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January 6, 2000

Dr. Mary S. Wolfe, Executive Secretary
National Toxicology Program
Board of Scientific Counselors
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Re: Comments on Styrene-7,8-oxide

Dear Dr. Wolfe:

On behalf of the Styrene Information and Research Center (SIRC), we are submitting the enclosed comments on the ***Draft Report on Carcinogens Background Document for Styrene-7,8-oxide*** (Draft Report). SIRC requests that these comments be made available to the National Toxicology Program's Board of Scientific Counselors Report on Carcinogens Subcommittee (Subcommittee), in preparation for the Subcommittee's meeting on January 20 and 21, 2000.

For further information, or if you have any questions concerning these comments, please do not hesitate to call me at the telephone number above, or Betsy Natz, SIRC's Executive Director, at (703) 741-5010. Additional contact information for SIRC and Ms. Natz is provided at the conclusion of SIRC's comments.

Sincerely yours,

Peter L. de la Cruz

Peter L. de la Cruz

Enclosure

COMMENTS OF THE STYRENE INFORMATION AND RESEARCH CENTER

Concerning the
DRAFT REPORT ON CARCINOGENS BACKGROUND DOCUMENT FOR STYRENE-7,8-OXIDE

Before the
NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS REPORT ON CARCINOGENS SUBCOMMITTEE

January 6, 2000

The Styrene Information and Research Center (SIRC) respectfully submits these comments to the National Toxicology Program (NTP) Board of Scientific Counselors Report on Carcinogens Subcommittee (Subcommittee), in preparation for the Subcommittee's meeting on January 20 and 21, 2000. The sole focus of these comments is the ***Draft Report on Carcinogens Background Document for Styrene-7,8-oxide*** (Draft Report).

SIRC is a non-profit organization formed in 1987 to explore the health effects of styrene, and act as a liaison between the styrene industry and U.S. and international regulatory agencies in disseminating the results of state-of-the-art research. SIRC's membership includes styrene manufacturers and users representing more than 95% of the industry. SIRC member companies are either directly involved in the manufacturing or processing of styrene monomer or use derivatives of styrene for the fabrication of consumer products that include, but are not limited to, boats, tubs, shower stalls, storage tanks, pipes, pollution-control devices and automotive components.

As manufacturers of consumer-oriented products, SIRC's members have invested heavily in a thorough understanding of styrene's health effects. Styrene research accounted for approximately fifty percent of SIRC's 1999 budget, and the industry has spent well over $12 million on scientific research on styrene since SIRC's inception. SIRC has also conducted extensive reviews of the comprehensive database concerning styrene and styrene-7,8-oxide (SO). In light of the attention given to data on styrene in the Draft Report, SIRC hopes that these comments will prove to be a valuable resource for the Subcommittee in reviewing this document.

I. Overview

According to NTP, the sole focus of NTP's criteria for listing a chemical in the *Report on Carcinogens* is whether a substance is either known or reasonably anticipated to be a *Human* carcinogen (*see, e.g.,* page *i* of the Draft Report). As detailed below, while there is positive occurrence data on SO in animals, these data do not support the conclusion that SO is Reasonably Anticipated to be a Human Carcinogen in the United States due to exposure and mode of action considerations.

SO is not deliberately produced in any significant amount in the United States and emissions are anticipated to be minimal. The 1996 Toxics Release Inventory (TRI) reported 32 pounds of total SO emissions. For 1997, the TRI emissions figure for SO is 11 pounds. Because SO is not a chemical in commerce, potential human exposure to SO is extremely low. As a result, SO may not be an appropriate candidate for the *Report on Carcinogens*.

Moreover, based on its years of research and review, SIRC is extremely concerned that the Draft Report presents an incomplete and one-sided perspective on the possible carcinogenicity of SO. The document relies largely on secondary reviews, and SIRC believes that a significant amount of effort would be required for the Draft Report to adequately reflect the underlying data in this area. As currently written, the Draft Report cites data on styrene as support for the conclusion that SO is carcinogenic in humans; however, the Draft Report fails to cite data that do not support such a conclusion. This is a very serious deficiency in scientific method and leads to an inaccurate conclusion regarding SO. In addition, because of the role that the NTP list of carcinogens plays in public health, this failing constitutes a fatal flaw in the development of Federal policy.

II. Comments on specific sections of the Draft Report

Based on SIRC's own research and its reviews of the extensive database in this area, the following insights and suggestions regarding specific sections of the Draft Report are offered for the Subcommittee's consideration:

Summary Statement

Discussions in this section concerning tumors at multiple tissue sites and genotoxicity data require the revisions detailed below. In addition, this section should reflect human metabolism capabilities and mode of action based upon cell proliferation.

Section 2.1: Human Exposure (Use)

SIRC asks that the Subcommittee re-examine references used in the Draft Report to describe the known uses of SO. Specifically, SO is not *used* as a reactive diluent for epoxy resins. Nor is SO *used* in the production of reinforced plastics or boat making.

Section 2.2: Human Exposure (Production)

This section should reflect that SO is *not* deliberately produced in any significant amount. The 1996 TRI, which is *not* a measure of production for chemicals substances, lists only 5 companies that reported SO in waste streams. The total reported as emissions was 32 pounds. Another 36,198 pounds in waste streams was burned for energy recovery. For 1997, the TRI release number for SO

is 11 pounds. SO is not a chemical in commerce and potential human exposure to SO is extremely low.

Section 2.7: Human Exposure (Occupational exposure)

The primary exposure to SO is not from the metabolism of styrene. In 1996, Rappaport and coworkers reported that approximately 70% of blood SO in reinforced plastics workers was from inhalation of atmospheric SO and only 30% from the metabolism of styrene. Reported occupational exposures to SO are comparatively low (less than 55 ppb) in the workplace. Section 2.8 cites the Rappaport data; thus, there is internal contradiction between Section 2.8 and the second paragraph of Section 2.7.

A statement in Paragraph 1 indicates that exposures are found primarily in workers in the paints industry. This information is not reflected in the earlier production and use sections of the Draft Report, and, to the best of SIRC's knowledge, is not accurate.

Section 2.8: Human Exposure (Biological indices of exposure)

A correction is required to the statement in Paragraph 1 to reflect that SO was found in the blood, not urine, of 4 workers exposed to styrene as reviewed by IARC, 1985.

Section 3: Human Cancer Studies

The study by Wong *et al.*, 1994, should not be dismissed in the Draft Report as simply an "early study" that "found little evidence for an association of styrene exposure with lymphoreticular cancers." It is the study with the longest follow-up period (average 19.5 years) and was published after the study by Kogevinas *et al.*, 1994, which covers a period of 13 years in comparison. In addition, the results of Wong *et al.*, Okun *et al.*, 1985, and Coggon *et al.*, 1987, are not properly characterized in this section of the Draft Report. There was not "little evidence for an association." There was no evidence for an association of styrene with lymphohematopoietic (LH) cancers in any of the three studies mentioned.

In addition, the characterization of the results of the Kogevinas *et al.* study is not accurate. While the study reported an increased trend in LH cancer compared with average exposure and time since first exposure, there was no increase noted in relation to duration of exposure or cumulative exposure. This occurs because there are many short-term workers in this industry such that those with the highest average exposure have the lowest cumulative exposure and lowest duration of exposure. Kogevinas and coworkers pointed out that the increase was mostly among short-term workers and was found only in one of the 8 subcohorts. This was the Danish cohort (the same as that reported by Kolstad *et al.*, 1994).

Results from Kolstad *et al.* should be interpreted cautiously because there are no individual exposure assessments in this cohort. An average exposure for laminators was estimated for each calendar year based on workplace measurements and modeling. All employees in all the companies included were assigned the exposure of a laminator without consideration of their job in the company. Evidence that the companies were actually involved in reinforced plastics manufacture and the duration of exposure by individuals are not well established. More than 60% of these workers were employed by these companies for less than 1 year.

Matanoski *et al.*, 1997, presented a retrospective case-control analysis of the data generated in the late 1980's. There was no new follow-up on deaths, and exposures were only estimated in general ranges. It should be noted that Matanoski *et al.* studied 8 styrene-butadiene rubber (SBR) plants. The recent SBR studies of Delzell and coworkers, 1996, were updates on the studies reported by Matanoski and Meinhardt; their cohort included 7 of the 8 Matanoski plants and the two Meinhardt plants. Delzell and coworkers updated mortality records, reassessed exposures, and added at least 5 years at risk to the follow-up. Results from the earlier Meinhardt and Matanoski data should be interpreted only in light of the updated data. While the re-analysis by Matanoski reported associations between styrene exposure in SBR workers and lymphoma, lymphosarcoma, and myeloma, no such associations were found in the data 5 years later, and no such associations were found in reinforced plastics workers exposed to 10 to 100 fold higher styrene levels without the confounding, butadiene-related chemical exposure.

Moreover, the final, summary paragraph of this section of the Draft Report deserves correction to more accurately reflect the outcome of the studies published since the 1994 IARC review. Specifically, the only studies published since the 1994 IARC review of styrene which represent new data are the studies of SBR workers by Delzell and coworkers. They conclude that there is no evidence for styrene-related cancer in SBR workers.

Section 4.1: Studies of Cancer in Experimental Animals (Carcinogenicity studies of orally administered SO in mice)

Regarding the review of carcinogenicity studies in mice, the interpretation of the liver tumor data requires further attention by the Subcommittee. It is true that males only at the low dose had increased liver tumors. However, the interpretation of this study in the Draft Report goes far beyond the conclusion of Lijinsky *et al.*, 1986. Lijinsky and coworkers concluded:

> The fact that chronic treatment of the animals with styrene oxide does not lead to development of tumors elsewhere in the body, except perhaps in the liver of male mice, suggests that styrene oxide is not readily absorbed from the stomach or that it is inactivated.

While there was decreased survival of the high dose male and female mice, more than 50% survived longer than 78 weeks, which is considered adequate survival by current Environmental Protection

Agency (EPA), Food and Drug Administration (FDA), and NTP's own guidelines. Thus, the lack of increased liver tumors at the high dose cannot be dismissed by reduced survival. No difference between males and females was seen in either survival or tumor frequency in the liver at the high dose; thus a chemically-induced sex difference would not be expected at the low dose.

The Draft Report's discussion in this section should note that oral administration of SO caused cellular damage in the forestomach which was evident in the subchronic study and persisted throughout the chronic study. Secondly, if the human data on styrene are appropriate to understand SO carcinogenicity, then the mouse data are also appropriate, especially since most of styrene's metabolism occurs in the liver. There have been five chronic studies of styrene in mice. Four by gavage (NCI, 1979a, 1979b, Ponomarkov and Tomatis, 1978) and one by inhalation (Cruzan *et al.*, in press). Increased liver tumors were not found in any of these five studies of styrene.

Section 4.2: Studies of Cancer in Experimental Animals (Carcinogenicity studies of orally administered SO in rats)

While the Draft Report's review of the studies in rats is written accurately, it could be further strengthened by including reference to the 8 chronic studies of styrene in rats by inhalation, gavage and drinking water . The weight-of-evidence, dose response, historical background data, etc. clearly indicate no tumorigenic effects from styrene in rat studies. This section of the Draft Report should point out that oral administration of SO caused cellular damage in the forestomach of rats which was evident in the subchronic studies and persisted throughout the chronic studies.

Section 4.5: Studies of Cancer in Experimental Animals (Summary)

The statement "SO administration also was associated with an increased incidence of hepatocellular neoplasms in male mice" should be reconsidered as an overly-broad characterization of the reported study by Lijinsky *et al.* Further, the second paragraph should be withdrawn, as it provides a commentary on human exposure that is out of place in a summary discussion of the animal data that is the focus of this section of the Draft Report.

Section 5.4.1.2: Genotoxicity (Mammalian Systems)(*In vitro* assays)(hprt locus forward mutation test)

Paragraph 2 of this section contains a discussion of Bastlova and Podlutsky, 1996. As accurately reflected in the Draft Report, the authors reported increased mutations at the hprt locus in human T lymphocytes exposed to SO. In addition, however, this section should reference the decreased frameshift and deletion mutations observed, that the increase was in splicing mutations, and that these data contradict Ames data indicating frameshift mutations from SO.

Section 5.4.1.4: Genotoxicity (Mammalian Systems)(*In vitro* assays)(Sister chromatid exchanges)

Paragraph 3 reports on studies by Uuskala *et al.*, 1995, showing that GSTM1 genotype had no influence on the formation of SCE in human donors, but that lymphocytes from individuals having GSTT1 generated a greater incidence of SCE from *in vitro* exposure to SO than lymphocytes from GSTT1 negative donors (Ollikainen *et al.*, 1998). However, Ollikainen *et al.* actually reported that GSTT1 positive donors developed fewer SCE *in vitro* than GSTT1 negative donors, and further stated that GSH is therefore important in the detoxification of SO in humans.

Based on the metabolism data, SO is detoxified largely by epoxide hydrolase in humans. GSH conjugation accounts for less than 1% of SO detoxification. Thus, it is submitted for the Subcommittee's consideration that an *in vitro* difference between donors who are GSTT1 positive and those that are negative is not reflective of an impact in humans *in vivo*.

Section 5.4.1.5: Genotoxicity (Mammalian Systems)(*In vitro* assays)(DNA damage/ repair tests)

This section references several studies allegedly reporting increased DNA strand breaks from *in vitro* exposure to SO. The referenced assays, however, do not measure the presence of DNA strand breaks. Rather, they measure the presence of alkaline-labile sites and/or DNA strand breaks. These assays use alkaline conditions under which strand breaks are caused during the assay at sites such as N-7-guanine adducts, 8-oxo-guanine adducts, *etc.*

Section 5.4.2.4: Genotoxicity (Mammalian Systems)(*In vivo* assays)(DNA damage/ repair)

Regarding the discussion of DNA strand breaks *in vivo,* SIRC respectfully submits the same comment applies as is provided above for Section 5.4.1.5.

Section 5.5: Genotoxicity (Mammalian Systems)(Summary)

Regarding SO genotoxic properties, SIRC urges the Subcommittee to revisit the summary in this section, because it appears to represent the data as uniformly positive. This is not the case, as demonstrated in Table 5-1 of the Draft Report that accompanies NTP's discussion. SIRC respectfully requests that the summary be revised to accurately report the information presented in Table 5-1 of the Draft Report.

Further, Table 5-1 does not include all the data presented in the text. Specifically, negative results for S. typhimurium TA97, TA98, and TA1537, with metabolic activation (p. 23) were not listed in the Table. Negative genotoxicity with metabolic activation for L5178 cells (p. 24) and Chinese hamster V79 cell mutation (p. 24) were also not included.

Further, Section 5 of the Draft Report omits the study by Richter and Vamvakas, 1998, which demonstrated a lack of posttranslation modification of histones (a response to DNA single and double strand breaks) and p53 gene mutations in LLC-PK1 cells. The authors conclude that SO induces forestomach tumors by a non-genotoxic mode of action as a result of cytotoxicity.

Section 6.1.1: Other Relevant Data (Absorption, distribution, metabolism, and elimination)(Absorption and pharmacokinetics of SO)

Paragraph 1 incorrectly reports that studies on mandelic acid and phenylglyoxylic acid in the urine of workers were from exposure to SO when the studies were actually based on worker exposure to styrene. Moreover, in paragraph 3, the half-life (3.4 minutes) calculated by Bidoli *et al.*, 1980, is not the most recent or accurate reported value. More recent studies by Langvardt and Nolan, 1991, and Kessler *et al.*, 1992, independently calculated half-lives of 24 to 28 minutes, indicating that SO is considerably less reactive than suggested by Bidoli *et al.*

Section 6.1.2.1: Other Relevant Data (Absorption, distribution, metabolism, and elimination)(Metabolism and elimination)(Metabolism)

In regard to paragraph 3 of this section, the study by Herrero *et al.*, 1997, demonstrates that SO is different from many other epoxides. Most epoxides are removed from biological tissues by reaction with glutathione. This reaction is dependent on tissue GSH levels and is subject to GSH depletion. In contrast, the major route for removal of SO is epoxide hydrolase. For SO there is a very low Km; thus, SO is removed very efficiently.

After Figure 6.1, the Draft Report contains the statement that, "small quantities of mercapturic acid derivatives of SO have been detected in the urine from workers at a plastics factory," citing Maestri *et al.*, 1997. Clarification of the word "small" is desirable here; these derivatives account for less than 0.1% of styrene excretion products in humans (Sumner *et al.*, in press). A more accurate description would be "trace quantities."

Section 6.2: Other Relevant Data (Adduct formation)

Paragraph 5 of this section currently does not contain reference to the important paper by Cantoreggi and Lutz, 1992, who administered SO by gavage to rats. They detected no DNA adducts in liver and approximately 0.4 adducts per 10^7 nucleotides in forestomach. As stated by Dr. Lutz's group throughout its publications, genotoxic carcinogens produce adduct levels at least 100-fold higher than does styrene or SO. Thus, it is extremely unlikely that SO induces tumors by a primarily genotoxic mode.

Section 6.3: Other Relevant Data (SO-induced squamous cell proliferation in rodent forestomachs)

Paragraph 2 of this section contains the mode of action statement, "a mechanism in which genotoxicity is combined with promotion by increased cell proliferation," which is attributed to Lutz *et al.*, 1993. This attribution is not accurate. Dr. Lutz reported that the likely mechanism for SO tumorigenicity in the forestomach was "marginal genotoxicity with strong promotion by increased cell proliferation." Thus, the Draft Report omits two key descriptive terms in Dr. Lutz's statement: "marginal" genotoxicity and "strong" promotion.

In the discussion of Dalbey *et al.*, 1996, this section needs to indicate that a dose-response for cell proliferation was established in the study, which explains why Maltoni demonstrated a dose-related increase in forestomach tumors between 50 and 250 mg/kg/day, while the Lijinsky studies found no difference at higher doses because both doses used by Lijinsky were above the plateau for increased cell proliferation.

Section 6.4: Other Relevant Data (Summary)

In the mode of action summary, the statement in sentence 6 requires further clarification. Specifically, the proportion of R- and S- SO that is formed in any *in vitro* experiments is not discussed in the Draft Report. In addition, the relevance of this observation to the mode of action is not stated. Similarly, the statement in sentence 7 that the mode of action is "largely unknown" does not accurately reflect the conclusions of the reported studies in this area. Increased tumors are found only at the site of contact, after prolonged tissue damage and increased cellular repair and increased replication, with evidence of only traces of DNA adducts (100-fold less than for genotoxic carcinogens). The incidence of tumors paralleled the increase in cell proliferation. Without the cellular damage and cell proliferation, increased tumors are not likely. Based on the known potencies of DNA adduct formation from genotoxic carcinogens, the minuscule level of DNA adducts from SO exposure, and the cytotoxicity and cell proliferation that parallels tumor incidence, a genotoxic mode of action is unlikely.

III. Conclusion

SIRC respectfully submits that SO has a low reactivity with macromolecules; *e.g.*, levels of adducts in forestomach DNA are about 1 per 10^7 nucleotides. Styrene oxide is rapidly detoxified by epoxide hydrolase, in contrast to many other epoxides. In *in vitro* systems where there is no epoxide hydrolase present, SO-induced genotoxicity is obvious. Overall, there are more negative than positive *in vivo* genotoxicity tests reported.

Gavage administration of SO resulted in tissue damage and repair, resulting in increased cell proliferation and forestomach tumors. The dose response for increased tumors matched that for increased cell proliferation. Increased liver tumors in low dose male mice are not likely related to

SO administration. No sex difference in liver tumor incidence was seen at the high dose, liver tumors were not increased in the high dose mice which lived long enough to develop liver tumors if SO really induced liver tumors, and increased liver tumors have not been seen in any of five chronic studies of styrene. Thus, in the absence of tissue damage, increased tumor formation from SO is unlikely.

Human exposures to SO are extremely low. Reinforced plastics workers will be exposed only to trace quantities of SO; the general population to even less. Human epoxide hydrolase has an even lower Km for SO than in rats and mice; therefore, this trace amount is quickly detoxified.

In conclusion, SO is not Reasonably Anticipated to be a Human Carcinogen at the extremely low potential human exposure levels found in the United States. SIRC urges the Subcommittee to make substantive revisions to the Draft Report to ensure that all relevant studies are cited and considered and that the narrative portions of the Draft Report accurately reflect the existing data and underlying studies.

Respectfully submitted,

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