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Committee on Science, Space & Technology, Subcommittee on Investigations & Oversight
and
Committee on Small Business, Subcommittee on Health Care & Technology

Joint Hearing: "How the *Report on Carcinogens* Uses Science to Meet its Statutory Obligations, and its Impact on Small Business Jobs"

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Presenter

My name is Dr. James Bus. I am employed as Director of External Technology, Toxicology and Environmental Research and Consulting, by The Dow Chemical Company (Midland, Michigan).

Since receiving my Ph.D. from Michigan State University in 1975, I have:

- Authored or co-authored more than 100 scientific papers, reviews and books in my field.
- Served as the president of the Society of Toxicology and the American Board of Toxicology, and currently am the president of the Academy of Toxicological Sciences.
- Been a member of the National Academy of Sciences (NAS) Board of Environmental Sciences and Toxicology.
- Served as a member of the Science Advisory Boards of the US Environmental Protection Agency (EPA), US Food and Drug Administration (FDA) and the US National Toxicology Program (NTP).

Executive Summary

I am here today as a concerned scientist and represent the Styrene Information and Research Center, of which my employer is a founding member, and I very much appreciate the opportunity to provide these comments regarding concerns about the scientific integrity of the processes the NTP uses in the development of the *Report on Carcinogens (RoC)*.

I, Dow, and the styrene industry are keenly interested in protecting the health and safety of workers, customers and the public. Objective, evidence-based reviews of scientific research are essential elements of our decision making about our products and facilities.

The National Toxicology Program (NTP) is globally recognized as an "authoritative body;" chemical classifications in its *Report on Carcinogens* carry significant consequences for businesses large and small, including regulatory actions and commercial impacts. Thus, it is essential that *RoC* classifications represent the highest quality scientific evaluations.

The primary issues with the process NTP used for the 12th *RoC*, and with the new process NTP implemented for future *RoC* assessments, are expanded upon in these comments. However, these concerns may be summarized by highlighting the following key points I hope the Joint Committees will please consider:

1) **The *RoC* is *Ad Hoc* and lacks explicit criteria needed to assure its reviews of scientific information are transparent and scientifically consistent.**

   While NTP prides itself on an effective *RoC* assessment process, the fact is that the process is – by NTP's own admission – largely *ad hoc* and does not document the fundamentally required specifics of the scientific approach NTP uses to assess the data on which its carcinogen listings are based.

Additionally, it is completely silent about criteria needed to guide scientific evaluations at several key process stages. For example, draft "Monographs" provide the primary rationale for *RoC* classifications. Yet the recently updated *RoC* process states reviews of the Monographs only include "external scientific input, **as needed** (*e.g.*, consultants, *ad hoc* presentations, expert panels)" **(emphasis added).**

A 2011 NAS assessment of the EPA review of formaldehyde details a number of scientific best practices for assessments of chemicals in general and points out that *ad hoc* review processes cannot be relied on to produce scientifically valid assessments; indeed, evidence based approaches are now being used by other institutions such as the Institute of Medicine.

2) **The *RoC* process lacks adequate checks and balances, including peer review and addressing outside/conflicting data.**

Although NTP insists that public comments are repeatedly solicited, and considered, the reality is that NTP's main approach to outside input is posting comments in an on-line docket. NTP has not dealt with public comments or sought peer review opinions on data contradictory to its conclusions. For the 12th *RoC*, NTP provided only minimal response to public comments after the Secretary had signed-off on the final *Report*. For the new *RoC* process NTP has clearly indicated, **as a matter of policy**, that it no longer will respond to public comments at all.[1]

In addition, NTP's current process limits review by its own Board of Scientific Counselors (BSC) to NTP's initial draft "concept document," which is akin to an outline of what NTP's review intends to examine. Peer review of the critical draft Monographs by external Expert Panels is left entirely to the discretion of the NTP, including the key steps of selection of expert panel members and identification of review charge questions.

Finally, interagency peer review of draft Monographs is reduced to providing "inputs" that will only be considered at the discretion of NTP and are not further shared with the Expert Panels or the public. Towards the end of the process, draft Monographs are simply presented to the NTP BSC for its information only, denying this senior advisory body from any meaningful peer review of the Monograph.

3) **The *RoC* process does not employ scientific best practices, relies on outdated approaches and has not adopted recent NAS recommendations.**

Both past and current *RoC* assessment processes fly in the face of scientifically accepted hazard assessment procedures – *i.e.*, an evidence-based approach to weighing the full body of data.

NTP acknowledges it used the outmoded "strength of evidence" approach in the 12th *Report on Carcinogens*,[2] essentially utilizing only data that support a conclusion of carcinogenicity. In fact, other regulatory bodies that employ the more scientifically robust evidence-based assessment process have reached opposing conclusions on substances NTP has listed as carcinogens.

NTP's process for the 12th *RoC*, as well as its new process, ignored clear and pertinent direction from the National Research Council's National Academy of Sciences (NAS) regarding several fundamental best practices necessary to assure that toxicology-related assessments of chemicals are conducted in an evidence based, objective and scientifically credible manner. In the case of formaldehyde for the 12th *RoC*, NTP dismissed NAS' conclusions that NTP's approach in classifying formaldehyde was scientifically inaccurate.

In summary, the current *RoC* process falls well short of producing evidence-based listing decisions.

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[1] NTP Board of Scientific Counselors Meeting, 15 Dec 2011, statement of Dr. John Bucher. The statement referred to can be found at 6:15 minutes of the recording that is available at https://www.box.com/shared/static/ea274f5a6547994936ac.wma.

[2] "Peer Review of Draft Substance Profiles for the 12th *Report on Carcinogens*," slide 6 of presentation by Mary S. Wolfe of NTP to the NTP Board of Scientific Counselors Meeting, 24 Feb 2009; available at http://ntp.niehs.nih.gov/files/Wolfe20090224.pdf.

Additionally, the current *RoC* program does not address the original intent of Congress to identify only serious carcinogen concerns. NTP instead seemingly attempts to justify listing all substances nominated for consideration. Further, the *RoC* program is now duplicative of other federal carcinogen classification programs which use more robust assessment practices and which have been put in place since the *RoC* program began.

Given the above facts, I strongly urge Congress to oversee a thorough assessment of the current *RoC* program (ideally through an NAS review of the *RoC*), and to begin an ongoing evaluation to determine the *RoC's* fundamental relevancy and to ensure that any future *RoC* listings are evidence-based, provide accurate public health information and reflect the highest scientific standards in its processes.

This will increase the confidence of the public and industry in the *RoC's* listings and their application to science-informed decision-making.

Background

The *Report on Carcinogens* (*RoC*) is a Congressionally mandated report that lists substances that the Secretary of Health and Human Services (HHS) has determined are "known" or "reasonably anticipated" to cause cancer and to which significant numbers of Americans are exposed. The HHS Secretary has delegated responsibility for preparation of the *RoC* to the staff of the National Toxicology Program (NTP), which is housed administratively at the National Institute of Environmental Health Sciences (Research Triangle Park, NC). The Congressional directives for the *RoC* are sparse (see page fourteen of these comments), and NTP has managed this program without meaningful oversight.

NTP has attempted to provide the public with some perspective about its *RoC* listings by stating:

> "A listing in the *RoC* does not by itself establish that a substance will cause cancer in an individual. Many factors, including the amount and duration of an exposure, and an individual's susceptibility to a substance, impact whether a person will develop cancer or not. Formal risk assessments, that take into account these factors, are the purview of the appropriate federal, state, and local health regulatory and research agencies."[3]

NTP has published 12 editions of the *RoC* – the 11th Edition was issued in 2004, and the 12th Edition was published June 10, 2011.[4]

The NTP is globally recognized as an "authoritative body," and chemical classifications in the *RoC* carry significant consequences for businesses large and small, including regulatory actions (*e.g.*, OSHA Hazard Communications Standard labeling requirements, TSCA reporting requirements and California's Proposition 65)[5] and commercial impacts.

Because objective, evidence-based reviews of scientific research are essential elements of both informing the public about the potential risks which may be associated with individual substances and decision making by industry about its products and facilities, the reality of these impacts make it essential that *RoC* classifications represent the highest quality scientific evaluations.

My comments focus on three key shortcomings in the process NTP uses to prepare and develop its *RoC* assessments, and are based in part on issues revealed in the review of styrene in the recent 12th *RoC*, namely:

- **The *RoC* is *Ad Hoc* and lacks explicit criteria needed to assure its reviews of scientific information are transparent and scientifically consistent.**
- **The *RoC* process lacks adequate checks and balances, including peer review and addressing outside/conflicting data.**
- **The *RoC* process does not employ scientific best practices, relies on outdated approaches and has not adopted recent NAS recommendations.**

Each of these shortcomings is discussed in more detail in the following pages.

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[3] NTP's "Questions & Answers about the *RoC*, What does a listing in the *RoC* Mean?" Available at http://ntp.niehs.nih.gov/go/7249.
[4] *Report on Carcinogens* 12th Edition; available at http://ntp.niehs.nih.gov/go/roc12.
[5] NTP's "Questions & Answers about the *RoC*, What does a listing in the *RoC* Mean?" Available at http://ntp.niehs.nih.gov/go/7249.

The *RoC* is *Ad Hoc* and lacks explicit criteria needed to assure its reviews of scientific information are transparent and scientifically consistent.

The NAS expert panel members who prepared a 2011 assessment[6] of the EPA Integrated Risk Information System (IRIS) review of the chemical formaldehyde expressed concern about the fact that, in preparing its formaldehyde assessment, EPA referred to its own guidelines but did not follow them, employing instead what appeared to be a largely *ad hoc* process.[7]

Chapter seven of the NAS report lays out a "Roadmap" in which the Panel details a number of scientific best practices for assessments of chemicals in general and points out that *ad hoc* review processes cannot be relied on to produce scientifically valid assessments.

These concerns indirectly but convincingly call into question the validity of the process NTP used to conduct each of the assessments published in the 12th *RoC*. Even though NAS criticized some of the conclusions of EPA's draft IRIS review, the IRIS process is designed to rely on EPA's well-described, detailed and extensive evidence-based guidelines, which include its "Guidelines for Carcinogen Risk Assessment."[8]

In contrast, NTP's process for the *Report on Carcinogens* is almost entirely *ad hoc*. For example, the *Report on Carcinogens* has no supporting guidelines for carcinogen hazard or risk assessment and its listing criteria are filled with ambiguous non-scientific terms and are devoid of any details of how data are to be evaluated to apply the listing criteria.

NTP's newly revised *RoC* process, which is described in a brief five-page document titled "Process for Preparation of the *Report on Carcinogens*,"[9] includes a series of bureaucratic steps but is completely silent about the scientific processes that should occur at each state of the process. In fact, NTP itself characterizes parts of the new *RoC* process as "*ad hoc*." Given the lack of specific procedures and the fact that so many of the *RoC* process steps are completely at NTP's discretion, the overall process is, in effect, *ad hoc*.

To describe how external peer review input is supposed to occur, this document simply includes a footnote on page three that links to an NTP webpage for "Special Emphasis Panels." Following this link on NTP's website reveals:

> "The NTP uses ad hoc scientific experts, referred to as special emphasis panels (SEPs), as needed, to provide independent scientific peer review and advice on targeted issues. Such issues include the strength of the scientific evidence of the potential for harm from specific environmental or occupational exposures, the identification of toxicology knowledge gaps and data needs, and the evaluation of new/revised alternative toxicological methods of multi-agency interest that might improve or reduce, refine or replace the use of animals. These panels help ensure transparent, unbiased, and scientifically rigorous input to the program for its use in making credible decisions about human health hazards, setting research and testing priorities, and evaluating test methods for toxicity screening. The *Report on Carcinogens*, Office of Health Assessment and Translation and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods use SEPs to conduct evaluations. Special emphasis meetings are typically announced and open to the public."[10]

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[6] *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde*, Board on Environmental Studies and Toxicology, National Research Council of the National Academies, 189 pages, 2011, National Academies Press, Washington, D.C; available at http://www.nap.edu/catalog/13142.html.

[7] *Ibid.*, p. 80.

[8] *Guidelines for Carcinogen Risk Assessment*, Risk Assessment Forum, United States Environmental Protection Agency, 166 pages, 2005; available at http://www.epa.gov/raf/publications/pdfs/CANCER_GUIDELINES_FINAL_3-25-05.PDF.

[9] *Process for Preparation of the Report on Carcinogens*, 11 Jan 2012; available at http://ntp.niehs.nih.gov/NTP/RoC/Thirteenth/Process/FinalRoCProcesswithFig.pdf.

[10] *Special Emphasis Panels*, last updated 2 May 2011, http://ntp.niehs.nih.gov/go/166, accessed on line 20 Apr 2012.

Furthermore, a key step of the NTP process includes preparation of a draft "Monograph" which contains NTP's primary scientific rationale for its *RoC* classification decisions. However, a flowchart of the *RoC* process published by NTP states the Monograph is reviewed by "external scientific input, **as needed** (*e.g.*, consultants, ***ad hoc*** presentations, expert panels)"[11] **(emphasis added).**

NTP's process provides no criteria for how or when "external scientific input" is to be solicited or if and when it may be needed. Equally important, no criteria are provided for identification of the critical studies upon which the assessment detailed in the Monograph is to be based, how these studies will be evaluated, how studies that NTP considers to be critical will be selected or how consistent and transparent evidence-based evaluations of the overall body of scientific evidence can be assured, all matters that the NAS panel explicitly identified as necessary in its Chapter seven "Roadmap" in its review of the IRIS formaldehyde assessment.

NTP's review of formaldehyde for the 12th *RoC*, found that exposure to this substance was associated with leukemia, and on that basis NTP's panel voted to recommend that formaldehyde be listed as a "known carcinogen" in the *RoC*. Yet the NAS panel that reviewed formaldehyde found that the available data do not support a leukemia concern.[12] The NAS panel suggested that only an inadequate assessment of the data could result in a leukemia finding for formaldehyde. NTP has subsequently responded to the NAS review, dismissing its relevance to NTP's review of formaldehyde by highlighting the small differences between the nature of the EPA and NTP reviews.[13]

In summary, since the EPA formaldehyde review used an *ad hoc* process that resulted in a scientifically unsupported conclusion for formaldehyde, it follows that the NTP process for formaldehyde is also suspect. By extension, NTP's process is therefore generally suspect with respect to its ability to implement transparent, credible and evidence-based reviews. In the view of the NAS formaldehyde panel's Chapter seven, a process this *ad hoc* cannot be relied on to produce scientifically valid assessments.

The *RoC* process lacks adequate checks and balances, including peer review and addressing outside/ conflicting data.

Before discussing the lack of an adequate peer review process at NTP for the *Report on Carcinogens*, it is important to understand what appropriate and effective peer review consists of.

According to a 2004 bulletin published by the White House's Office of Management and Budget (OMB):

> "Peer review is one of the important procedures used to ensure that the quality of published information meets the standards of the scientific and technical community. It is a form of deliberation involving an exchange of judgments about the appropriateness of methods and the strength of the author's inferences. Peer review involves the review of a draft product for quality by specialists in the field who were not involved in producing the draft."[14]

The OMB Bulletin further indicates:[15]

- "The peer reviewer's report is an evaluation or critique that is used by the authors of the draft to improve the product. Peer review typically evaluates the clarity of hypotheses, the validity of the research design, the quality of data collection procedures, the robustness of the methods employed, the appropriateness of

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[11] *Process for Preparation of the Report on Carcinogens*, 11 Jan 2012, Figure 1; available at http://ntp.niehs.nih.gov/NTP/RoC/Thirteenth/Process/FinalRoCProcesswithFig.pdf.

[12] *NAS Formaldehyde Review*, *op. cit.*, pp. 108-110, 112.

[13] *Addendum to the 12th Report on Carcinogens*, National Toxicology Program, 30 Nov 2011; available at http://ntp.niehs.nih.gov/ntp/roc/twelfth/Addendum.pdf.

[14] *Final Information Quality Bulletin for Peer Review*, Executive Office of the President, Office of Management and Budget, p. 4, 16 Dec 2004; available at http://www.whitehouse.gov/sites/default/files/omb/memoranda/fy2005/m05-03.pdf.

[15] *Ibid.*, pp. 3-4.

the methods for the hypotheses being tested, the extent to which the conclusions follow from the analysis, and the strengths and limitations of the overall product."

- "Peer review should not be confused with public comment and other stakeholder processes. The selection of participants in a peer review is based on expertise, with due consideration of independence and conflict of interest."

Simply stated, effective peer review provides needed checks and balances, is conducted by "specialists in the field who were not involved in producing the draft" and is scientifically essential "to ensure...the quality of published information" and "to improve the product."

The Obama Administration has more recently reinforced a similar theme in several of its directives relation to the use of scientific information and scientific integrity. For example:

- A January 18, 2011 Executive Order by President Obama further directed that "[r]egulations shall be based, to the extent feasible and consistent with law, on the open exchange of information and perspectives among...affected stakeholders in the private sector, and the public as a whole."[16]
- A December 17, 2010 memo by the Director of the White House Offices of Science and Technology Policy, directs heads of executive departments and agencies to ensure that their scientific programs are based on "...honest investigation, open discussion, refined understanding, and a firm commitment to evidence.".[17]
- A March 9, 2009 "Memorandum on Scientific Integrity" to the heads of executive departments and agencies states "[t]he public must be able to trust the science and scientific process informing public policy decisions. Political officials should not suppress or alter scientific or technological findings and conclusions." It also says "[w]hen scientific or technological information is considered in policy decisions, the information should be subject to well-established scientific processes, including peer review where appropriate..."[18]

In contrast to these policies, the NTP process does not conform to the President's directives and advocacy in favor of transparency, integrity and sound science In contract, NTP's current review process, is starkly different from President Obama's directives relating to the use of science as well as OMB's description of peer review:

- **NTP's Board of Scientific Counselors (BSC)**

  In the past, the BSC's review served as both a peer review and a check and balance to the NTP office. With the exception of the 12th *RoC*, the BSC was asked to critically review NTP's scientific reasoning and then to vote on the NTP's recommendation found in the draft Monograph. Over the years, on three occasions, the BSC overturned the NTP's draft recommendation as a result of its peer review.[19] For the 12th *RoC*, the BSC had a more limited role due to a change in NTP policies was not asked to vote on NTP's listing decision.[20]

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[16] Improving Regulation and Regulatory Review, Executive Order 13563 of January 18, 2011, Federal Register, v. 76, no. 14, pp, 3821-3823; available at http://www.gpo.gov/fdsys/pkg/FR-2011-01-21/pdf/FR-2011-01-21.pdf.

[17] Memorandum for the Heads of Executive Departments and Agencies, Memorandum: Scientific Integrity, 17 Dec 2010; available at http://www.whitehouse.gov/sites/default/files/microsites/ostp/scientific-integrity-memo-12172010.pdf.

[18] *Memorandum on Scientific Integrity*, Administration of Bararck. H. Obama, 9 Mar 2009; available at http://regs.dot.gov/requirements/DCPD-200900137.pdf.

[19] *12th Report on Carcinogens, Appendix C*; available at http://ntp.niehs.nih.gov/ntp/roc/twelfth/roc12.pdf, p. 470 (lists these substances); the outcomes of the BSC deliberations can be found by reviewing the documents related to each review (available on request from NTP).

[20] *NTP Report on Carcinogens Review Process*, last updated 3 Oct 2011, http://ntp.niehs.nih.gov/go/29353, accessed 20 Apr 2012.

In the newly announced process, review by the BSC is limited to its initial draft "concept document,"[21] which is akin to an outline of what NTP's review intends to consider for a particular substance.

As a nearly final process step, NTP is also to "present information"[22] to the BSC about each draft Monograph and any reviews by an NTP Special Emphasis Panel (if convened). This step appears to be intended simply to inform the BSC in a public forum about NTP's conclusions, and it denies this senior advisory body any opportunity to conduct a peer review of the draft Monograph.

As a result, NTP will not use the BSC as a peer review body in the future.

- **Interagency Review**

  Draft Monographs have historically been subject to interagency peer review, but the results of these reviews have not been made public. These reviews were formalized as a part of NTP's process and gave experienced scientists at other Federal agencies with an interest in substances under review the opportunity to provide NTP with a critical peer review of the draft Monographs.

  For the 12th *RoC*, this process involved "...an interagency scientific review group..." which was "...provided with all relevant information (including the background document, the expert panel report, and any public comments received to date) on the candidate substances and asked to apply the listing criteria to this information and make a recommendation on the listing status of the candidate substance."[23] As with previous *RoC* reviews, the deliberations and results of this interagency review were not made public.

  In addition, in the case of styrene in NTP's 12th *RoC*, the meeting of one of the review panels was scheduled just four days following the close of the comment period; this made it exceptionally unrealistic to imagine that the reviewers would be able to appropriately consider the public comments received by NTP.

  NTP's flowchart of its most recent *RoC* review process still includes "Interagency Input" and "Interagency Review" as line items.[24] However, while in the past, this review was formalized when NTP "provided all relevant information" to its interagency partners, interagency "input" is now "invited" and any input received is "considered," along with input from other stakeholders.

  In essence, NTP has reduced interagency review to one of several stakeholder processes it uses to gather information. This is not peer review, however, as explained in OMB's 2004 Bulletin on Peer Review, which says "[p]eer review should not be confused with public comment and other stakeholder processes."[25]

  The bottom line is that NTP is free to do what it pleases with this "input," as NTP's process includes no formal guidelines for addressing such input.

- **Special Emphasis Panels**

  As previously referenced in these comments, NTP clearly states that its Special Emphasis Panels are, "*ad hoc* scientific experts..." who serve "...as needed, to provide independent scientific peer review and advice on targeted issues."[26]

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[21] *Process for Preparation of the Report on Carcinogens*, 11 Jan 2012, p.2; available at http://ntp.niehs.nih.gov/NTP/RoC/Thirteenth/Process/FinalRoCProcesswithFig.pdf.

[22] *Process for Preparation of the Report on Carcinogens*, 11 Jan 2012, Figure 1; available at http://ntp.niehs.nih.gov/NTP/RoC/Thirteenth/Process/FinalRoCProcesswithFig.pdf.

[23] *NTP Report on Carcinogens Review Process*, last updated 3 Oct 2011, http://ntp.niehs.nih.gov/go/29353, accessed 20 Apr 2012.

[24] *Process for Preparation of the Report on Carcinogens*, 11 Jan 2012, Figure 1; available at http://ntp.niehs.nih.gov/NTP/RoC/Thirteenth/Process/FinalRoCProcesswithFig.pdf.

[25] *OMB Peer Review Bulletin, op. cit.*, p. 4.

[26] *Special Emphasis Panels*, last updated 2 May 2011, http://ntp.niehs.nih.gov/go/166, accessed on line 20 Apr 2012.

In addition, NTP states that "[m]embers of NTP panels are scientists with relevant expertise and knowledge selected by the NTP from the public and private sectors. The final selection of membership is based upon providing a balanced and unbiased group of highly qualified individuals."[27]

For the *RoC*, such panels are instructed to determine "...whether the scientific evidence is adequate for applying the listing criteria..."[28] Special Emphasis Panels are included in the current NTP *RoC* process description and flowchart, but under different names:[29]

- NTP seeks "external scientific input, as needed" as it completes its draft Monograph.
- The *RoC* process includes a near-final step of "peer review of draft *RoC* Monograph by NTP Peer-Review Panel."

When each of these steps is first mentioned in the description of the updated *RoC* process and flowchart, they are footnoted with a reference to NTP's "*ad hoc*" and "as needed" Special Emphasis Panels.

The above descriptions of NTP's listing criteria and the roles of its Special Emphasis Panels seem similar to how OMB's 2004 Bulletin describes the peer review process. However, as explained beginning on page eleven of these comments, in its past practices, NTP has failed to adhere to evidence-based approaches which meet "...the standards of the scientific and technical community" and which assure that peer reviewers are "...not involved in producing..." NTP's draft Monographs.

At the present time, however, even the need for peer review of the critical draft Monographs by any non-NTP body, including NTP's self-described "*ad hoc* expert panels," is left entirely to the discretion of the NTP; this total discretion extends to the essential steps of selecting expert panel members who have appropriate expertise and identifying the review charge questions, which guide the reviews.

- **Role of the HHS Secretary**

The statue which created the *Report on Carcinogens* requires that the Secretary of Health and Human Services approve the publication of the listing decisions in the *Report on Carcinogens*.[30]

- In the 12th *RoC*, the Secretary received briefing papers from NTP and held meetings with members of the public who objected to the recommendations in the draft report. This provided some level of supervision of NTP's decisions.
- Under the new process for future assessments, the *Report* signed by the Secretary is afforded secondary importance by the fact that the NTP will publish the results of its assessments on the Internet for the public to begin using immediately upon completion and then every two years send forward the assessments completed up to that point for formal publication in the *Report on Carcinogens*.[31]
- It is hard to imagine that the Secretary would be inclined to overrule one of these assessments that had already made available to the public on the Internet up to 2 years previously.

This process change has now given the Director of the NTP full authority to write the assessments, subject them to some form of peer review to a panel of NTP's own choosing, complete the report, and publish it on the Internet without any supervision or review by any person outside of direct organizational control of the NTP Director.

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[27] *Process for Preparation of the Report on Carcinogens*, 11 Jan 2012, page 3, footnote 7; available at http://ntp.niehs.nih.gov/NTP/RoC/Thirteenth/Process/FinalRoCProcesswithFig.pdf.
[28] *Ibid.*, p. 4.
[29] *Process for Preparation of the Report on Carcinogens*, 11 Jan 2012, Figure 1; available at http://ntp.niehs.nih.gov/NTP/RoC/Thirteenth/Process/FinalRoCProcesswithFig.pdf.
[30] Public Services Health Act, as amended,§301(b)(4); available at http://energycommerce.house.gov/108/pubs/109_health.pdf.
[31] *Process for Preparation of the Report on Carcinogens*, 11 Jan 2012; available at http://ntp.niehs.nih.gov/NTP/RoC/Thirteenth/Process/FinalRoCProcesswithFig.pdf.

For a *Report* that has such important potential consequences for public health and the economy, this lack of proper checks and balances is inappropriate.

To summarize, NTP selects the scope of work for each Monograph, creates its Monographs in-house with limited external input or oversight, selects its own review committees "as needed," and approves and publishes the final content on the Internet.

In addition to the general issues that NTP's *Report on Carcinogens* has with its peer review process, as outlined above, the case of styrene in the 12th *RoC* also reveals a very specific concern about NTP's approach to peer review:

- NTP's current description of its *RoC* process include the following statement about peer review:

  "...all scientific information used to evaluate the potential carcinogenicity of a candidate substance must come from peer-reviewed, publicly available sources." Similar descriptions have been in place for some time at NTP.[32]

- Unfortunately, while this statement is clear, NTP did not follow it during its review of styrene during the 12th *RoC*. As part of NTP's styrene review, NTP reinterpreted two studies in ways that differed from the study authors' peer reviewed published conclusions. As a result, NTP was able to claim that styrene met its listing criteria and subsequently classified styrene as "reasonably anticipated to be a human carcinogen" in the 12th *RoC*.

  The styrene industry challenged NTP's approach in its public comments and testimony at public meetings to no avail.[33] Additionally, when NTP was questioned about its reinterpretation of these studies by two Members of Congress,[34] NTP, in a meeting with the Congressmen, first said that NTP could not conduct a peer review because the novel statistical analysis "was submitted to NTP over the phone."[35] In response to a written question, NTP later baldly stated that "no formal analysis of the results of any epidemiology study was presented as part of this process."[36]

None of the above reflects either transparent or credible peer review, and do not meet even the minimum standards of transparency, collaboration and participation which the Obama administration recognized in its 2009 memorandum about scientific integrity.[37]

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[32] *Ibid.*, p. 3.
[33] Letter from Jack Snyder, Styrene Information and Research Center, to Linda Birnbaum, Director of NTP, 22 Oct 2009; available at http://ntp.niehs.nih.gov/ntp/roc/twelfth/2009/Styrene/SIRC20091022.pdf.
[34] Questions 5 and 6, letter from John Shadegg and Rick Boucher, Congressmen, to Linda Birnbaum, Director of NTP, 22 Oct 2010.
[35] Question 5, letter John Shadegg and Rick Boucher, Congressmen, to Linda Birnbaum, Director of NTP, 22 Oct 2010.
[36] Reply to Question 6, letter to The Honorable John Shadegg from Linda Birnbaum, Director of NTP, 20 Dec 2010.
[37] *Memorandum on Scientific Integrity*, Administration of Bararck. H. Obama, 9 Mar 2009; available at http://regs.dot.gov/requirements/DCPD-200900137.pdf.

The *RoC* process does not employ scientific best practices, relies on outdated approaches and has not adopted recent NAS recommendations.

As previously noted in these comments (see page five), the National Academy of Sciences has specifically outlined some fundamental best scientific practices which are necessary to assure that toxicology-related assessments of chemicals are conducted in an evidence based, objective and scientifically credible manner.

These current best practices are detailed in Chapter seven of the NAS formaldehyde panel's report, which provides a "roadmap" for preparing hazard and risk assessments. In the view of the NAS panel, the roadmap provides the most effective process for developing the most scientifically valid assessments.

The NAS panel observed that successful approaches for reviewing and evaluating scientific data have several common elements, namely:

1. Transparent and explicitly documented methods;
2. Consistent and critical evaluation of all relevant literature;
3. Application of a standardized approach for grading the strength of evidence;
4. Addressing peer review and public comments; and
5. Clear and consistent summative language.[38]

The *Report on Carcinogens'* failure to meet these tests is especially egregious with regard to the first four:

1. Transparent and documented methods

As previously described on pages five and six of these comments, NTP's *RoC* process, while arguably open to the public, is *ad hoc* and lacks the explicit criteria needed to assure a consistent and transparent process.

2. Consistent and critical evaluation.

The NAS report specifically discussed the importance of a including a systematic, tabular analysis ("evidence table") of all the relevant studies as a specific best practice in conducting scientifically valid assessments.

The NAS report states that such tables should "...summarize the details and findings [of the research studies] in evidence tables. Typically, such tables provide a link to the references, details of the study populations and methods, and key findings. They are prepared in a rigorous fashion with quality-assurance measures, such as using multiple abstractors (at least for a sample) and checking all numbers abstracted."

Examining NTP's approach to its review of styrene for the 12th *RoC* is helpful in evaluating NTP's process:

- During the time that styrene was being reviewed by NTP but before the 12th *RoC* was finalized, several letters from various of Members of Congress were sent to NTP regarding NTP's styrene review. One of these letters, authored by then Congressmen John Shadegg (R-AZ) and Rick Boucher (R-VA), asked NTP to provide answers to eleven specific questions about the styrene review. One of these questions requested than NTP provide the Congressmen with a list of studies that supported a link between styrene and cancer and specifically how the data from these studies supported a cancer concern.[39]

[38] *NAS Formaldehyde Review, op. cit.* p. 157.
[39] Question 7, letter from John Shadegg and Rick Boucher, Members of Congress, to Linda Birnbaum, Director of NTP, 22 Oct 2010.

- NTP's reply to this letter did not provide the requested analysis. Instead, it referred to NTP's preliminary Styrene Background Document that "includes more than 500 studies." NTP further stated that the analysis of the studies was "complex," implying that it was not feasible for NTP to provide the requested study-by-study analysis.[40] Additionally, the published Styrene Substance Profile in 12th *RoC* does not include a table of this nature.[41]

This is just one example of how the process NTP used to prepare the *RoC* falls considerably short of this specific best practice as recommended by NAS.

3. Standardized approach to grading evidence.

The NAS panel identified a weight-of-the-evidence approach as a vital component of any standardized approach to evaluating scientific evidence so that the evaluation results in a balanced toxicity assessment.[42] This approach requires the use all the relevant data to develop the most plausible hypothesis regarding potential human toxicity.

In contrast, for the *RoC*, NTP uses a strength-of-the-evidence approach for its assessments. Such assessments differ from a weight-of-the-evidence review in that their conclusions are based primarily on data which supports an adverse effect ("positive data"). Even if there is a substantial body of data which fails to support an adverse effect ("negative data"), NTP typically does not use this data to as a counter-weight to the positive data. NTP may, as they often state, "consider" the negative data, but they do not "use" it.

This interpretation of the *RoC* process is supported by a number of examples, three of which follow:

- During a public 2010 NTP Board of Scientific Counselor's meeting, Dr. Gloria Jahnke of NTP presented and explained the NTP draft profile for glass wool fibers.

  Following this presentation, Dr. Mitzi Nagarkatti of the University of South Carolina School of Medicine (a member of the BSC panel), asked Dr. Jahnke: "I'm just wondering whether there were not studies on other animals such as mice, or they were done and found not to be carcinogenic."

  Dr. Jahnke replied: "The inhalation study of monkeys was negative. So, I'm not recording negative data here; I am recording data that supports our call. So that's why you didn't see it."[43]

- During a public 2009 NTP Board of Scientific Counselor's meeting regarding styrene and several other chemicals which were subsequently listed in the 12th *RoC*, a senior NTP official stated that *RoC* reviews are based on a "strength of the evidence" approach.[44]

- In a summary of a paper that reviews NTP's listing of styrene in the 12th *RoC* and is currently "In press" in the journal *Human and Ecological Risk Assessment*, the authors conclude:

  > "The NTP classification of styrene as 'reasonably anticipated to be a human carcinogen' based on 'limited' evidence of carcinogenicity in humans, 'sufficient' evidence in animals, and supporting mechanistic data is not scientifically supported, given that the available data do not meet these criteria. Styrene should not have been listed as 'reasonably anticipated to be a human carcinogen' in the NTP's 12th *Report on Carcinogens*."[45]

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[40] Reply to Question 7, letter to The Honorable John Shadegg from Linda Birnbaum, Director of NTP, 20 Dec 2010.
[41] *12th Report on Carcinogens, Styrene*, pp. 383-391, 2011; available at http://ntp.niehs.nih.gov/ntp/roc/twelfth/roc12.pdf.
[42] *Ibid.*, pp. 151-166.
[43] NTP Board of Scientific Counselors Meeting, June 21, 2010. The discussion referred to can be found at 12:30 minutes of the recording that is available at www.box.net/shared/static/sxqzg12pkr.mp3.
[44] "Peer Review of Draft Substance Profiles for the 12th *Report on Carcinogens*," slide 6 of presentation by Mary S. Wolfe of NTP to the NTP Board of Scientific Counselors Meeting, 24 Feb 2009, http://ntp.niehs.nih.gov/files/Wolfe20090224.pdf.
[45] Goodman, J.E., Rhomberg, L., "Why Styrene Should Not Be Classified as a Human Carcinogen And Does Not Belong in the NTP's 12th *Report on Carcinogens*," *Daily Environment Report*, BNA, 12 Mar 2012; available at http://www.gradientcorp.com/alerts/pdf/Styrene.pdf.

4. Addressing peer review and public comments.

The NAS Panel's "New IRIS assessment process" includes seven specific steps; step five of this new process is described as "Revise Assessment: Address peer review and public comments; prepare response to comments document."[46]

Although external public comment is solicited as an element of NTP's *RoC* process, NTP has stated, **as a matter of policy**, it will not offer any written response to such inputs for future *RoC* reviews.[47] This is in direct contradiction to the best practices articulated by the NAS Panel; this also minimizes the existence of differing scientific viewpoints. Several additional examples of NTP's failure to consider public and peer review comments evident from the styrene review are outlined below:

- Dr. Elizabeth Delzell, the author of a study that was inappropriately used to support NTP's classification of styrene in the 12th *RoC*, wrote a letter to NTP in which Dr. Delzell complained that NTP applied a novel statistical manipulation to her peer reviewed published data to change the result of the study and to incorrectly suggest a cancer concern for styrene, and that NTP had also improperly interpreted other studies.[48]

  In the same exchange of letters between Members of Congress[49] and NTP referred to on page eleven of these comments, NTP was asked about this situation. NTP first responded that it was unaware of Dr. Delzell's letter, even though it had long been posted to NTP's *RoC* docket; when made aware of Dr. Delzell's letter, NTP responded that it would be addressed at the completion of the *RoC* review,[50] well after its consideration could have any impact on the outcome of the *RoC* review.

- NTP did provide a response to certain issues raised by the public (including Dr. Delzell's questions), at the same time the final *RoC* was released, on June 10, 2011.[51] However NTP's response, which is simply "too little, too late," is critically flawed in two ways:

  1. NTP's response to comments came well after any opportunity for them to have any influence, if justified, on the outcome of the *RoC* review.
  2. NTP failed to respond at all to many additional public comments, as a matter of policy.[52]

  Each of these flaws is contrary to the best practices outlined in the OMB Bulletin on Peer Review and the NAS Panel's recommendations.

- In the same exchange of letters referred to earlier, NTP was asked more generally about how NTP would respond to scientific input received as part of the public comment process relating to the 12th *RoC*. NTP's response was similar to their response to Dr. Delzell, except that NTP went on to add that the various review groups were "provided access" to public comments "prior to their meetings"[53] related to the 12th *RoC* process.

  However, simply making information "available" to reviewers by posting it to a publicly-available docket or via some other mechanism is inconsistent with best practices. Such reviewers are often volunteers with limited time availability, and it is the role of review's sponsor to make this process efficient and to bring potentially conflicting areas of data interpretation to the attention of reviewers.

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[46] *NAS Formaldehyde Review*, *op. cit.* p. 154.
[47] NTP Board of Scientific Counselors Meeting, 15 Dec 2011, statement of Dr. John Bucher. The statement referred to can be found at 6:15 minutes of the recording that is available at https://www.box.com/shared/static/ea274f5a6547994936ac.wma.
[48] Letter from Dr. E. Delzell, University of Alabama to Dr. B. Shane, NTP, .5 Feb 2009; available at http://ntp.niehs.nih.gov/files/20090205Delzell.pdf.
[49] Question 8 in letter from John Shadegg and Rick Boucher, Members of Congress, to Linda Birnbaum, Director of NTP, 22 Oct 2010.
[50] Response to Question 8 in letter to The Honorable John Shadegg from Linda Birnbaum, Director of NTP, 20 Dec 2010.
[51] *NTP Response to Issues Raised in the Public Comments for Candidate Substances for the 12th Report on Carcinogens*, National Toxicology Program, 50 pages, 2011; available at http://ntp.niehs.nih.gov/ntp/roc/twelfth/2011/ResponsePublicComments2011.pdf.
[52] *Ibid.*, p. 1.
[53] Response to Question 10 in letter to The Honorable John Shadegg from Linda Birnbaum, Director of NTP, 20 Dec 2010.

Review

In summary, NTP's process for the *RoC* fails four of the National Academy of Sciences Panel's for quality hazard assessments:

- NTP's data evaluation methods are not well documented and are not employed consistently or transparently.
- From the early stages of a review, all but the data supporting a cancer concern are largely ignored.
- There is no standardized approach for grading scientific evidence.
- NTP's policy going forward is to NOT provide comments on public input and NTP "considers" input from the public but seldom actually uses it.

Oversight of the *RoC* by the Congress is needed now.

In creating the *Report on Carcinogens,* the U.S. Congress sought to identify those substances that are "known" or "reasonably anticipated to be" human carcinogens. The statutory language is brief.

Within the scientific context of carcinogen classification, the statutory phrase "reasonably anticipated to be a human carcinogen" is neither plain nor clear, but the Joint House-Senate Comparative Summary provides guidance.

> "...the phrase 'suspected carcinogens' [was replaced] with 'substances...reasonably anticipated to be carcinogens', in order to make it absolutely clear in the statute that there must be reasonable ground for designating a substance as a putative carcinogen."[54]

The final legislative language was a clear departure from earlier proposals that would have expansively listed substances as "suspect" carcinogens based on much looser criteria, such as "sound theoretical grounds."[55]

NTP has strayed from its legislative mandate by interpreting "reasonably anticipated" to mean suspect or theoretical carcinogens. This dilution of the basic evaluation criteria has led to excessive hazard identifications not intended by Congress.

NTP updated its *RoC* process in January 2012.[56] The changes made by NTP have weakened its process for reviewing scientific data even further by:

- Removing the long-standing authority of the Board of Scientific Counselors to peer review NTP substance assessments;
- Removing NTP's responsibility to respond at any time to public comments;
- Making the way in which peer review will be conducted *ad hoc* and entirely within the discretion of the authors of the assessment; and
- Effectively removing the Secretary of Health and Human Services from supervising NTP's *RoC* assessments before they are made public on the Internet.

In addition, in today's difficult economic climate, Congressional oversight could result in a substantial savings for the Federal budget. Congress may want to consider whether or not the *Report on Carcinogens* is redundant and should either be combined with other assessment functions or possibly sunset.

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[54] Joint House-Senate Comparative Summary and Explanation of Title II of H.R. 12460 and H.R. 12347, as Reported by the Committee on Interstate and Foreign Commerce, the Senate Bill, S. 2450, and the House Amendment in the Nature of a Substitute. 124 Congressional Record H38657 (1978) (statement of Rep. Rogers).

[55] 124 Congressional Record H34938 (1978) (statement of Rep. Rogers).

[56] *Process for Preparation of the Report on Carcinogens*, 11 Jan 2012; available at http://ntp.niehs.nih.gov/NTP/RoC/Thirteenth/Process/FinalRoCProcesswithFig.pdf.

This idea is supported by the fact that there is a great deal of redundancy among the hazard and risk assessment activities of the Federal government as applied to chemicals.

- When the *Report on Carcinogens* was first authorized in 1978, it was unique in its functions; however, other, more thorough, hazard assessment programs have outstripped it in terms of quality and usefulness.
- At the present time, however, seven different Federal agencies, including NTP, perform hazard and/or assessments on chemicals, including two other agencies within HHS alone – FDA and ATSDR – that overlap NTP's mission related to the *Report on Carcinogens*.
- Since 2011, just for the chemical styrene, four reviews have recently been completed or are currently underway, namely:
  - 2011 – National Toxicology Program's *Report on Carcinogens*.
  - 2011 – Agency for Toxic Substances and Disease Registry's Toxicological Profile.
  - 2012 – United States Environmental Protection Agency's IRIS Assessment.
  - 2012 – EPA's office of Chemical Safety and Pollution Prevention Review – announced, but start date is uncertain.

Summary

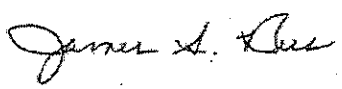
As demonstrated in the preceding pages of this testimony, the current *RoC* process falls well short of producing evidence-based listing decisions. Simply stated, the current process for the *Report on Carcinogens*:

- Lacks explicit criteria needed to assure a consistent and transparent assessment process.
- Does not meet even minimum standards of peer review and ignores nearly all public comments.
- Fails to use many current scientific best practices

Conclusions

I urge Congress and these Committees to actively oversee a thorough assessment of the *RoC* – ideally through an NAS review – to ensure that any future *RoC* listings are evidence-based, provide accurate public health information and reflect the highest scientific standards in its processes, and to begin to determine the *RoC's* fundamental relevancy going forward. This will increase the public's and industry's confidence in the *RoC's* listings and their application to science-informed decision-making.

Respectfully submitted,



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