NATIONAL TOXICOLOGY PROGRAM
U.S. Department of Health and Human Services

National Institute of Environmental Health Sciences
111 T.W. Alexander Drive
P.O. Box 12233
Research Triangle Park, NC 27709

December 23, 2010

Jack Snyder
Executive Director
Styrene Information and Research Center
1300 Wilson Boulevard, Suite 1200
Arlington, Virginia 22209

Dear Mr. Snyder:

I am responding to your Information Quality Request for Correction of Information ("the Request") dated October 26, 2009, and submitted by the Styrene Information and Research Center (SIRC) pursuant to Section 515(a) of the Treasury and General Government Appropriations Act for Fiscal Year 2001[1] (the Information Quality Act or IQA) and the guidelines issued by the Office of Management and Budget (OMB Guidelines),[2] the U.S. Department of Health and Human Services (HHS) (HHS Guidelines),[3] and the National Institutes of Health (NIH Guidelines).[4] SIRC requests corrections to the "Final Report on Carcinogens Background Document for Styrene" (Background Document) issued by the National Toxicology Program (NTP). In the Request, SIRC asserts that the Background Document fails to meet the objectivity and utility requirements of the OMB, HHS, and NIH Guidelines. I have reviewed the request and would like to respond to your concerns.

Report on Carcinogens (RoC) Background Document

Before I respond to issues raised in the Request, I would like to briefly provide information about the Background Document and its development. A background document is a reference document that compiles and summarizes publicly available information from both positive and negative studies on a candidate substance. It may be prepared with the assistance of a consultant(s) with expertise and/or knowledge relevant to the specific candidate substance. The

[1] P.L. 106-554, 44 U.S.C. 3516 note.
[2] *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility and Integrity of Information Disseminated by Federal Agencies*, 67 Fed. Reg. 8452 (February 22, 2002).
[3] *HHS Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public*, available at http://aspe.hhs.gov/infoquality/Guidelines/part1.shtml.
[4] *HHS Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public*, Part II.I (National Institutes of Health), available at http://aspe.hhs.gov/infoquality/Guidelines/NIHinfo2.shtml.

background document follows a general format and is not intended to develop or present opinions regarding the listing status for the candidate substance. It serves as a resource that review groups can use in applying the RoC listing criteria[5] during evaluation of a candidate substance and in formulating their opinion on whether to recommend listing the substance in the RoC. In the current RoC review process,[6] the NTP prepares the background document as a draft that is peer reviewed at a public meeting with opportunity for public comment. The draft background document is posted on the NTP RoC website, and its availability announced through the NTP listserv[7] and other NTP publications.

An external scientific panel peer reviews the draft background document. The NTP convenes an external, scientific panel for each candidate substance. The expert panel meeting is announced in the Federal Register at least 60 days prior to the event, and the public is invited to attend and provide oral and/or written comments on the draft background document and/or the listing status of the candidate substance. All comments received within this time period become part of the public record that is reviewed by the expert panel and posted on the RoC Website. The panel is given a two-part charge: (1) peer review the draft background document and once the peer review is completed, (2) apply the RoC listing criteria to the relevant scientific evidence, make a recommendation regarding the listing status of the candidate substance, and provide a scientific justification for that recommendation. The panel submits a report that contains (1) its peer-review comments on the draft background document (Part A) and (2) its recommendation on listing status of the candidate substance and the scientific justification for that recommendation (Part B). The NTP posts the expert panel reports (Parts A and B) on the RoC Website and publishes a Federal Register notice inviting public comment on the expert panel's listing recommendation and scientific justification (Part B). Following the meeting, the NTP reviews the expert panel's peer-review comments and any public comments as it finalizes the background document on the candidate substance. The final version of the background document is posted to the RoC Website.

I would like to clarify one part of the RoC review process raised in your letter, page 6, 2nd bullet: "[i]n addition, the Background Document was finalized several weeks before the close of the public comment period on the Expert Panel's report." The NTP published a Federal Register notice following the expert panel meeting for styrene (73 Fed. Reg. 52059).[8] The notice 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 (Expert Panel Report, Part B). It did not include solicitation of public comments on the expert panel's peer-review comments (expert panel report, Part A), which as noted above, is not part of the RoC review process.

[5] RoC listing criteria are available at http://ntp.niehs.nih.gov/go/15209.
[6] NTP Report on Carcinogens Review Process is available at http://ntp.niehs.nih.gov/go/29353.
[7] The NTP listserv is an email distribution list used to disseminate information on NTP activities. Subscription to the NTP listserv is available on the NTP Website at http://ntp.niehs.nih.gov/go/getnews.
[8] Notice is available at http://ntp.niehs.nih.gov/go/29682, see July 21-22, 2008, Topic: Styrene.

IQA Background and Applicability to the Background Document

With respect to specific text of the Background Document for styrene, we believe it satisfies the applicable information quality guidelines. Regarding the "objectivity" criterion,[9] the Background Document presents information on peer-reviewed studies with both positive and negative findings in an accurate, complete, and unbiased manner. As noted in the RoC review process, the information included in the sections Human Cancer Studies, Studies in Experimental Animals, and Other Relevant Data, "must come from publicly available, peer-reviewed sources."[10] According to the OMB Guidelines, "[i]f 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."[11] The draft Background Document was peer-reviewed by an independent, external scientific panel at a public meeting. The expert panel advised the NTP on the content and completeness of the draft Background Document taking into consideration the individual publications and public comments. Following completion of the peer review, the expert panel voted 10 yes/0 no that the draft Background Document with the recommended changes was "adequate for drawing conclusions about the carcinogenicity of styrene and for applying the RoC listing criteria."[12] Additionally, the NTP believes that the "utility" criterion[13] is satisfied. The Background Document is useful to the reader. It is a public resource document that provides information from published, publicly available studies on styrene including its use, production, exposure, toxicology, and carcinogenicity, and is available in both electronic and printed formats.

Detailed Discussion of Asserted IQA Deficiencies and Requested Corrections

On pages 4-98 of the Request, SIRC raises specific issues with regard to study findings and information presented in the Background Document and requests changes to the document. We respond below to these requests for changes, pointing out those instances where we agree with SIRC's comments and will make corrections to the document and others where we disagree and will not make the requested changes, many of which would affect the objectivity and utility of the Background Document. In responding to those comments, we point out instances where the NTP relied upon scientific advice gathered from its technical and subject matter experts during peer review of the draft Background Document. We also note where changes requested by SIRC would make the presentation of information more consistent with its own interpretations of study findings.

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[9] According to the OMB Guidelines, "[o]bjectivity" focuses on "whether disseminated information is being presented in an accurate, clear, complete, and unbiased manner" and whether it is "accurate, reliable, and unbiased." 67 Fed. Reg. at 8459.

[10] NTP Report on Carcinogens Review Process, Draft Background Documents, available at http://ntp.niehs.nih.gov/go/29353.

[11] OMB Guidelines, 67 Fed. Reg. at 8459.

[12] Styrene Expert Panel Report. Part A – Peer review of the draft background document on styrene, available at http://ntp.niehs.nih.gov/go/29682 see July 21-22, 2008, Topic: Styrene.

[13] According to the OMB Guidelines, 67 Fed. Reg. at 8459, "[u]tility" refers to the "usefulness of the information to its intended users, including the public."

A. Executive Summary

The Executive Summary of the Background Document summarizes technical and factual information provided within the individual chapters. On pages 4-7 of the Request, SIRC provides opinion and interpretation regarding information provided in the Executive Summary of the Background Document. SIRC also comments and provides opinion on information found in various chapters of the Background Document. The issues identified by SIRC are individually raised later in the Request, and NTP's responses are outlined for human, animal, and mechanistic data in parts B-D, below. Part E responds to the complaint that the Background Document fails to provide an integrated opinion on proposed inconsistencies in the human, animal, and mechanistic data.

B. Asserted IQA Deficiencies for Human Data

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. In presenting the results, the NTP typically, when available, included findings for the overall population, workers with highest exposure, and any exposure-response analysis. The NTP also reported the risk estimate (or effect estimate), the 95% confidence interval (CI), the number of exposed cases or deaths when relevant, and the statistical *P* value. Strengths and limitations in the study design noted by the expert panel or NTP were included in square brackets [].

1. Shift from the Reinforced Plastics Industry to the SBR Industry

On pages 24-27 of the Request, SIRC proposes that the Background Document "shifted its focus to styrene-butadiene rubber (SBR) workers. In doing so, however, the Background Document failed to meet the reliability requirement of the IQA, because lower exposure studies with confounding exposures cannot be more significant than higher exposure studies with few confounding exposures. It also failed the clarity and completeness requirements, as it provided no explanation of this profound shift." On page 27, SIRC proposes that text from the draft Background Document be added back to the Background Document, page 156, lines 1-17, "[t]hus, workers from the reinforced plastics industry are the most relevant study population."

- NTP response: The final Background Document reports the strengths and weaknesses of studies from both industries and does not identify which industry is the most appropriate study population. The text proposed by SIRC requests the NTP to draw conclusions and include SIRC's interpretative opinion. The NTP has instead chosen to accept the advice provided by the RoC expert panel to remove the statement and simply emphasize the strengths and limitations of the body of evidence from epidemiological studies in both industries.[14] A discussion of these limitations is provided in Section 3.6 of the Background Document.

[14] Styrene Expert Panel Report, Part A: Peer Review Comments on the Draft Background Document, page 10, bullet 2, available at http://ntp.niehs.nih.gov/go/29682, see July 21-22, 2008, Topic: Styrene.

2. Mischaracterization of Kolstad *et al*. (1995, 1994)

On page 27 of the Request, SIRC states regarding the study by Kolstad *et al*. (1995, 1994) reported on pages 93-96 and 103, "the Background Document inaccurately describes the methodology employed by this study and the resulting data." SIRC, on pages 29-30, proposes replacement text for the Background Document "to accurately describe the study methodology and contextualize the study within the framework of the study authors' approach to exposure characterization" and to describe the Kolstad studies. The proposed SIRC text also includes providing SIRC's opinion regarding the utility of this study for evaluating the carcinogenicity of styrene, "…it is not reasonable to conclude that this study provides evidence of increased cancer from styrene exposure."

- NTP response: Information on the Kolstad study in the Background Document follows a standard format and is accurate; no changes are needed. The document describes the methods (e.g., study population, exposure assessment) and reports the findings from the two major studies of the cohort by Kolstad (1994, 1995). The Background Document also notes any major strengths or limitations in square brackets [], including the limitation in exposure assessment noted by SIRC. However, the Background Document does not draw conclusions relative to the study's findings as SIRC proposes. The NTP will not replace the text in the Background Document with that proposed by SIRC for the following reasons: (1) The factual information from the Kolstad study in the text proposed by SIRC is already provided in the Background Document. (2) The Background Document reports many more of the findings from the Kolstad study than SIRC proposes to include. SIRC's text reports only one risk estimate from one publication, which would limit and bias information about the Kolstad study because it selectively reports the study and its findings. (3) SIRC proposes to include text in the description of the study that the NTP could not identify in publications of the Danish cohort reported by Kolstad, "[i]n a typical RPC facility only 10% to 20% of the workforce were laminators." (4) SIRC proposes to include, "it is not reasonable to conclude that this study provides evidence of increased cancer from styrene exposure," which represents SIRC's interpretation of the study's findings.

3. Kogevinas (1994a, 1993) Mischaracterized

On page 30 of the Request, SIRC states that the Background Document, pages 96-98 and 105-106, retains "erroneous statements about that study." SIRC proposes that "[t]he Background Document's interpretation of these studies is thus inaccurate at best and biased at worst. An objective reading of this study is that the epidemiologic evidence the authors evaluated does not support a causal relationship between styrene exposure and any type of human cancer." SIRC requests that the Background Document be edited and proposes substitute language on pages 32-33 of the Request, "[t]he Kogevinas study comprised eight subcohorts that had different criteria for inclusion, different exposure assessments, and different years of follow-up…NTP concurs with the authors that the study does not demonstrate a causal association but only does not exclude that possibility."

- NTP response: Information on the Kogevinas studies in the Background Document follows the standard format and is accurate; no changes are needed. The Background Document describes the studies' methodologies and reports the findings, both positive and negative, and does not draw conclusions relative to the studies' findings. The NTP

will not replace the text in the Background Document with text proposed by SIRC because it would limit and bias information about the Kogevinas studies, as it selectively reports details about the studies and their findings. For example, SIRC proposes that the Background Document only report information from Table 3 of Kogevinas and not include information about the findings for the overall population and the workers with highest exposure (Table 2 of Kogevinas) and about exposure-response relationships (Table 4 of Kogevinas). Information from all three tables is included in the Background Document (pages 96-98 and Table 3-1, specifically pages 105-106). SIRC also proposes that the NTP adopt SIRC's interpretation of the data, "the NTP concurs… that the study does not demonstrate a causal association but only does not exclude that possibility." The NTP will not add this statement to the Background Document. Furthermore, SIRC has erroneously stated the conclusion of the Kogevinas studies. Kogevinas *et al*. (1994a) states, "[i]n conclusion, these findings leave the question open of whether an excess risk of neoplasms of the lymphatic and hematopoietic tissues occurs among workers exposed to styrene."

4. Misinterpretation of Delzell Studies

On pages 33-40 of the Request, SIRC addresses studies by Delzell and includes text from her comments on the expert panel's conclusions. SIRC requests that the Background Document (pages 113-126 and Table 3-4, specifically pages 130-132) be revised and proposes text on pages 39-40, "[t]he multi-plant study included 17,924 male workers…analysis of styrene exposure and NHL risk revealed a non-significant trend across increasing cumulative styrene exposure categories."

- NTP response: Information on the Delzell studies in the Background Document follows the standard format and is accurate; no changes are needed. The Background Document describes the studies' methodologies and reports the findings, both positive and negative, from both external and internal analysis. The Background Document contains the information covered by SIRC plus additional details and findings. The NTP will not replace the text in the Background Document with text proposed by SIRC because it would limit and bias information about the Delzell studies, as it (1) selectively reports details about the studies and their findings and (2) does not provide data to support the summary statements. For example, the SIRC text does not include data for the risk estimates from the internal analysis of cumulative and/or peak exposure to styrene in models that include butadiene and DMDTC or discuss the analysis of exposure to styrene peaks. The Background Document provides this information on pages 122-126 including Table 3-2 (leukemia, page 123) and Table 3-3 (NHL and NHL+CLL, page 126).

  The NTP would point out that the Background Document does not state that the available epidemiologic evidence supports "a causal relationship between styrene exposure and any type of human cancer" as stated by SIRC on page 34 of the Request.

  The Request discusses many points from the Expert Panel Report, Part B. The NTP would point out that conclusions reached by the expert panel and reported in the Expert Panel Report, Part B, are independent of the Background Document. The expert panel's role in the multi-step, scientific RoC review process was to act as an independent review

body and the panel's listing recommendation for styrene, and scientific justification were a product of the panel's independent review. Per its review process for the RoC, the NTP solicited public input on the Expert Panel Report, Part B and those comments are posted on the NTP Website[15] and were considered by the NTP in its deliberations on styrene.

5. AML, CML, and ALL Development

On pages 40-41 of the Request, SIRC discusses information in the Background Document on the development of these cancer types and proposes that the document does not include data to support the statement (page 159), "AML, CML, and adult ALL arise from the same pluripotential stem cell" and requests that the text be changed to what appeared in the draft Background Document, "[a] possible causal effect between styrene and leukemia is only expected for subgroups originating from a common stem cell."

- NTP response: In not including the statement from the draft Background Document in the final Background Document, the NTP has chosen to accept the advice of the RoC expert panel to remove it, to keep the remainder of the sentence, "only a few studies have assessed specific sub-diagnoses of leukemia (Flodin *et al*. 1986…Sathiakumar *et al*. 2005)," and to add the panel's explanatory text.[16] Page 159, lines 1-10 of the Background Document gives details and references identified by the expert panel in support of the statement, "(AML, CML, and adult ALL arise from the same pluripotential stem cell, based on observations of specific genetic re-arrangements in these 3 subtypes of leukemia, which comprise about 80% of adult leukemias. For example, the blast crisis of CML, 90% of which have the Philadelphia chromosome, cannot be distinguished from AML. An estimated 10% of adult ALL cases have the Philadelphia chromosome, which suggests a common stem-cell origin for these leukemias (Bloomfield *et al*. 1978, Jacobs 1989, Yunis 1983). There is considerable overlap between CLL and NHL; CLL and NHL (85%) are B-cell malignancies (Delzell *et al*. 2006) and CLL is the same disease as small lymphocytic lymphoma (Delzell *et al*. 2006, Harris *et al*. 2000). Delzell *et al*. 2006 grouped NHL+CLL in their data analyses.)"

6. Unbalanced Discussion of Coyle *et al*. (2005)

On page 45 of the Request, SIRC requests that discussion of Coyle *et al*. be deleted or replaced with the following language, "[a] review of Coyle et al. (2005) by Burns et al. (2006) noted that these results are likely to be an example of an ecological fallacy. Ambient styrene exposures in the Houston, TX area average 0.018 ppb. Industrial exposures are about 3 million times greater, but no excess risk of breast cancer has been found in these populations."

- NTP response: The Background Document, pages 148-149, provides information on the ecological study by Coyle *et al*. following its standard format to include the methodology and findings. In addition, the NTP in square brackets [] identified the limitations of the ecological study design for interpreting any association between environmental styrene exposure and breast cancer risk. No changes are needed to the Background Document.

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[15] See public comments for styrene, 73 Fed. Reg. 52059 (September 8, 2008), available at http://ntp.niehs.nih.gov/go/9920.

[16] Styrene Expert Panel Report, Part A: Peer Review Comments on the Draft Background Document, page 10, item 2, bullet 1, star 2, available at http://ntp.niehs.nih.gov/go/29682, see July 21-22, 2008, Topic: Styrene.

The NTP did not include the letter by Burns *et al*. because it is a *Letter to the editor* and does not contain primary data or synthesize information as a review.

7. Improper Characterization of Lymphohematopoietic Malignancies

On pages 45-46 of the Request, 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."

- NTP response: SIRC does not identify any inaccuracies in the statement in the Background Document that require correction. The information given on page 192 and in the summary table on pages 171-172 dealing with lymphohematopoietic cancers in the styrene monomer and polymer industry clearly addresses the issues of statistical significance raised by the styrene industry. In addition, SIRC proposes to include its interpretation of the studies' findings, i.e., "do not provide evidence for a causal association between styrene exposure and cancer…." The NTP will not add this text to the Background Document.

8. Improper Characterization of Pancreatic Cancer

On pages 46-48 of the Request, SIRC discusses information on pancreatic cancer in the Background Document. SIRC identifies a statement in the summary on page 192, lines 19-25, "[a]mong the highest styrene-exposed group…and the other two were nonsignificant [Kogevinas et al., 1994a, Ruder et al. 2004])," and in its supporting tables that SIRC proposes contain errors. SIRC requests two corrective actions to the Background Document:

(1) SIRC on page 48 requests that the text, page 174, lines 5-17, "[i]ncreased risks (1 significant and 2 non-significant) of pancreatic cancer were observed…but not in all studies (Ruder *et al*. 2004)," should be revised to read, "[a]mong Danish companies where more than 50% of the workers were employed in RPC manufacture (Kolstad et al. 1995), there was no measurable increase in incidence...There were no significant increases in death from pancreatic cancer among the other three studies of RPC workers (Kogevinas et al., 1994; Ruder et al., 2004; Wong et al., 1994)."

- NTP response: Information provided in the Background Document is accurate and complete in presenting a summary of findings for incidence of pancreatic cancer in the four studies of reinforced-plastics worker. The NTP will not make the changes requested by SIRC because the proposed text is selective and misleading about the findings from the studies, which would bias the presentation of information. For example, SIRC proposes to delete information presented in the Background Document on page 174 reported by Kolstad *et al*. (1995) about the "significant risks of pancreatic cancer among individuals with probable high styrene exposure (workers from plants employing 50% to 100% laminators) and among individuals exposed to styrene for greater than one year."

(2) SIRC requests on page 48 of the Request that the text, page 192, lines 19-25, "[a]mong the highest styrene-exposed group in the reinforced-plastics industry, there was an excess…and the other two of which were nonsignificant (Kogevinas *et al*., 1994a; Ruder *et al*., 2004)," should be revised to read, "[n]o statistically significant increases in death from pancreatic cancer were observed in the reinforced-plastics industry cohort studies."

- NTP response: Information provided in the Background Document is accurate and complete in summarizing the findings for pancreatic cancer in the four studies of reinforced-plastics workers. The NTP will not make the changes requested by SIRC because the proposed text is incomplete as it does not include information about the increased mortality across the four cohort studies for individuals in the highest styrene-exposed group or about the significant and nonsignificant increases in pancreatic cancer risk reported in these studies. The proposed SIRC text would limit and bias the presentation of information about the studies.

SIRC has identified several statements and supporting tables in the Background Document that it believes need correction. The NTP will respond to each of the nine bullets on pages 47-48 of the Request:

- SIRC: The text on page 174 is inconsistent with that in Table 3-8, page 169 for pancreatic cancer, which lists the studies as showing nonsignificant excess of cancer. NTP response: Kolstad *et al*. 1995 reported a RR (internal analyses) of 2.2 (95% CI = 1.1 to 4.5). Table 3-8 reports findings (+ or -) for the total cohort and not the findings for workers with "high exposure probability" noted in the text on page 174.
- SIRC: Table 3-9 lists "expected cases" in Kolstad studies as 34.2, but that number does not appear in the publication. NTP response: The expected number of cases 34.2 is found in Table 4 of Kolstad *et al*. 1995.
- SIRC: Table 3-10 indicates that 7.7 pancreatic cancer cases were expected in the Kolstad study and the manuscript indicates it is 12.7. NTP response: 12.7 is the rate (see Table 5 of Kolstad *et al*.), not the expected number of cases.
- SIRC: The footnote * to Table 3-9 reads, "'*Note that in the Kolstad *et al*. studies…50% to 100% of the workers were laminators.' The footnote is incorrect. Kolstad says that 50 to 100% of the employees were involved in RPC; only an unknown fraction were laminators…" NTP response: The NTP assumes that SIRC's comments refer to Table 3-10, which has the footnote *. The NTP appreciates SIRC bringing this error to our attention. In an erratum to the Background Document, the NTP will correct the footnote to state:

  > Note that Kolstad *et al*. classified employees at companies with 50% or more of workers involved in reinforced plastics as probable high exposure, and that most of the companies were boat yards or manufacturers of containers by hand lamination.

- SIRC: Footnote d for Table 3-9 states the Kogevinas study included "[l]aminators, excluding the Danish workers included by Kolstad *et al*." The Danish workers from Kolstad *et al*. were not included in the "laminators" category in Kogevinas. NTP response: The NTP assumes that SIRC's comments refer to Table 3-10, which has the footnote "d." The footnote for the Kogevinas study stating that the findings are for laminators is correct.
- SIRC: The text on page 174, lines 11-14 refers to the "'high' exposure group in the

Kolstad study as the group in which 50 to 100% were laminators. This is wrong; as only an unknown fraction were laminators." NTP response: The NTP appreciates SIRC bringing this error to our attention. In an erratum to the Background Document, the NTP will correct the text as follows:

> The NTP will delete the text in parentheses, "(workers from plants employing 50% to 100% laminators)," from the sentence, "Kolstad *et al*. (1995) reported significant risks of pancreatic cancer among individuals with probable high styrene exposures (workers from plants employing 50% to 100% laminators)…for greater than one year."
>
> The NTP will add the following sentence: "The authors classified employees at companies with 50% or more of workers involved in reinforced plastics as probable high exposure, and most of the companies were boat yards or manufacturers of containers by hand lamination."

- SIRC: The text on page 174, lines 15-17 reads, "…a slightly higher risk was seen among long-term than among short-term workers and earlier start dates (Kolstad *et al*. 1995), but not in all studies (Ruder *et al*. 2004)." This statement is not supportable as the differences in incidence rates and 95% confidence intervals are so slight and overlapping. NTP response: The text in the Background Document is accurate; no changes are needed. The risk is ~10% higher for long-term workers and 40% higher for earlier start dates, although the 95% confidence intervals overlap.
- SIRC: Data from Kolstad *et al*. 1995 cannot be combined in a meta-analysis with the three other studies as was done in Tables 3-8 and 3-9 because Kolstad reported incidence data and the three studies reported mortality data. NTP response: Table 3-8 is not a meta-analysis, but reports relative occurrence of cancer in 12 cohort studies. Table 3-9 is also not a formal meta-analysis. The table reports the observed cases, expected cases, and SMRs for selected cancers for each study individually and then sums the observed and expected cases of selected cancers across studies. The title of the table denotes that mortality and incidence data are provided. The strengths and limitations of this approach (including pooling incidence and mortality data) are discussed on page 167 of the Background Document and included in square brackets [].
- SIRC: Tables 3-8 and 3-9 contains values for "expected deaths," but these values are not present in the original articles and need to be identified. NTP response: Table 3-8 has the results for major cancer sites for 12 separate populations and does not have values for expected deaths. In Table 3-9, the number of expected deaths for the different studies is from data in the original article or can be calculated (e.g., expected cases = observed cases/SMR) from data provided in the article.

9. Characterization of Non-Statistically Significant Data

On page 50 of the Request, SIRC requests that the NTP "delete any conclusions or inferences based on non-statistically significant data, unless accompanied by a statement that the data are statistically insignificant or that the data do not support a finding of an effect. This correction request applies to the entire Background Document and is not limited to human data."

- NTP response: It is the NTP's practice to report in the Background Document the statistically significant and statistically nonsignificant findings in a study. In the

description of individual studies, the NTP generally provides the risk estimates, 95% CI (or notes if not reported), and *P* values as reported by the study authors. In summarizing information across studies for specific tumor sites, the Background Document may not include the statistical details; however, the NTP clearly identifies the risk estimates as statistically significant or statistically nonsignificant, or provides the *P* value or 95% CI. NTP followed this practice in the examples highlighted by SIRC. The NTP would note that the RoC expert panel convened to peer review the draft Background Document in general found that the approaches used by the NTP to summarize the literature in Section 3 Human Cancer Studies "were consistent with standard epidemiological practices and provided a sound basis for evaluating the human carcinogenicity of styrene."[17] As recommended by the expert panel,[18] the NTP included the modifier "non-statistically significant" in reporting risk estimates where appropriate. The NTP will additionally clarify statistically significant findings. The following clarifications will be made in an addendum to the Background Document:

- Page xii, lines 19-22 and page 192, lines 14-17: "In 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."
  - The NTP will add "(both statistically significant and statistically non-significant)" after "increased."
- Page xii, line 30 to page xiii, line 2 and page 192, lines 25-27: "The risk of pancreatic cancer…increased with cumulative exposure in the multi-plant cohort."
  - The NTP will add the "*P* value" for cumulative exposure "(*P* = 0.068)."
- Page 178, lines 27-30: "In analyses of subtypes of leukemia, the risk…and increased risk was also seen for myeloid leukemia with chromosomal aberrations in a nested case-control study of the Danish workers (Kolstad *et al*. 1996)."
  - The NTP will add "statistically non-significant" before "increased risk" and add "based on small number of cases" after "Danish workers."
- Page 181, lines 19-24: "The nested case-control study from the Matanoski cohort of 58 lymphohematopoietic cases and 1,242 controls found two- to three-fold increased risks for lymphoma, lymphosarcoma, and myeloma and styrene exposure (increase of 1 ppm in TWA) (Matanoski *et al*. 1997), and the risk of myeloma increased with increasing cumulative exposure to styrene using the step-down regression analysis and taking into account butadiene exposure and other variables."
  - The NTP will add "statistically significant" before "increased risks" and add "(*P* = 0.023)" after "cumulative exposure."
- Page 184, lines 20-22: "An increased risk of renal-cell cancer was also associated with exposure to styrene-butadiene rubber in the population case-control study from Canada (Parent *et al*. 2000)."
  - The NTP will add "statistically significant" before "increased risk."

[17] Styrene Expert Panel Report. Part A – Peer review of the draft background document on styrene, page 7, available at http://ntp.niehs.nih.gov/go/29682, see July 21-22, 2008, Topic: Styrene.
[18] Ibid.

- Page 184, lines 25-29: "Increased risk of breast cancer was suggested in an ecological study (Coyle *et al*. 2005), which assessed styrene exposure by toxic release inventory data; [however, this study was limited by the ecological design and poor characterization of styrene exposure, which was based only on residence in counties with varying environmental toxic releases]."
  - The NTP will add "statistically significant" before "increased risk."

C. Asserted IQA Deficiencies for Animal Data

1. NCI Oral Study

SIRC has concern about the inclusion in the Background Document of information for the additional analyses of historical controls from NCI studies. On page 51 of the Request, SIRC states, "[i]t found 'increased' incidence in mouse tumors in two National Cancer Institute (NCI) studies that NCI itself said provide, respectively, 'no more than suggestive evidence' and 'no evidence' of tumors. It did so by substituting historical control data from laboratories for the historical control data contained in the NCI (1979a) [19] study, in violation of sound and objective scientific practices, and by introducing interpretive bias into its characterization of the NCI (1979a) study." On page 55 of the Request, SIRC proposes corrective actions regarding the discussion of the NCI study (1979a) including that "the original conclusion of NCI should be retained; the study provides no more than suggestive evidence of carcinogenicity of styrene."

- NTP response: The information for the NCI study is presented appropriately; no changes are needed. The tumor incidence in the high-dose styrene group is 21%, not 18% as SIRC states. These data, shown in Table 4-1 on page 198 of the Background Document, are from Table 5 of NCI (1979a). The value (9.1%) reported by SIRC for tumor incidence in control mice at Litton is inappropriately calculated because it results from combining untreated and corn oil gavage control rates that are significantly different. The original conclusion by NCI is included in the Background Document on page 197, "NCI (1979a) concluded that there was suggestive evidence for carcinogenicity of styrene in male $B6C3F_1$ mice, but no convincing evidence was obtained for either sex." Historical control data reported in the NCI study for untreated controls are also included in the Background Document.

  The NTP would point out that information regarding the additional analyses of historical controls is presented appropriately and noted as separate from the original publication. The NTP's review of lung tumor incidence in historical controls from NCI studies conducted at other laboratories and included in the Background Document on pages 196-197 is clearly identified as information not present in the original publication by inclusion in square brackets [] and is available to readers to use their scientific judgment in reviewing. This information was present in the draft Background Document (pages 164-165, dated May 22, 2008) released for public comment (73 Fed. Reg. 29139)[20] and peer reviewed by the Styrene Expert Panel at its meeting on July 21-22, 2008. The NTP has chosen to follow the advice of the RoC expert panel regarding the appropriate inclusion

[19] NTP. 1979a. *Bioassay of Styrene for Possible Carcinogenicity*. Technical Report Series No. 185. NCI-CG-TR-185. Bethesda, MD: National Institutes of Health. 108 pp.
[20] Notice is available at http://ntp.niehs.nih.gov/files/RoC_73_FR_98_508.pdf.

of the historical control data from the NCI studies in the Background Document and their use in assessing the concurrent control group tumor incidence in the NCI styrene study.[21]

SIRC suggests that the NTP compare the findings of the NCI study (TR 185 1979a) with the NCI study of β-nitrostyrene and styrene (TR 170, 1979b).[22]

- NTP response: The information about the NCI study of β-nitrostyrene and styrene (TR 170) is included in the Background Document on page 212 and in Table 4-9 on page 213. The Background Document presents the low-dose lung tumor response accurately and enables the reader to reach his/her own conclusions as to the relevance of the findings with respect to styrene carcinogenicity in mice.

SIRC suggests that the statement in the Background Document, "[[h]owever, because of poor survival of the high-dose male mice there were substantially fewer animals at risk for late-occurring lung tumors]," is "not complete and reflects interpretative bias."

- NTP response: The NTP added the statement, "[[h]owever, because of poor survival….lung tumors]," to the Background Document based upon advice from the RoC expert panel and as such it is included in square brackets [].[23]

2. Inappropriate use of Huff *et al*. (1984)

On page 51 of the Request, SIRC states, "[i]t combined data on fibroadenoma and adenocarcinomas, even though doing so does not represent sound and objective scientific practice and is misleading." SIRC requests, page 56, that reference to the Huff *et al*. (1984) study be removed from the Background Document on multiple pages.

- NTP response: Background documents present factual information from the publicly available, peer-reviewed scientific literature. The information provided from the Huff (1984) study is presented accurately as provided in the original publication. No changes to Table 4-4 (page 205) are needed. As noted in the table in [], "[[s]tatistics not reported by NTP for benign and malignant tumors combined because of lack of information on the histogenesis of the tumors.]"

  Page 204, lines 18-26, reports details from Huff (1984).

  The information on page 216, lines 7-9 for Huff is accurate and refers to data on fibroadenoma of the mammary gland, which was significantly higher in the high-dose group versus controls by pairwise comparison and had a significant dose-related trend (see Table 4-4, page 205), and does not refer to combined mammary gland tumors.

  No changes to text are needed on pages 195, 208, and 209 because it all refers to factual information from Huff (1984). Huff (1984) referred to on page 195 identifies the study as

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[21] Styrene Expert Panel Report. Part A – Peer review of the draft background document on styrene, page 15, items 3, and 4, bullet 3, available at http://ntp.niehs.nih.gov/go/29682, see July 21-22, 2008, Topic: Styrene.

[22] NTP. 1979b. *Bioassay of a Solution of Beta-Nitrostyrene and Styrene for Possible Carcinogenicity*. Technical Report Series No. 170. NCI-CG-TR-170. Bethesda, MD: National Institutes of Health. 98 pp.

[23] Styrene Expert Panel Report. Part A – Peer review of the draft background document on styrene, page 21, bullet 3, available at http://ntp.niehs.nih.gov/go/29682, see July 21-22, 2008, Topic: Styrene.

included in Section 4 Studies of Cancer in Experimental Animals. Page 208 identifies Huff (1984) as a study that reviewed Jersey *et al*. 1978. Information from Huff (1984) on page 209 pertains to leukemia.

3. Use of historical controls

On page 51 of the Request, SIRC states, "[i]t deleted references in the draft to decreased incidence of tumors on the basis of unsupported statements about historical experience, in violation of NTP's own policy on use of historical controls." SIRC requests on page 58 that "the language from the draft Background Document (page 173, Table 4-4) should be restored and the discussion of the study should be consistent with these findings."

- NTP response: The NTP chose to follow the advice of the RoC expert panel and to remove the text, "decreased incidence of total benign and malignant tumors and total mammary tumors in females in the high-dose group," from Table 4-4, page 173 of the draft Background Document.[24]

4. Temporal observation of tumors

On page 58 of the Request, SIRC identifies text that it proposes is not clear to the reader, "[l]ung tumors were reported to occur at an earlier age in the styrene-treated progeny than in control progeny, [but this may be…was not reported.]" SIRC requests, page 59, that the text be deleted or revised.

- NTP response: The NTP added the phrase, "[but this may be the result of higher mortality in the styrene-treated mice rather than an effect of styrene]," to the Background Document based upon advice from the RoC expert panel and as such it is included in square brackets []. The phrase is sufficiently clear.

5. Effects in Experimental Animals Are Species-Specific and Not Applicable to Humans

On page 62 of the Request, SIRC requests the following correction, "[t]he Background Document (pages 214-216) summary of the animal studies should be revised to note that the effects are 'limited,' not 'sufficient,' and are species-specific."

- NTP response: Section 4.5 of the Background Document presents a summary of the cancer findings for individual studies along with any comments on the study, which are present in square brackets []. This information is also presented on pages 217-219 in tabular form, Table 4-11. Summary of studies in mice and Table 4-12. Summary of studies in rats. The Background Document does not include an assessment of the animal studies and reach a conclusion that the effects are "sufficient" as SIRC proposes. The NTP will not revise the text because SIRC requests that the Background Document include SIRC's evaluation of the animal studies as "limited" and "species-specific."

D. Asserted IQA Deficiencies for Mechanistic Data

On page 62 of the Request, SIRC states that the information "is treated in a very biased and incomplete fashion in the Background Document" and on pages 62-71 raises several issues identified below that SIRC believes should be corrected.

[24] Ibid., page 18, item 12, bullet 3.

1. Styrene Metabolism

a. Biased description of the state of the science

On page 66 of the Request, SIRC requests that the Background Document on page 383 "be revised to state that, while two hypotheses have been considered, cytotoxic effects of styrene metabolites in the mouse lung is the plausible mechanism of action."

- NTP response: The Background Document on page 383, lines 9-13 states, "[t]he proposed mechanisms for the carcinogenicity of styrene include both genotoxic and epigenetic pathways. These mechanisms, which are not necessarily mutually exclusive, include: (1) metabolic conversion of styrene to styrene-7,8-oxide and subsequent induction of DNA damage in the target tissue and (2) cytotoxic effects of styrene metabolites in the mouse lung." As a resource for scientific information on styrene, the Background Document would not limit presentation to a single theory, as SIRC proposes, or state which is the "plausible mechanism of action" so as not to bias the presentation of information to the reader. The NTP will not revise text in the Background Document because SIRC requests inclusion of its assessment of the two hypotheses.

b. Failure to reference Hofmann et al. (2006)

On page 66 of the Request, SIRC requests that "section 5.5 (pages 368-384) should integrate Hofmann et al. (2006) into the discussion. The findings of Hofmann et al. (2006) should be supported."

- NTP response: The Background Document includes Hofmann *et al*. (2006) on page 259, lines 6-12 and accurately cites the authors' finding that mean styrene-7,8-oxide levels in mouse lungs were about 2 times higher than in rat lungs at equal styrene exposure conditions. The Background Document would not "integrate" or provide "support for" Hofmann *et al*. (2006) as SIRC proposes so as not to bias the presentation of information to the reader.

c. The role of CYP2F2-mediated metabolites (alternative hypothesis to SO-mediated tumorigenesis)

On page 67 of the Request, SIRC requests that NTP delete text on lines 19-23, page 383 in the Background Document, "[s]tyrene is mutagenic through the formation of styrene-7,8-oxide (*in vitro*). A number of studies reported a positive association between occupational exposure to styrene and the frequency of chromosomal aberrations, with some studies reporting exposure-response relationships. Some authors have suggested…higher risk for styrene genotoxicity or carcinogenicity." SIRC provides replacement text, "[i]t has been proposed that styrene-7,8-oxide, a major metabolite of styrene, is responsible for any genotoxicity and tumorigenicity from styrene. However, oral administration of styrene-7,8-oxide to mice did not produce lung tumors. SO levels in rat lungs up to 8 fold higher than the level that produces tumors in mice do not produce tumors in rats."

- NTP response: This section of the Background Document is a summary of information from earlier sections that contain detailed descriptions of the studies. It summarizes findings related to the two proposed mechanisms for the carcinogenicity of styrene: "(1) metabolic conversion of styrene to styrene-7,8-oxide and subsequent induction of DNA damage in the target tissues and (2) cytotoxic effects of styrene metabolites in the mouse

lung." The text on lines 19-23 provides information in support of the genotoxicity of styrene, is accurate, and is appropriate to the section; no changes are needed. The NTP will not revise the text as SIRC proposes because it would limit and bias information to the reader by deleting the summary of supporting information for the genotoxicity of styrene and only provide information about the proposed nongenotoxic mechanism of styrene, discussed in the subsequent paragraph.

On page 68 of the Request, SIRC requests that NTP add text to page 384, lines 7 and 14 of the Background Document. On line 7, SIRC requests that NTP add "Cruzan et al. (2002) concluded that mouse lung tumors were unrelated to the total SO lung levels. Hofmann et al. (2006) likewise concluded that mouse lung tumors were not caused by SO." On line 14, SIRC requests that the NTP add "[s]imilar toxicity and tumors in the lungs of mice, but not rats, and CYP2F metabolism in a series of related compounds, add weight to the hypothesis. Lack of tumorigenicity by analogs of these compounds that cannot be metabolized to the same metabolites further strengthens this mode of action for styrene."

- NTP response: The Background Document, lines 24-30 on page 383 through lines 1-14 on page 384, presents theories regarding why lung tumors have been observed in mice but not in rats in long-term inhalation studies from Cohen *et al*. (2002). The text beginning on page 384, line 7 is from Cruzan *et al*. (2002). This reference will be added in an erratum to the Background Document as follows:

  "An alternative mechanism (Cruzan *et al*. 2002) is that interspecies differences in styrene toxicity…lung."

d. Unbalanced discussion of 4-vinylphenol vs. SO

On page 68 of the Request, SIRC requests that the Background Document's discussion of the effects of styrene metabolites should be expanded to note the concordance between Kaufmann *et al*. (2005) and Gamer (2004).

- NTP response: NTP could not find any data on 4-vinylphenol or styrene oxide in the study reported by Gamer (2004).

2. Styrene Genotoxicity

On page 71 of the Request, SIRC requests that corrections noted on pages 68-71 should be incorporated into the Background Document along with additional text proposed by SIRC, "[t]he bacterial mutation assays were nearly all negative…The positive *in vitro* genotoxicity studies of styrene occurred at concentrations of styrene not achievable in humans…The *in vivo* genotoxicity assays of styrene in rodent assays are overwhelmingly negative…*In vivo* assays have indicated that exposure to styrene results in increased SCE (summarized in Cruzan et al., 2009)."

- NTP response: Information in the Background Document is accurate and complete in providing details about the genotoxicity studies and summarizing the findings; no changes are needed. The NTP will not incorporate the edits or additional text proposed by SIRC into the Background Document because it would limit and bias information about the genotoxicity studies, as it selectively reports details and highlights negative findings. In addition, the NTP will not add the statement, "[i]n summary, the genotoxicity data for

styrene are not convincing of a genotoxic mode of action," because SIRC requests inclusion of its interpretation of the findings in the Background Document.

3. Additional Corrective Actions for "Other Data" Section of Background Document

On page 71 of the Request, SIRC asks for confirmation that the estimate of dermal uptake for Luderer *et al*. (2005) is correct on page 222, lines 21-24 of the Background Document.

- NTP response: Luderer *et al*. (2005) is the report from the scientific expert panel convened by the NTP Center for the Evaluation of Risks to Human Reproduction to carry out an assessment of the potential reproductive and developmental hazards of styrene. It is not a review, although the Background Document can include secondary publications. The statement is from section 1.2.4.2, page 118 of Luderer *et al*. 2005 and is correct.

On page 71 of the Request, SIRC requests that phenylglycine be deleted from Figure 5-1 (page 226 of the Background Document) or that an alternate figure for the metabolism of styrene be used because phenylglycine is a hypothesized metabolite.

- NTP response: Figure 5-1 is accurate; no changes to the Background Document are needed. Manini *et al*. (2002b) detected phenylglycine in both human and rat urine: (1) Figure 2, which is a chromatogram from human urine of a worker exposed to styrene, identifies peak 1 as phenylglycine. (2) Table 2 lists phenylglycine as being identified in rats exposed to styrene. (3) Table 5 states the median level of phenylglycine in 10 workers was 5.4 mg/g creatinine at the end of their shift.

On pages 71-72 of the Request, SIRC requests on pages 229-230 of the Background Document that "the summary of the study should indicate that it is an inhalation study followed by isolation of the cells for analysis." SIRC also requests that the sentence on page 230, "Clara cells are the predominant cell type in mouse lung, while type II cells predominate in rat lung," should be deleted or expanded upon.

- NTP response: Page 229, lines 16-18 of the Background Document references Section 5.4.3.1 (pages 278-284) where details of Boogaard *et al*. (2000b) are provided on page 281 and in Table 5-7, pages 282-283. Page 281, lines 1-3 read, "DNA adducts also were detected…CD-1 mice and male Sprague-Dawley rats were exposed to [ring-U-^{14}C]styrene at 160 ppm by nose-only inhalation for 6 hours (Boogaard *et al*. 2000b). Tissues were collected either immediately or 42 hours after exposure."

  On page 230, lines 1-3 of the Background Document, the information regarding the predominant type of cells in mouse versus rat lung is information provided by the authors. This text is the same paragraph carried over from page 229, lines 16-19 for Boogaard *et al*. (2000b).

On page 72 of the Request, SIRC requests that the information regarding "total CYP450" be deleted on page 235, line 1 because SIRC could not find the information in Wenker *et al*. (2001c).

- NTP response: Wenker *et al*. (2001c) reports that the purpose of the study was to assess interindividual variation in styrene toxicokinetics and to correlate this variation with the individual metabolic capacity for cytochrome P450 (CYP), CYP2E1, CYP1A2, and

CYP2D6. The metabolic capacity was assessed by phenotyping with chlorzoxazone (CYP2E1), caffeine (CYP1A2), dextromethorphan (CYP2D6), and antipyrine (CYP450). The NTP ascribed CYP450 to mean total cytochrome P450 enzymes because Wenker *et al*. noted that antipyrine clearance was used as a measure of general oxidative capacity.

On page 72 of the Request, SIRC states that information regarding styrene metabolism by pulmonary microsomes in *Cyp2e1*-knockout mice relative to wild-type mice from Carlson (2003, Table 2) should be "73%" not "about one-half" as stated in the Background Document, page 235, line 20.

- NTP response: The text in the Background Document is accurate; no changes are needed. The reference to "about one-half" is from Carlson (2003, page 864), which states, "when pulmonary microsomes were used, the styrene-metabolizing activity in the knockout mice was about one-half that of the wild-type mice."[25] Table 2 of Carlson (2003) reports data on metabolism of *R*- and *S*-enantiomers of styrene in lung microsomes of knockout versus wild-type mice. *R*-enantiomer in knockout mice is 0.72 vs. 1.27 in wild-type mice, a ratio of 0.57. *S*-enantiomer in knockout mice is 0.27 vs. 0.53 in wild-type mice, a ratio of 0.51. For total styrene oxide, the ratio is 0.55 (0.99 in knockout mice / 1.80 in wild-type mice).

On page 72 of the Request, SIRC requests that on page 237 of the Background Document "the discussion and summary of Arand et al. (1999) should be revised to note that the study involved mutant forms of the enzyme, and the relevance of the study to styrene metabolism in an intact organism is unclear."

- NTP response: Information in the Background Document for Arand *et al*. (1999) is accurate; no changes are needed. The comments referred to in the Background Document are to findings with the wild-type enzyme. The studies included both mutant and wild type enzymes. The NTP will not add the text, "the relevance of the study…is unclear," because SIRC requests inclusion of its interpretation of the study in the Background Document.

On page 72 of the Request, SIRC requests that the text on page 246, lines 8-10 of the Background Document, "[t]here was suggestive evidence that occupational exposure to styrene was associated with increased serum prolactin," be deleted or contextually clarified.

- NTP response: Reference to "increased serum prolactin" is accurate; no changes to the Background Document are needed. It is the conclusion reached by the expert panel convened to assess the potential reproductive and/or developmental hazards of styrene by the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR). The CERHR Expert Panel Report on Styrene is included in NTP (2006) as Appendix II. The panel reached this conclusion based upon findings from four published studies listed in footnote 20[26] (see pages II-130 – II-131 in Appendix II).

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[25] Carlson, G.P. (2003). *In vitro* metabolism of styrene to styrene oxide in liver and lung of cyp2e1 knockout mice**.** J Toxicol Environ Health, Part A, 66:861–869.

[26] Arfini, G., Mutti, A. and Vescovi, P., *et al*. (1987). Impaired dopaminergic modulation of pituitary secretion in workers occupationally exposed to styrene: further evidence from PRL response to TRH stimulation. J Occup Med, 129: 826-30; Bergamaschi, E., Mutti, A., Cavazzini, S., Vettori, M. V., Renzulli, F. S. and Franchini, I. (1996).

On page 72 of the Request, SIRC suggests that the Background Document discussion of Cohen *et al*. (2002) should include a citation to Filser *et al*. (1999).

NTP response: Cohen *et al*. (2002) is a review that discusses Filser *et al*. Given that Filser is included within Cohen *et al*., the paper by Filser *et al*. was not reviewed for this section. Filser *et al*. (2002) is separately discussed in the Background Document on page 263, lines 3-11.

On page 73 of the Request, SIRC requests that the Background Document provide a distinction between information presented from a review versus original research.

- NTP response: The NTP's practice is to use publicly available, peer-reviewed primary scientific publications when available; however, publicly available, peer-reviewed secondary sources providing summaries of large bodies of literature such as on metabolism, modeling, and from general toxicity studies, can be used in Section 5 Other Relevant Data. The NTP appreciates the suggestion that background documents distinguish information from reviews versus original research and will consider this suggestion for future background documents.

On page 73 of the Request, SIRC requests that the Background Document, page 280, lines 8-28 be amended "to note that the significance of DNA adducts in NMRI mice exposed to 175 or 350 ppm (Vodicka et al. 2001b, 2006a) is not clear because exposure to these levels is lethal to some CD-1 and B6C3F1 mice (up to 50% at 250 ppm). Morgan et al., (1993) and Cruzan et al. (1997)."

- NTP response: SIRC proposes text that extrapolates the findings from the studies by Morgan *et al*. and Cruzan *et al*. to the findings of Vodicka *et al*. The NTP has no information regarding the differential sensitivity of these strains to styrene; therefore, we will not add the proposed text, "the significance of the DNA adducts in NMRI mice…is not clear because exposure…Cruzan *et al*. (1997)," to the Background Document.

On page 73 of the Request, SIRC states, on page 328, lines 4-28 "[t]he Background Document lists human chromosomal aberration (CA) studies and indicates that positive results were observed in studies with higher levels of exposure, but that statement is inaccurate…"

- NTP response: The Background Document states, page 328, lines 29-30 [emphasis added by NTP], "[[i]n general, 'positive' results were observed in studies with *higher levels of exposure or in the high-exposure subgroup*.]" The statement is not inaccurate as SIRC proposes; no changes are needed. SIRC's analysis has some inaccuracies. For example, SIRC listed the results from Vodicka *et al*. 2004c, a study in the lower levels of exposure group, as "positive"; however, chromosomal aberrations in the two exposure groups versus controls were either the same or statistically significantly lower (see Table 5-13, page 323 of the Background Document). As stated in the Background Document, page 330, lines 5-8, "[s]tudies that did not find any significant increases in chromosomal

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Peripheral markers of neurochemical effects among styrene-exposed workers. Neurotoxicology, 17: 753-9; Luderer, U., Tornero-Velez, R., Shay, T., Rappaport, S., Heyer, N. and Echeverria, D. (2004). Temporal association between serum prolactin concentration and exposure to styrene. Occup Environ Med, 61: 325-333; Mutti, A., Vescovi, P. P., Falzoi, M., Arfini, G., Valenti, G. and Franchini, I. (1984). Neuroendocrine effects of styrene on occupationally exposed workers. Scand J Work Environ Health, 10: 225-8.

aberrations in workers exposed to styrene include Thiess *et al*. (1980), Watanabe *et al*. (1983, 1981), Nordenson and Beckman (1984), Mäki-Paakkanen (1987), Jablonicka *et al*. *(*1988), Sorsa *et al*. (1991), Biró *et* a*l*. (2002), and Vodicka *et* a*l*. (2004c, 2004a)."

On page 74 of the Request, SIRC requests that the text in the Background Document, page 360, lines 17-18, "[h]owever, most of the studies published prior to 1994 were negative, while most of the studies published after 1994 were positive," include additional discussion and "attempt to explain this curious result and its implications for attributing SCE to styrene exposures…"

- NTP response: The NTP appreciates SIRC bringing this statement to our attention and agrees that the meaning is not clear. We will delete the statement in an addendum to the Background Document.

On page 74 of the Request, SIRC states that there are inconsistencies between the text of the Background Document and Table 5-18 that should be corrected.

- NTP response: Beginning on page 366, line 16, the Background Document describes the cytogenetic findings (chromosomal aberrations, sister chromatid exchange, and micronuclei) as follows, "[a] meta-analysis of studies of occupational exposed workers reported a positive association between styrene exposure level (higher levels) and chromosomal aberration frequency. Studies in occupationally exposed workers show conflicting responses with SCE and micronuclei formation" and not as stated by SIRC, "results of clastogenic effects are inconclusive." This text is consistent with results for cytogenetic findings indicated in Table 5-18 as (+) = weakly positive and ± = similar number of positive and negative results or multiple studies with positive and negative results. The NTP agrees with SIRC that characterization of mutations in Table 5-18 is not consistent with the text. In an addendum to the Background Document, the NTP will change the designation for Mutations as follows:

  Mutations – *In vivo* Humans will change from "(+)" to "inconclusive."

On page 75 of the Request, SIRC states that information from Melnick (2002) included on pages 368-369 of Background Document is inappropriate.

- NTP response: There is no information from Melnick (2002) on page 368 of the Background Document. The text from Melnick (2002) on page 369, lines 6-10 of the Background Document is accurate. Inclusion of information about structurally related compounds, such as epoxides for styrene oxide, is consistent with information typically discussed in the "Other Relevant Data" section of background documents. The NTP would point out that the Background Document, page 369, lines 6-7 states that styrene-7,8-oxide and other epoxides are *reactive* compounds not *highly reactive* [emphasis added by NTP] as stated by SIRC.

On page 75 of the Request, SIRC disagrees with text in the Background Document, page 375, lines 22-25 presented for Gadberry *et al*.

- NTP response: The Background Document states, page 375, lines 22-25, "[s]tudies by Gadberry *et al*. (see Section 5.2.2.3) showed that styrene-7,8-oxide administered by i.p. injection caused pulmonary toxicity in mice, suggesting that styrene-7,8-oxide is responsible for the pneumotoxicity and that systemically available styrene-7,8-oxide can

enter the lung cell." This text is accurate and supported by the authors' statements; no changes to the Background Document are needed.

On pages 75-76 of the Request, SIRC states that information for Cohen *et al*. (2002) on pages 376-377 of the Background Document is incomplete and proposes its observations about the data for inclusion. SIRC states, "[t]he Cohen model assumes that all metabolism of styrene occurs in the liver and does not include lung metabolism. Thus it cannot explain mouse and rat differences. The conclusions from Cohen *et al*. about styrene oxide lead logically to the conclusion that SO is not responsible for the cytotoxicity from styrene in mouse lung terminal bronchioles."

- NTP response: The NTP will not revise the Background Document because the conclusion is not a conclusion cited in the paper by Cohen *et al*. (2002).

E. Asserted Failure to Discuss Inconsistencies or Lack of Concordance among Human, Animal, and Mechanistic Data

On page 79, SIRC requests that the Background Document be revised extensively "so that it completely and objectively presents the lack of concordance among human, animal and mechanistic data."

- NTP response: NTP would like to point out that the Background Document presents the scientific information from human, animal, and mechanistic studies on styrene. The NTP will not revise the Background Document's discussion to present only "the lack of concordance among the human, animal, and mechanistic data" as SIRC requests because it would provide a limited and biased presentation of the information. The NTP convened an expert panel to peer review the draft Background Document and determine its adequacy for use in the evaluation of styrene for the RoC. Following completion of their peer review, the expert panel voted 10 yes/0 no "that the draft background [document] with the recommended changes in the expert panel report is adequate for drawing conclusions about the carcinogenicity of styrene and for applying the RoC listing criteria."[27]

SIRC Assertion That the Expert Panel's Peer Review of the Draft Background Document Does Not Immunize the Final Background Document from this Correction Request

With respect to specific text of the Background Document for styrene, we believe it satisfies the applicable information quality guidelines. Regarding the "objectivity" criterion,[28] the Background Document presents information on peer-reviewed studies with both positive and negative findings in an accurate, complete, and unbiased manner. According to the OMB Guidelines, "[i]f the data and analytic results have been subjected to formal, independent, external peer review, the information may generally be presumed to be of acceptable

[27] Styrene Expert Panel Report. Part A – Peer review of the draft background document on styrene, page 1, available at http://ntp.niehs.nih.gov/go/29682, see July 21-22, 2008, Topic: Styrene.

[28] According to the OMB Guidelines, "[o]bjectivity" focuses on "whether disseminated information is being presented in an accurate, clear, complete, and unbiased manner" and whether it is "accurate, reliable, and unbiased." 67 Fed. Reg. at 8459.

objectivity."[29] As noted in the RoC review process, the information included in the sections Human Cancer Studies, Studies in Experimental Animals, and Other Relevant Data, "must come from publicly available, peer-reviewed sources."[30] In addition, the draft Background Document was peer reviewed by an independent, external scientific panel at a public meeting. Additionally, the NTP believes that the "utility" criterion[31] is satisfied. The Background Document is useful to the reader. It is a public resource document that provides information from published, publicly available studies on styrene including its use, production, exposure, toxicology, and carcinogenicity, and is available in both electronic and printed formats.

Request for Correction of the Background Document's Executive Summary

On pages 85-98 of the Request, SIRC provides a revised Executive Summary for the Background Document. SIRC states that underlined text denotes additions and strikeout of text denotes deletions.

- NTP response: The Executive Summary summarizes information for exposure, human cancer studies, studies in experimental animals, and other relevant information detailed in the individual sections of the Background Document. The changes to the Executive Summary that SIRC proposes misrepresent and/or limit the information currently presented, or they make the presentation of information more consistent with the interpretations of study findings by SIRC. As this would provide a biased presentation to the reader, the NTP will not make the requested changes.

Conclusion

As noted above, 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. It follows a general format and does not contain any opinion regarding the listing status for the candidate substance. It serves as a resource that the review groups can use in applying the RoC criteria during evaluation of the candidate substance and in formulating their opinion on whether to recommend listing the substance in the RoC. The Background Document for styrene includes factual information from studies on styrene. Each of the three scientific review groups, including the expert panel, acted as an independent review body. Each group used the factual and technical information available in the Background Document and public comments to assess the scientific evidence for the carcinogenicity of styrene, to apply the RoC listing criteria, and to make a listing recommendation. Similarly, the NTP used the Background Document, public comments, and the recommendations from the three scientific review bodies to reach its preliminary policy decision on styrene, which is presented in the Draft Substance Profile for Styrene.[32]

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[29] OMB Guidelines, 67 Fed. Reg. at 8459.
[30] NTP Report on Carcinogens Review Process, Draft Background Documents, available at http://ntp.niehs.nih.gov/go/29353.
[31] According to the OMB Guidelines, "[u]tility" refers to "the usefulness of the information to its intended users, including the public." 67 Fed. Reg. at 8459.
[32] Available at http://ntp.niehs.nih.gov/files/StyreneProfile1_5_ref_change_v3.pdf.

In conclusion, we believe that the Background Document on Styrene satisfies the OMB, HHS and NIH Guidelines issued pursuant to the IQA. The NTP identified several edits to the Background Document that will be made by issuing "Erratum and Addendum to the Final Report on Carcinogens Background Document for Styrene" (enclosed). The document as a PDF file will be posted with the Background Document on the RoC Website (http://ntp.niehs.nih.gov/go/10091 see Styrene) within five days of the date of this letter. It will be included as hardcopy in printed Background Documents.

SIRC may appeal our agency's decision either in writing or electronically within 30 days of receiving this response. Your request should state the reasons for your appeal. It does not need to reference a tracking number. The request may be sent electronically to InfoQuality@od.nih.gov or in hard copy to the Associate Director for Communications, Office of the Director, National Institutes of Health, Building 1, Room 344, 9000 Rockville Pike, Bethesda, Maryland 20892. If the appeal is sent in hard copy, please clearly mark the appeal and outside envelope with the phrase "Information Quality Appeal."

Sincerely,

John R. Bucher, Ph.D.
Associate Director, NTP

Enclosure

Erratum and Addendum to the Final Report on Carcinogens
Background Document for Styrene

The following corrections are made to the Final Report on Carcinogens Background Document for Styrene.

1. Table 3-10, page 187. The footnote * is corrected to read: "Note that Kolstad *et al*. classified employees at companies with 50% or more of workers involved in reinforced plastics as probable high exposure, and that most of the companies were boat yards or manufacturers of containers by hand lamination."

2. Page 174, lines 12-13. The following text in parentheses, "(workers from plants employing 50% to 100% laminators)," is deleted from the sentence: "Kolstad *et al*. (1995) reported significant risks of pancreatic cancer among individuals with probable high styrene exposures (workers from plants employing 50% to 100% laminators), and among individuals exposed to styrene for greater than one year."

   The following sentence is added: "The authors classified employees at companies with 50% or more of workers involved in reinforced plastics as probable high exposure, and most of the companies were boat yards or manufacturers of containers by hand lamination."

3. Page 384, lines 7-9. The reference is added: "An alternative mechanism (Cruzan *et al*. 2002) is that interspecies differences in styrene toxicity are most likely explained through CYP2F-generated metabolites (2f2 in mice, 2F4 in rats, and 2F1 in humans) in the mouse lung."

The following clarifications are made to the Final Report on Carcinogens Background Document for Styrene. New text is shown in italics.

1. The terms "statistically significant" and/or "statistically non-significant" and/or the *P* value are added to clarify the reported findings as follows:
   - Page xii, lines 19-22 and page 192, lines 14-17: "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."
   - Page xii, line 30 to page xiii, line 2 and page 192, lines 25 to 27: "The risk of pancreatic cancer was slightly higher among the Danish workers with longer term employment and earlier start date, and increased with cumulative exposure *(P = 0.068)* in the multi-plant cohort."
   - Page 178, lines 27-30: "In analyses of subtypes of leukemia, the risk of myelogenous leukemia (chronic and acute) was slightly higher than for all leukemia (Kogevinas *et al.*1994a), 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)."

- Page 181, lines 19-24: "The nested case-control study from the Matanoski cohort of 58 lymphohematopoietic cases and 1,242 controls found two- to three-fold *statistically significant* increased risks for lymphoma, lymphosarcoma, and myeloma and styrene exposure (increase of 1 ppm in TWA) (Matanoski *et al*. 1997), and the risk of myeloma increased with increasing cumulative exposure *(P = 0.023)* to styrene using the step-down regression analysis and taking into account butadiene exposure and other variables.
- Page 184, lines 20-22: "A *statistically significant* increased risk of renal-cell cancer was also associated with exposure to styrene-butadiene rubber in the population case-control study from Canada (Parent *et al*. 2000)."
- Page 184, lines 25-29: "*Statistically significant* increased risk of breast cancer was suggested in an ecological study (Coyle *et al*. 2005), which assessed styrene exposure by toxic release inventory data; [however, this study was limited by the ecological design and poor characterization of styrene exposure, which was based only on residence in counts with varying environmental toxic releases]."

2. Page 360, lines 17-18. The following sentence is deleted: "However, most of the studies published prior to 1994 were negative while most of the studies published after 1994 were positive."

3. Table 5-18, page 367. The designation for Mutations – *In vivo* Humans is changed from "(+)" to "inconclusive."