June 25, 2013

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

Nancy Beck, PhD, DABT
American Chemistry Council

American® Chemistry Council

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

ACC:

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

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

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

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.

<u>Suggested Improvement:</u>

- 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

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

Evidence integration should include:

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

<u>Suggested Improvement</u>

- ❑ Use mechanistic and MOA data as more that 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

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.

<u>Suggested Improvement:</u>

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

5. Objectively Evaluate Associations vs. Causation

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.

<u>Suggested Improvements:</u>

- 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

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!

- 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.