November 22, 2011

BY ELECTRONIC MAIL

The Honorable Kathleen Sebelius
Secretary of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

RE: Comments on the Department of Health and Human Services, National Toxicology Program's Report on Carcinogens

Dear Secretary Sebelius:

The U.S. Small Business Administration (SBA) Office of Advocacy (Advocacy) submits these comments on the Department of Health and Human Services (HHS), National Toxicology Program's (NTP), Report on Carcinogens (RoC) and on the proposed RoC review process.[1] Advocacy is familiar with the concerns underlying the NTP's decision to review the RoC process as identified by small businesses, including the quality of scientific research and procedural transparency. The efforts of NTP to review the RoC process by inviting public comment are welcomed, however, the proposed review process does not make any substantial or necessary changes.[2] In fact, the NTP's removal of peer review and public comment opportunities in the proposed review document will further hinder the RoC by decreasing the level of transparency.[3]

Advocacy urges the HHS to review and evaluate the RoC's purpose and objectives and to consider whether, if substantial changes cannot be made, the RoC should continue to play a role in the federal government's chemical risk assessment program. Further, the RoC is duplicative of another federal chemical assessment program, the Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS). Advocacy's concern reflects those of small businesses for which a less than robust RoC may have a substantial, negative economic impact.

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[1] Federal Register, Vol. 76, No. 2010, October 31, 2011. Retrieved from http://ntp.niehs.nih.gov/ntp/PressCtr/FRN/2011/76FRN210ROC20111031.pdf.
[2] National Toxicology Program's Proposed Review Process for the Report on Carcinogens available at http://ntp.niehs.nih.gov/?objectid=3756DE0C-FA7A-404B-3F72194C30ABD961.
[3] HHS (2011). Proposed Report on Carcinogens Review Process. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, Research Triangle Park, NC. Retrieved from http://ntp.niehs.nih.gov/NTP/RoC/Thirteenth/Process/ProposedROCReviewProcess2011.pdf.

Office of Advocacy

Congress established the Office of Advocacy under Pub. L. No. 94-305 to advocate the views of small entities before Federal agencies and Congress. As Advocacy is an independent body within the U.S. Small Business Administration (SBA), the views expressed by Advocacy do not necessarily reflect either the position of the Administration or the SBA.

The RoC Background

The RoC was congressionally mandated in 1978, as part of the Public Health Services Act, in response to Americans' concerns regarding the relationship between their environment and cancer. It was to be a science-based, public health report to identify 'substances' in the environment that may potentially increase the risk of cancer.[4] The biennial publication provides information on cancer studies that support a listing, potential sources of exposure to humans, and current federal regulations to limit exposures. The RoC lists chemicals as either "known to be a human carcinogen" or as "reasonably anticipated to be a human carcinogen."

Notably, on the NTP's website, and in a fact sheet on the 12th RoC published by the NTP, the NTP explains that a listing in the RoC does not "by itself establish that a substance will cause cancer in an individual."[5] Further, the RoC studies were neither designed for, nor intended to inform regulatory decision-making. However, the listings are used by several organizations primarily as substantive guidance documents and to regulate potential human carcinogens. Such organizations include the U.S. Congress, Federal and State agencies including EPA, the Occupational Safety and Health Administration (OSHA), private businesses and unions. Although the RoC was a novel approach when mandated, it overlaps today with other more robust federal chemical assessment programs, such as EPA's IRIS.

Accurate and Reliable Chemical Assessments are Vital for Small Businesses

Small businesses are growing more concerned with the RoC because of the impact that the report may have on their business. The placement of a chemical in a RoC has the potential to substantially stigmatize the chemical post-listing. The stigmatism may lead to substantial adverse economic impacts for small businesses that use that chemical, including de-selection of American products in the marketplace by businesses and consumers, an increase in the likelihood of additional regulations and, an increase in fears of using or buying products manufactured with a labeled chemical.

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[4] U.S. Department of Health and Human Services, National Toxicology Program website. Retrieved from http://ntp.niehs.nih.gov/?objectid=72016262-BDB7-CEBA-FA60E922B18C2540.

[5] U.S. HHS (2011). Fact Sheet on the 12th RoC. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, Research Triangle Park, NC, p. 2. Retrieved from http://www.niehs.nih.gov/health/materials/fact_sheet_the_report_on_carcinogens.pdf; *see also* National Toxicology Program website http://www.niehs.nih.gov/news/sya/sya-roc/.

Government agencies should also be aware that technical labels used in the RoC can be misinterpreted and mislead the public about the true nature of risks to health and safety. For example, although the RoC lists chemicals as "reasonably anticipated to be a human carcinogen" or "known to be a human carcinogen," it includes the caveat that "listing of substances in the RoC only indicates a potential hazard and does not establish the exposure conditions that would pose cancer risks to individuals in their daily lives."[6] However, because consumers, businesses and government bodies are likely to be more aware of how the chemical is labeled than the disclaimer that appears in the RoC, and because negative labeling can stigmatize a chemical, an accurate risk characterization is vital.

The call for accurate and consistent risk characterizations based on reliable scientific processes is supported by President Obama's Executive Order 13563 "Improving Regulation and Regulatory Review," issued on January 18, 2011. The E.O. states that the regulatory system "must promote predictability and reduce uncertainty and identify and use the best, most innovative and least burdensome tools for achieving regulatory ends."[7]

The President's 2009 Memorandum on Scientific Integrity states, "Science and the scientific process must inform and guide decisions of my Administration … The public must be able to trust the science and scientific processes informing public policy decisions."[8] Likewise, small businesses and the public must be able to rely on the scientific integrity and procedures that produce chemical risk characterizations.

Once a substance has been listed in the RoC, the substance may be delisted. However, the process for delisting is a substantial obstacle to having a chemical removed from the RoC. This difficulty is highlighted by the attempt to delist glass wool as "reasonably anticipated to be a human carcinogen" that was listed in the 7th RoC published in 1994. After more than ten years of research, glass wool was nominated for delisting in 2004. However, instead of delisting the substance the NTP modified the substance profile which excluded certain varieties of glass wool that are "not biopersistent" in the lung. In the 12th RoC glass wool does not appear either as a delisted substance or as a listed substance, causing additional confusion. The listing to 'delisting' process for glass wool took more than 20 years.[9]

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[6] U.S. HHS (2011). Report on Carcinogens, Twelfth Edition. U.S. Department of Health and Human Services, Public Health Service, National Toxicological Program, Research Triangle Park, NC, p 3.

[7] Executive Order 13563, Improving Regulation and Regulatory Review (76 Fed. Reg. 32088) (January 18, 2011).

[8] Presidential Memorandum for the Heads of Executive Departments and Agencies on Scientific Integrity. March 9, 2009. Retrieved from http://www.whitehouse.gov/the_press_office/Memorandum-for-the-Heads-of-Executive-Departments-and-Agencies-3-9-09/.

[9] Richard B. Belzer, "The Report on Carcinogens: What Went Wrong; What can be Done to Fix It", Working Paper, Revised October 24, 2011, p. 3. Retrieved from http://www.rbbelzer.com/uploads/7/1/7/4/7174353/111103_regcheck_working_paper_on_roc.pdf.

Small Businesses' Primary Concerns with the Report on Carcinogens are not Addressed in the NTP's Proposed Review Process

Comments made by small businesses since the NTP's June 10, 2011 release of the 12th RoC have highlighted substantive and procedural problems throughout the program. Small businesses' primary concerns with the 12th RoC, and the RoC in general, relate to the quality of scientific analysis, the robustness of the scientific process, including procedures for peer review and public comment procedures, and that the RoC is duplicative of other federal chemical risk assessment programs, particularly the IRIS. The NTP's proposed review process does not improve on these major concerns and will in fact aggravate the existing problems.

RoC's Scientific Analysis and Methods Need Improvement

The 12th RoC included new listings for both styrene and formaldehyde. Small businesses have taken issue with styrene's listing as "reasonably anticipated to be a human carcinogen" and formaldehyde's listing as "known to be a human carcinogen." Styrene is used by thousands of mostly smaller companies in the composites and recreational boat building industries. Formaldehyde is used in numerous products from plywood to embalming fluid and toothpaste.

Substantively, Advocacy is concerned with the quality of scientific analysis undertaken by NTP's researchers in drafting the 12th RoC. The RoC focuses on a selected set of studies and not a weight of evidence assessment. Neither a mode of action analysis nor an understanding of how exposure to a certain chemical leads to cancer are required.[10] It is sufficient for the RoC to show "causality" from human studies defined as a "credible association that cannot be explained by chance, bias, or confounding."[11] However, the RoC only cites data from workers exposed to the highest exposure of formaldehyde[12] and ignores data from negative studies.[13] Because of this, the RoC has been criticized as only undertaking a labeling exercise with almost no value for estimating cancer risk or supporting risk-based decision-making.[14]

Further, the RoC's listing of styrene as a "reasonably anticipated to be a human carcinogen" conflicts with several other studies that have concluded to the contrary. One recent European Union study, a review of the styrene health effects database by scientists, determined that styrene should not be classified or regulated as a carcinogen. [15]

[10] U.S. HHS (2011). Addendum to the 12th Report on Carcinogens. U.S. Department of Health and Human Services, Public Health Service, National Toxicological Program, Research Triangle Park, NC, p 2. Retrieved from http://ntp.niehs.nih.gov/ntp/roc/twelfth/Addendum.pdf.
[11] *Id.* at 2.
[12] C. Richard Titus, "Formaldehyde in the 12th Report on Carcinogens." Kitchen Cabinet Manufacturers Association. July 2011.
[13] Belzer, *supra* note 9 at 26.
[14] *Id.* at 2.
[15] European Chemicals Agency (2008). European Union Risk Assessment Report: Styrene. Draft for Publication, June 2008, United Kingdom. Retrieved from

A second report in 2009 by a blue ribbon panel of internationally recognized epidemiologists concluded that the, "available epidemiologic evidence does not support a causal relationship between styrene and exposure and any type of human cancer."[16]

The University of Alabama's Dr. Elizabeth Delzell, a styrene researcher, argues that there "is not sufficient science to conclude that styrene causes lymphoma, leukemia or other cancers."[17] Also, the International Agency for Research on Cancer decided to list styrene as a "possible" and not a "probable" carcinogen in a 2002 review.[18] Notably, HHS' own Agency for Toxic Substances and Disease Registry (ATSDR) recently reviewed the same data but instead of finding that styrene was a "reasonably anticipated to be a human carcinogen", found only that styrene "may be a weak carcinogen."[19]

Further, the RoC's listing of formaldehyde as "known to be a human carcinogen" contradicts the National Academy of Sciences' recent independent review of the Draft IRIS Review of Formaldehyde.[20] The NAS found that IRIS' scientific evaluation of formaldehyde did not support its conclusion that formaldehyde caused blood cancers. NTP explained the different hazard characterizations by stating that the NAS critique of the IRIS had 'limited applicability' because the, "NAS document is not an independent hazard assessment."[21]

NTP's proposed review process does not include methods to rectify the RoC's lack of mode of action analysis as well as the understanding of how exposure to chemicals leads to cancer which would lend increased credibility to the RoC.

Peer Review and Public Comment Opportunities are Insufficient

The RoC listings should receive appropriate independent peer review. Advocacy is concerned that the NTP's procedures do not allow for sufficient opportunity for peer review or public comment and are, therefore, insufficiently transparent. Similar concerns

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http://echa.europa.eu/doc/trd_substances/styrene/rar/trd_rar_uk_styrene.pdf; *see also* http://www.box.net/shared/zjy9h7xc6hh66erlmca2.

[16] Boffetta *et al*, "Epidemiologic Studies of Styrene and Cancer: A Review of the Literature", J Occup Environ Med., Vol. 51, N. 11, 1275-1287, November 2009. Retrieved from http://www.box.net/shared/static/mfusvfim1x.pdf.

[17] Letter from Elizabeth Delzell, University of Alabama, to Barbara Shane, Executive Secretary, National Toxicology Program, Board of Scientific Counselors, NIEHS, February 5, 2009, retrieved from http://www.box.net/shared/static/slm4m8tp7a.pdf.

[18] World Health Organization, International Agency for Research on Cancer, "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene", Vol. 82, Lyon: IARC Press, 2002, retrieved from http://monographs.iarc.fr/ENG/Monographs/vol82/mono82-9.pdf.

[19] Styrene Information and Research Center, "Styrene Industry Will Contest Vigorously the Unwarranted listing of Styrene in 12th Report on Carcinogens", Statement by Jack Snyder, Executive Director, June 10, 2011, retrieved from http://www.styrene.org/news/pdfs/06-10-11-statement-ntp-listing.pdf.

[20] NAS. (2011). Review of EPA Formaldehyde April 8 2011 Committee to Review EPA's Draft IRIS Assessment of Formaldehyde. National Academy of Sciences, Washington, D.C.

[21] NTP, *supra* note 10, at 1.

were previously raised following the 11th RoC which prompted the NTP to review and improve its procedures for the 12th RoC review process.

Peer review of the 12th RoC began with an external panel review of the draft background document. The reviewers do not conduct an independent and objective review of the science, but instead are asked to determine whether NTP's policies are supported by its science. The Board of Scientific Counselors (BSC) then undertakes a second scientific peer review. However, for the 12th RoC the BSC was not charged with the review of NTP's decision regarding listing status. Instead, the BSC was asked only to determine, "whether the scientific information cited in the draft substance profile for a candidate substance is technically correct, clearly stated and supports the NTP's policy decision regarding its listing."[22]

Although the NTP procedures provide peer reviewers with access to the scientific data, peer reviewers on the three styrene peer review panels were not informed of the scientific criticisms of NTP's position on styrene.[23] Peer reviewers lack access to, and therefore cannot comment on, public comments and scientific controversies.[24] With the limited time and resources of the peer reviewers, it is difficult for the peer reviewers to review all of the materials and often rely on NTP staff to summarize important information for them. Insufficient opportunity for peer review and public comment decreases transparency and confidence in the NTP process.

Unfortunately, the proposed RoC review process does not bolster opportunity for either peer review or public comment and even takes away from the current opportunities. For example, under the 'Scientific evaluation' phase the new process requires external scientific input only 'as needed'. NTP's explanation for when scientific input is 'needed' is based on "The nature, extent, and complexity of the scientific information on a candidate substance",[25] which does not describe specific circumstances or requirements. Further, this phase only includes one opportunity for public participation, whereas in the 12th RoC this phase included three opportunities. Under the 'Public Release of Draft RoC Monograph and Peer Review' phase, instead of having the NTP BSC peer review the draft, the review may be conducted either by the BSC or an 'ad hoc panel'. There is no explanation of when it is appropriate to choose either the BSC or the ad hoc panel and why this change was made. In the 'HHS Approval and Release' phase the NTP has abandoned the requirement of the NTP to respond to public comments. Advocacy notes that there are additional opportunities for interagency comment early on in the

[22] Bergeson & Campbell PC, "NTP Proposes to Revise RoC Review Process." November 1, 2011. Retrieved from http://www.lawbc.com/tsca/memoranda-2011-51-mobile.html.
[23] Letter from Jack Snyder, Styrene Research and Information Center & John Schweitzer, American Composites Manufacturers Association to the Hon. Kathleen Sebelius, Secretary, U.S. Department of Health and Human Services, May 24, 2011, retrieved from http://www.styrene.org/news/pdfs/05-24-11-letter-to-HHS.pdf.
[24] Letter from Cal Dooley, American Chemistry Council, to David Lane, Assistant to the President & Cass Sunstein, Administrator, Office of Information and Regulatory Affairs, Office of Management and Budget, September 21, 2011.
[25] NTP, *supra* note 3, p 3.

'Nominations and Selection' and 'Scientific Review' phases, however, interagency review should not take away from the opportunity for the public to comment.

The RoC is Duplicative

Advocacy is concerned about the duplication of work between the RoC and the IRIS. Duplication can lead to inconsistent findings which in turn may increase public uncertainty over the human health and environmental risks. Currently, there is no interagency process to promote uniformity and ensure coordination between agencies with chemical risk assessment responsibilities. Within HHS itself, for example, there are two agencies that duplicate the NTP's hazard assessment objective: the U.S. Food and Drug Administration (FDA) and the ATSDR.

The duplication of federal chemical risk assessment programs is highlighted by the RoC and EPA's IRIS assessments. The IRIS is a human health assessment program that evaluates risk data on effects that may result from exposure to environmental contaminants. The IRIS compiles a database that describes the health effects of substances and contains quantitative and descriptive information on cancer and non-cancer effects. Thus, the IRIS not only duplicates, but exceeds the scientific analyses undertaken by the RoC as the quantitative hazard characterization is not performed by the RoC. The NTP's proposed review process does not address the overlap between the RoC and the IRIS or other federal chemical risk assessments.

Conclusion

Small businesses are concerned that the continued lack of rigorous scientific inquiry and methodology, procedural inadequacies, and the duplication of assessments will have a substantial, negative economic impact on their business. The NTP's proposed review process falls short of making the necessary changes by which to turn the RoC into a transparent and science-based process. If such changes cannot be made HHS should review and evaluate the RoC's purpose and objectives and consider whether the RoC continues to play an important and useful role in the federal government's chemical risk assessment program. If my office can be of any further assistance, please contact me or Sarah Bresolin Silver at (202) 205-6790 or sarah.bresolin@sba.gov.

Sincerely,

/s/

Winslow Sargeant, Ph.D.
Chief Counsel for Advocacy

/s/

Sarah Bresolin Silver
Assistant Chief Counsel

Copy to: The Honorable Cass R. Sunstein, Administrator
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