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Via email to InfoQuality@od.nih.gov

John T. Burklow
Associate Director for Communications
Office of the Director
National Institutes of Health
Building 1, Room 344
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Bethesda, MD 20892

Re: Information Quality Act Appeal – Styrene Background Document [1]

Dear Mr. Burklow:

This appeal by the Styrene Information and Research Center, Inc. (SIRC) is being submitted under the Information Quality Act (IQA)[2] and implementing guidelines issued by the Office of Management and Budget (OMB),[3] the U.S. Department of Health and Human Services (HHS)[4] and the National Institutes of Health (NIH).[5] SIRC filed its Request for Correction (RFC) of the Final Report on Carcinogens Background Document for Styrene on October 26, 2009, and the National Toxicology Program (NTP) provided a response dated December 23, 2010 (NTP's Response) which SIRC received on January 14, 2011.[6]

[1] SIRC is not aware of any NIH tracking number being assigned to its original Request for Correction.

[2] Pub. L. No. 106-554, § 515, 114 Stat. 2763A-153 to 2763A-154, 44 U.S.C. § 3516 note (2000).

[3] *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies*, 67 Fed. Reg. 8452 (Feb. 22, 2002).

[4] HHS, *Guidelines for Ensuring the Quality of Information Disseminated to the Public*, available at http://www.hhs.gov/infoquality/part1.html**.**

[5] NIH, *Guidelines for Ensuring the Quality of Information Disseminated to the Public*, available at http://aspe.hhs.gov/infoquality/Guidelines/NIHinfo2.shtml.

[6] NTP's response was received by SIRC via Federal Express delivery on January 14, 2011. Consistent with the NIH procedures regarding appeals, copies of both SIRC's RFC and NTP's response are attached. They are: letter of October 26, 2009, from Jack Snyder, Executive Director, SIRC to John Burklow, Associate Director for Communications, Office of the Director, NIH; and letter of December 23, 2010, from John R. Bucher, Associate Director, NTP to Jack Snyder, Executive Director, SIRC.

In response to SIRC's RFC, NTP's Response does acknowledge the need to make roughly a dozen corrections to the Background Document and provides some additional clarifications. While these are appreciated, the bulk of NTP's Response consists of formulaic statements to the effect that NTP followed its procedures, and thus the Background Document must be correct. Consistent with the IQA, SIRC's RFC principally addressed the substantive science issues raised by the Background Document. In contrast, NTP's Response studiously avoids the substance of the science and reiterates procedural conclusions like "the Background Document follows the standard format" (p. 5) and "NTP has chosen to accept the advice of the RoC expert panel" (p. 7).

NTP's Response reflects a fundamental misunderstanding of the objectivity criterion under the IQA, as we demonstrate with the examples that appear below. For the Background Document to comply with that criterion, it must be "accurate [and] reliable," contain "the best available . . . science," and present that information in a "complete and unbiased manner . . . within the proper context." It currently does not. The Background Document also violates the "utility" criterion of the IQA because it does not enable a reader to make an informed judgment about the carcinogenicity of styrene.

Finally, NTP fails to rebut the single procedural argument that SIRC *did* make in its RFC – that NTP finalized the Background Document before the close of the public comment period on the Expert Panel's draft report. Those comments were invited to address the Panel's scientific justification for listing styrene, a justification that is based on and inseparable as a factual matter from the manipulations and characterizations of the data that the Expert Panel introduced into the final Background Document through its review comments on the draft, which NTP adopted across the board. We recognize that NTP's procedural approach attempts to sever the Background Document from the Panel's scientific justification, but we view these as interdependent. Thus the Background Document was finalized before NTP had even received all of the public comments on what became fundamental (and problematic) elements of the final Background Document.

The balance of this appeal explains the foregoing assertions and demonstrates how NTP failed to comply with the requirements of the IQA in crafting its reply and why NIH should grant SIRC's appeal and revise the Background Document – and the Substance Profile based on it – accordingly. Because this appeal and the Background Document it addresses are so fundamental to HHS' final listing decision regarding styrene, NTP should not include any decision about styrene in the 12th *Report on Carcinogens (RoC)* until these corrections and associated changes are made in the Draft Profile on styrene.

I. THE IQA REQUIREMENTS OF OBJECTIVITY AND UTILITY

Congress enacted the IQA to ensure and maximize the "quality, objectivity, utility and integrity of information . . . disseminated by Federal agencies" like NIH.[7]

[7] Pub. L. No. 106-554, *supra* note 2, at § 515(a).

"Objectivity" is centrally relevant in cases of scientific health assessments such as the Report on Carcinogens (RoC). "Objectivity" means that information must be *accurate, reliable* and *unbiased*.[8] Moreover, "influential" scientific information like the RoC that bears on assessment of health risks must be based on "*the best available . . . science . . . conducted in accordance with sound and objective scientific practices*."[9] Science that is not the best available, or that is generated by practices that are chosen to produce a given effect, is not objective. NTP's Response fails to rebut (or even address, in some cases) the RFC's demonstration that the Background Document, in many places, is not objective in this respect.

Objectivity must also be reflected in the way that information is presented. To be objective, information must be presented in an *accurate, clear, complete* and *unbiased* manner, which includes presentation in the proper context.[10] In particular, the Background Document is a prime example of a case in which, "in disseminating . . . information to the public, other information must also be disseminated in order to ensure an accurate, clear, complete and unbiased presentation."[11] Influential scientific information bearing on assessing health risks – like the Background Document – must present "each significant uncertainty identified in the process" and "peer-reviewed studies . . . that fail to support any estimate of risk."[12] Again, NTP's Response does not rebut SIRC's demonstration in the RFC that the Background Document fails this aspect of the objectivity criterion in many instances.

Finally, the IQA also aims to ensure the "utility" of information that comes from Federal agencies. "Utility" is equally as important as objectivity and requires that information, as it is presented, be useful to its intended users, including the public.[13] SIRC's RFC demonstrated that the Background Document is not useful because it does not allow a reader to make a reliable judgment about the carcinogenicity of styrene due to NTP's failure to report valid alternative interpretations of fundamental scientific studies. NTP's Response does not overcome that showing.

II. NTP'S RESPONSE DEMONSTRATES THAT IT FUNDAMENTALLY MISUNDERSTANDS THE REQUIREMENTS OF THE OBJECTIVITY AND UTILITY CRITERIA

To satisfy the objectivity and utility criteria, the Background Document generally should:

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[8] 67 Fed. Reg. 8549 (emphasis added).

[9] *Id*. at 8457 (emphasis added).

[10] *Id.* at 8459 (emphasis added).

[11] *Id*.

[12] *Id.* at 8457-58.

[13] *Id.* at 8459; *cf.* 44 U.S.C. § 3504(e)(1)(B) (2006).

(1) Inventory all the relevant, peer-reviewed literature on a particular point; and
(2) Present the methodologies and findings of those studies in an accurate and complete manner, which includes discussing their strengths, limitations and data to the extent they may be relevant to plausible scientific interpretations.[14]

There is probably no dispute among the parties on these steps (although, as shown below, NTP did not always follow them). And so far as it goes, NTP's "standard format" of describing data could accomplish these functions.[15] But no matter how hard NTP strives to characterize the function of a Background Document as a ministerial, descriptive summary of studies, it cannot escape several complexities forced on it by the requirements of objectivity and utility – and merely asserting that it "follow[ed] the standard format" is insufficient to dismiss these inherent challenges.

Below we describe four ways in which the Background Document violates the demands of the objectivity and utility requirements, in each case noting one or more examples. Each of those examples is then explained at greater length.

- **Omission of Analysis of Study Results by the Original Author**
  The views of the relevant scientific community on a particular study are certainly relevant to whether it, or conclusions drawn from it, are "reliable" or represent the "best available . . . science." This is most certainly the case when the principal author of a published study offers interpretations that contradict those in the Background Document. A complete discussion of the study must at least note the fact of this disagreement.
    - Specifically, NTP failed to acknowledge that the principal investigator in Delzell et al. (2006) flatly disagreed with the Expert Panel's characterization of her findings, a characterization that NTP incorporated into the final Background Document.

- **Reliance on a Study Hampered by Methodological Limitations**
  At some point, the methodological limitations of a study may render its findings unreliable, or at least far less reliable than other studies not so limited. It is not sufficient for the Background Document to note the limitations of a study but then to present the resulting data as if they were equally significant as other, more reliable results – especially when these findings, *without* a necessary qualifier about their limitations,

[14] We stress that we are not suggesting that the Background Document needs to contain interpretations. Rather, it should summarize studies so that readers can make informed judgments when more then one plausible interpretation of the data is possible. However, as we note below, in several instances NTP crafted the Background Document to promote a particular interpretation of the data, while ignoring other plausible interpretations without providing any justification for doing so.

[15] *See*, *e.g.*, NTP's characterization on page 4 of NTP's Response: "The NTP would like point out that the Background Document for styrene follows a standard format for reporting the human cancer studies. In general, the approach was to describe the study population(s), exposure assessment, and methods of statistical analysis, and to extensively report the findings including results for the overall population and any subgroups."

become part of the scientific justification for listing. Such a presentation almost assures that judgments based on the Background Document will fail to reflect the best available science and will be unreliable.

- Specifically, NTP relied on results from Kolstad et al. (1995, 1994) that were not statistically significant to support a finding of an effect.

- **Unexplained Departure from Standard NTP Practice**
  Multiple times in the Background Document, NTP departs from standard NTP practices without acknowledging that departure. Where NTP departs from a standard practice, such as its use of historical controls, the IQA requirement for "sound and objective scientific practice" obliges NTP to:
  - Note the prior policy;
  - Provide a justification for departing from the policy, including whether the departure is a special exception based on particular data, or instead a program-wide decision prompted by the evolving state of scientific understanding; and
  - Inform the public whether NTP will be applying this new position uniformly in the future.

  NTP must follow this process not only to satisfy the IQA, but also to comply with general principles of administrative law and due process.
  - Specifically, 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;
  - NTP relied on Huff et al. (1984), even though NTP has not typically combined the particular tumor types in question for over two decades; and
  - NTP relied on results that were not statistically significant in Kolstad et al. (1995, 1994) to support a finding of an effect.

- **Omission of Contextual Information Regarding the State of the Science**
  By definition, studies based on hypothesis testing are premised on one of several competing theories about causation. In some cases, each of those theories may be supported by roughly equivalent bodies of work and enjoy comparable support within the scientific community. In other cases, however, the weight of evidence is strongly toward one hypothesis and away from others. Thus, the state of the science provides essential context and must be addressed for the presentation of information to be considered complete and accurate. For example, a discussion on the possible reasons for the variety of finch beaks observed in the Galapagos would not be expected to explain even-handedly that natural selection and "intelligent design" were two alternative explanations. Rather, the discussion must provide the context that, based on the published literature, creationism was a less plausible interpretation of the data.[16] A report would certainly not be "biased" if it did so; to the contrary, it would be biased and misleading if it did not.

[16] *See, e.g.,* National Research Council, SCIENCE, EVOLUTION, AND CREATIONISM (2008), available at http://www.nap.edu/catalog.php?record_id=11876&utm_medium=etmail&utm_source=National%20Academies%20Press&utm_campaign=NAP+mail+eblast+1.21.11+-+Readers+Choice+Final&utm_content=customer&utm_term=.

- Specifically, NTP relied on Huff et al. (1984), even though the statistical approach of combining tumors in the study was shown to be erroneous a few years after completion of the study; and
- NTP failed to acknowledge the conclusion in Boffetta et al. (2009) that is contrary to the conclusion of the Background Document regarding the characterization of lymphohematopoietic malignancies.

As noted above, simply stating that NTP has followed its standard format does not explain how NTP has grappled with and resolved these unavoidable issues. Nor does the objectivity requirement allow NTP to justify its actions by simply stating that they "were consistent with the Expert Panel." NTP sometimes accepts and sometimes rejects the suggestions of expert panels, as is clear from the disparate treatment of expert panel recommendations regarding substances being reviewed for inclusion in the 12th RoC.[17] In all cases, the IQA and the Administrative Procedure Act (APA) require NTP to give adequate reasons for its choices. NTP's actions must be based on a rational interpretation of underlying data, which must be generated, analyzed and presented objectively. When that analysis is unsound and unreliable and its presentation is biased and incomplete, the resulting characterization can become arbitrary and capricious under the APA – as has occurred here.

SIRC does not dispute that it is difficult to craft a textual summary that accurately and completely characterizes a collection of studies in light of the scientific context in which they are situated. But that is NTP's obligation under the IQA. As the following examples show, the styrene Background Document does not meet those obligations, despite what NTP's Response says in its defense.

III. SPECIFIC EXAMPLES

A. NCI Oral Study (failure to explain departures from standard NTP practice)

In the final Background Document, NTP developed and used a new historical control analysis to evaluate the NCI (1979a) study, in which NCI had concluded that its mouse tumor data were within the historical control range and provided no more than suggestive evidence of cancer. SIRC proposed that NTP delete the new analysis as "not reflect[ing] sound and objective scientific practice." SIRC cited the following as evidence "suggest[ing] an attempt to bias the interpretation of the NCI study to support a preferred hypothesis."

[17] *See*, *e.g.*, NTP's determinations regarding glass fibers. The Expert Panel Report Part B: Recommendation for Listing Status, and the Scientific Justification for the Recommendation for Glass Fibers states: "by a vote of 8 yes/0 no that glass wool fibers . . . should not be classified either as known to be a human carcinogen or reasonably anticipated to be a human carcinogen." (Available at http://ntp.niehs.nih.gov/Ntp/roc/twelfth/2009/june/GWF_PartB.pdf.) NTP's draft substance profile for glass fibers proposes to classify as reasonably anticipated to be a human carcinogen. If the simple statement that NTP elected to follow an expert panel's recommendation is sufficient justification for a cancer classification, than the simple statement that NTP did *not* follow a recommendation should suffice to *invalidate* the resulting classification. If an expert panel's recommendation is not to be dispositive, then additional explanation is always required, and citing a recommendation is not a sufficient basis for the agency's action.

- NTP's new historical control analysis used animals from a laboratory different than that used in NCI (1979a). NTP justified this action as being required to obtain a sufficient number of controls for studies that used corn oil as the vehicle for administration of the test substance. The Background Document failed to note, however, that NCI's own earlier analysis of control data from NTP studies had concluded that: (i) use of corn oil had no impact on the incidence of lung tumors; and (ii) historical controls for mouse tumor studies should be drawn only from studies conducted by the same laboratory because there are different rates of lung tumors in controls from different laboratories.[18]
- NTP failed to address its departure from its traditional practice of not engaging in additional analyses of historical controls, or to explain why this is the sole study among the hundreds referenced in the Background Document for which it chose this unusual approach.

NTP offers two reasons for its departure from the norm (p. 12). First, NTP argues that its new analysis of historical controls is clearly presented, so that the reader should not confuse these with the data in the original study; and it "has chosen to follow the advice of the RoC expert panel." As to the first response, potential confusion was never SIRC's complaint; SIRC wanted the new analysis removed altogether as being "not valid."

NTP's second response is that it "has chosen to follow the advice of the RoC expert panel." As discussed above, however, mere citation to the Expert Panel does not take the place of explaining why NTP changed its scientific position regarding (i) the effect of a corn oil vehicle for administration of the test substance, and the (ii) appropriateness of mixing controls from different labs, or why NTP was justified in changing its practice regarding historical controls in this case but no others. As to the corn oil issue, NTP's own analysis of the NTP historical control database (Haseman et al., 1985) concluded that use of corn oil vehicle in the NCI study specifically *did not* impact lung tumor incidence in B6C3F1 mice in NCI-NTP carcinogenesis bioassays. NTP thus failed to justify why its novel historical control analysis using corn oil historical controls was a scientifically necessary alternative approach in the face of the authors' own published conclusions. Remarkably, the Background Document does not even reference Haseman et al. (1985), despite that fact that the lead author was listed as a contributing consultant on the Background Document (page iii).[19]

As to the issue of mixing controls, NTP also has published its position that, because of significant inter-laboratory variability in the incidence of background mouse lung tumors, historical control tumor analyses for this endpoint should be restricted to tumor incidences

[18] These issues and comparison with NCI (1979b) and Ponomarkov (1978) are discussed on pages 51-55 of SIRC's initial Request for Correction.

[19] References demonstrating standard NTP practice: Haseman JK, Huff, J, Boorman, GA. 1984. Use of historical control data in carcinogenicity studies in rodents. *Toxicologic Pathology* 12: 126-135; Haseman JK, Huff JE, Rao GN, Arnold JE, Boorman GA, McConnell EE. 1985. Neoplasms observed in untreated and corn oil gavage control groups of F344 rats and (C57Bl/6N x C3H/HeN)F1 (B6C3F1) mice. JNCI. 75: 975-984.

observed within the same testing laboratory (Haseman et al. 1984). The basis for this concern is specifically evident in the NTP Background Document analysis: the lung tumor incidence in control animals in the laboratory conducting the NCI bioassay was 3-fold higher than the control incidence in the laboratory selected for the NTP analysis – a point that SIRC made in its RFC (p. 55). Again, despite NTP's own opposing recommendations for use of such historical data, no justification was provided in the Background Document for alternative use of inter-laboratory historical control data.[20]

Objectivity requires that NTP give reasoned explanations for deviations from established practice like the use of new historical control analysis in the Background Document, particularly since NTP's novel analysis was key to supporting its conclusion that the animal tumorigenicity data justified the proposed "reasonably anticipated as a human carcinogen" RoC listing. NTP fails to provide sound and reliable justification for this substantial deviation.[21] Thus the portion of the Background Document containing this analysis continues to violate the objectivity requirement of the IQA and must be corrected. NTP's decision to engage in new historical control analysis is also arbitrary and capricious under the APA, and cannot be used as the basis for listing styrene as a reasonably anticipated human carcinogen.

B. Delzell et al. (2006) (failure to include analysis of study results by the original author)

The final Background Document contains an extended and substantial discussion of studies of styrene-butadiene rubber (SBR) industry workers by Delzell et al. (2006). NTP re-interpreted Delzell et al. to assert an association even though the authors themselves did not conclude that styrene caused cancer. It did so largely at the direction of the Expert Panel, which asserted that there is increased risk of Non-Hodgkin lymphoma (NHL), and NHL combined with chronic lymphocytic leukemia (CLL), caused by styrene and not by butadiene in the SBR cohort:

> In the Delzell study there was an exposure-response relationship for NHL and NHL plus chronic lymphocytic leukemia (CLL) that was not attenuated by control for butadiene and

[20] See, e.g., Keenan C, Elmore S, Francke-Carroll S, Kemp R, Kerlin R, Peddada S, Pletcher J, Rinke M, Schmidt SP, Taylor I, and Wolf DC. 2009. Best Practices for Use of Historical Control Data of Proliferative Rodent Lesions. Toxicologic Pathology 37: 679-693. The authors of this paper, including representatives of NTP, NIEHS, FDA, and USEPA, recommended consensus principles to guide the use of historical control data from chronic rodent bioassays. Their first consensus principle is that the "current control group is the most relevant comparator for determining treatment-related effects in a study." In preparing the Background Document, NTP departed from these consensus principles without adequate explanation.

[21] In developing a new analysis or interpretation of the original study using additional data, NTP also departed from its policy stating that it only relies on peer-reviewed studies in preparing the Background Document. The new analysis should have first been published in a peer review journal. That process would have provided the necessary scientific scrutiny and comparison with consensus practices. NTP has never done this. Ironically, Boffetta et al., which NTP declines to reference, is a peer-reviewed publication critically discounting the Expert Panel's conclusions, as discussed below.

> only mildly attenuated by control for dimethyldithio-carbamate (DMDTC) (which may not have been appropriate to control for).[22]

Dr. Delzell reviewed the Expert Panel report and the final Background Document, and her comments were submitted to NTP. In response to the foregoing quote, she said flatly:

> To the extent that the above statement implies that the epidemiologic results for NHL from the two studies constitute strong evidence of a causal relation with styrene, I do not agree. Results for styrene and NHL from both studies are unconvincing . . . . As the Background document points out frequently, the papers and report on the UAB study did not include any statistical tests of exposure-response trends for styrene and NHL or NHL/CLL.
>
> In the case of styrene and NHL, such supportive epidemiologic evidence is not sufficient for a conclusion of causality. The epidemiologic studies, including the UAB study, are, at best, weakly supportive. The Background document downplays the fact that studies of reinforced plastics industry workers do not provide clear support for a causal relationship between styrene and NHL, citing exposure misclassification, short follow-up, large proportions of short-term employees, etc., as explanations. However, reinforced plastics industry workers on average experienced styrene exposure concentrations much higher than those in the synthetic rubber industry. Even short-term workers in the reinforced plastics industry could have had cumulative styrene exposures similar to, or above, the median cumulative exposure of 17 ppm-years estimated for all styrene-exposed decedents (or the median of 30 ppm-years among NHL decedents) in the UAB study (Delzell et al., 2006). Thus, the lack of a clear association between styrene and NHL in the studies of reinforced plastics industry workers is an important shortfall of the evidence for the hypothesis that styrene causes NHL.[23]

Thus the author of a key publication in the Background Document directly disagrees with NTP's characterization of the publication's conclusion. However, the Background Document makes no reference to the author's disagreement.[24] Such a stunning omission signals a failure to present the relevant science accurately and objectively. The motives for this omission are inevitably called into question, moreover, by NTP's additional failure to discuss Boffetta et al. (2009), which was provided to NTP before SIRC filed its RFC. Boffetta et al. (2009) also included an evaluation of Delzell et al. (2006) and, like Dr. Delzell, concluded that styrene was not causally associated with the cancers claimed in the Background Document. *See* Part III.E below.

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[22] Scientific Justification, at 2.

[23] Comments of Dr. Delzell, included as Attachment A to SIRC's comments on the draft Expert Panel Report (Oct. 23, 2008), available at http://ntp.niehs.nih.gov/index.cfm?objectid=20A477F2-F1F6-975E-7472FC6B0DA56D9C#styrene.

[24] Conceivably NTP will respond that this is because it finalized the Background Document before the close of the comment period for the Expert Panel's report. This is precisely why that sequence of events was so illogical and detrimental to the quality of the final Background Document. *See* Part IV below.

C. Huff et al. (1984) (failure to provide contextual information regarding the state of the science, and failure to acknowledge departure from standard NTP practice)

NTP's response with regard to Huff et al. (1984) is the mirror image of its response to NCI (1979a). Regarding NCI (1979a), NTP departs from the study authors' conclusions and its own standard practice to support an interpretation. With regard to Huff, et al. (1984), NTP supports the study author's finding of an effect despite the fact that the statistical approach of combining tumors taken in Huff et al. (1984) was shown to be erroneous a few years later and, as a result, NTP has not typically combined the particular tumor types in question for over two decades.[25]

In its RFC, SIRC noted (p. 56) that combining various types of mammary tumors as done in Huff et al. (1984) is not appropriate because fibroadenomas are not related to adenocarcinomas. McConnell et al. (1986)[26] demonstrated that mammary fibroadenomas should not be combined with malignant mammary tumors unless a continuum has been demonstrated within a given study. No such continuum was demonstrated in the Beliles et al. (1985) drinking water study that Huff et al. (1984) was reanalyzing. Therefore, combining them does not represent "sound . . . and objective scientific practice" and is misleading. SIRC thus requested that discussions of Huff et al. (1984) or such combinations of tumors be removed from the Background Document.

NTP responds (p. 13) that no changes are needed to the discussion on Huff et al. (1984) in the Background Document because the text in question "all refers to factual information from Huff (1984)." Again, this was never the criticism posed by SIRC. The discussion of Huff et al. (1984) is misleading because it presents an approach to combining tumors that has since been discredited. NTP should delete any reference to Huff et al. (1984) in the Background Document; if it retains references to the study, NTP must explain why it is departing from standard practice, and how inclusion of Huff et al. (1984) constitutes sound and objective scientific practice in light of the findings of McConnell et al. (1986).

D. Kolstad et al. (1995, 1994) (relying on a study hampered by methodological limitations, and failure to acknowledge departure from standard NTP practice)

The serious methodological flaws with Kolstad et al. (1995, 1994) prompted the EU to characterize the study's estimate of the number of exposed workers as "highly questionable," particularly because the assessment of which workers had "high" or "low" exposures was regarded as unreliable. In line with the EU's conclusion that Kolstad presented "no evidence [of] an increased cancer risk," SIRC explained that the *accurate* summary of Kolstad is that, "[b]ased on this methodology and data, it is not reasonable to conclude that this study provides evidence of increased cancer from styrene exposure." NTP rejected SIRC's request for correction because "the Background Document does not draw conclusions relative to the study's findings," and NTP declined to include "SIRC's interpretation of the study's findings" (NTP's Response, page 5).

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[25] McConnell E.E., *Solleveld H.A., Swenberg J.A., Boorman G.A. Guidelines for Combining Neoplasms for Evaluation of Rodent Carcinogenesis Studies* J. Nat'l Cancer Inst. 76: 283-289 (1986).

[26] *Id*.

Instead, the Background Document simply acknowledges "a methodological limitation of this study" and then proceeds to present data from Kolstad, most of which showed nonsignificant increases for cancer (*see esp*. pp. 95-96). That description of the study is then repeated in NTP's draft Substance Profile, which cites Kolstad et al. (1995, 1994) in support of an effect.[27]

OMB's IQA Guidelines state: "[I]t is clear that agencies should not disseminate substantive information that does not meet a basic level of quality."[28] In the case of RoC Background Documents, meeting that level of quality requires "us[ing] the best available . . . science," reflecting "sound and objective scientific practices," and being "reliable."[29] NTP faces a challenge. It must either:

- Omit studies that are as flawed methodologically as Kolstad et al. (1995, 1994);
- "[D]raw conclusions" about their reliability; or
- Ensure that it does not allow methodologically limited data to shed its limitations and emerge unqualified in shorter or more influential documents.

But NTP cannot leave the matter as it stands now.

As noted above, most of the increases that Kolstad et al. (1995, 1994) described were not statistically significant. As with its flawed use of Huff et al. (1984), NTP's inclusion of data that are not statistically significant and suffered from recognized methodologic limitations to support a finding of an effect also departs from generally accepted scientific norms. NTP does not address this fundamental issue; thus the references to nonstatistically significant and methodologically limited data should be removed or validated in some substantial (and presumably highly qualified) fashion.

E. Improper Characterization of Lymphohematopoietic Malignancies (failure to provide contextual information regarding the state of the science)

SIRC requested that NTP revise a statement in the Background Document relating to the characterization of lymphohematopoietic malignancies in the styrene monomer/polymer industries to be consistent with Boffetta et al. (2009). Again, NTP responded that the statement in the Background Document is correct and that it would not include SIRC's "interpretation of the studies' findings . . . ." (NTP's Response, p. 8). However, SIRC was not asking NTP to include SIRC's opinion or interpretation. Rather, SIRC was asking NTP to incorporate a direct quote from Boffetta et al. (2009) reflecting those authors' conclusion upon reviewing the same four studies that the Background Document presents on the topic: "In the styrene monomer and polymer industries, studies of styrene production workers, while limited by small size, *do not provide evidence for a causal association between styrene exposure and cancer, including lymphohematopoietic malignancies*" (emphasis added).

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[27] Draft Substance Profile at 2-4.

[28] 67 Fed. Reg. 8452.

[29] *Id*. at 8457, 8457 and 8459, respectively.

The Background Document must present "each significant uncertainty identified in the process" of assessing the risk of styrene. The IQA requires NTP to discuss "peer-reviewed studies . . . that fail to support any estimate of risk."[30] NTP's Response itself captures the profound uncertainties that remain to this day regarding the different interpretations that can be drawn from the human studies. NTP's Response states (p. 8):

> SIRC requests specific revisions to the statement in the Background Document on page 192, "[i]n the styrene monomer and polymer industries, the risk of lymphohematopoietic malignancies was also increased 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," to be consistent with Boffetta et al. (2009), "[i]n the styrene monomer and polymer industries, studies of styrene production workers, while limited by small size, do not provide evidence for a causal association between styrene exposure and cancer, including lymphohematopoietic malignancies."

Yet the Background Document conceals this uncertainty by omitting any reference to Boffetta et al. (2009).[31]

Even more troubling than this omission, however, is NTP's insistence that "[t]he information given on page 192" does not require correction. The statement on page 192 ("the risk of lymphohematopoietic malignancies was also increased in most of the studies") is clearly not an accurate characterization of the four studies summarized in Table 3-8 (pp. 171-72). As that table shows, only one of the four studies (Hodgson and Jones) found a statistically significant increase in any LH cancers ("all LH," both by standard incidence ratio and standard mortality ratio). As Boffetta et al. (2009) explained, there was no trend among these by length of service. All the other findings among the four studies were not statistically significant and almost completely offsetting:

- Hodgson and Jones: 3 (+), 3(-)
- Bond: 6 (+), 5(-)
- Nicholson: 1(+), 2 (-)
- Frentzel, Beyme et al. [none]

[30] *Id*. at 8457-58.

[31] SIRC submitted Boffetta et al. in a letter dated December 16, 2008, available at http://ntp.niehs.nih.gov/index.cfm?objectid=20A477F2-F1F6-975E-7472FC6B0DA56D9C#styrene. While this was after the close of the comment period on the draft Expert Panel report, SIRC had repeatedly advised NTP that the Boffetta et al. Blue Ribbon Panel's work was in progress and had requested an extension of the comment period to accommodate submission of its manuscript. NTP denied SIRC's request for an extension. In any event, NTP has a continuing obligation to maintain the quality of the Background Document, particularly while the 12th RoC is still in development. *See* 67 Fed. Reg. 8459 (Feb. 22, 2002) (OMB IQA Guidelines) ("Agencies shall treat information quality as integral to every step of an agency's development of information, including creation, collection, maintenance and dissemination . . . . The agency's administrative [correction] mechanisms . . . shall apply . . . regardless of when the agency first disseminated the information.").

It is simply wrong to describe this random scatter of data as showing that "the risk . . . was . . . increased in most of the studies."

NTP's Response notes that the Background Document does not express an opinion concerning a particular listing status in the Report on Carcinogens. While it is true that NTP does not explicitly express an opinion in the Background Document, NTP's selective presentation of data and published conclusions clearly conveys a variety of toxicological and epidemiological conclusions. As a result, the tailored Background Document can more readily be cited in NTP's draft Substance Profile in support of the overt statement of those same conclusions. Failing to acknowledge a contrary and scientifically credible conclusion in the published, peer-reviewed literature is an inaccuracy in the final Background Document. Also, as noted above regarding Delzell, NTP failed to address that the Background Document relied on a non-peer reviewed and non-published novel evaluation of Delzell developed by the Expert Panel and directly contrary to the published findings of Boffetta et al. Unless the full range of science is presented completely and accurately, the reader is left with the inaccurate impression that only those conclusions presented by NTP are viable.

IV. NTP FINALIZED THE BACKGROUND DOCUMENT BEFORE REVIEWING PUBLIC COMMENTS ON RELEVANT ISSUES

In its RFC, SIRC explained that:

- NTP finalized the Background Document after it had received the Expert Panel's draft report but before the deadline for submission of public comments on the draft; and
- NTP adopted essentially every recommendation of the Expert Panel, making significant changes in the final Background Document that rendered it even less objective and useful within the meaning of the IQA.

Thus, by the time NTP had received comments explaining the problems with the Expert Panel's draft report, the damage was done: the Background Document had been revised to incorporate those problems, which in turn have been carried into the draft Substance Profile. SIRC pointed out that this improper procedure undermined the normal presumption of objectivity that attaches to a peer-reviewed document – but obviously, this procedure is also inherently illogical (and thus arbitrary and capricious).[32]

In response, NTP repeatedly insists that the Expert Panel's peer review comments on the draft Background Document were Part A of its report, and that NTP had not sought comment on Part A, but only on Part B (the Expert Panel's proposed cancer classification and scientific justification therefore). It may be, as a matter of procedural formality, that "conclusions reached

[32] *See, e.g.*, Illinois Public Telecommunications Ass'n v. FCC, 117 F.3d 555, 566 (D.C. Cir. 1997) ("The Commission's failure to provide an explanation for this seemingly illogical decision is arbitrary and capricious.").

by the expert panel and reported in the Expert Panel Report, Part B, are independent of the Background Document" (Response at 6). In reality, however, that statement is demonstrably false. The conclusions set out in the Expert Panel's scientific justification for listing are woven throughout the Panel's peer review comments, which are self-evidently constructed to maximize apparent support for those conclusions. This can be readily seen by comparing the two at any corresponding points. Compare, for example, the two documents on the significance of Delzell et al. (2006):

Scientific Justification (p. 2):

> The strongest evidence for cancer in humans is the association between styrene exposure and non-Hodgkin lymphoma (NHL). This evidence comes from the Delzell et al. (2006) analysis in the styrene-butadiene industry and the Kogevinas (1994a) study in the reinforced plastics industry. In the Delzell study there was an exposure-response relationship for NHL and NHL plus chronic lymphocytic leukemia (CLL) that was not attenuated by control for butadiene and only mildly attenuated by control for dimethyldithiocarbamate (DMDTC) (which may not have been appropriate to control for). It is very unlikely that such a strong exposure-response trend could be due to chance, bias, or confounding.

Peer Review Comments:

> The Delzell et al. 2006 report also analyzes leukemia, NHL and NHL-CLL data for three-chemical exposures, butadiene, styrene, and DMDTC. Both butadiene and styrene in single-agent models are associated with significantly increased risks for all leukemias in the two highest exposed groups and both show a dose response (although no trend information is provided). When both of these chemicals are in the model, both chemicals show increases in RR with increasing dose, but when DMDTC is added to the model as reported by Graff et al. 2005, the styrene risk disappears. Using a different exposure measure [in Table 12], namely number of styrene peaks, styrene in the single chemical model has RR values for all leukemia that are slightly higher than those of butadiene alone (except at the highest quartile). Both styrene and butadiene are associated with significant excesses of all leukemias at the highest quartile for number of peak exposures. Both have apparent positive dose responses for each chemical. Using a two-chemical model, an increasing frequency of peak styrene exposures in relation to the risk of all leukemias is associated with higher RR values for styrene than butadiene. The RRs remain significant only for styrene at high peak doses. The higher risks for styrene compared with butadiene remain even in the three-chemical (styrene+butadiene+DMDTC) model.[33]
>
> Add results for CLL and NHL combined and for NHL alone that are described in Delzell et al. 2006 (See Part A: Additional Information above). These studies found an exposure-response relationship with cumulative exposure to styrene for CLL and NHL combined or NHL alone that was not attenuated when butadiene was added to the model. These results should also be added to Section 3.8 (Summary for selected cancer sites).[34]

[33] Part A at 8.

[34] *Id*. at 12.

As is obvious, therefore:

- The Expert Panel's peer review comments embodied the same judgments as its scientific justification;
- By incorporating those comments into the final Background Document, NTP produced a document that more consistently supported those judgments; and
- By finalizing the Background Document before it received public comments on the draft Expert Report, NTP ensured the comments would not have any effect on the Background Document.

We acknowledge that NTP has previously taken the position that, because the Expert Panel is an independent advisory committee operating under the Federal Advisory Committee Act (FACA), its reports are not agency disseminations subject to the IQA. Regardless, it is clear that when NTP incorporates recommendations of the Expert Panel into the Background Document in a way that at least "reasonably suggests that the agency agrees with the information, this appearance of having the information represent agency views makes agency dissemination of the information subject to th[e IQA] guidelines."[35] Accordingly, NTP should reopen the Background Document and revise it in light of the comments filed on the draft Expert Report. NTP should also change the process of soliciting comments described above for the 13th and future RoCs.

V. CONCLUSION

For the above-stated reasons, which highlight only a few of the flaws in NTP's Response, the Background Document of September 29, 2008, does not conform to the requirements of the Information Quality Act, must be withdrawn and, if reissued, corrected. Similarly, all subsequent NTP documents based on the flawed Background Document – in particular, the draft substance profile issued in December 2008 – should be withdrawn and, if reissued, revised consistent with the corrected Background Document.

[35] 67 Fed. Reg. at 8454.

SIRC and its members would welcome the opportunity to meet and discuss these issues or provide clarifications to assist the review and correction of the Background Document. Please do not hesitate to contact me for any further information.

Sincerely,

/S/

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Enclosures: SIRC IQA Request for Correction (October 26, 2009)
NTP's Response (December 23, 2010)