



MODERNIZING PROBLEM FORMULATION

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Key Scientific Improvements Needed in IRIS

- Problem formulation, including plan for conducting the assessment
- Data acquisition protocol
- Data evaluation protocols for each major type of study: epi, animal tox, mechanistic for determining quality & reliability
- Transparent framework for integrating results - weight of evidence methodology - to evaluate mode(s) of action, cause and effect, etc.
- Accurate characterization of potential risks associated with exposures at environmental levels (including uncertainties)
- Independent peer review, responsiveness to scientific issues raised and accountability that these are addressed

Weight of Evidence Framework for Integration of Lines of Evidence

**Critical Reviews
in Toxicology**

<http://informahealthcare.com/txc>
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informa
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REVIEW

A survey of frameworks for best practices in weight-of-evidence analyses

Lorenz R. Rhomberg¹, Julie E. Goodman¹, Lisa A. Bailey¹, Robyn L. Prueitt¹, Nancy B. Beck², Christopher Bevan³, Michael Honeycutt⁴, Norbert E. Kaminski⁵, Greg Paoli⁶, Lynn H. Pottenger⁷, Roberta W. Scherer⁸, Kimberly C. Wise², and Richard A. Becker²

Outcome of the December 2012 Workshop organized by
ACC's Center for Advancing Risk Assessment Science and Policy
<http://arasp.americanchemistry.com/>

Recommendations on Best Practices for WoE from Rhomberg et al. 2013

- Articulating the central organizing elements
- Modernizing problem formulation
- Specific best practices for data acquisition, data evaluation, WoE (integration) and drawing conclusions
- Implementing Best Practices

Modernizing Problem Formulation

Improving the problem formulation phase is a key to making risk assessment:



Steps Needed to Modernize Problem Formulation



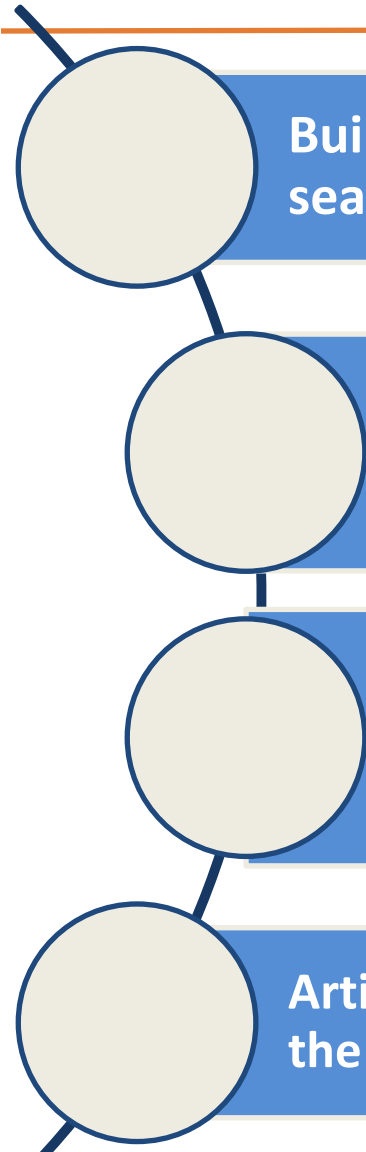
Intended purpose of the assessment (incl. how outcomes will be used (which programs & for which RA & RM purposes))

Identify uses, sources and exposures, key potential exposure scenarios & populations

Identify and summarize conclusions of recent relevant peer reviewed evaluations (e.g., ITER, ATSDR, NTP, IARC; journal publications)

Summarize the potential hazards of key concern for the assessment

Steps Needed to Modernize Problem Formulation



Building from the Preamble: articulate the specifics: lit search strategy, data evaluation protocols, etc.

Preliminary identification of hypothesized modes of action for production of these toxicities: absolutely necessary for cancer endpoint evaluations

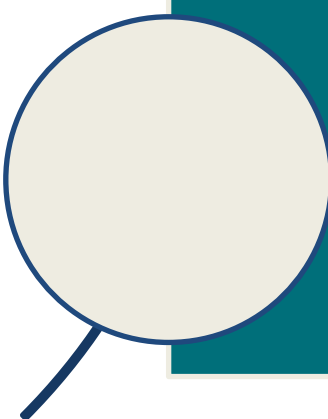
Define the framework that will be used for study integration (e.g., WHO/IPCS Key Events DR Framework; Hypothesis-Based WoE Framework, etc.)

Articulate the key scientific issues that need to be addressed in the evaluation of the hypothesized Modes of Action

Stakeholder Meeting: Open and Frank Discussion



**Of the Problem Formulation
documentation (analysis plan)**



**Of the key scientific issues that need to be
addressed in the assessment and
specifically for evaluation of the
hypothesized Modes of Action**

Modernizing Problem Formulation: A Necessity



ARTICULATE SPECIFIC HYPOTHESES: Chloroform Example

Hypothesis A: : CHCl_3 acts via a mutagenic MoA, a MOA which entails a linear, non-threshold dose-response, to produce a cancer risk to humans at typical exposure levels....

Hypothesis B: CHCl_3 acts via a cytotoxic MoA, a MOA which entails a non-linear, threshold dose-response, such that cancer risk to humans only arises at cytotoxic exposure levels

A Clear Path Forward for IRIS

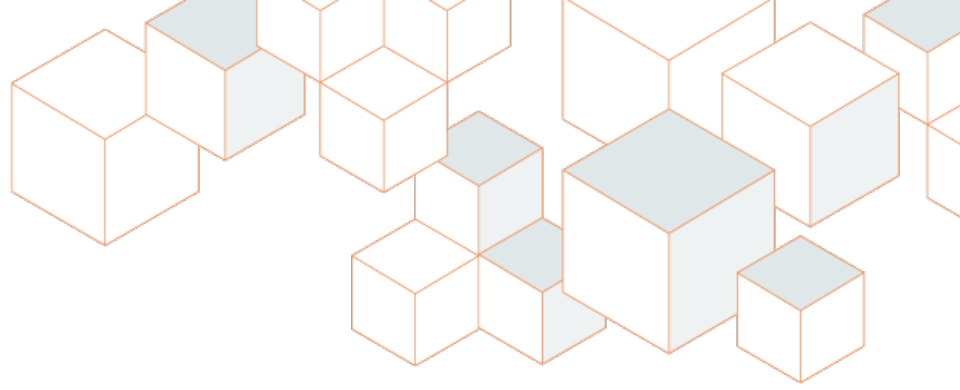
1) Modernize problem formulation – make MoA a central element (articulate specific hypotheses for each MoA)

2) A priori – detail the specific weight of evidence framework that will be used for integrating results



3) Use best practices for data acquisition, data evaluation, WoE, risk characterization, peer review, revision and finalization

4) Implement immediately and incorporate continuous improvement procedures



THANK YOU

