



MICHAEL P. WALLS
VICE PRESIDENT
REGULATORY & TECHNICAL AFFAIRS

November 27, 2012

Dr. Lori White
Designated Federal Officer for the BSC
Office of Liaison,
Policy and Review Division of NTP, NIEHS
P.O. Box 12233, K2-03
Research Triangle Park, NC 27709

Regarding: NTP Approach for Systematic Review and Evidence Integration for Literature-based Health Assessments.

Dear Dr. White:

The American Chemistry Council (ACC) appreciates the opportunity to provide comments to the National Toxicology Program (NTP) Board of Scientific Counselors (BSC) on NTP's approach to the review and integration of evidence in literature-based health assessments. In our view, it is incumbent on NTP to enhance the transparency of and opportunities for public comment on its approach to review and integration of evidence.

ACC¹ and its members make substantial, ongoing investments in research to support product development, health, safety and environmental protection, and to abide by product stewardship and regulatory policies. We have a significant interest in a National Institute of Environmental Health Sciences (NIEHS)/NTP hazard evaluation process that leads to assessments that consider all relevant scientific data in an unbiased and rigorous manner. We are committed to promoting high quality science generally and risk assessment in particular (including hazard evaluation). Our significant interest in the approaches NTP will use for evidence based assessments and systematic reviews is also a function of the precedent NTP reviews will have for other government assessment programs.

¹ The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a \$720 billion enterprise and a key element of the nation's economy. It is one of the nation's largest exporters, accounting for ten cents out of every dollar in U.S. exports. Chemistry companies are among the largest investors in research and development. Safety and security have always been primary concerns of ACC members, and they have intensified their efforts, working closely with government agencies to improve security and to defend against threats to the nation's critical infrastructure.



We are greatly disappointed in the limited opportunities that have been provided for meaningful stakeholder engagement as the NTP develops its approaches for Systematic Review and Evidence Integration for Literature-based Health Assessments (hereinafter referred to as Systematic Review). For the June 2012 BSC meeting, stakeholders were provided a one-page overview describing the plans of the Office of Health Assessment and Translation (OHAT) to develop an approach to systematic review. After the June meeting slide presentations were also made available to the public. Unfortunately, neither a written detailed description nor slides were provided to the public before that meeting, and thus there was no meaningful opportunity for stakeholders to review information, provide comment, and engage with the NIEHS/NTP staff or the BSC.

Additionally, in late November, in preparations for the December 2012 meeting, NIEHS/NTP posted a draft report from an August 28-29, 2012 meeting of the BSC working group. That group apparently met with no public notice. This draft report (which is post-dated December 11, 2012, the date of the future meeting) is accompanied by an appendix which includes another draft report authored by NTP (entitled: Draft NTP Approach for Reaching Conclusions For Literature Based Evidence Assessments) that was apparently made available to the working group in August, or perhaps even earlier. This report was not provided to the public before being posted for the December 11, 2012 meeting, thus stakeholders have not had any real opportunity to review the report because NTP has not sought public comment on it. In addition, the posted report is missing appendices that include important study templates and data extraction forms that have been developed, further precluding any public comment on these important documents.

Furthermore, in materials recently released by NTP² it appears that that NTP intends to use the December meeting to not only discuss the BSC working group report but also expects to “release a revised draft of the NTP approach before the December 11, 2012 meeting of the BSC.” As described in the Agenda, NTP will discuss OHAT implementation of this revised Systematic Review approach. This revised draft had not been released as of 11pm November 26, 2012. Therefore, there will be no opportunity for public review and comment on the revised NTP document before close of the public comment period on November 27th and little, if any, opportunity for public review and comment before the December 11th meeting. Consequently, any public comment allowed at the December meeting (which we note is limited to 7-10 minutes per organization), will be on the prior draft developed in August and considered by the BSC working group. In short, NTP has provided no opportunity for the public to have a meaningful and timely dialogue on the development, revisions and implementation of the Systematic Approach.

NTP has implemented a truncated, inadequate review process which appears to bypass robust public review and comment.³ This lack of transparency is contrary to existing procedural standards and contrary to President Obama’s commitment to building the public trust by establishing “a system of transparency, public participation, and collaboration.”⁴ NTP should demonstrate both a commitment to transparency and an interest in public input.

Therefore, ACC requests the following:

² See: http://ntp.niehs.nih.gov/NTP/About_NTP/BSC/2012/December/Cvr_LiteratureBasedEvi_508.pdf

³ ACC finds it very troubling that NTP appears to have adopted procedures which limit opportunity for public review and comment, as a similar truncated approach was used by NTP in late 2011 to inhibit meaningful public input into the organization’s procedural changes to the development of the Report on Carcinogens.

⁴ See: http://www.whitehouse.gov/the_press_office/TransparencyandOpenGovernment

- 1) NIEHS/NTP must embrace and fully adhere to the President's commitment to transparency and public involvement and adopt, as standard operating procedure, open meetings of all FACA committees, including all meetings of FACA workgroups.
- 2) NIEHS/NTP should adopt a practice of simultaneous public dissemination of every program document, draft or final, which it circulates to its BSC (including BSC working groups) for review as a standard operating practice.
- 3) NIEHS/NTP should release the revised draft "NTP Approach for Reaching Conclusions for Literature-Based Evidence Assessments," for a 60-day public comment period, and then provide an opportunity for meaningful oral public presentation to the BSC. This action should be completed before NTP proceeds with implementation.

ACC is also concerned about many of the technical and science policy procedures proposed in the draft approach. As NTP is currently revising the document, it does not seem useful to provide detailed comment on an older draft. When we are provided with sufficient opportunity to review and analyze the forthcoming NTP revisions, we will share with you and the BSC our comments on the revised draft Systematic Approach. In the attachment to this letter, based upon a cursory review of the August draft, several examples illustrate our concerns with the substance of the Systematic Approach.

In conclusion, we believe that NIEHS/NTP should provide more transparency and encourage public input into this important process. We strongly recommend that NIEHS/NTP follow well-established standards for stakeholder engagement and good government. It is imperative that NIEHS/NTP share the revised and most current draft approaches with stakeholders for comment and input before peer review and well before NIEHS/NTP begins implementation. The process currently employed by NIEHS/NTP does not allow for sufficient and meaningful engagement.

If we can provide additional information, or if you have any questions regarding our comments, please feel free to contact me at (202) 249 6400 or mike_walls@americanchemistry.com.

Sincerely,

[Redacted]

Michael P. Walls
Vice President
Regulatory & Technical Affairs

cc:

Linda Birnbaum, Ph.D.
Dr. John Bucher, Ph.D.
Caya Lewis, M.P.H.

Appendix

Based upon a cursory review of the August draft, several examples below illustrate our scientific concerns with the substance of the Draft Systematic Approach (provided in August 2012 to the BSC working group).

- The approach appears highly biased towards greater consideration of epidemiological data, when most toxicological data is experimental, *in vitro*, or uses animal models. In the flow diagram for the review, non-human data does not appear to be appropriately considered as it is not evaluated until Step 7.
- Table 3 starts with evaluating individual studies, but then considers aspects of each study to increase or decrease confidence in the “body of evidence” rather than in the individual study.
- Table 3 develops a confidence rating “in the body of evidence” without any consideration of data other than epidemiological data.
- When discussing bias, NTP does not require that outcomes in epidemiological reports be pre-specified.⁵
- Confidence in the “body of evidence” does not appear to include consideration of plausibility, mode of action, or relevance of the dosing to environmental exposures that are of concern.
- Evaluation of non-human data is not given sufficient weight or systematic consideration. The document should consider systematic approaches adopted by OECD and REACH that include using the Klimisch scoring system or use of the ECVAM ToxRTool.⁶
- In the draft approach a two-fold change in effect is considered “large” without any consideration of the severity or reversibility of that endpoint.
- NTP has developed an approach that can start with studies of low quality but somehow lead to moderate or high confidence in the “body of evidence” and thus based on these low quality studies, later conclude that the associations found imply a causal link. This jump to causality would not be supported by the evidence, yet NTP believes this is implicit based on the proposed systematic review approach.
- NTP adopts a Globally Harmonized System (GHS) approach to hazard, but has not considered, or conducted any research regarding, how this information will be communicated to and understood by the public in a non-occupational scenario. While the working group has suggested alternative terminology, these must also be sufficiently vetted before being implemented. Getting the risk communication wrong will have very large unintended consequences for public health and personal decision making.

⁵ See, for instance, articles such as S. Young, A. Karr, “Deming, data and observational studies. A process out of control and needing fixing”, *Significance*, September 2011; available at:

<http://www.niss.org/sites/default/files/Young%20Karr%20Obs%20Study%20Problem.pdf>.

⁶ See: Schneider, K., Schwarz, M., Burkholder, I., Kopp-Schneider, A., Edler, L., Kinsner-Ovaskainen, A., Hartung, T., and Hoffmann, S. (2009). ToxRTool, a new tool to assess the reliability of toxicological data. *Toxicology Letters* 189:138-144 and Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology* 25:1-5.

