DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of
Environmental Health Sciences
P. O. Box 12233
Research Triangle Park, NC 27709
Website: www.niehs.nih.gov

June 8, 2011

Mr. Jack Snyder
Executive Director
Styrene Information and Research Center, Inc.
801 North Quincy Street, Suite 700
Arlington, Virginia 22203

Re: Information Quality Act (IQA) Request for Reconsideration (RFR) – Styrene Background Document

Dear Mr. Snyder:

I am responding on behalf of the National Institute of Environmental Health Sciences (NIEHS) to your February 11, 2011, Request for Reconsideration (RFR), submitted on behalf of the Styrene Information and Research Center (SIRC). The RFR requests withdrawal or correction of information disseminated by the National Toxicology Program (NTP) concerning the Background Document for styrene.

NTP is located administratively within NIEHS. However, NTP officials and personnel did not participate in this response to your RFR in order to ensure an objective process.

We have reviewed and considered your RFR pursuant to the Department of Health and Human Services (HHS) Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public and the National Institutes of Health (NIH) Guidelines for Ensuring the Quality of Information Disseminated to the Public (http://aspe.hhs.gov/infoquality/guidelines/nihinfo2.shtml and http://aspe.hhs.gov/infoquality/guidelines/index.shtml). We have also reviewed your October 26, 2009, Request for Correction of Information, the December 23, 2010 response from NTP, and the Background Document. This information was used in assessing the merits of your appeal. This letter follows the interim response to your RFR from Betsy Dean, Office of Science Policy Analysis, Office of Science Policy, Office of the Director, NIH, dated April 8, 2011.

Upon review, we conclude that NTP complied with NIH and HHS Information Quality Act (IQA) Guidelines with respect to the Background Document. As a result, your RFR is denied. The reasons for this determination are as follows:

1. The Background Document is meant to be an unbiased compendium of carcinogenicity and toxicology information, including both positive and negative findings, from publicly available, peer-reviewed literature. As stated in the NTP response, "a background document is a resource for evaluating candidate substances for the RoC [Report on Carcinogens] that compiles and

summarizes publicly available information from both positive and negatives studies on the substance. It follows a general format and does not contain any opinion regarding the listing status for the candidate substance." Drawing such conclusions about the data described or including interpretative information and evaluation would amount to a usurpation of the functions of the independent, external scientific panel members, for whom the information in the Background Document is intended.

2. You assert that "NTP's response demonstrates that it fundamentally misunderstands the requirements of the objectivity and utility criteria" and that the Background Document fails to meet the "objectivity" criterion of the IQA. According to OMB guidelines, "Objectivity" focuses on "whether disseminated information is being presented in an accurate, clear, complete, and unbiased manner" and whether it is "accurate, reliable, and unbiased." The Background Document contains information from publicly available, peer-reviewed sources. According to OMB guidelines, "If the data and analytic results have been subjected to formal, independent, external peer review, the information may generally be presumed to be of acceptable objectivity." Moreover, each of three scientific review groups, including the expert panel, acted as an independent review body and used the information available in the Background Document and public comments to assess the scientific evidence for carcinogenicity of styrene. The expert panel voted unanimously that the draft Background Document with their recommended changes was "adequate for drawing conclusions about the carcinogenicity of styrene and for applying the RoC listing criteria." Hence, we agree with NTP's conclusion that the Background Document satisfies applicable IQA guidelines with respect to objectivity.

3. You similarly assert that the Background Document fails to meet the "utility" criterion of the IQA. According to OMB guidelines, "Utility" refers to the "usefulness of the information to its intended users, including the public." As noted, a background document is a resource for evaluating candidate substances for the RoC that compiles and summarizes publicly available information from both positive and negative studies on the substance. Review groups utilize the information contained in a background document in formulating their opinion on whether or not to recommend listing a substance in the RoC. In this case, the draft Background Document was peer reviewed by an independent expert panel at a public meeting. Additionally, public comments were received. The Background Document is useful to its intended audience, including the public. Hence, we agree with NTP's conclusion that the Background Document satisfies applicable IQA guidelines with respect to utility.

In your RFR, you reiterate "four ways in which the Background Document violates the demands of the objectivity and utility requirements." Each of these was addressed, at some length, in NTP's response of December 23, 2010. We briefly summarize our views on these examples here.

1. "Omission of analysis of study results by the original author." The Background Document describes the study's methodologies and reports the findings, both positive and negative, of Delzell et al., 2006. As previously pointed out by NTP, "[T]he Background Document does not state that the available epidemiologic evidence supports 'a causal relationship between styrene exposure and any type of human cancer.' "

2. "Reliance on a study hampered by methodological limitations." You state that, "NTP relied on results that were not statistically significant in Kolstad et al. (1995, 1994) to support a finding of an effect." The Background Document describes the methods and reports the findings of Kolstad et al., 1994, 1995. It also notes the limitations of this work, as you mention. In addition, as noted on page 11 of the NTP response, NTP has issued an addendum to the Background Document to modify page 178, lines 27-30, to read, "In analyses of subtypes of leukemia, the risk…and *statistically non-significant* increased risk was also seen for myeloid leukemia with chromosomal aberrations in a nested case-control study of the Danish workers, *based on small number of cases* (Kolstad et al., 1996)." [*Italics indicate clarifications made.*]

3. "Unexplained departure from standard NTP practice." You state that, "NTP used a new historical control analysis to evaluate NCI (1979a), which departs from NTP's practice of not engaging in additional analyses of historical controls." The Background Document describes the methods and reports the findings of the NCI oral study (1979). The original conclusion by NCI is included. Historical control data reported in the NCI study are also included. Information regarding additional analyses of historical controls is clearly identified as information not present in the original publication and is available to readers to use their own scientific judgment in reviewing. Provision of information about historical tumor rates in groups of control animals for consideration in evaluating a given tumor response is standard NTP practice and consistent with information reported in NTP Technical Reports.

4. "Omission of contextual information regarding the state of the science." You state that, "NTP relied on Huff et al. (1984), even though NTP has not typically combined the particular tumor types in question for over two decades…" The Background Document presents the methods and findings of Huff et al. (1984). Specifically, the Background Document notes in Table 4-4 that, "Statistics not reported by NTP for benign and malignant tumors combined because of lack of information on the histogenesis of the tumors." Information on page 216, lines 7-9, refers to data on fibroadenoma of the mammary gland and does not refer to combined tumors. NTP did not rely on Huff et al. (1984). The study and its findings were included in the Background Document as part of the relevant, peer-reviewed literature on styrene. With respect to characterization of lymphohematopoietic malignancies, on page xii, lines 19-22, and page 192, lines 14-17, NTP amended the Background Document in an addendum to read, "In the styrene monomer and polymer industries, the risk of lymphohematopoietic malignancies was also increased *(both statistically significant and statistically non-significant)* in most of the studies (as well as the total number of observed cases across studies), but these workers might also have been exposed to benzene." [*Italics indicate clarifications made.*]

Finally, your RFR again asserts that "NTP finalized the Background Document before reviewing public comments on relevant issues." As explained in the original NTP response, upon public release of the Expert Panel Report, NTP invited public comment on the expert panel's recommendation on the listing status of styrene in the 12th RoC and the scientific justification for that recommendation, i.e., Expert Panel Report, Part B. Consistent with the RoC review process, NTP did not invite public comments on the expert panel's peer review comments, i.e., Expert Panel Report, Part A. NTP had previously invited and received public comment on the draft Background Document, and the expert panel heard additional public comments at its meeting. Conclusions of the expert panel are indeed independent of the Background Document. Further, NTP's website on the "RoC review process" discusses public release of NTP response documents

in the paragraph titled "Preparation of Draft RoC and Transmittal" (http://ntp.niehs.nih.gov/?objectid=FA925F34-F1F6-975E-775C81773747D452). This paragraph states that, at the time the 12th RoC is publicly released, "…the NTP posts the BSC's peer review report, the NTP 's response to that report, and the NTP 's response to the expert panel peer review comments on the draft background documents on the RoC website. In addition, for the 12th RoC, the NTP will prepare a response to public comments received on candidate substances since issuance of the expert panel report and will post the response on the RoC website."

We thank you for your interest and contribution to the RoC process.

Sincerely,

Allen Dearry, Ph.D.
Senior Advisor