

August 1, 2012  
Trimethylbenzenes Listening Session

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# COMMENTS ON THE TOXICOLOGICAL REVIEW OF TRIMETHYLBENZENES

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# OVERVIEW OF ARASP

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- ❑ Promotes risk assessment, science methodologies and policies that support the generation and the use of best available and relevant science in chemical risk assessments.
- ❑ Encourage use of mode of action and consistent scientific data evaluation processes (including weight of evidence) in risk assessments.

# ADDITIONAL IMPROVEMENTS NEEDED

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- ❑ The recommendations we are making have objective of ensuring IRIS assessments are scientifically sound and defensible
- ❑ Will point out areas where the current assessment falls short in meeting NAS recommendations and suggest improvements
- ❑ These improvements can be implemented without undue delay & would improve scientific quality and efficiency / timeliness of IRIS

# ADDITIONAL IMPROVEMENTS NEEDED

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- Preface
- Preamble
- Tables and figures
- Design of Assessments
  - Literature search
  - Study inclusion / exclusion criteria
  - Study evaluation protocols (study reliability and data quality and for integrating studies)
  - Systematic application of Weight of Evidence framework

# PREFACE

## Recommendations for Improvement



- ❑ The preface should include the following:
  - Rationale for selecting the chemical for initial or re-review.
  - Potential uses of IRIS values in regulatory activities.
  - Any MOU currently in place that could have impacted the assessment.
  - Summary of similarities/differences between the draft assessment values and other agencies' values that EPA considered when developing the assessment.
  - Explanation of the scope of an IRIS assessment.

# PREAMBLE

## Recommendations for Improvement

- ❑ The preamble should be specific for the chemical.
- ❑ Any “standard practices” employed by the Agency should be clearly referenced.
  - ❑ Section 3.1 notes standard literature search practices but doesn’t provide a reference or detail on these standard practices.
  - ❑ Section 3.2 describes types of epidemiological studies, but does not lay out clear criteria for how the studies will be prioritized or considered by the Agency.
  - ❑ Section 4, states that the Agency will evaluate “design and methodological aspects that can increase or decrease weight” but does not provide how the methodological aspects would lead to a decrease or increase in confidence in the studies ability to support a causal relationship.

# PREAMBLE

## Recommendations for Improvement

- ❑ Section 5 describes some elements that may be considered when weighing evidence for an effect but does not show how these elements will be used or how evidence will be weighed and integrated.
  - Section 5.1 begins with criteria for causality but later appears to change focus to whether or not an ‘association’ exists.
  - This section also notes several references for reviewing evidence but it is unclear if or how these were followed by the Agency (eg., CDC 2004 cited as an example of a way to clarify how epidemiological evidence contributes to the overall WOE using specific descriptors but not applied in assessment).

# PREAMBLE

## Recommendation for Improvement

The criteria for employing the various uncertainty factors (UFs) should be clearly defined and explained.

- ❑ Section 7.6, states that the UF for human variation is reduced only if the point of departure is derived specifically for susceptible individuals. In general, in this section it is unclear what is guidance and what is common practice. Clear criteria for the application of UFs would be most helpful for this section.
- ❑ EPA should provide a discussion on how the Agency considers the UFs in totality to ensure that there is not any compounding conservatism which leads to a final RfD/RfC that is below background levels, or generally not scientifically defensible.
- ❑ Need transparent procedures for applying UF's.

# TABLES AND FIGURES

## Recommendation for Improvement

*ACC's ARASP comments that were presented at the listening session for Ammonia are also applicable to the Draft TMB assessment.*

- Evidence tables and figures need more information:
  - Support credible WOE
  - Highlight consistencies / inconsistencies across the studies including dose-response results
  - Include reasons for study inclusion /exclusion
  - Characterize state of knowledge on MOA
  - Include statistical information, e.g., power, confidence, etc.

# DESIGN OF THE ASSESSMENT

## Recommendation for Improvement

- ❑ **Develop a formal study design protocol for each IRIS assessment, including :**
  - ❑ literature search strategy
  - ❑ study inclusion / exclusion criteria
  - ❑ description of methods to be used to evaluate individual studies for data quality and reliability
  - ❑ specify methods to be used to analyze individual studies for dose response of reported effects
  - ❑ specify the framework and methods that will be used to conduct the weight of evidence evaluation to integrate results across studies
- ❑ **Distribute the study design protocol for review and comment, then hold “listening session” for discussion of the study design protocol**
  - ❑ would provide more meaningful input at arguably the key step - the start of the evaluation
  - ❑ promote a clearer understanding by EPA and stakeholders on studies that need to be considered (and why) , methods of analysis needed (and why), etc.
  - ❑ would improve timelines and efficiency too

# RELEVANT STUDIES WERE INAPPROPRIATELY EXCLUDED

## Studies Required by EPA Were Not Included

- ❑ EPA OPPT required and used reached the C9 aromatics studies to evaluate and characterize potential hazards of these substances.
- ❑ The C9 aromatics testing results have been submitted to EPA and most have been published in scientific literature too
- ❑ But the draft IRIS assessment never even discusses these in any detail.
- ❑ At a minimum, the EPA OPPT test rule and resulting studies, and HPV challenge program results should have been presented in the draft assessment and EPA's OPPT rationale for using the C9 aromatics studies fully presented too.
- ❑ The action by EPA IRIS to not use these studies leads to presentation of an unbalanced picture of regulatory science and could unjustifiably undermine OPPT's hazard assessment determinations, regulatory actions and company product stewardship programs.

# DATA EVALUATION PROCEDURES

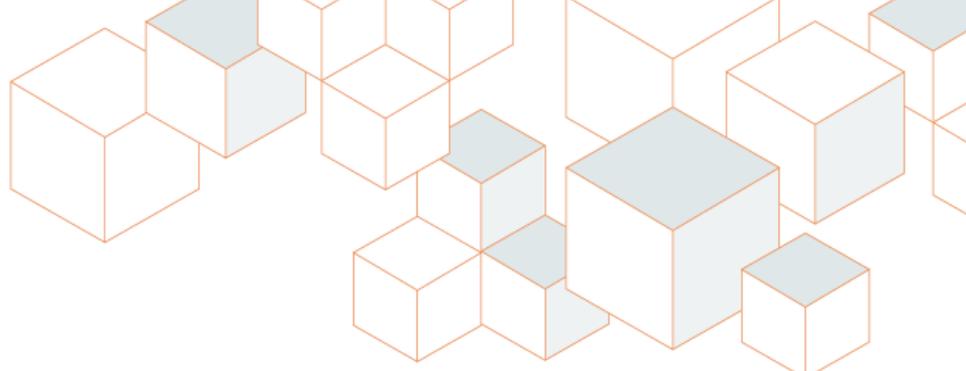
## Where are the Data Evaluation Protocols?

- ❑ NAS was clear, recommending EPA “Establish protocols for review of major types of studies, such as epidemiologic and bioassay.”
- ❑ EPA provides a general discussion in the Preamble of some of the elements that are evaluated in studies of different types.
- ❑ BUT - no mention is made of using pre-defined, objective protocols for evaluating study quality and data reliability.
- ❑ Existing data evaluation procedures are available and being used by EPA OPPT, OECD, ECHA, etc.:
  - ❑ Klimisch Code System (incl. ECETOC modified approach)
  - ❑ ECVAM ToxRTool Software (both in vivo and in vitro)

# WEIGHT OF EVIDENCE

## Where is the WoE Framework?

- ❑ NAS recommended EPA “standardize [the] approach to using weight-of-evidence”
  - ❑ EPA must adopt a consistent weight of evidence framework, formulated upon a mode of action evaluation procedure so that data from all relevant studies can be systematically reviewed, given appropriate weight, and integrated in a manner that provides a robust understanding of the mode of action and the potential hazards and risks that environmentally relevant levels of exposure could pose.
1. Cannot exclude the Clark et al. (1989) and Douglas et al. (1993) test guideline compliant studies.
  2. WoE analysis is more than just assigning descriptors of toxicity
  3. The WoE analysis must be transparent and explicitly describe why certain studies were given greater weight compared to others and how study results are integrated.



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# THANK YOU FOR THIS OPPORTUNITY TO PROVIDE RECOMMENDATIONS FOR IMPROVING IRIS

ACC'S CENTER FOR ADVANCING RISK ASSESSMENT SCIENCE AND POLICY (ARASP)

