Weighing evidence of biological relevance: from empirical testing in rats to 21st century mode of action analysis

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Can we at least agree on the basic reasons for toxicity testing?

- Get the ***necessary information*** about chemicals and products to safeguard human and environmental health by using

  appropriate test systems to evaluate the responses to chemicals, together with …..

  robust interpretive tools to extrapolate from test systems (animals or human cells in vitro) to humans or species in the environment

The Early Days of Regulatory Toxicology

The "Poison Squad" and the Advent of Food and Drug Regulation

By Carol Lewis

U.S. Food and Drug Administration Consumer Magazine
November-December 2002

"O, they may get over it but they'll never look the same,
That kind of bill of fare would drive most men insane.
same."

Chorus from "Song of the Poison Squad" Lew Dockstader's Minstrels, October 1903

A century ago, 12 men sat down to a plate of food laced with poison and came back for more. Blessed by Congress, the dinner was the first in a series of meals containing steadily increasing doses of suspected toxic chemicals. What better animal to test toxicity in humans, than a human?

The infamous five-year human feeding experiment took place in the basement of the Agriculture Department's former Bureau of Chemistry, located on what is now Independence Ave., in Washington, D.C.

Complete with kitchen and dining room and backed by a government laboratory, the project was the brainchild of scientists from the Bureau of Chemistry (now the Food and Drug Administration). Chief chemist Harvey W. Wiley, M.D., considered by many to be the founding father of the FDA, spearheaded the effort to such tests himself. Wiley hoped to learn "whether preservatives should ever be used or not, and if so, what preservatives and in what quantities." Ultimately, if Wiley could prove from his studies that food adulteration went beyond flagrant cheating to obvious harm, then both the public and Congress would likely support a national policy.

'None But the Brave Can Eat the Fare'

Three years after Wiley's initial request, Congress enacted new controls over imported foods, including provisions for the inspection and rejection of adulterated shipments. Historians write that greater knowledge about the safety of common preservatives, it was believed, would serve to strengthen enforcement of these new laws. Therefore, Congress included funding in the chemical division's 1902 budget

Next week he'll give them mothballs, a la Newburgh or else plain;
O, they may get over it but they'll never look the

separate scientific facts on food safety from the recurrent food safety scares that had fast become the subject of growing public mistrust, inflammatory publications, and Congressional hearings. Wiley's earliest concerns stemmed from the widespread use of borax as a food preservative. And, in fact, fraud was so widespread that even products labeled "pure" were often counterfeits, such as purported "pure Vermont maple syrup" that was little more than colored and flavored Iowa corn syrup.

At the same time, however, manufacturers argued that certain preservatives, such as sulfur, were indispensable in processing products such as wines and raisins. Nevertheless, the public was becoming increasingly concerned about all kinds of toxic substances reportedly found in foods.

Although Wiley believed the burden of proving the safety of preservatives should fall on the manufacturers of such additives, still, he boldly asked Congress during Senate hearings on food adulteration in 1899 for money to conduct

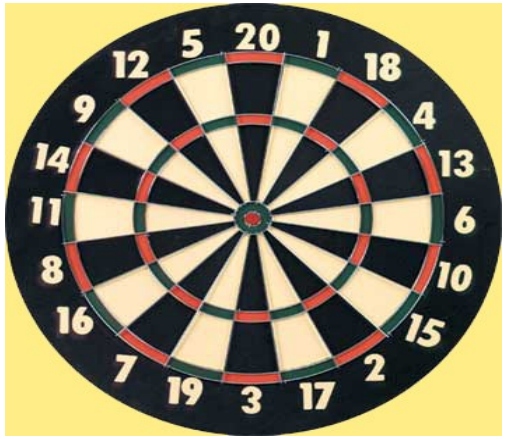
appropriations to carry out the proposed "hygienic table trials."

Wiley and other scientists quickly assembled the first dozen young, able-bodied Department of Agriculture volunteers--dubbed the "Poison Squad" by newspapers--and fed them wholesome meals containing potentially harmful substances. The initial five preservatives studied were borax, salicylic acid, sulfuric acid, sodium benzoate, and formaldehyde. Dosages ranged from one-half gram daily to four grams by the end of the five-year study. Each subsequent group of a dozen men tested one preservative, and in all of the five years, there was never a shortage of volunteers.

The squad pledged to eat all their meals at the "hygienic table." They agreed not to consume any outside foods or beverages, except water. Even that had to be measured and reported. Each participant recorded his weight, temperature and pulse rate before each meal, and what he ate.

Harvey Wiley, USFDA

A key question:



What do we need to know?

- Any possibility of response? *
  - labeling, categorization
- Expected likelihood of response at a given dose?
  - risk assessment
- **No reasonable likelihood of response?**
  - safety assessment

** however, cf. Paracelsus*

"The quality of risk analysis will improve as the quality of input improves. As we learn more about biology, chemistry, physics, and demography, we can make progressively better assessments of the risks involved. Risk assessment evolves continually, with reevaluation as new models and data become available."

"Science and Judgment in Risk Assessment"
(National Research Council, 1994)

Key Definitions in the New EPA Cancer Guidelines

Default – A generic approach, the use of which must be justified on the basis of the lack of adequate chemical-specific data

Mode of Action - "a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation."

Biologically Based Dose-Response (BBDR) Model – "predictive tool used to estimate potential human health risks by describing and quantifying the key steps in the cellular, tissue and organismal responses as a result of chemical exposure."

Value of Mechanistic Data for Risk Assessment

- Identify
  - Key biological (precursor) events
  - Human relevance of animal findings
  - Dose response for extrapolation
  - Life stage susceptibilities
- Understand
  - Common pathways of toxicity (cumulative risk assessment)
- Promote
  - Consistent harmonized approaches to risk assessment for all health endpoints

Parallel Efforts to Understand How Compounds caused Effects

MODE-OF-ACTION STUDIES (1970's to the Present)

- Vinyl chloride metabolites and liver cancer (Gehring)
- Saccharin and bladder tumors (Cohen)
- Formaldehyde induced nasal tumors (CIIT)
- Hydrocarbon nephropathy
- Dioxins
- Arsenic

USEPA/IPCS Mode of Action Framework

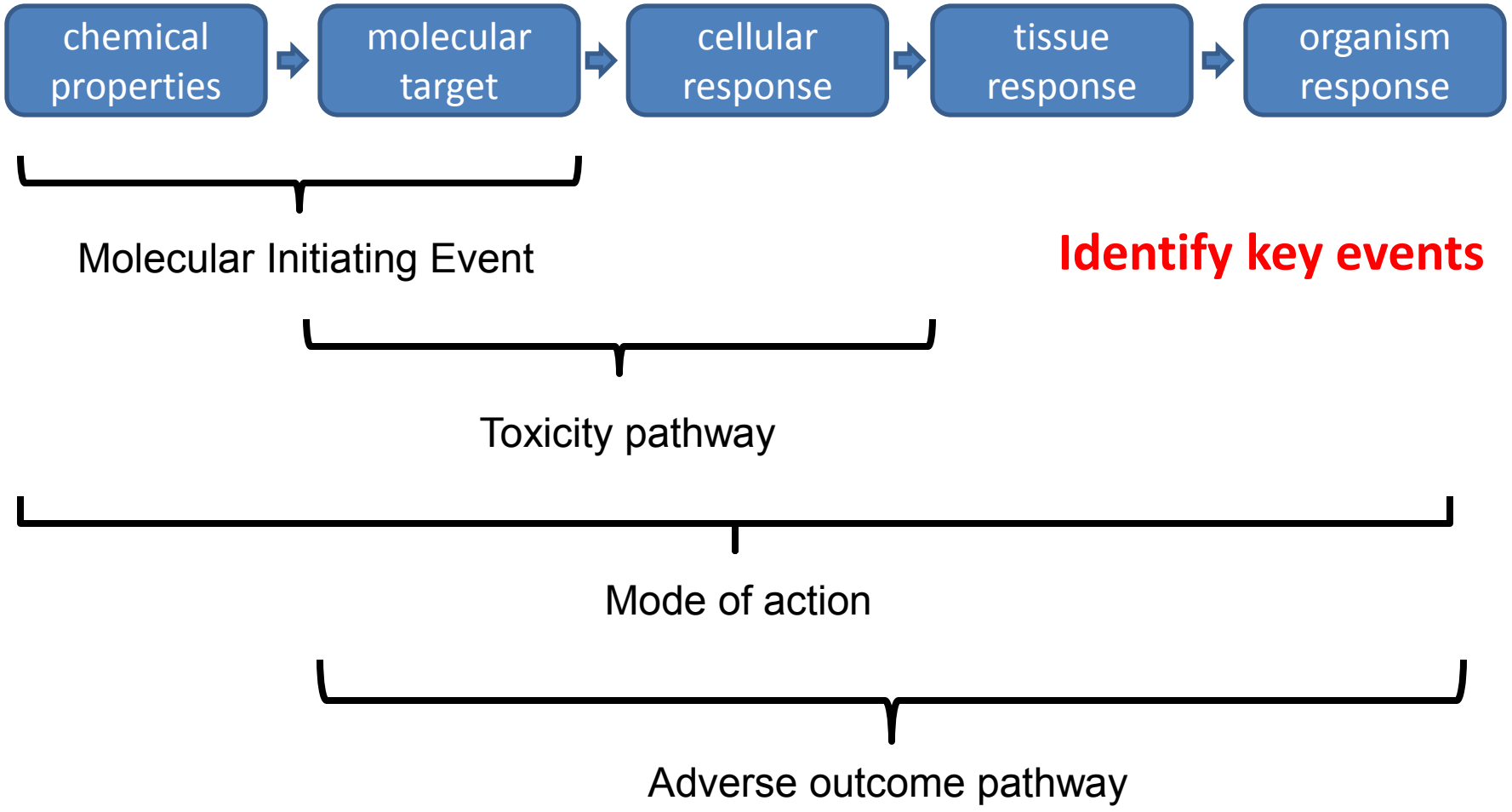
- Postulated mode of action
  - Identify sequence of key events on the path to cancer
- Experimental support
  - Concordance of dose-response for key events with that for tumors
  - Temporal relationships for key events & tumors
- Biological plausibility & Coherence
- Strength, consistency & specificity
- Other modes of action
- Identify uncertainties
- Conclusion

ILSI/IPCS Human Relevance Framework

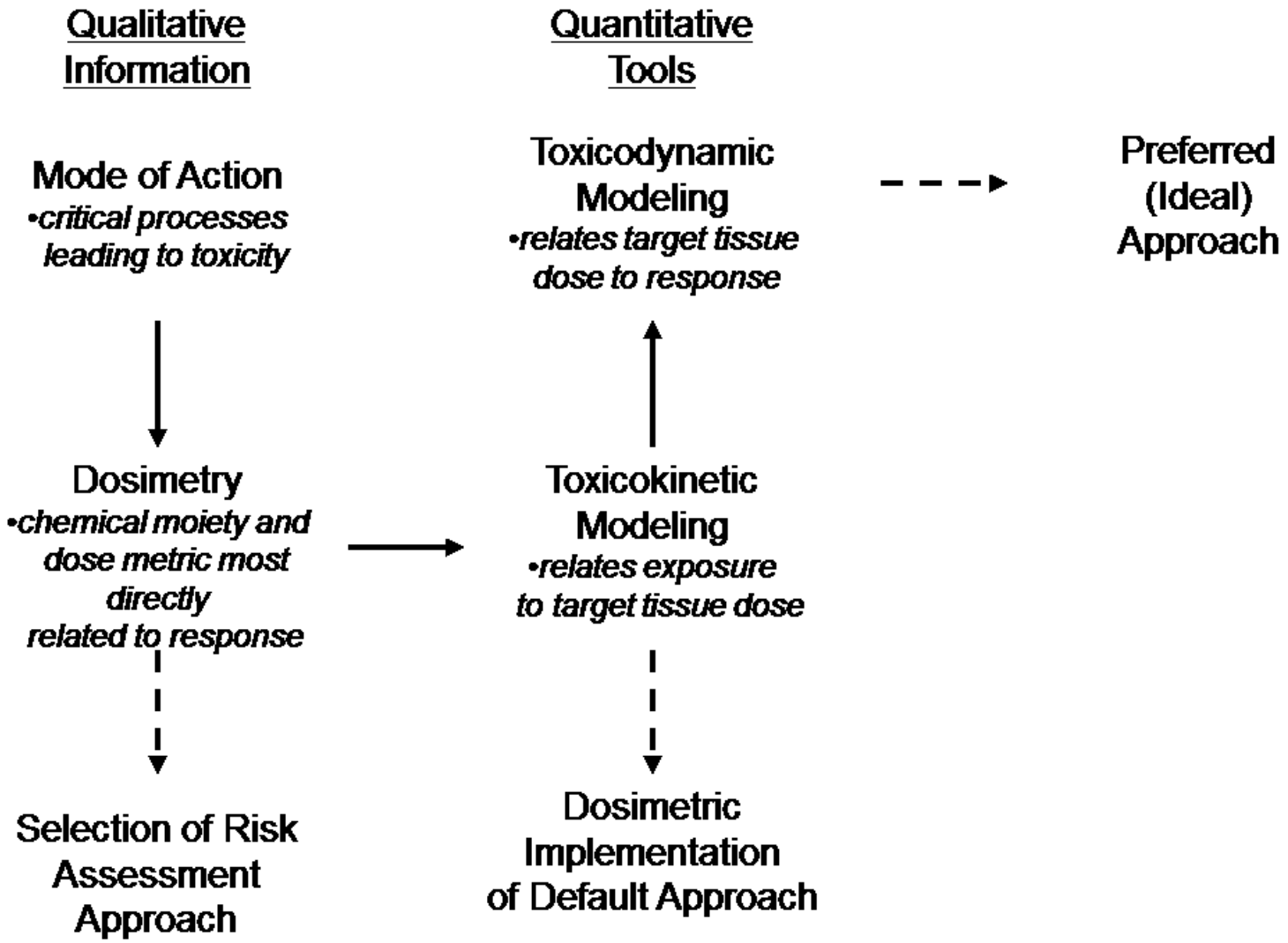
- Adjunct to Mode of Action analysis
  - Comparability or concordance analysis of the key events & relevant biology between the laboratory species & humans
  - extended human relevance analysis to include mutagenic carcinogens & noncancer end points
- Based on three considerations:
  - Is the Weight of Evidence sufficient to establish a MOA in animals (MOA Framework)?
  - Are the key events in the animal MOA plausible in humans?
  - Taking into account kinetic/dynamic factors, is the animal MOA plausible in humans?

AOPs help bring something new to the table

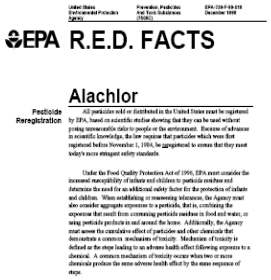
Chemical-agnostic response-response relationships



Mode-of-Action Directed Risk assessment



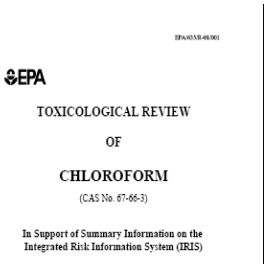
Some Examples of Mode-of-Action Directed Risk Assessments at USEPA


EPA R.E.D. FACTS

Alachlor

Pesticide Reregistration

Alachlor - ". . . a margin of exposure (MOE) approach (indicative of a non-linear dose response) should be used for the risk assessment."


EPA

TOXICOLOGICAL REVIEW

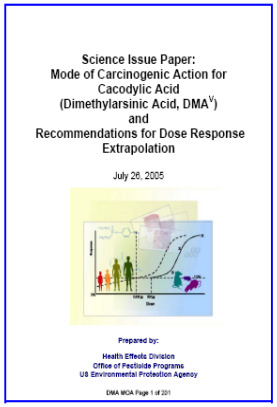
OF

CHLOROFORM

(CAS No. 67-66-3)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

Chloroform – ". . . a nonlinear approach is more appropriate for low-dose extrapolation."


Science Issue Paper:
Mode of Carcinogenic Action for Cacodylic Acid (Dimethylarsinic Acid, DMA^{V}) and Recommendations for Dose Response Extrapolation

July 26, 2005

Prepared by:

Health Effects Division
Office of Pesticide Programs
US Environmental Protection Agency

Cacodylic Acid – ". . . nonlinear default approach (i.e., derivation of a reference dose or margin of exposure) is regarded as the more appropriate dose response extrapolation approach. . ."

Additional Applications of Mode of Action in Risk Assessment

Application	Examples
Determination of human relevance	Atrazine, MTBE (USEPA)
Cross-chemical extrapolation	Vinyl fluoride (IARC)
Criterion for cumulative risk assessment	Organophosphates (USEPA)
Precursor/biomarker selection	Liver weight (USEPA)
Harmonization of cancer/noncancer approaches	Perchlorate (USEPA)
Selection of dosimetric approach	Vinyl chloride, EGBE (USEPA)
Development of CSAFs	Boron and compounds (USEPA)
Development of BBDR model	Formaldehyde (USEPA)

Hierarchy of Dosimetric Approaches: Changing Nature of Uncertainty

Generic Default

Categorical Default

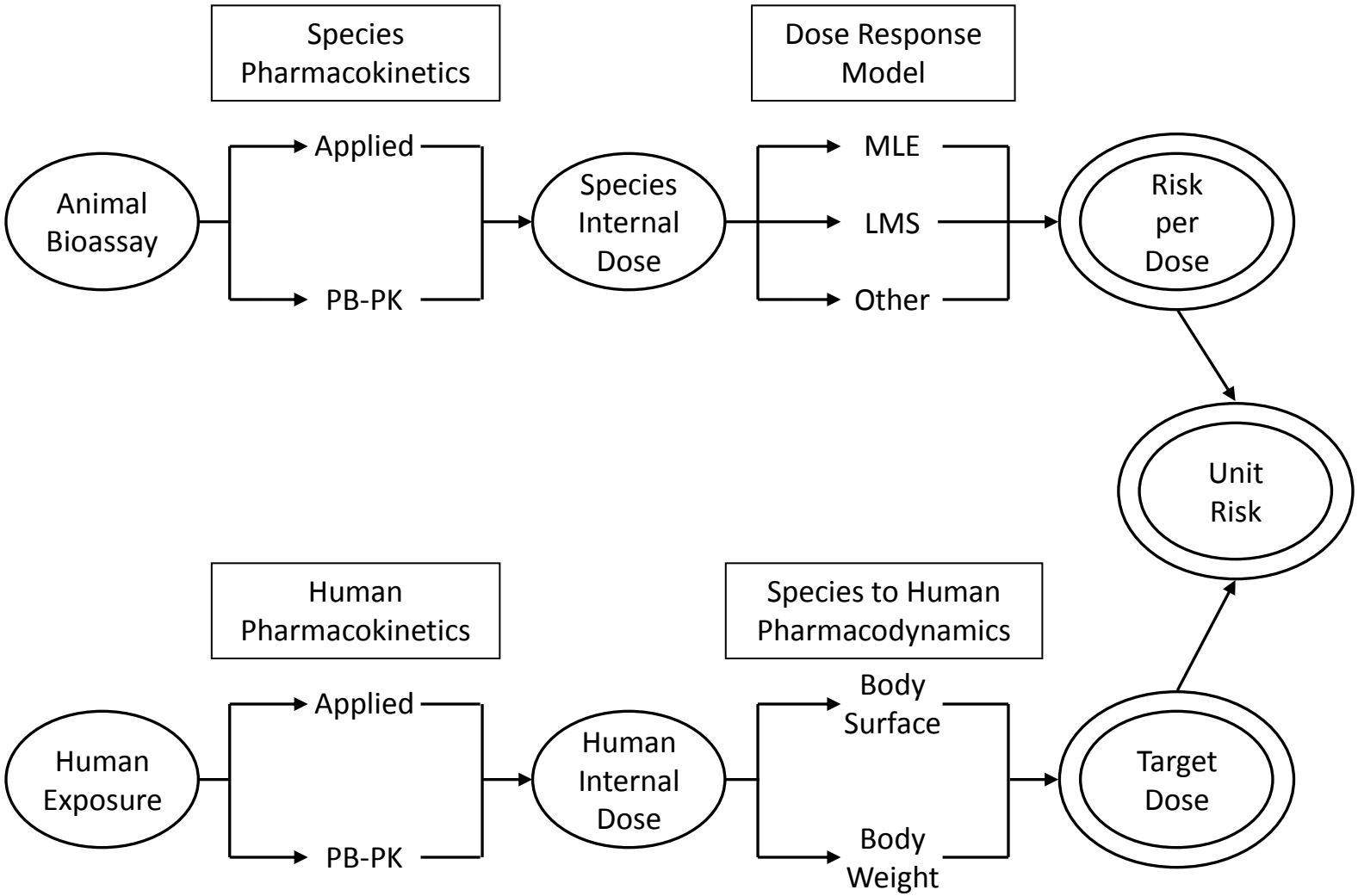
Data-Derived Uncertainty Factor

Chemical-Specific Adjustment Factor

Physiologically Based Pharmacokinetic Model

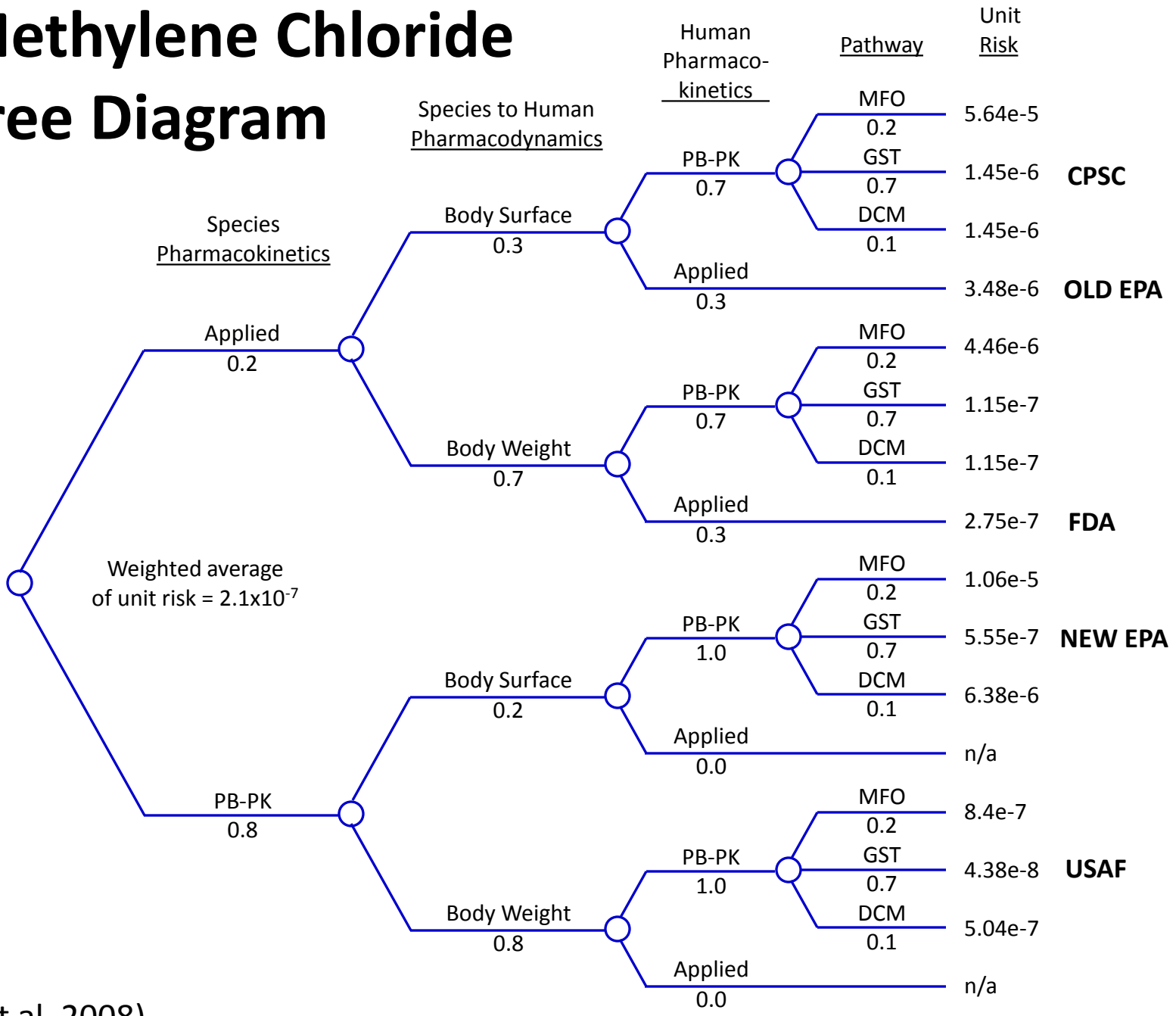
Biologically Based Dose-Response Model

Decision Analysis Framework for Methylene Chloride



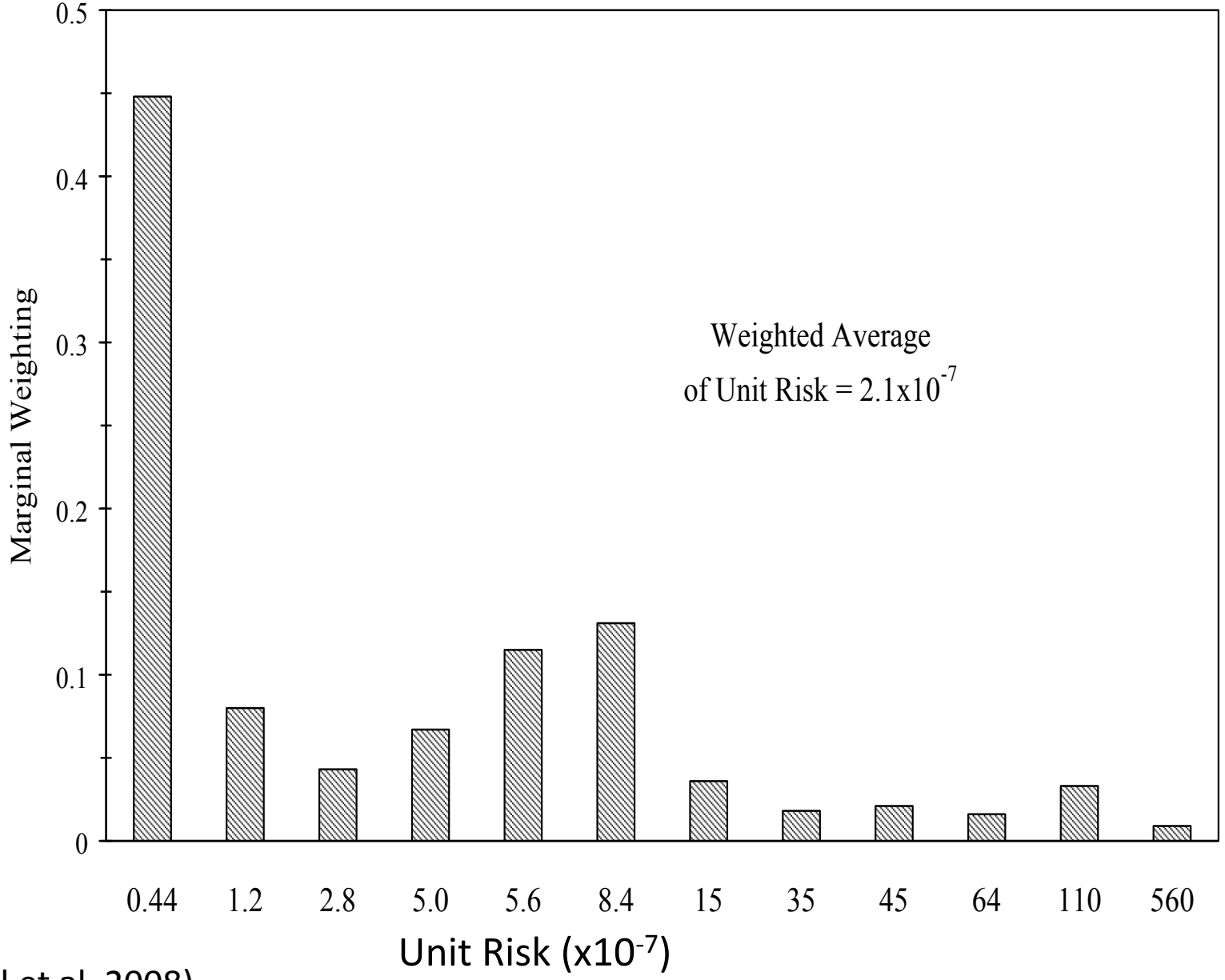
(Clewell et al. 2008)

Methylene Chloride Tree Diagram



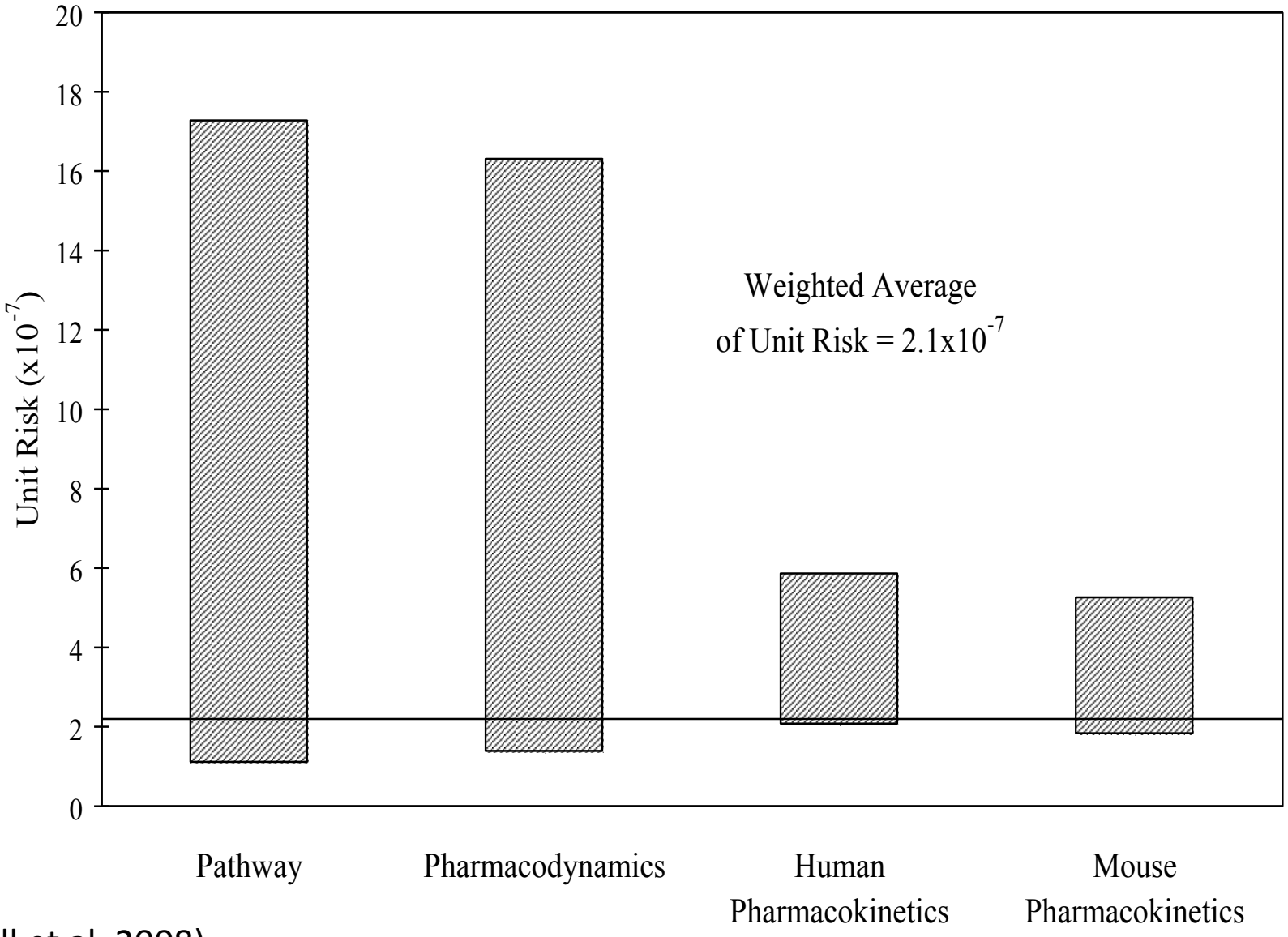
(Clewell et al. 2008)

Unit Risk Distribution for DCM



(Clewell et al. 2008)

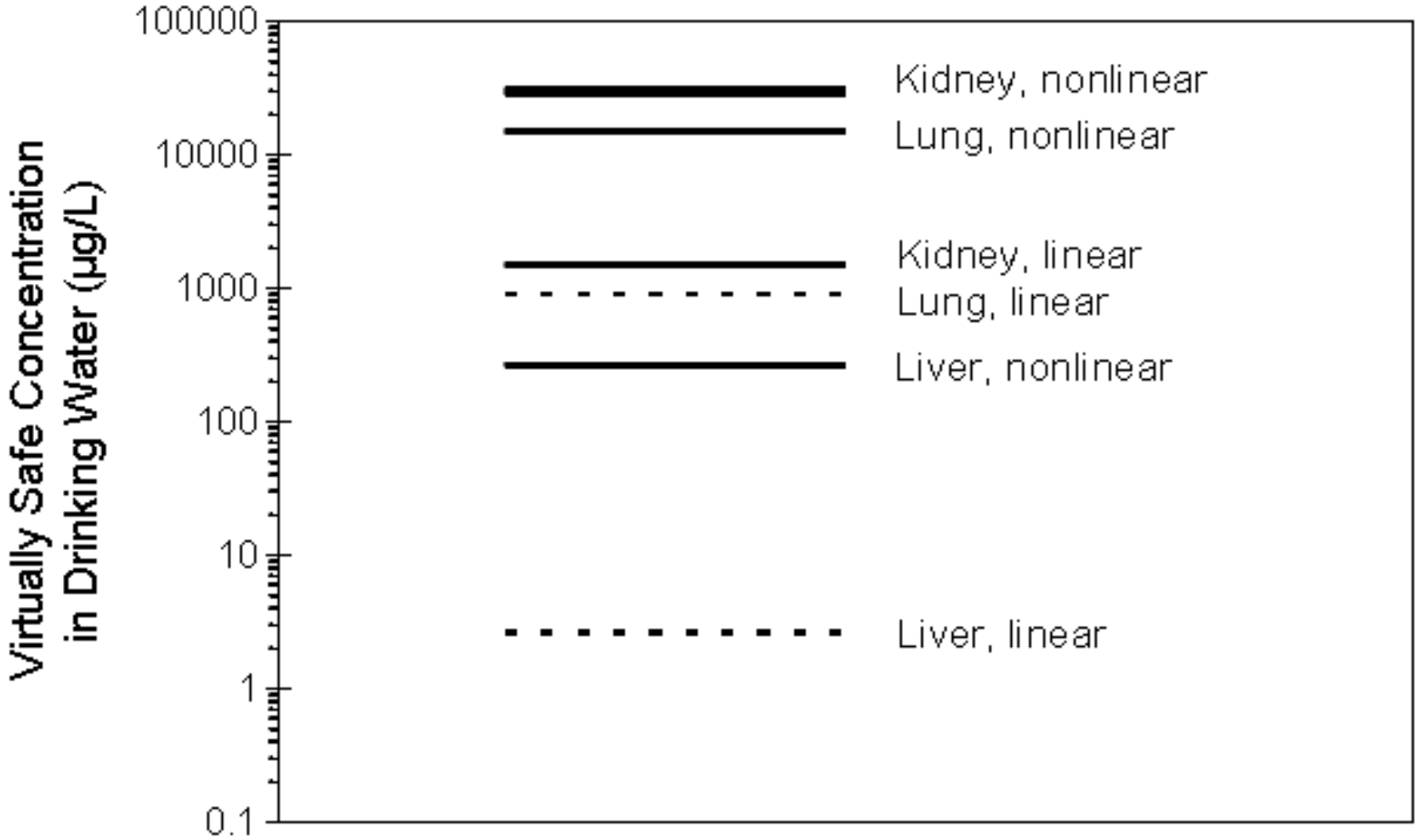
Relative Impact of Decisions on Risk



(Clewell et al. 2008)

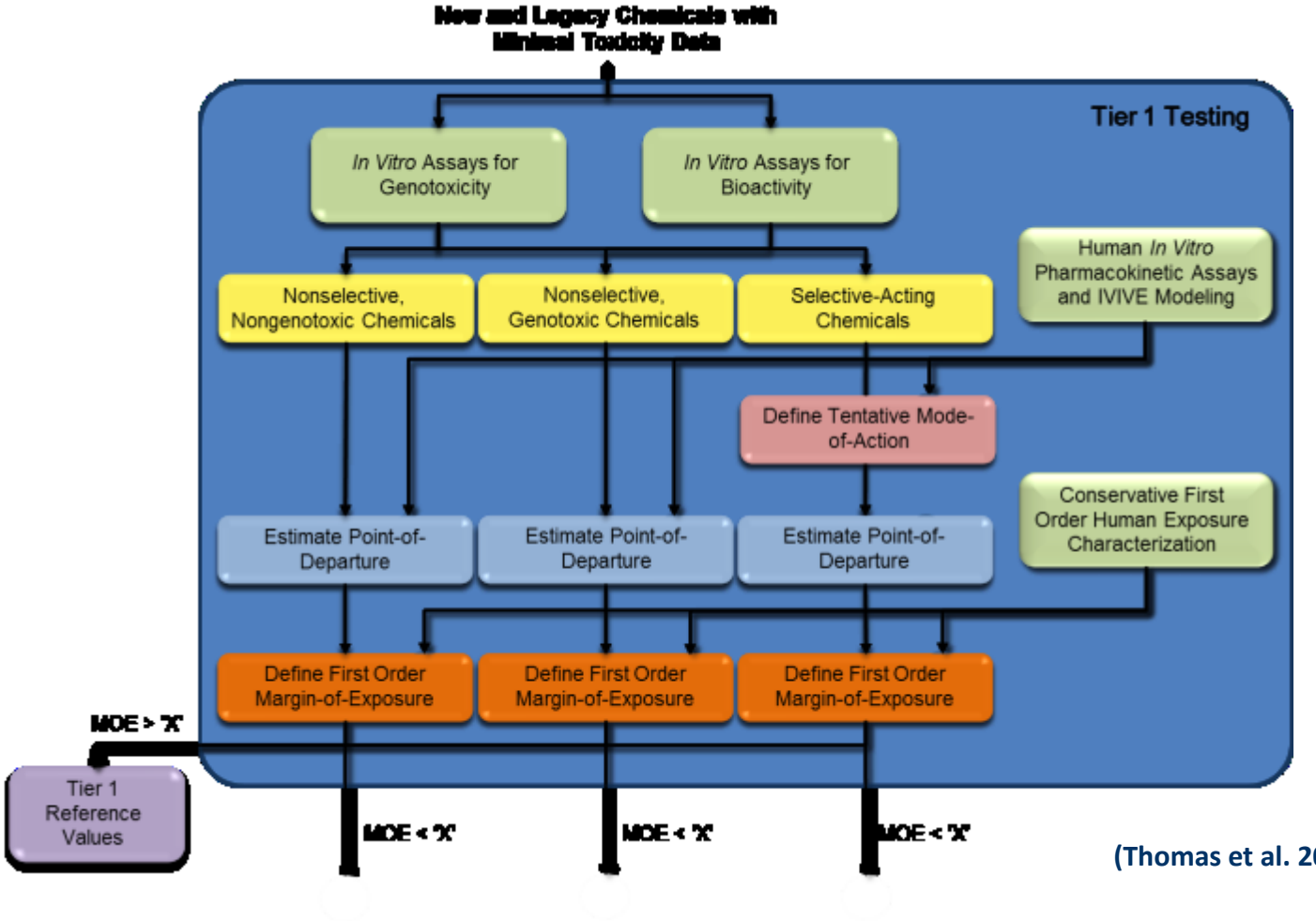
Comparison of virtually safe concentrations for trichloroethylene in drinking water

Dashed lines indicate approaches that are not recommended.
Broader solid line identifies the preferred approach based on biological plausibility.



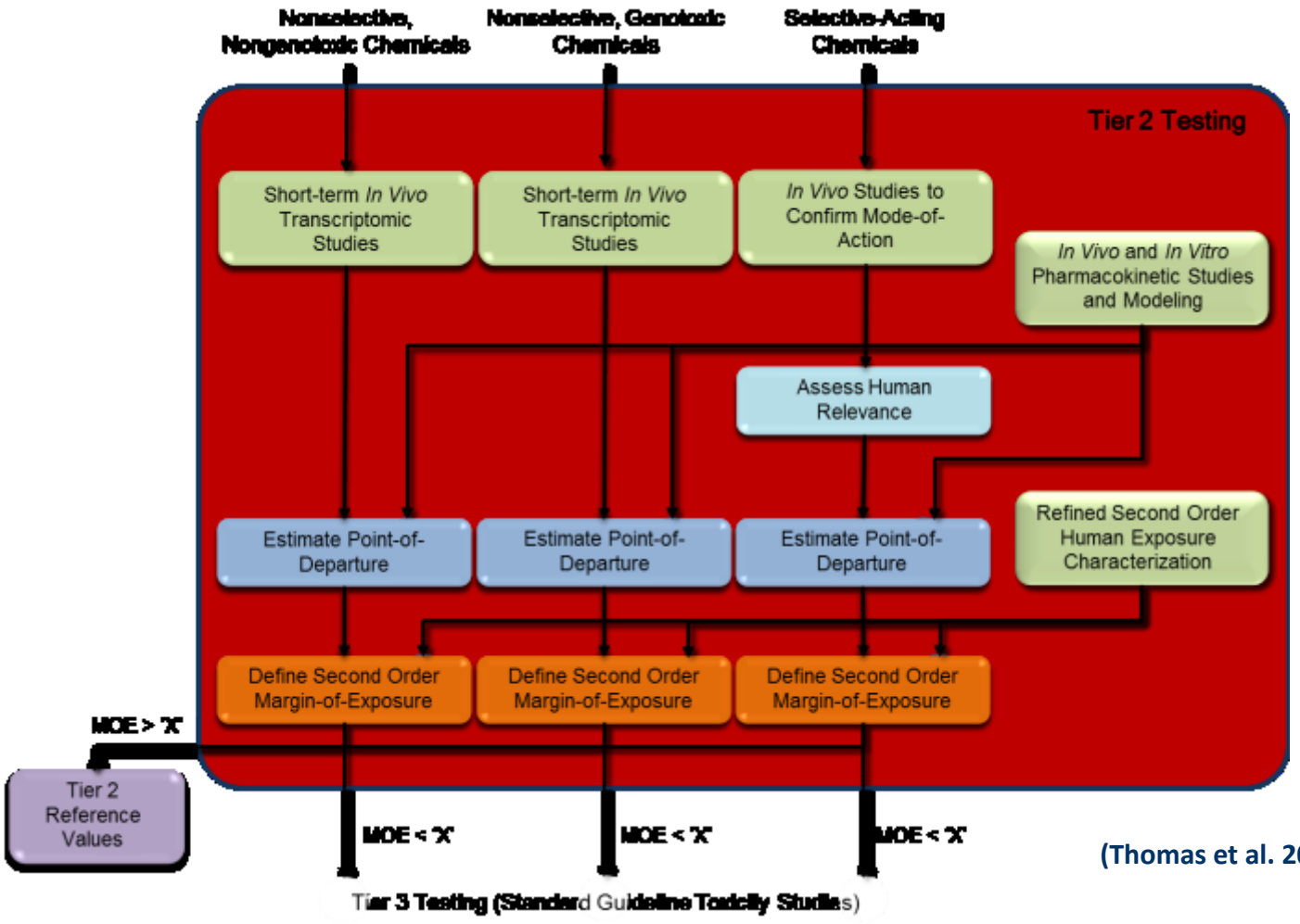
(Adapted from Clewell and Andersen, 2004)

Tiered Approach for 21st Century Risk Evaluation – Tier 1



(Thomas et al. 2013)

Tiered Approach for 21st Century Risk Evaluation – Tier 2



(Thomas et al. 2013)