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February 6, 2009

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RE: Comments for the Consideration of the NTP Board of Scientific Counselors on
1. Draft Substance Profile for Styrene
2. Deficiencies in NTP's Review of Styrene

Dear Dr. Shane:

The Styrene Information and Research Center¹ (SIRC) appreciates the opportunity to provide comments in response to the National Institute of Environmental Health Sciences' (NIEHS') December 22, 2008 *Federal Register* notice, announcing the February 24, 2009 meeting of the National Toxicology Program Board of Scientific Counselors (BSC), and making available a Draft Substance Profile for Styrene. **73 Fed. Reg. No.246, 78364 (December 22, 2008)** The BSC's review of the Substance Profile is a process step in the NTP'S consideration of styrene for possible listing in the 12th *Report on Carcinogens (RoC)*.

Executive Summary

The Styrene Draft Substance Profile, which has been submitted to the BSC for peer review, states "Styrene is *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity in humans, sufficient evidence of carcinogenicity in experimental animals, and supporting mechanistic data." The BSC is

¹ The Styrene Information and Research Center's (SIRC's) mission is to evaluate existing data on potential health effects of styrene, and develop additional data where it is needed. SIRC has gained recognition as a reliable source of information on styrene and helping ensure that regulatory decisions are based on sound science. For more information, visit <http://www.styrene.org>.

charged with determining whether this Draft Substance Profile is technically correct and supports the classification of “reasonably anticipated,” in accordance with NTP’s classification criteria.²

These comments will show the Draft Substance Profile on styrene CANNOT be found to be technically correct and supportive of this classification because:

- The human data do not provide “limited” evidence of styrene’s potential carcinogenicity; in fact, there is no evidence of a causal relationship between styrene exposure and cancer in humans. [1st Clause of NTP Criteria]
- Animal studies do not present “sufficient” evidence of styrene’s potential carcinogenicity; in fact, they provide only *limited* evidence of carcinogenicity – clear evidence by one route of administration and no more than suggestive evidence by another. [2nd Clause of NTP Criteria]
- The draft profile asserts that styrene’s mode of action is relevant for humans; in fact, available data do not support genotoxicity through styrene-7,8-oxide as the mode of action for mouse lung tumors. [3rd Clause of NTP Criteria]
- The BSC has not been informed of this evidence by the Draft Substance Profile because it inexplicably deviates from accepted scientific practice by
 - *reinterpreting* – on a first-time basis – three key published studies contrary to the findings of their authors, without highlighting this to reviewers,
 - creating an improper historic control group, contrary to previous NTP policy,
 - failing to characterize or seriously consider null studies,
 - not discussing that its conclusions differ dramatically from those of respected groups that have previously assessed the hazard potential of styrene,
 - not identifying legitimate differences in the interpretation of the existing data, and
 - providing a *highly selective* presentation of the existing evidence on styrene, despite the fact that the larger body of evidence on styrene has been brought to the staff’s attention in prior public comments.

Thus, the BSC is being asked to review a Draft Substance Profile that cannot be considered complete. Instead, the carcinogenicity of styrene must be judged by the BSC using both the Draft Profile AND the larger body of science on styrene, which is presented only in these and other public comments. We realize that this situation greatly complicates the task of the BSC. However, this effort is vitally important because the BSC is the last peer review in the RoC process. The health of our workers and neighbors, and the health of our industry itself, depends on the BSC’s conducting an independent and thorough review of the NTP staff’s

² There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded,

or

There is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset,

or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

proposal to classify styrene as “reasonably anticipated.” We believe that such a review will find no valid justification for listing styrene in the *Report on Carcinogens*.

1. The Human Data Do Not Provide “Limited” Evidence of Carcinogenicity

The Draft Profile says “There is limited evidence of the carcinogenicity of styrene in humans based on studies of workers exposed to styrene showing (1) increased mortality or incidence of lymphohematopoietic cancer and (2) increased levels of DNA adducts and genetic damage in lymphocytes from exposed workers.” “The two cohort studies with the largest number of person-years, an incidence study of male Danish workers (Kolstad *et al.* 1995, Kolstad *et al.* 1994) and a European multinational mortality study of male and female workers (which included a subset of the Danish workers) (Kogevinas *et al.* 1994) were considered to be the most informative studies in the reinforced plastics industries. In the styrene-butadiene industry, the major study was the large multi-plant cohort mortality study of male and female styrene-butadiene workers in the United States and Canada by Delzell and colleagues (Delzell *et al.* 2006, Graff *et al.* 2005)...”

The NTP reached the above conclusions by inappropriately *re-interpreting* the conclusions of both Kogevinas *et al.* and Delzell *et al.*

Independent evaluations of the styrene epidemiologic data submitted to the NTP completely disagree with those conclusions. Their evaluations unanimously conclude the existing data do not support a determination of “limited” evidence of cancer in humans exposed to styrene.

- a. Boffetta Panel Report (2008, submitted to *Journal of Occupational & Environmental Medicine*)³ reviewed the styrene epidemiology data and concluded: “The available epidemiologic evidence does not support a causal relationship between styrene exposure and any type of human cancer.”
- b. Teta (2008, see styrene RoC docket Emulsion Polymers Council letter of July 7, 2008) concluded: “The NTP review is generally unbalanced in that weakly positive, often non-statistically significant and imprecise measures of association are listed, without discussing relevant non-positive and subgroup results in the context of consistency of these results with an occupational risk.”
- c. Goodman (2008, see styrene RoC docket letter of Feb. 5, 2008 and ACMA letter of July 7, 2008) concluded: “We addressed the question as to whether styrene exposure can lead to an increased risk of these malignancies based on the Bradford Hill Criteria, taking all of the above factors into consideration. We found that, based on these criteria, the epidemiology data does not support an association between styrene exposure and pancreatic or lymphohematopoietic cancer risk.”
- d. Rhomberg (2008, see styrene RoC docket letter of Feb. 5, 2008 and NMMA letter of July 7, 2008) concluded: “Although some positive associations were reported in certain exposure groups of some cohorts in some studies, so, too, were null and negative effects. There were no *consistent* findings of effect for any cancer type in the RPC, SBR, or PS industries.”
- e. Delzell (2008, see styrene RoC docket SIRC letter of Oct. 23, 2008) concluded: “Results for styrene and NHL from both studies are unconvincing.”

³ The members of the Panel were: Dr. Hans-Olov Adami, Chairman, Department of Epidemiology, Harvard University School of Public Health; Dr. Philip Cole, Professor Emeritus, Department of Epidemiology, School of Public Health, University of Alabama, Dr. Paolo Boffetta, Coordinator of the Genetics and Epidemiology Cluster at IARC, Dr. Dimitrios Trichopoulos, Professor of Epidemiology, Harvard University School of Public Health, and Dr. Jack Mandel Professor and Director, School of Public Health, University of Toronto, and formerly of Emory University.

The Boffetta et al. report noted above was a project sponsored by SIRC, and expedited to address the fact that the Styrene Expert Panel, and subsequent NTP documentation, justified the finding of “limited” human data by **upgrading the conclusions** of Delzell et al. (2006) and Kogevinas et al. (1994). In previous comments to NTP, SIRC pointed out the need for external peer review of these reinterpretations of published data, and offered the report of the Boffetta panel to provide such peer review. The Boffetta et al. report was submitted directly to NTP staff by the authors, at the same time that it was provided to SIRC. SIRC further formally submitted the report in its letter of December 16, 2008 (see styrene RoC docket), requesting that the report be added to the styrene docket. **The Boffetta et al. report clearly contradicts NTP’s upgraded conclusions on which the styrene classification is based. Further, Boffetta et al.’s conclusion that there is *no causal relationship* between styrene exposure and human cancer is based on consideration of the full body of styrene epidemiological data. And yet the Draft Substance Profile continues to try to justify styrene’s “reasonably anticipated” classification based on these inappropriate reevaluations.**

It is important to realize that, in order for a chemical to be characterized as having "limited" evidence, there must be a positive finding in which a causal explanation is credible; it is not simply applied when the data are inconsistent or inconclusive. The mere presence of some positive evidence in some studies is not by itself grounds to conclude that a causal explanation is credible. *Importantly, the conclusions cited in the Draft Profile as limited evidence of carcinogenicity in humans are contrary to the conclusions of the authors cited (Kogevinas et al., 1994 and Delzell et al., 2006).*

CONCLUSION: As evaluated in the five reports above, there is no evidence of a causal relationship between styrene exposure and cancer in humans. Therefore, the draft profile’s characterization of the human data as “limited” is not consistent with the NTP classification criteria.

2. The Available Animal Studies Do Not Present “Sufficient” Evidence of Carcinogenicity

The Draft Profile states: “There is sufficient evidence for the carcinogenicity of styrene in experimental animals based on the induction of tumors in multiple studies in mice exposed to styrene **by two routes of exposure**. The most robust studies are a two-year inhalation study in CD-1 mice (Cruzan *et al.* 1998) and a two-year oral gavage study in B6C3F1 mice (NCI 1979).”

The inhalation study by Cruzan et al. (**2001, not 1998 as stated in the Draft Profile**) found increased lung tumors in male and female CD-1 mice.

The NCI (1979) mouse study provides no more than *suggestive* evidence of increased lung tumors.

- a. The NCI did not conclude that there was sufficient evidence of cancer in this study. The NCI (1979) concluded “The findings of an increased incidence of a combination of adenomas and carcinomas of the lung provided **suggestive** evidence for the carcinogenicity of styrene in male B6C3F1 mice. However, it is concluded that, under the conditions of this bioassay, **no convincing evidence** for the carcinogenicity of the compound was obtained in F344 rats or B6C3F1 mice of either sex.” The reviewers recommended either “suggestive evidence” or “no evidence.”
- b. The Draft Substance Profile’s conclusion is based on a new historical control analysis developed by the NTP for the RoC review. The original NCI study used a historical control of mice tested at the same facility (Litton), while the NTP in its Draft Profile developed its analysis from mice used in testing primarily at a nearby facility (Hazelton). The Draft Profile’s rationale for using historical controls from a different facility was based on an attempt to obtain sufficient numbers of historical control studies which employed corn-oil gavage dosing. However, an earlier analysis published by the NTP demonstrated that use of corn-oil as

a vehicle had no impact specifically on the incidence of mouse lung tumors, and thus the Draft Profile's rationale for use of corn-oil gavage historical controls from a different laboratory cannot be justified. Further, NTP's earlier analysis of the historical control database also concluded that significant inter-laboratory variation in historical control tumor incidence precluded use of inter-laboratory controls to facilitate interpretation of bioassay tumor responses. Examination of 91-week and 104-week mouse studies at Litton and Hazleton demonstrated that control male B6C3F1 mice at Litton had a significantly higher incidence of lung tumors than at Hazleton and, **therefore, the data from Hazleton are not appropriate for comparison to Litton studies and the Draft Substance Profile's development of a new historical control analysis was improper.**

- c. A companion study conducted at the same time at the Litton facility of a mixture of 30% β -nitrostyrene and 70% styrene used approximately the same doses of styrene and did not produce increased lung tumors in mice.
- d. IARC (2002) concluded that these studies provided only limited evidence of cancer in animals.

CONCLUSION: The animal studies provide at best only *limited* evidence of carcinogenicity – clear evidence by one route of administration and no more than suggestive evidence by another. Therefore, the draft profile's classification of the animal data as "sufficient" does not conform to the NTP classification criteria.

3. The Available Data Indicate that the Mode of Action is Not Relevant for Humans

The Draft Substance Profile states: "The mechanisms of styrene carcinogenicity are not fully known. The 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 including styrene-7,8-oxide and 4-vinylphenol in the mouse lung, resulting in cellular proliferation, pulmonary hyperplasia, and tumor formation (Cohen *et al.* 2002, NTP 2008, Cruzan *et al.* 2002)." "The majority of genotoxic effects (DNA damaging) associated with styrene exposure are thought to be due to styrene-7,8-oxide." "The primary metabolite of styrene, styrene-7,8-oxide, is listed in the *Report on Carcinogens as reasonably anticipated to be a human carcinogen* based on sufficient evidence in experimental animals. Styrene-7,8-oxide induced increased incidences of 5 forestomach tumors in rats and mice and liver tumors in male mice after oral administration (NTP 2004)."

3.a. Styrene-7,8-oxide is not likely involved in mouse lung tumors

The first proposed mode of action above states that any genotoxic mode of action for styrene is caused by the metabolite styrene-7,8-oxide (SO). However, increased mouse lung tumors from the inhalation of styrene is unrelated to the presence of SO in the lungs.

- 3.a.1. Gavage administration of SO did not result in increased lung tumors in mice, despite equivalent lung level of SO.
- 3.a.2. A lung explant study showed 8-fold more SO in lungs of rats exposed to styrene at non-tumorigenic air concentration than in mice at a tumorigenic concentration.
- 3.a.3. CYP2E1 produces mostly S-SO; inhibition of CYP2E1 or use of CYP2E1-knockout mice did not reduce the lung toxicity from styrene exposure.
- 3.a.4. Similar cytotoxicity and tumors in mouse, but not rat, lungs has been demonstrated in at least two similar chemicals that are not metabolized to epoxides like SO, namely ethylbenzene and cumene.

3.b. Furthermore, it is unlikely that styrene acts via a genotoxic mode of action.

The Draft Profile asserts that metabolism of styrene to SO and subsequent DNA damage in the target tissue is the likely mode of action. While it is true that styrene is metabolized to SO in mouse lung terminal bronchioles, there is no evidence that this leads to genotoxicity. The only assays of styrene genotoxicity in mouse lung are negative.

3.b.1. Kligerman et al.⁴ found no increase in CAs in the lungs of mice exposed to high levels of styrene by inhalation for 2 weeks.

3.b.2. Brunnemann et al.⁵ found no increase in mouse lung tumors in an initiation assay in A/J mice administered i.p. styrene.

3.c. The mode of action for styrene induced mouse lung tumors involves cyp2f2 metabolism, which is negligible in humans

The second proposed mode of action above states that tumors may be formed as a result of cytotoxicity from styrene metabolites SO or 4-vinylphenol. SO (at least S-SO) does not play a role in styrene induced lung cytotoxicity. As noted above, inhibition of CYP2E1 or in 2E1-KO mice, cytotoxicity from styrene is not reduced. Furthermore, 4-vinylphenol is likely the proximate cytotoxic metabolite of styrene.

3.c.1. Inhibition of CYP2F2 inhibits the toxicity from 4-vinylphenol.

3.c.2. Metabolism studies show two further metabolites from 4-vinylphenol; 4-hydroxystyrene-7,8-oxide and 3,4-dihydroxystyrene, whose formation are inhibited by inhibition of CYP2F2, but not CYP2E1.

3.c.3. Production of similar ring-hydroxylated metabolites from ethylbenzene and cumene in mice.

The Draft Profile equates DNA adducts with genotoxicity. DNA adducts are repaired and only lead to genotoxicity if they cause misreplication of DNA to daughter cells. For styrene, DNA adducts are not more prevalent in mouse lung tissue than in liver tissue and are not more prevalent in mouse tissues than in rat tissues. Thus, if the DNA adducts from styrene were “genotoxic,” they should lead to increased tumors in rats as well as in mice.

CONCLUSION: The available data do not support genotoxicity through styrene-7,8-oxide as the mode of action for mouse lung tumors.

4. Absence of Scientific Rigor in NTP RoC Process

The preceding sections 1-3 present the heart of our scientific concerns with the Substance Profile, and our conviction that the Draft Substance Profile does not provide a reasonable scientific footing to justify an RoC listing of styrene.

⁴ Kligerman, A.D., Allen, J.W., Bryant, M.F., Campbell, J.A., Collins, B.W., Doerr, C.L., Erexson, G.L., Kwanyuen, P., and Morgan, D.L., 1992. Cytogenetic studies of mice exposed to styrene by inhalation. *Mutat. Res.* 280: 35-43

⁵ Brunnemann, K.D., Rivenson, A., Cheng, S.C., Saa, V. and Hoffmann, D., 1992. A study of tobacco carcinogenesis. XL VII. Bioassays of vinylpyridines for genotoxicity and for tumorigenicity in A/J mice. *Cancer Let.* 65: 107-113

SIRC does, however, have significant concerns as to how the *RoC* process has *produced* a Substance Profile that fails to transparently address major scientific issues critical to a rational scientific evaluation of styrene, and we believe it is important for the BSC to understand these concerns.

A key intent of the new *RoC* process was to allow for increased public comment and input. However, from SIRC's experience throughout NTP's assessment of styrene, it is clear that NTP interprets this to mean that they need only post comments in the docket, but in no way are required to consider those public comments or highlight scientific issues in dispute for subsequent reviewers.

SIRC has provided the information contained in this current comment letter to NTP on *multiple* occasions and in great detail⁶, yet NTP has consistently ignored SIRC's comments and has refused to include discussions of the fundamental scientific challenges we have raised to question NTP's interpretation of the styrene data, apparently believing that simply adding our comments to the styrene docket sufficiently meets the requirements of considering public comments. This approach effectively prevents subsequent reviewers, such as the BSC, from independently reviewing the NTP staff's proposed decisions.

That NTP refuses to acknowledge public input – even to explain why our comments are being dismissed – shows a profound imbalance in governmental due process which blindsides those who have the duty to peer review their work, including the BSC. And, as SIRC has learned, it is an imbalance that has so far gone unchecked. Even more profoundly disturbing is the NTP's selective use and interpretive bias with regard to the peer reviewed literature, that fails to meet accepted standards of scientific rigor and objectivity, logical honesty, and fairness in governmental proceedings.

5. Request to Board of Scientific Counselors to Thoroughly Assess the Scientific Validity of the Styrene Draft Substance Profile

The February 24, 2009 meeting of the NTP Board of Scientific Counselors will be the first time the BSC will consider substances proposed for listing in the *RoC* which have been reviewed according to the NTP's new *RoC* process. SIRC therefore wishes to draw to the BSC's attention the stubborn resistance on the part of NTP to engage in a comprehensive, transparent assessment of the full body of scientific evidence on styrene.

The BSC should be clear in assessing the Draft Substance Profile for Styrene that the justification provided by the NTP Draft Substance Profile for classifying styrene as “reasonably anticipated” to be a carcinogen is highly selective, *does not present a scientifically balanced review*, and relies to a large degree on the Draft Profile's *upgrading* of the conclusions of published authors. The Draft Substance Profile does not acknowledge or explain why the agency has set aside these study authors' conclusions, nor why myriad data which contradict its conclusion were *ignored* – data which *have* been considered in other hazard assessments of styrene.

⁶ July 19, 2004 – SIRC response to Nomination of Styrene for Review for 12th Report on Carcinogens,
July 7, 2008 – SIRC Comments on NTP Report on Carcinogens, Draft Background Document for Styrene
October 23, 2008 – SIRC Comments on NTP *RoC*, Styrene Expert Panel's Listing Status for Styrene and Scientific Justification
All of these documents can be found in the styrene public comments docket on the NTP/12th RoC website

According to the new *RoC* process, the BSC is asked to determine “whether the scientific information cited in the draft substance profile for a candidate substance is technically correct and supports the NTP’s decision regarding its listing in the *RoC*.” Further, the *RoC* process notes that “The BSC is not asked to review the NTP’s decision regarding listing status.”

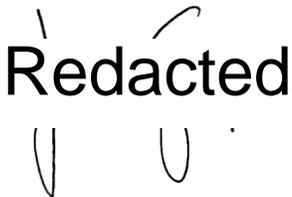
SIRC believes that NTP’s Draft Substance Profile for Styrene most certainly cannot be characterized as “technically correct.” Indeed, if it were technically correct, we do not believe that it could justify a classification of “reasonably anticipated.”

Therefore, SIRC respectfully urges the BSC to seriously examine the scientific thoroughness and accuracy of the styrene Draft Substance Profile, and to question NTP as it finds appropriate on issues such as NTP’s upgrading of conclusions on published data, its omission of large amounts of data that contradict its conclusions, and its failure to acknowledge or reflect extensive comments provided by the public that outline valid arguments why styrene should not be given such an inappropriately severe classification.

6. Conclusion

We believe that if NTP were to move forward to list styrene in the 12th *RoC*, it would be based on a misuse of published data, and a straightforward effort to ignore all data which contradict its selectively crafted conclusion that styrene is “reasonably anticipated” to be a carcinogen. For NTP to seek to inform the public that styrene is a carcinogen of such high concern, based on such narrow evidence, would serve only to ignite wholly unwarranted alarm around a chemical that has safely and productively been used for decades. The impact of such a scientifically weak classification would be significant on industries across the United States, and indeed would have global implications, raising needless concern and attention around a substance that helps to enhance the safety and quality of life. The *RoC* process – certainly in the case of styrene – is poised to do a grave disservice to the public it is intended to accurately inform.

Very truly yours,


Redacted

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ATTACHMENT: Detailed SIRC Comments on Styrene Draft Substance Profile

**ATTACHMENT TO STYRENE INFORMATION & RESEARCH CENTER COMMENTS ON
NTP DRAFT SUBSTANCE PROFILE FOR STYRENE**

February 6, 2009

**Detailed Comments Addressing NTP's Draft Substance Profile Validation for Classifying Styrene as
"Reasonably Anticipated to Be a Human Carcinogen"**

1. Human Studies

The NTP criteria indicate that for there to be limited evidence of carcinogenicity, "a causal interpretation is credible". The guidelines do not specify what makes a causal interpretation credible; however, inconsistent or inconclusive results do not make an association credible. In the styrene human data, the NTP have asserted a causal association that is contrary to the conclusions of the authors of the primary studies and to three additional independent reviews.

The limited evidence consists of:

1. Increased leukemia in the Kolstad et al. (1994) study;
2. Increased total lymphohematopoietic cancers in Kogevinas et al. (1994) and
3. increased NHL or NHL-CLL combined in Delzell et al. (2006).

It should be noted that the increased leukemia from the Kolstad study was not carried into the Kogevinas study even though the members of the Kolstad study made up more than 30% of the Kogevinas study.

1.1. The Kolstad et al. (1994) study.

The Kolstad cohort is treated in the draft Document and Profile as evaluating high exposure and low exposure, but there is no individual exposure assessment in the study. The authors reviewed the Danish industry registry for companies that might be involved in reinforced plastics (RPC). They then asked the company owners if they were involved in RPC. They also asked two suppliers of styrene-based resin material to identify if each company listed was involved in RPC. The resin suppliers identified 386 companies with 36,525 employees as involved to some extent in RPC. The company owners identified 277 companies with 28,518 employees as ever involved in RPC. The suppliers and owners agreed on 233 companies with 26,784 employees. Kolstad et al. performed the rest of the analyses using the responses from the resin suppliers because they found a significant increase using the suppliers' assessment and did not find one using owners' assessment in a subset of the cohort. They further asked the suppliers if more or less than 50% of each company's workforce was involved in RPC.

No attempt was made to determine how many workers were laminators, the group with the highest styrene exposures. The evaluation of high vs. low exposures was based on whether more or less than 50% of the workers may have been involved in RPC. RPC workers in the category where less than 50% were involved in RPC had the same exposure as workers in companies where more than 50% were involved in RPC, but were deemed to have low exposure. The authors estimated that 43% of the cohort was involved in RPC, but not all of those were exposed to styrene or were laminators. In a typical RPC facility only 10 to 20% of the workforce were laminators. Thus one can estimate that between 4 and 9% of the cohort were laminators. There were 32 leukemias among those who worked less than 1 year and were more than 10 years from first employment; this was reported as a significant increase. No attempt was made to determine if any of the 32 cases was actually exposed to styrene. **It does not seem reasonable to conclude that this study provides evidence of increased cancer from styrene exposure.**

1.2. The Kogevinas et al. (1994) study

The Kogevinas study was comprised of 8 subcohorts that had different criteria for inclusion, different exposure assessments, and different years of follow-up, but an average of 13 years. The workers in the Kolstad study were from companies where more than 50% of the workers were estimated to be involved in RPC but were included under “other exposed workers,” not under laminators. There was no increase in any cancer type by job classification. Kogevinas and coworkers estimated a cumulative exposure and duration of exposure for each member of the cohort. They then estimated an average exposure by dividing the cumulative exposure by the duration. The authors reported a significant increased trend in total lymphohematopoietic cancers in relation to average exposure, but not cumulative or duration. (Note: it seems unusual and not indicative of a causal effect that neither the numerator nor the denominator was significant, but the dividend was). Table 3 in Kogevinas et al. (1994) lists 74 SMRs and their 95% CIs, each representing an analysis of a particular subset or categorization of the subjects in a study. Of these, six are statistically significant:

- all neoplasms (SMR = 91, 95% CI = 83-99)
- all neoplasms, < 10 years since first exposure (SMR = 84, 95% CI = 72-97)
- lymphatic and hematopoietic cancers, < 2 years exposure, 10-19 years since first exposure (SMR = 183, 95% CI = 112-283)
- lymphatic and hematopoietic cancers, < 2 years exposure, < 10 years since first exposure (SMR = 43, 95% CI = 16-93)
- non-Hodgkin's lymphoma (SMR = 0, 95% CI = 0-99); and
- leukemia, < 2 years exposure, 10-19 years since first exposure (SMR = 215, 95% CI = 103-395).

Four of these six are significant decreases in cancer incidence. Based on 5% probability of false positive results, one would expect 4 statistically significant outcomes in this study. Unless one assumes all four of the false positive results were the four decreases, one or two of the significant increases is likely to represent a false positive. The authors did not conclude that this study provided evidence of carcinogenicity from styrene; they concluded “These findings leave open the possibility of an excess risk of neoplasms of the lymphatic and hematopoietic tissues among workers exposed to styrene.” **They did not conclude there was a causal association, just that the study did not rule one out. NTP has re-interpreted this study a providing a causal association.**

1.3. The Draft Profile does not include the results from two other RPC cohorts. Wong et al. (1994)⁷ evaluated cancer risks among 15,826 US RPC workers with an average follow-up of 19 years. Unlike the imprecise exposure estimates used in Kolstad et.al. (1994), individual exposures in this study were estimated using a job-exposure matrix based on individual worker histories and time-weighted job-specific exposure levels. There was no increased risk of cancer in relation to styrene exposure in that cohort. In another RPC cohort, Ruder et al. (2004)⁸ reported no increase in lymphohematopoietic cancers in a cohort of more than 5000 RPC workers with an average follow-up of 26 years (> 2000 workers confirmed as high exposure by industrial hygiene surveys). **While these studies were smaller than the Kogevinas et al study, both had longer follow-up times and refined exposure analyses and found no increase in any type of cancers of lymphatic or hematopoietic tissues.**

1.4. The Draft Profile cites increased NHL and NHL-CLL combined in the US SBR cohort as evidence of a causal association of styrene with cancer. None of the RPC cohorts, with much higher cumulative exposures to styrene,

⁷ Wong, O., Trent, L.S., and Whorton, M.D., 1994. An updated cohort mortality study of workers exposed to styrene in the reinforced plastics and composites industry. *Occup. Environ. Med.* 51: 386-396.

⁸ Ruder, A.M., Ward, E.M., Dong, M., Okun, A.H., and Davis-King, K., 2004. Mortality patterns among workers exposed to styrene in the reinforced plastic boatbuilding industry: an update. *Am. J. Ind. Med.* 45: 165-176.

had increased NHL or CLL. Dr. Delzell commented that the elevated RRs for NHL and CLL-NHL among workers with nonzero exposure to styrene reflect, to some extent, unexplained and substantial **deficits** of deaths from NHL and CLL-NHL in the **styrene-unexposed** group. These deficits were seen when the workers unexposed to styrene were compared to the general population at large (Delzell et al., 2006, tables 21 and 22). The deficit observed in this “external” comparison was statistically significant for CLL-NHL, based on 2 observed compared to 8.1 expected deaths during the time period 1968-1998 (standardized mortality ratio=0.25, 95% confidence interval, 0.03-0.89). She further has pointed out that the Draft Profile and Background Document assert there was an increased trend for NHL and NHL-CLL combined, but the basis for this conclusion was not provided since there were no statistical tests of any relationship to exposure. **Dr. Delzell concluded “Results for styrene and NHL from both studies are unconvincing.” The NTP re-interpreted her results to indicate a causal association.**

1.5. Draft Substance Profile Rejection of External Peer Review of Study Reevaluations

SIRC sponsored, and expedited, a review of the styrene epidemiological data by a blue ribbon panel of internationally reputable scientists (Boffetta et al., 2008)⁹, in large part to address the fact that the Styrene Expert Panel, and subsequent NTP documentation now including the Draft Substance Profile, justified the finding of “limited” human data by **upgrading the conclusions** of Delzell et al. (2006) and Kogevinas et al. (1994). On several occasions in written comments to NTP staff, SIRC has pointed out the critical need for external peer review of these *reevaluations* of the conclusions of published studies. We offered the report of the blue ribbon panel to provide such peer review. The Boffetta et al. report was submitted directly to NTP staff by the authors, at the same time that it was provided to SIRC, and has been included in the styrene RoC docket (see SIRC letter of December 16, 2008). **Boffetta et al. clearly contradicts the upgraded conclusions of published authors as cited in the Draft Substance Profile, and upon which the styrene classification is based. The Draft Substance Profile ignores Boffetta et al.’s conclusion that there is *no causal relationship* between styrene exposure and human cancer – a conclusion that is based on consideration of the full body of styrene epidemiological data. The Draft Substance Profile continues to justify styrene’s “reasonably anticipated” classification based on these inappropriate reevaluations.**

1.6. Summary of Epidemiology Data

The NTP has re-interpreted two studies (Kogevinas et al., 1994; Delzell et al., 2006) involving styrene workers to assert a causal association where the authors themselves did not conclude that styrene caused cancer. Independent reviews of these studies agreed with the authors, not with the NTP (Boffetta et al., 2008). In all these studies, there were more cases of significant *deficits* of cancer than *increases* of cancer. No consistent pattern of increases was found among studies. Therefore, the available epidemiologic evidence does not support a causal relationship between styrene exposure and any type of human cancer, and the NTP classification criteria are not met.

⁹ The members of the Panel were: Dr. Hans-Olov Adami, Chairman, Department of Epidemiology, Harvard University School of Public Health; Dr. Philip Cole, Professor Emeritus, Department of Epidemiology, School of Public Health, University of Alabama, Dr. Paolo Boffetta, Coordinator of the Genetics and Epidemiology Cluster at IARC, Dr. Dimitrios Trichopoulos, Professor of Epidemiology, Harvard University School of Public Health, and Dr. Jack Mandel Professor and Director, School of Public Health, University of Toronto, and formerly of Emory University. This report has been submitted for publication to the *Journal of Occupational & Environmental Medicine*.

2. Animal Cancer Studies

The NTP *RoC* criteria for listing as “reasonably anticipated” based on animal data requires two studies of clear evidence of increased cancer in two or more species or by two or more routes. For styrene, the *RoC* Draft Substance profile asserts that styrene caused a clear increase in lung cancer in both sexes in a mouse inhalation study (Cruzan et al., 2001) and in male mice by gavage in which there were 20 male and 20 female control mice and 50 male and 50 female in each of the two treated groups (NCI, 1979a).

There are four gavage studies of styrene which provide conflicting data and no more than suggestive evidence of carcinogenicity. The results are summarized below:

Styrene in B6C3F1	0, 150, 300	increase in high dose males, within historical control range NCI: Suggestive evidence	NCI, 1979a
Styrene/ β -nitrostyrene in B6C3F1	0, 204, 408	increase in low dose males NCI: no convincing evidence	NCI, 1979b
Styrene in O20	0, 1350	increased lung tumors m&f Severe lung toxicity 50% mortality by week 20	Ponomarkov, 1978
Styrene in C57Bl	0, 300	no increase in lung tumors	Ponomarkov, 1978

Details of Mouse Studies

NCI (1979a) administered styrene in corn oil by gavage to 20 male and 20 female control mice and 50 male and 50 female in each of the two treated groups, 150 and 300 mg/kg day (NCI, 1979a). There was an increased trend for lung tumors in males and the high dose was significantly elevated compared to the concurrent control (0, 12 and 18% at 0, 150 and 300 mg/kg/day styrene in corn oil). The report identifies 2 studies of chemicals dissolved in corn oil at the same laboratory, including the styrene study. They concluded that this was insufficient to assess the historical control range and relied on the incidence in control mice from several diet studies performed at the same laboratory at about the same time. The historical control incidence of the studies they selected averaged 12% with a range up to 20%. The primary reviewer of the styrene report recommended that this study provided suggestive evidence of carcinogenicity, while the secondary reviewer recommended that the study was negative. The NCI concluded that the styrene incidence was within the historical range and the styrene difference from control provided no more than suggestive evidence.

The Draft Substance Profile reasons that using untreated mice as the historical control was incorrect, so they developed a novel new historical control using corn oil controls from the two studies at Litton, plus 12 additional studies at nearby Hazleton Laboratories from the first 110 TR numbers. The Hazleton studies included nearly all NCI studies done at Hazleton with a lower TR number than the styrene study (TR185). This control had an average incidence of lung tumors of 4%. Therefore, the Draft Substance Profile concludes that the control incidence in the Litton styrene study was not low, the incidence in the styrene study was outside the historical control range, and the NCI study provided clear evidence of carcinogenicity of styrene by oral gavage.

Although the Draft Substance Profile posits that corn oil controls were needed because of the potential for this vehicle to influence tumor outcome, NTP's own analysis of the NTP historical control database concluded that corn oil specifically did not impact lung tumor incidence in B6C3F1 mice in NCI-NTP carcinogenesis bioassays (Haseman et al., 1985). Further, NTP analysis reported that the incidence of mouse lung tumors exhibited significant interlaboratory variability and recommended that use of historical control tumor incidence values to facilitate bioassay interpretation should be restricted to values developed within the testing laboratory (Haseman et.al. 1984).

The Draft Substance Profile fails to assess whether there was a difference in lung tumor rates in male B6C3F1 mice at Litton versus Hazleton. The NCI used a group of diet studies from Litton as comparison, with an average incidence of 12% and range to 20%. The Substance Profile compares the styrene study to the incidence in 14 control groups administered corn oil from Litton (2 studies) and Hazleton (12 studies). We examined not only all the corn oil control studies at Hazleton, but also all the diet studies at Hazleton conducted about the same time as the styrene study. We found 2 additional corn oil studies not included in the NTP database (total 14) and 14 diet studies of approximately 91 weeks. The average incidence (and range) for the corn oil studies was 4% (range 0-18%) based on 10/256 male mice and for diet studies was 2% based on 6/260 male mice (0-11%). These data confirm the conclusion of Haseman et al. (1985) that the use of corn oil has little impact on the incidence of tumors in the NCI-NTP carcinogenicity studies, and particularly so in B6C3F1 mice.

A laboratory difference in lung tumor incidence was further supported by examining 104-week studies at the two labs. The incidence at Hazleton was 11% (7 studies, range 2-18%) and at Litton was 19% (40 studies, range 0-45%). Thus, actual historical control group incidence was quite different between Litton and Hazleton labs and was much higher than the incidence used by NTP for analysis of the styrene results.

Three conclusions can be drawn from this analysis:

1. The overall incidence of alveolar/bronchiolar adenomas or carcinomas in male control mice at Litton in studies TR000-TR190 of ~91 weeks duration was 9.1%. The incidence in the high dose styrene exposed males (18%) was lower than the incidence in the control males of 2 of 16 Litton studies in this number range.
2. The incidence of alveolar/bronchiolar adenomas or carcinomas in male mice at Litton was much greater than at Hazleton (overall 9.1% vs., 3.1% for 91 week studies; 19 vs. 11% for 104 week studies). Therefore, the control data at Hazleton is not a valid comparison for Litton studies.
- 3. The NCI conclusion that TR185 provides suggestive evidence is the correct interpretation of the study and the Draft Substance Profile's conclusion of clear evidence is not valid. The original conclusion of the NCI should be retained; the study provides no more than suggestive evidence of carcinogenicity of styrene.**

Other Studies in Animals

The NCI also conducted a gavage study of commercial β -nitrostyrene (TR170) in B6C3F1 mice. Commercial β -nitrostyrene is 30% β -nitrostyrene and 70% styrene. Therefore, the mice that received β -nitrostyrene received 2.3 times as much styrene. The β -nitrostyrene doses were 87.5 and 175 mg/kg 3 days per week for 78 weeks, followed by 14 weeks of observation. The styrene doses were 204 and 408 mg/kg/day 3 days per week. Note that the daily doses of styrene were greater than those of styrene by itself (TR185). Again the incidence of alveolar/bronchiolar adenomas or carcinomas in the control male mice was 0 of 20. 11 of 50 male mice dosed at 204 mg/kg/day styrene developed lung tumors, while only 2 of 36 males dosed at 408 mg/kg had lung tumors. Fourteen male high-dose mice died during week 40, which was attributed to a handling accident. The average

weekly doses of styrene in TR170 and TR185 were: low dose - 87.5 vs. 107 mg/kg/day averaged over 7 days/week, and high dose – 175 vs. 214 mg/kg/day averaged over 7 days/week. (Calculated by daily dose x days/week dosed/ 7 days/week.) Thus at similar doses, styrene (dosed with β -nitrostyrene) did not increase lung tumors in male mice.

3. Mode of Action Data

3.1. Styrene Genotoxicity Data

The bacterial mutation assays were nearly all negative, but positive results were reported for chromosomal aberrations (CA) and sister chromatid exchanges (SCE) in *in vitro* assays. The positive *in vitro* genotoxicity studies of styrene occurred at concentrations of styrene not achievable in humans, under conditions of styrene metabolism, but of inhibited downstream metabolism of styrene oxide. This is in contrast to the *in vivo* situation, where styrene oxide is rapidly removed.

The *in vivo* genotoxicity assays of styrene in rodent assays are overwhelmingly negative. Five of seven micronucleus (MN) assays were negative. One study reported increased MN at 7 days, but not at 1 or 21 days of exposure to styrene; a subsequent publication by this laboratory indicated the positive results could not be duplicated. Eleven of twelve studies of CA in experimental animals were negative, including one in the lungs of mice exposed to styrene by inhalation at concentrations that caused lethality in some mice. *In vivo* assays have indicated that exposure to styrene results in increased SCE.

The Draft Profile lists the human studies of CA and SCE as positive. Critical reviews of the individual studies have reported deficiencies in many of the studies reporting increases, including inappropriate control populations (either by size or characteristics), and non-standard assay conditions. Although Bonassi et al. (1996), included in the Draft Profile, concluded there were increased CAs in workers exposed to greater than 30 ppm styrene, others, not included in the Draft Profile, have disagreed (Scott and Preston, 1994; Speit and Henderson, 2005; Nestmann et al., 2005; IARC, 2002). As stated by IARC (2002), "Inconsistent results have been reported for chromosomal aberrations, micronuclei, and sister chromatid exchange in approximately 30 studies of workers exposed to styrene in various industries."

DNA adducts have been reported in humans, rats and mice exposed to styrene. These are measures of exposure; they do not demonstrate genetic damage likely to lead to the development of tumors. In mice, Boogaard et al. (2000) found lower levels of DNA adducts in lung than in liver and found no greater levels in mice than in rats. The adducts found in animals and humans were at less than 1 in 10^7 nucleotides, and were largely N-7 adducts which are quickly repaired. In serial human studies reported by Vodička et al., there was no accumulation in workers over several years.

The Draft Profile reports styrene-related DNA strand breaks. The actual studies are Comet or DNA unwinding assays. These are notably subject to false positive results and are not sensitive to identify genotoxic or non-genotoxic modes of action. One COMET assay conducted by the inhalation route of exposure (Kligerman *et al.*, 1993), the route of exposure of most relevance to humans showed no genotoxic effect of styrene in female Fischer rat peripheral blood lymphocytes following exposure at 125 to 600 ppm for 6 hours/day for 2 weeks. Vodička *et al.* (2001) reported equivocal results for a COMET assay for styrene in which mice were exposed by inhalation for up to 21 days at 175 to 350 ppm for 6 hours/day. Overall, the results for styrene in COMET assays conducted by relevant routes of exposure present no substantive evidence of a clear genotoxic effect *in vivo*.

There are two assays of styrene genotoxicity on mouse lung. Kligerman et al. (1993) found no increase in CAs in mice exposed for 14 consecutive days at 125, 250 or 500 ppm styrene by inhalation. Exposure at 250 or 500 ppm resulted in lethality in 30 to 50% of the mice. These exposure levels were greater than those of the chronic inhalation studies (20-160 ppm). Thus, it is unlikely that increased CAs were a factor in the formation of lung tumors in mice exposed to styrene by inhalation. Furthermore, in a study to examine carcinogen initiators from cigarette smoke, Brunnemann et al., (1992) injected styrene ip for 7 weeks in A/J, a strain designed to be sensitive to the formation of lung tumors in mice, followed by 20 weeks of observation. Styrene did not cause an increase in lung tumors, indicating styrene provided no indication of tumor initiating potency.

In summary, the genotoxicity data for styrene are not convincing of a genotoxic mode of action.

3.2. Role of Styrene Oxide

The Draft Profile states “The mechanisms of styrene carcinogenicity are not fully known. The 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 including styrene-7,8-oxide and 4-vinylphenol in the mouse lung, resulting in cellular proliferation, pulmonary hyperplasia, and tumor formation (Cohen *et al.* 2002, NTP 2008, Cruzan *et al.* 2002).”

The above proposes that any genotoxic MOA is through styrene-7,8-oxide (SO) and that a cytotoxic MOA may also occur because of the formation of SO. The following comments evaluate whether the review the data on styrene and styrene oxide support the hypothesis that lung tumors in mice exposed to styrene occur as a result of the formation of SO.

Hypothesis: Styrene-7,8-oxide resulting from the metabolism of styrene causes genotoxic events, leading to cancer.

Facts that support this hypothesis:

- a. There is ample evidence that styrene is metabolized to styrene-7,8-oxide in liver and lung (IARC, 1994, 2002).
- b. Styrene inhalation exposure in animals and humans results in circulating levels of styrene-7,8-oxide. (Cruzan et al., 1998, 2001; reviewed in IARC, 2002)
- c. Low levels of SO-DNA adducts have been reported in animals and humans exposed to styrene (reviewed in IARC, NTP draft document).
- d. *In vitro* genotoxicity studies of styrene-7,8-oxide are positive, including bacterial mutagenicity, chromosomal aberrations (IARC, 1994; NTP draft document).

Facts that contradict this hypothesis

- a. Genotoxic carcinogens normally cause tumors at multiple sites in multiple species. **This is not true for styrene.** The only tumor type increased in 8 rat studies and 5 mouse studies is mouse lung tumors (IARC, 2002; EU, 2007, Cohen et al., 2002).
- b. **Administration of SO (up to 550 mg/kg) to mice did not result in increased lung tumors.** Lijinski et al., 1985 administered SO to rats and mice at 275 and 550 mg/kg/day. Severe necrosis of the forestomach and forestomach tumors were found. In low-dose males, there was an increase in liver tumors. There was

no increase in lung tumors. Dose-response for cell proliferation paralleled dose response for forestomach tumors; cell-proliferation plateaued at 200 mg/kg (Dalbey et al., 1996). Lutz and coworkers (1992) found very low level of DNA adducts, and proposed that genotoxicity did not explain the forestomach tumors.

- c. **Increased mouse lung tumors not related to level of SO in lungs.** Inhalation of styrene at 40 ppm resulted in increased mouse lung tumors (estimated SO level in terminal bronchioles = 4.38 nmoles/mL); gavage of SO at 550 mg/kg/day did not cause increased lung tumors (estimated SO level in terminal bronchioles = 5.56 nmoles/mL). Increased mouse lung tumors not related to level of SO in lungs. (Sarangapani et al., 2002)
- d. **Lung level of SO does not explain rat/mouse difference (Cohen, 2002).** Hofmann et al., 2005 demonstrated 8 fold higher SO in rat lung *ex vivo* exposed to 1000 ppm (2.05 nmole/ml) than in mouse lung exposed to 40 ppm (0.25 nmole/ml). They concluded that mouse lung tumors were not related to the presence of SO.
- e. **There is no increase in DNA adducts in target tissues.** Levels of SO-DNA adducts are very low – <1 in 10⁷ nucleotides and are not higher in mouse than rat or in mouse lung than mouse liver.
- f. **Genotoxicity studies in mouse lung are negative.** There was no increase in chromosomal aberrations in the lungs of mice exposed to 125, 250 or 500 ppm styrene for 2 weeks (Kligerman et al, 1992). There was no increase in lung tumors after the 20 weeks observation period when styrene was administered ip for 6 weeks in a lung tumor initiation in A/J mice (Brunnemann et al., 1994).
- g. **CYP2E1 metabolism does not affect styrene lung toxicity.** CYP2E1 metabolizes styrene primarily to S-SO (Green et al., 2001). A role for CYP2E1 metabolism of styrene in liver toxicity was demonstrated using both a CYP2E1 inhibitor and CYP2E1-knockout mice. However, inhibition of CYP2E1 did not reduce the lung cytotoxicity from styrene exposure; furthermore, the lung cytotoxicity of styrene was not diminished in CYP2E1-knockout mice compared to wild-type.

Conclusions of others

Cohen et al., 2002: Difference in lung tumor response is not explained by differences of SO in rat and mouse lung. Cruzan et al., 2002 concluded that lung tumors were not related to total SO. Hofmann et al., (2005) concluded that mouse lung tumors were unrelated to the level of SO in the lung.

3.3. The Role of CYP2F2-mediated metabolites (alternative hypothesis to SO-mediated tumorigenesis)

The tissues that are high in CYP2F are the primary tissues that experience cytotoxicity from styrene and a series of similar chemicals. CYP2F2 is expressed primarily in mouse lung Clara cells and nasal olfactory epithelium. These are the primary tissues of cytotoxicity from styrene. In rats, CYP2F4 is expressed primarily in the nasal olfactory epithelium; this is the only tissue in rats that experiences cytotoxicity from styrene exposure. Inhibition of CYP2F2 inhibits both the nasal and lung cytotoxicity from styrene exposure. CYP2F2 catalyzes the ring oxidation of styrene to 4-hydroxystyrene (also called 4-vinylphenol). Inhibition of CYP2F2 inhibits the formation of 4-hydroxystyrene. Furthermore, 4-hydroxystyrene is further metabolized to 4-hydroxystyrene-7,8-oxide and to 3, 4-dihydroxystyrene. Inhibition of CYP2F2 inhibits this metabolism and inhibits the cytotoxicity from 4-hydroxystyrene. The necessity of oxidation of the aromatic ring is further supported by the lack of lung cytotoxicity or increased lung tumors in mice exposed to 4-methylstyrene.

Similar cytotoxicity in lung of mice and nasal olfactory epithelium in mice and rats has been reported for several other chemicals of similar structure including coumarin, naphthalene, ethylbenzene, cumene, and divinylbenzene. Lung tumors in mice, but not rats, has been reported for all of these. For several, metabolism by CYP2F2 to cytotoxic metabolites has been demonstrated and analogs that block the CYP2F2 metabolism are not cytotoxic and/or do not produce lung tumors in mice.

A manuscript on this mode of action has been submitted for publication and is attached with these comments.

Summary Conclusions

Collectively, the data discussed above support the following conclusions relative to meeting the NTP's criteria for "reasonably anticipated to be a human carcinogen:"

1. There is no evidence of a causal relationship between styrene exposure and cancer in humans. The Draft Substance Profile's characterization of the human data as "limited" is not consistent with the NTP classification criteria.
2. The animal studies provide at best only *limited* evidence of carcinogenicity – clear evidence by one route of administration and no more than suggestive evidence by another. The draft profile's classification of the animal data as "sufficient" does not conform to the NTP classification criteria.
3. The available data do not support genotoxicity through styrene-7,8-oxide as the mode of action for mouse lung tumors.