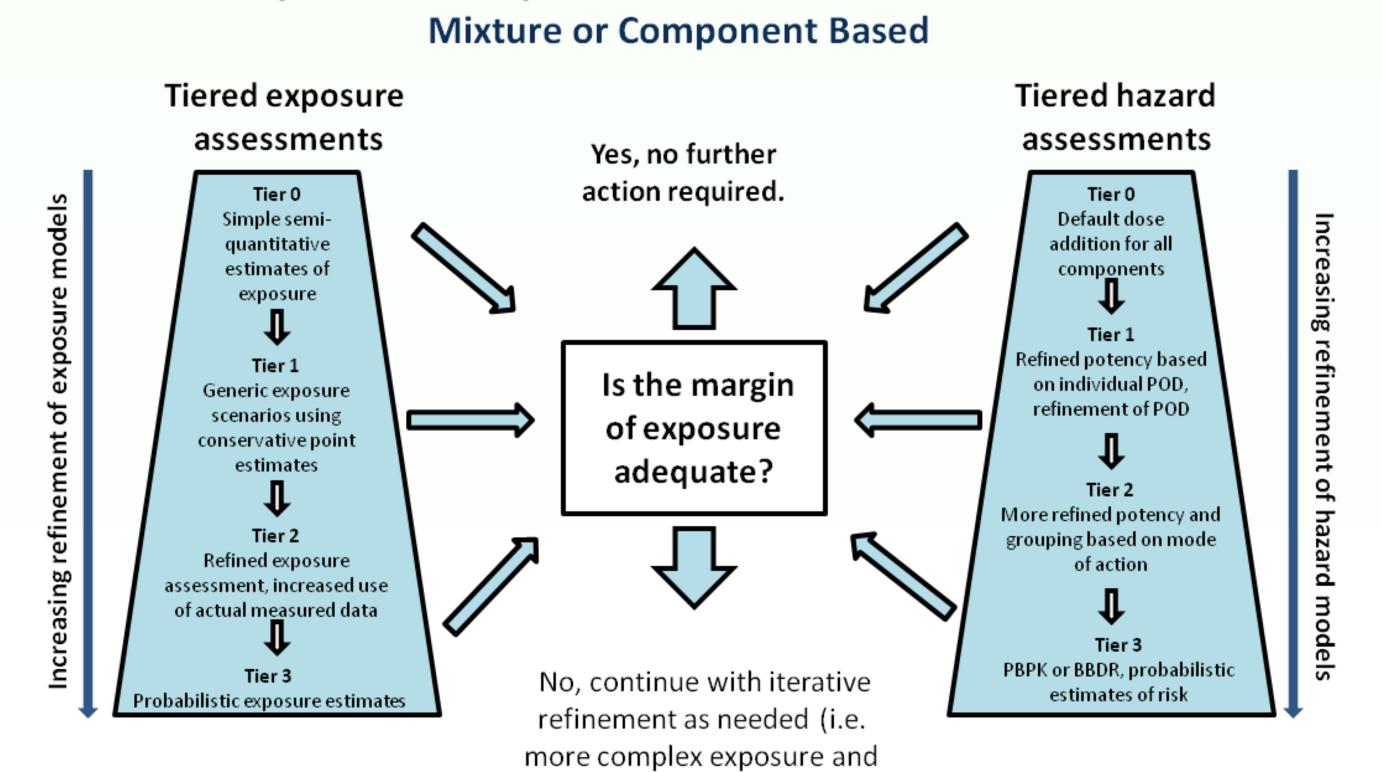
approach.

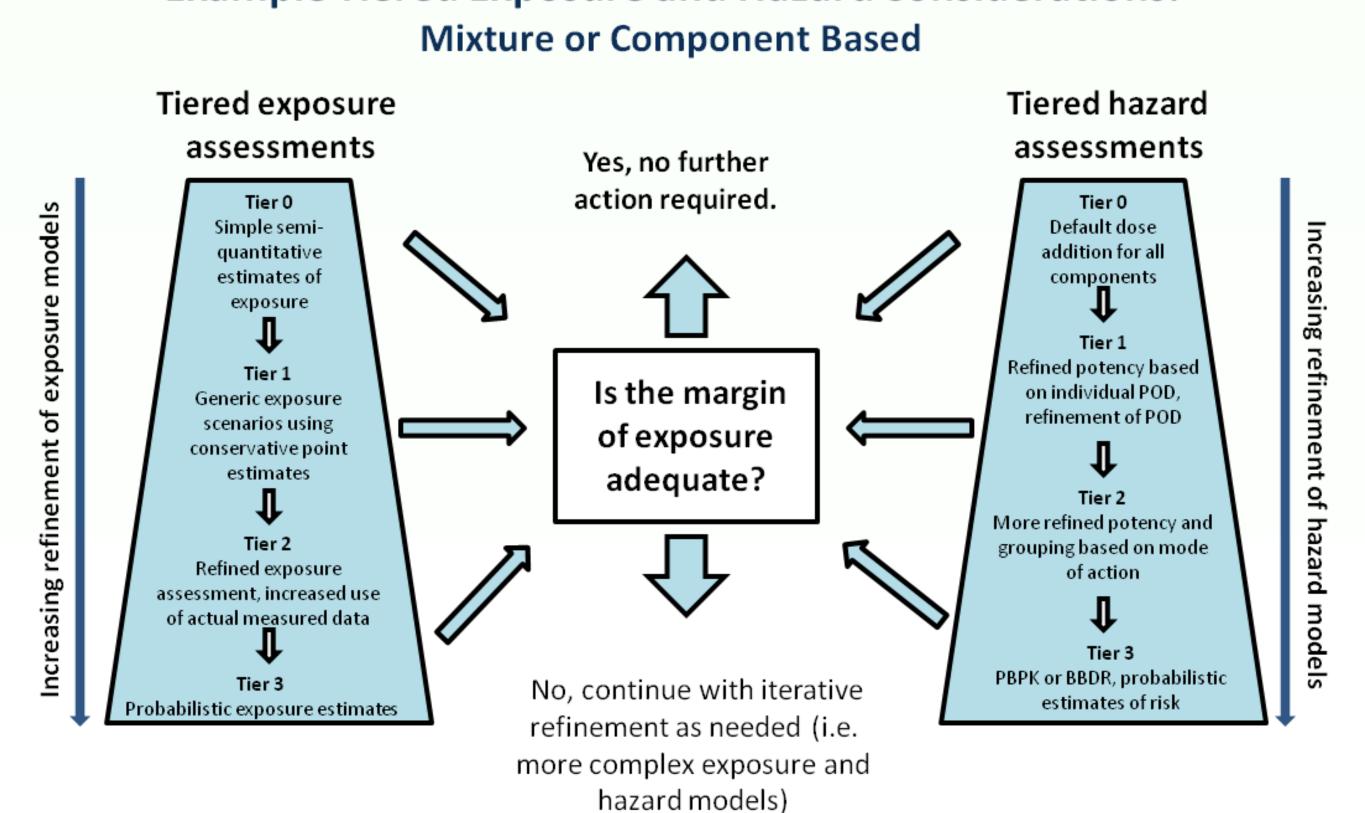
Problem Formulation for Combined Exposure Assessment

multiple chemicals. From Meek et al. (2011) (permission pending)

- What is the nature of the exposure?
- Is exposure likely, taking into account the context?
- Is there a likelihood of co-exposure within a relevant timeframe?
- What is the rationale for considering compounds in an assessment group?

Example Tiered Exposure and Hazard Considerations: Mixture or Component Based





INTERSPECIES INTERINDIVIDUAL DIFFERENCES **DIFFERENCES**

Figure 1. The Chemical Specific Adjustment Factor (CSAF) Scheme of the International

UNCERTAINTY FACTOR - 100

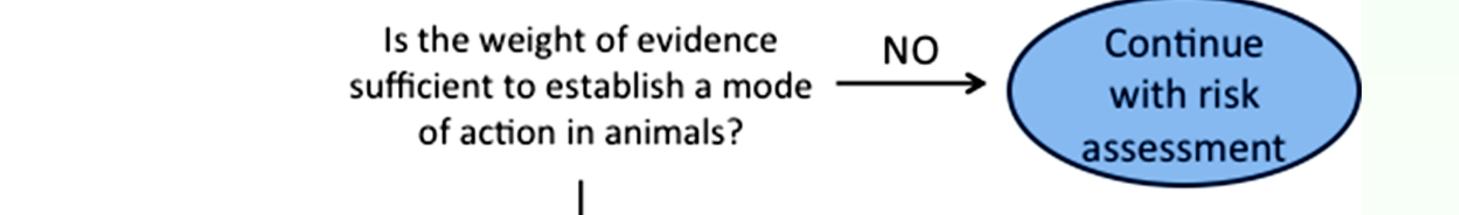
TOXICO-DYNAMIC TOXICO-KINETIC TOXICO-DYNAMIC $\mathsf{HD}_{\mathsf{UF}}$ $10^{0.5}$

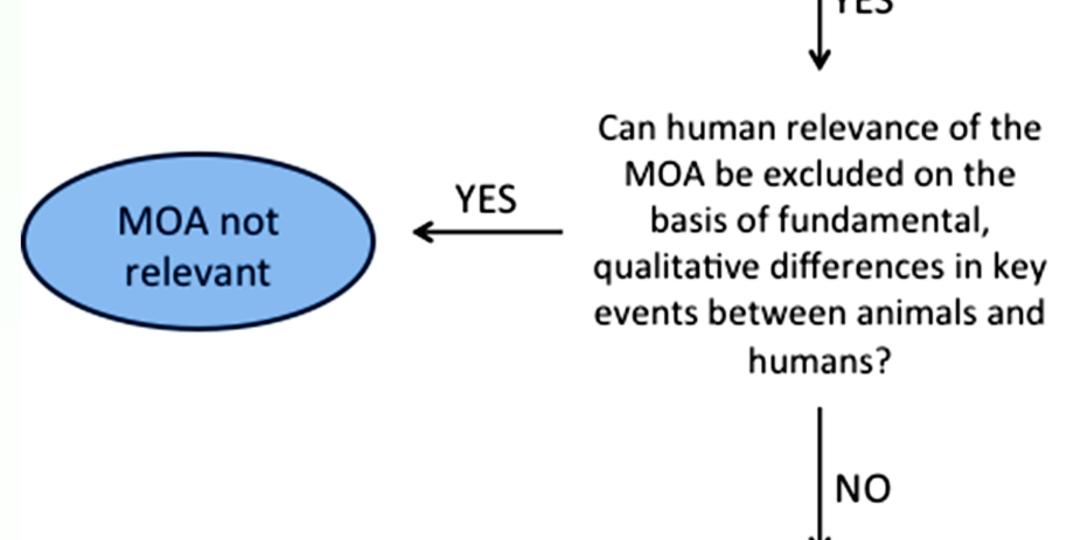
 AD_{UF} = Uncertainty factor for animal to human differences in toxicodynamics AK_{IJF} = Uncertainty factor for animal to human differences in toxicokinetics $HD_{UF} = Uncertainty factor for human variability in toxicodynamics$

 HK_{UF} = Uncertainty factor for human variability in toxicokinetics

Is the weight of evidence

Figure 3. The mode of action/human relevance framework (MOA/HRF). Adapted from WHO (2007).





Can human relevance of the MOA be reasonably ---- quanitative differences in assessment kinetic or dynamic factors between animals and humans?

<u>Critical effect</u>: As dose further increases, the critical effect is reached. This is the first adverse effect, or its known precursor, that occurs to the most [relevant or] sensitive species as the dose rate of an agent increases.^a Doses associated with such effects are Lowest Observed Adverse Effect Levels (LOAELs). The highest NOAEL below this LOAEL is generally used in the dose response, and the focus is on determining this NOAEL in a sensitive population.

Table 1. Continuum of effects associated with any exposure to xenobiotics reflecting a sequence of

Adaptive effects: This continuum starts at low dose with upstream indicators of change, or

sociated with such effects are often referred to as No Observed Adverse Effect Levels

(NOAELs). The concepts of homeostasis and hormesis are relevant here.

adaptive effects, where the organism's ability to withstand a challenge is enhanced. Doses as-

Compensatory effects: As dose increases, compensatory effects occur, which enable the organ-

ism to maintain overall function without further enhancement or significant cost. Doses asso-

ciated with such effects are also often NOAELs. Some of these effects might be judged to be

effects of differing severity (ARA, 2012).

the critical effect.

Adverse effects: As dose further increases, the critical effect is exceeded, and adverse effects are manifested as biochemical changes, functional impairments, or pathologic lesions. These progressively more severe effects impair the performance of the organism, and/ or reduce its ability to respond to additional challenges. At some point these adverse effects become manifestly overt and irreversible, and frank effects or clinical disease ensues.

(a) Note that the bracketed phrase "relevant or" is important since the most relevant specie is always preferred over the most sensitive specie (e.g., if data shows that the rat is more sensitive than the human, the human data are still preferred), but when such information is not available, data from the most sensitive specie are chosen. Also the term "precursor" in this definition is singular, meaning the immediate precursor, not just any prior effect. This restriction is important both because it ties the concept of critical effect into common medical practice of focusing on important endpoints, and because the resulting dose response---such as an RfD---is more meaningful, since without the restriction multiple and different RfDs can be estimated.