

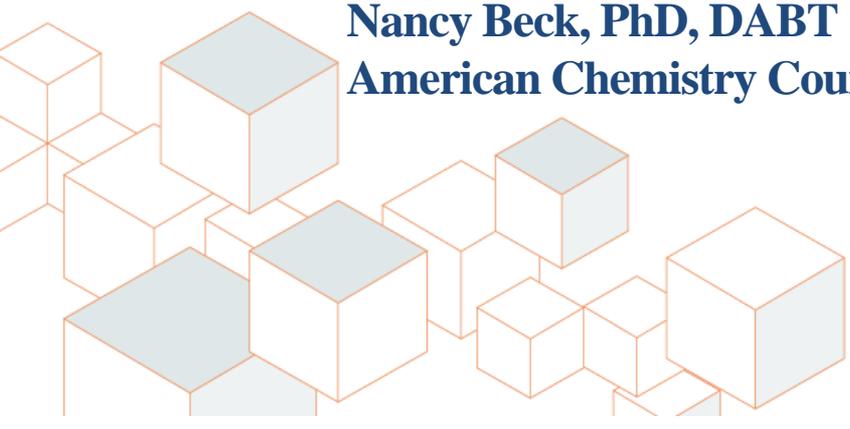
**June 25, 2013**

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**COMMENTS TO THE NTP BOARD OF SCIENTIFIC  
COUNSELORS ON THE OHAT DRAFT APPROACH  
FOR SYSTEMATIC REVIEW AND EVIDENCE  
INTEGRATION**

**On behalf of ACC and its Center for Advancing Risk  
Assessment Science and Policy**

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# ACC and its Center for Advancing Risk Assessment Science and Policy (ARASP)

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## ACC:

- Represents the leading companies engaged in the business of chemistry.
- Committed to improved environmental, health and safety performance through Responsible Care<sup>®</sup>.

## ARASP:

- Coalition of 19 organizations focused on development and application of scientifically sound methods for conducting chemical assessments.
- Members include chemical specific panels and other trade associations. See: <http://arasp.americanchemistry.com/>

# Standardized Systematic Review and Evidence Integration Approaches Are Needed

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These approaches must include:

- ❑ Consideration of exposure.
  - ❑ Standardized approaches and transparent criteria for reviewing the quality of scientific evidence (epidemiology, animal, mechanistic).
  - ❑ Frameworks for integrating evidence, from diverse data streams.
  - ❑ Guidance to ensure all relevant data are considered in a transparent, unbiased and rigorous manner.
- The NTP approach is a good step forward.
- However, substantive improvements are necessary to make the approach transparent, objective, and relevant.



# 1. Consideration of Exposure Information

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Hazard findings without a dose context limits the usefulness of the information.

- ❑ Provides only a partial conclusion that opens the door for misinterpretation.
- ❑ Results in undue fear and inappropriate risk-risk trade offs in the general population.

## Suggested Improvement:

- ❑ Be consistent with the PECO principles and ensure that each protocol has an exposure context.
  - This can easily be added during the scoping phase when the topic is prepared.



## 2. Evaluating Study Quality

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Existing tools and criteria are available and can be applied to soundly and objectively judge toxicological information in an unbiased manner.

- ❑ There is no need to fit toxicological data into an inappropriate clinical trial framework to judge its quality.

### Suggested Improvements:

- ❑ Reduce emphasis on “risk of bias.”
- ❑ Step 4 should include a robust evaluation of study quality and relevance.

# 3. Mode of Action is a Critical Component of Evidence Integration

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Evidence integration should include:

- Mechanistic/mode of action (MOA) data, when available.
- Considerations of biological plausibility, based on available evidence.

## Suggested Improvement

- Use mechanistic and MOA data as more than a modifier.
- Problem formulation stage should integrate hypothesized MOA's in each protocol.
  - The BPA protocol can be easily modified to incorporate this.

## 4. Objectively Determine Confidence in the Body of Evidence

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No justification is provided for using the four key features to determine the confidence in the body of evidence.

- ❑ The features chosen are based on GRADE and AHRQ which evaluate an entirely different type of database (medical/health care related vs. toxicological and observational).
- ❑ Applying these arbitrary features to observational/cross-sectional studies will give the studies higher confidence ratings than they deserve.

### Suggested Improvement:

- ❑ Cross-sectional studies should only rarely receive a confidence level higher than low.

## 5. Objectively Evaluate Associations vs. Causation

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The NTP Approach inappropriately assumes that causal relationships have been established when associations are described.

- ❑ Incorporating some of the Bradford-Hill considerations, as concepts during review, is not the same as proving causation.

### Suggested Improvements:

- ❑ Consider Hill considerations only when there is evidence of a statistically significant association.
- ❑ Statements about causality must be appropriately supported, not implicitly defined. The current approach only supports determinations of associations.



## 6. Risk Communication is Critical

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The Hazard Identification categories must accurately describe the level of scientific evidence and must also be understandable to the general public.

### Suggested Improvements:

- ❑ Revise the “Presumed” category.
  - ❑ NTP should consider language that is already familiar to the public health community (e.g., “likely”).
- ❑ Revise the definition of “Suspected.” As currently stated, it is not an appropriate term to describe low to moderate evidence.
  - ❑ A term describing weak evidence would be more suitable (e.g., “limited”).

# Thank You!



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- ❑ Getting Systematic Review right is important.
  - ❑ This approach will likely be adapted/adopted by a wide variety of stakeholders.
  - ❑ Appropriate review (e.g., EO 12866 review) and stakeholder engagement for this important guidance is necessary.
  - ❑ NTP must ensure that the approach is grounded in science and objectively uses all the evidence, from diverse data streams, based on its quality and relevance.