



Styrene Information and Research Center (SIRC)  
910 17th Street NW #500-B, Washington, DC 20006  
Phone: 202-787-5996 www.styrene.org

*This Document Submitted By Electronic Delivery*

June 7, 2013

James J. Reisa, Ph.D.  
Director, Environmental Studies and Toxicology  
National Research Council  
Keck Center of the National Academies  
500 Fifth Street, NW  
Washington, DC 20001

### **NRC Review of the NTP Report on Carcinogens Listing of Styrene: NTP Scientific Review Processes**

Dear Dr. Reisa:

This letter is a supplemental submission to the National Research Council (NRC) Committee charged with reviewing the National Toxicology Program's listing of styrene in the *Report on Carcinogens (RoC)*. In past submissions, the Styrene Information and Research Center (SIRC) has presented information to the Committee on the two alternative interpretations of the extensive scientific database on styrene, because we believed this would be particularly informative as the Committee carries out its charge to develop its own independent listing recommendation for styrene.

In this letter, SIRC addresses an additional matter—namely, the adequacy of the scientific review processes employed by the *RoC* staff responsible for developing the assessments used in the 12<sup>th</sup> *RoC*. Indeed, the adequacy or inadequacy of these procedures may partially account for how NTP could have arrived at an interpretation of the data that differs so substantially from previous hazard assessments of styrene.

While good scientific review processes may be secondary to sound scientific decision criteria, both are important to reaching valid and meaningful results. For example, well-designed test protocols are a cornerstone of experimental science, but protocols must be married to sound laboratory practices to produce verifiable data. By analogy, administrative review procedures are akin to sound laboratory practices. Scientists may apply their very best scientific judgment but without the checks and balances of rigorous peer review and other administrative review procedures, there is a significant chance of error.

SIRC's ability to offer observations on the scientific review processes used by the *RoC* staff is of necessity limited because NTP's processes are not transparent. However, Dr. John Bucher's presentation to your Committee on March 19, 2013 provided some insight into the deficit in such procedures. In addition, based on our observation of NTP's review of styrene, we can identify elements of the 12<sup>th</sup> *RoC* process where NTP

did not follow best practices as identified in previous NRC recommendations, evidence-based review procedures, or even the NTP's own draft Systematic Review framework.\*

In summary, we believe there were scientific procedural shortcomings in the following areas in the preparation of the 12<sup>th</sup> *Report on Carcinogens*. Further details are provided in "[Scientific Procedural Shortcomings in the NTP's 12<sup>th</sup> Report on Carcinogens](#)," which is attached to this letter.

### **Insights from Dr. Bucher's Presentation of March 19, 2013**

1. Criteria for the literature search both prior to and after the development of the assessment;
2. Interpreting the meaning of key terms in the NTP listing criteria.

### **Best practices that SIRC believes were not carried out in the 12<sup>th</sup> RoC Review**

3. Selecting studies for inclusion in the assessment;
4. Recording data from the studies;
5. Determining the quality of individual studies;
6. Handling alternative interpretations of the data;
7. Responding to issues raised by outside scientists;
8. Selecting members of the expert panels;
9. Managing the two internal review committees;
10. Ensuring that all these steps are conducted in a transparent and robust manner.

### **Insights from the 13<sup>th</sup> RoC**

11. New peer review and public comment processes.

### **Scientific and Administrative Practices**

12. Ensuring that scientific and administrative practices are mutually reinforcing.

SIRC has not been able to establish that the lack of scientific procedures and criteria for decision making throughout the 12<sup>th</sup> *RoC* development process was a cause of what SIRC believes to be the incorrect interpretation of the science in the case of styrene. However, we can say that the agency's lack of transparency and of publically available criteria made it exceedingly difficult for SIRC to understand how the scientific data were considered and to suggest alternatives in an effective manner. With the *RoC* staff's almost total discretion to deal with only the issues of their own choosing, the public's scientific arguments received no substantive response throughout the entire assessment process.

---

\* A draft framework for Systematic Review of non-cancer endpoints has recently been developed by the Office of Health Assessment and Translation (OHAT), a sister organization within the NTP. This letter and its attachment highlight twelve procedural areas where SIRC believes the 12<sup>th</sup> *RoC* was deficient. Several of these shortcomings are consistent with process elements that the OHAT framework seeks to improve and which the NRC has previously recommended federal agencies take action to address.

While SIRC and similar groups have sought the assistance of other portions of the Executive Branch as well as other branches of government, these other governmental organizations have naturally been reluctant to intervene in what they see as scientific decision making, leaving this role to scientific organizations such as the National Academy of Sciences. We would therefore respectfully suggest that the Committee provide guidance to the *RoC* staff to regarding the necessary objective scientific criteria and procedures to ensure that future decisions by the *RoC* staff are reached in a transparent and scientifically sound manner.

Sincerely,

A handwritten signature in black ink that reads "Jack Snyder". The signature is written in a cursive style with a large, looping initial "J" and "S".

Jack Snyder, Executive Director  
Styrene Information and Research Center

# SCIENTIFIC PROCEDURAL SHORTCOMINGS IN THE NTP'S 12<sup>TH</sup> REPORT ON CARCINOGENS

---

## Insights from Dr. Bucher's Presentation of March 19, 2013

- 1. Criteria for the literature search both prior to and after the development of the assessment:** In previous reports, the NRC has identified a carefully designed and comprehensive search strategy, including documented search criteria, as necessary in order to assure that important studies related to the substance are not overlooked.<sup>1</sup> These criteria were not publically available from NTP during the development of the 12<sup>th</sup> RoC.

At the NRC Committee meeting held on March 19, 2013, Dr. Bucher and staff indicated that NTP routinely monitors the literature during its process to ensure that newly published studies that may affect the outcome of the assessment are evaluated. However, upon questioning, NTP admitted that this process was *ad hoc* and conducted without a documented search strategy or formal criteria for evaluation. This informal approach was then confirmed in material submitted to the Committee by NTP on April 2, 2013.<sup>2</sup> This *ad hoc* process after the draft Substance Profiles were completed is indicative of NTP's process as these profiles were being developed.

*For example, SIRC does not know whether NTP's search found the four Mode of Action studies funded by SIRC and published between the time the draft profile underwent peer review by the Board of Scientific Counselors (2009) and the publication of the 12<sup>th</sup> RoC listing (2011). More importantly, if they were found, SIRC does not know NTP's scientific evaluation of the relevance of these studies for the RoC listing recommendation.*

- 2. Interpreting the meaning of key terms in the NTP listing criteria:** The RoC staff cites the listing criteria as the determinant of whether and how a substance is to be listed in the RoC. However, the listing criteria use a series of common words of general meaning that have no explicit definitions when used in the RoC criteria (*e.g.*, "credible," "can adequately be excluded," "compelling"). In the March 19, 2013 public meeting of this Committee, Dr. Bucher indicated that NTP does not have definitions or guidance for applying these terms for use by the staff and review panel members in order to ensure consistency. Currently, each

---

<sup>1</sup> "Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde, National Research Council," ISBN: 0-309-21194-8 (2011), p. 152, available at [http://www.nap.edu/catalog.php?record\\_id=13142](http://www.nap.edu/catalog.php?record_id=13142).

<sup>2</sup> Testimony of Dr. John Bucher, Associate Director National Toxicology Program to the National Research Council (NRC) Styrene Review Committee, Mar, 19, 2013, p. 4, available by request from the NRC:

"The NTP periodically monitored the scientific literature up to the release of the 12th RoC (June 2011) for any new studies that would warrant a re-review of the NTP's preliminary recommendations to the HHS Secretary for the listing status of formaldehyde and styrene. The databases searched were *PubMed* and *Web of Science*. Although many additional studies were identified, which were published between the peer-review date of the draft substance profile and release of the 12th RoC, the NTP did not feel that the findings of any of those studies would change its listing recommendation for styrene or formaldehyde."

member of the various review committees uses his or her own judgment about the proper meaning of these terms.

This situation appears to be still continuing with the latest reviews for the 13<sup>th</sup> RoC, as evidenced in the peer review for cumene, where the panel struggled with the term “compelling,” and the RoC staff simply kept repeating the word, without any clarifying definition.<sup>3</sup> Whether NTP or an expert panel applies these listing criteria, a clearly articulated definition of these terms is essential because decisions to list or not to list a substance can turn on the meaning applied to these key terms.

## Best practices that SIRC believes were not carried out in the 12<sup>th</sup> RoC Review

3. **Selecting studies for inclusion in the assessment:** All references identified in the search that are relevant to evaluating the substance need to be identified and carried forward. The NRC has recommended that criteria for including or excluding references need to be explicitly provided and reasons recorded for excluding studies from further consideration.<sup>4</sup> In any regulatory science review, the agency scientists should describe the criteria they use to determine which scientific papers to review and how those papers will be evaluated, and the proposed criteria should be open for public comment as early in the process as possible.<sup>5</sup>
4. **Recording data from the studies:** It is important that procedures be in place to assure that the data in the selected studies are carefully extracted and recorded. The NRC has recommended that evidence tables be used for this purpose and be constructed in a rigorous fashion.<sup>6</sup>
5. **Determining the quality of individual studies:** Studies differ in their study design and execution in ways that can affect the reliability of the outcome. The NRC has recommended that hazard and risk assessors institute a process by which the quality of individual studies is objectively and transparently assessed, using templates tailored to the type of research (*i.e.*, types of epidemiological and toxicological studies).<sup>7</sup>

---

<sup>3</sup> National Toxicology Program, “Peer Review of Draft Report on Carcinogens (RoC), Monographs for Cumene and 1-Bromopropane,” March 21–22, 2013, National Institute of Environmental Health Sciences, *Peer Review Report*, p. 17, available at [http://ntp.niehs.nih.gov/NTP/About\\_NTP/MonoPeerRvw/2013/March/PeerReviewRpt20130322\\_508.pdf](http://ntp.niehs.nih.gov/NTP/About_NTP/MonoPeerRvw/2013/March/PeerReviewRpt20130322_508.pdf).

The confusion that was generated by not having a definition of “compelling” is especially evident in the recording of the Cumene Peer Review at audio segments 1012 through 1015; recording available upon request from the National Toxicology Program.

<sup>4</sup> National Research Council Formaldehyde Review, 2011, p. 152.

<sup>5</sup> Bipartisan Policy Center, “Improving the Use of Science in Regulatory Policy,” p. 41 (Aug. 5, 2009), available at <http://www.bipartisanpolicy.org/sites/default/files/BPC%20Science%20Report%20fnl.pdf>.

<sup>6</sup> National Research Council Formaldehyde Review, 2011, p. 158.

<sup>7</sup> *Ibid.*.

6. **Handling alternative interpretations of the data:** As both the individual studies and groups of studies are evaluated within and across disciplines, alternative interpretations of the data can emerge. It is important that the rationale(s) for choosing among these alternative interpretations be documented and assessed completely in a transparent manner.

An open dialogue between the staff, agency review panels, and the outside scientific community is essential to draw upon the available expertise and diversity of scientific perspectives.<sup>8</sup> OMB's *Final Information Quality Bulletin for Peer Review* recognizes the value of obtaining diverse scientific input:

*On most controversial issues, there exists a range of respected scientific viewpoints regarding interpretation of the available literature. Inviting reviewers with competing views on the science may lead to a sharper, more focused peer review. Indeed, as a final layer of review, some organizations (e.g., the National Academy of Sciences) specifically recruit reviewers with strong opinions to test the scientific strength and balance of their reports.<sup>9</sup>*

7. **Responding to issues raised by outside scientists:** Often the scientists who know most about a particular set of studies related to a chemical are employed outside of the Federal Government. When reviewing a draft assessment prepared by the RoC staff, these scientists may identify serious issues that need to be addressed before the assessment should go forward. The earlier in the assessment development process that these issues are acknowledged, the more likely that they will be resolved appropriately.

*We would note that during the review of styrene, the RoC staff chose not to respond either in writing or orally to any of the scientific issues raised by outside scientists, relying on their promise instead to address public comments once the final listing decisions had been made and reviewed and the actual listing of styrene was signed by the Secretary of HHS and published. Without a response from the RoC staff, the review committees were left on their own, if they chose, to discover from the public comments what the key scientific issues were and what the NTP's position and justification on these issues might had been, had the RoC staff chosen to address them. Not surprisingly, the issues identified by the public therefore did not receive much attention.*

8. **Selecting members of the expert panels:** The National Academy of Sciences has procedures to ensure that their panels are balanced and broadly representative of various points of view while at the same time avoiding conflicts of interest. These procedures are necessary in order to obtain fair and objective reviews and to ensure acceptance by the public of the legitimacy of the panels. It appears that the RoC staff does not have a policy of allowing the

---

<sup>8</sup> *Final Information Quality Bulletin for Peer Review*, Memorandum from Joshua B. Bolten, Director, Office of Management and Budget to Heads of Departments and Agencies, Dec, 16, 2004, pp. 16-17, available at <http://www.whitehouse.gov/sites/default/files/omb/memoranda/fy2005/m05-03.pdf>.

See *supra* note 21 at 16-17 (stating that the two critical factors in selecting reviewers is expertise and balance).

<sup>9</sup> *Ibid*, p. 17.

public to challenge the balance of a RoC expert panel or the appearance of conflict of interest or bias on the part of the panel's members.

*We would note that during the styrene review, SIRC complained after the fact about the appearance of a professional conflict of interest on the Expert Panel for styrene. The NTP never responded to these complaints nor did the agency confirm that the Agency had in fact vetted the Expert Panel for conflict of interest.*

9. **Managing the two internal review committees:** The summaries of the meetings of the Interagency Committee and the NIEHS/NTP Scientific Review Group submitted recently by NTP to this NRC Committee reveal that RoC staff characterized the alternative hypotheses advanced by SIRC in a manner highly favorable to NTP's listing recommendation and presented poorly, if at all, the positive arguments submitted by SIRC.

*We would note that although SIRC is not privy to the information about whether or how SIRC's comments were provided to these panels, we do know that the interagency panel meeting was scheduled and took place only four working days after the close of the comment period when NTP received SIRC's comments. Thus, if SIRC's comments were provided to the panel immediately, the members had only four days to consider the alternative interpretations of the studies while NTP had distributed its draft listing decision and justification considerably earlier. In short the NTP process did not foster scientific discussion of interpretations of data contrary to those of the RoC staff, and the minutes from these meetings provided by NTP do not reflect a robust discussion of these matters.*

10. **Reviewing novel analyses advanced by staff or panel members:** The RoC staff appears to have no procedures for ensuring transparent and independent peer review of novel analyses developed by the staff or panel members during an assessment.

*We would note that we watched the styrene Expert Panel vote to list styrene in the RoC based largely on speculation by the panel's epidemiology subcommittee chair that a reanalysis of published data would support a carcinogen listing. This supposed reanalysis never was disclosed or published in the peer-reviewed literature. Yet this view of the subcommittee chair appeared to be very influential in the subsequent decision by the full panel to recommending listing styrene in the RoC.*

## Insights from the 13<sup>th</sup> RoC

11. **Ensuring that all these steps are conducted in a transparent and robust manner:** Subsequent to the 12<sup>th</sup> Report on Carcinogens (in which styrene was reviewed), the NTP has again modified its peer review and public comment process. NTP has (1) eliminated the review role of the Board of Scientific Counselors for the draft monographs, (2) given itself great discretion to fashion the type and nature of any peer review of the draft assessments, and (3) has eliminated *any* response from the RoC staff to public comments at any point in the process. These new procedures appear even less transparent and have the

potential to actually exacerbate the problems with the 12<sup>th</sup> RoC identified above. In SIRC's view, the RoC staff appears to be moving away from best practices rather than toward them, leaving more decisions to their own *ad hoc* judgments without the checks and balances of transparency, reproducibility or rigorous peer review that are cornerstones of good science.

In experimental science, the study report or manuscript must contain enough detail that other researchers can replicate the test protocol and compare their results with the original research. That replication or lack of replication will validate, modify or invalidate the insights learned from the initial study. This ability to replicate is very similar to the concept of transparency in administrative proceedings. Transparency is used prominently in President Obama's guidance, in Lisa Jackson's 2009 memo on transparency in EPA operations, in the Information Quality Act and in the National Research Council's review of EPA's Draft IRIS Assessment of Formaldehyde.<sup>10</sup>

## Scientific and Administrative Practices

- 12. Ensuring that scientific and administrative practices are mutually reinforcing:** Well-conducted scientific research and good administrative practices share common elements and should be mutually reinforcing. Both internal and external agency communications would benefit by ensuring transparency and meaningful, timely dialogue among the agency, its review panels and outside stakeholders. While these principles would benefit many types of administrative processes, they are essential in the field of "regulatory science," where scientific disciplines are used in support of value-based policy and decision-making. In this context, transparency includes clearly distinguishing the roles science, data interpretation, and regulatory policy. In this fashion, science will be respected while the administrative process benefits.

---

<sup>10</sup> January 20, 2009 Inaugural Address, available at <http://www.whitehouse.gov/blog/inaugural-address/>; "Memorandum for the Heads of the Executive Departments and Agencies on Scientific Integrity," from John P. Holdren, Director of the Office of Science and Technology (Dec. 17, 2010), available at <http://www.whitehouse.gov/sites/default/files/microsites/ostp/scientific-integrity-memo-12172010.pdf>; "Opening Memorandum to EPA Employees," from EPA Administrator Lisa P. Jackson (Jan. 23, 2009), available at <http://blog.epa.gov/administrator/2009/01/26/opening-memo-to-epa-employees/>; National Academy of Sciences "Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde," Chapter 7 "Roadmap for Revision" (Apr. 2011), available at <http://www.nap.edu/catalog/13142.html>.