DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR STYRENE

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Peer reviewers for the second draft of the Toxicological Profile for Styrene were:

George Cruzan, Ph.D., DABT
Toxicologist
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Bridgeton, NJ

Teresa Leavens, Ph.D.
Research Investigator, Biological Sciences Division
The Hamner Institutes for Health Sciences
Research Triangle Park, NC

Jean Rabovsky, Ph.D.
Retired Toxicologist
El Cerrito, CA

ATSDR would like to thank these scientists for their review of the document. When the reviewer's suggestions were followed, or when other revisions obviated the need to respond, no further response is provided herein. Revisions that may have obviated the need to respond included sections that were rewritten, moved, or deleted. Some of the editorial and format suggestions could not be followed without changing ATSDR established format. Additionally, several stylistic changes that were purely arbitrary were not incorporated. Other suggestions made by the reviewers that ATSDR decided not to follow are discussed below. In the discussion that follows, "PR" refers to the appropriate page of the assembled peer review document, "P" indicates a page number in the second draft of the profile, and "L" indicates the line number on that page.

Review comments provided by Dr. George Cruzan:

PR5, chronic inhalation MRL: Dr. Cruzan noted several limitations to the Benignus study including: (1) two of the four studies on reaction time were not generally considered to be reaction-time studies, (2) selectivity of color discrimination studies, and (3) time-response effects were only found because Benignus assumed that there was and estimated effects for different of exposure. The reviewer provided an analysis of the Benignus study conducted by four independent consultants for the Styrene Information and Research Center.

Response: The opinions of the four independent consultants were presented in an unpublished document; it is ATSDR's policy not to include unpublished documents and/or non-peer-reviewed reports in the toxicological profile. ATSDR agrees with the reviewer that there are some imitations to the Benignus analysis; however, the LOAEL identified in this paper is supported by similar LOAEL values for a number of individual studies examining reaction time, color discrimination, and other neurological effects.

PR5, Section 3.6: Dr. Cruzan noted that in all of the studies cited on increases in prolactin levels in humans, the prolactin levels were within the normal range.

Response: Although the prolactin levels were within the normal range, significant associations with styrene exposure were found; additionally, there is a note that the clinical significance of the alterations in the absence of reproductive effects is not known. ATSDR's discussion of this effect is consistent with NTP's Expert Panel report on the reproductive and developmental toxicity of styrene.

PR6, P22: Dr. Cruzan suggested adding the Dalton paper regarding the lack of change in the odor detection ability.

Response: The ability to detect standard odors and odor detection threshold was considered a neurological end point and Dalton et al. (2002) was discussed in the neurological effects section.

PR6, P29: Dr. Cruzan suggested adding a paper by Ska et al. (2003) examining neurotoxicity in volunteers exposed to 20 or 50 ppm styrene for 8 hours.

Response: This paper was ordered, but was not received in time for incorporation into the profile; it will be added to the first draft of the post-public comment toxicological profile.

PR385, P100, L4-6: Dr. Cruzan stated that the worker exposure data from the NIOSH study is 24 years old and a current assessment is in order.

ATSDR Response: The data were derived from the National Occupational Exposure Survey, which has not been updated since 1983.

All other comments provided by Dr. Cruzan were addressed as suggested.

Review comments provided by Dr. Teresa Leavens:

PR18, P5: Dr. Leavens noted that there is little support for the statement that children would likely have the same effects as adults and suggested deleting the statement.

Response: In the absence of data on the contrary, it is assumed that children and adults would have similar targets of toxicity, although there may be differences in sensitivities. The statement that children would have similar effects as adults was retained because there is no evidence for styrene or similar compounds that this would not be true.

PR18, P5: Dr. Leavens suggested deleting the sections of Chapter 1 dealing with children's health (How can styrene effect children? and How can families reduce the risk of exposure to styrene?) because the answer to the question of how can styrene effect children is that they would have the same effects as adults and thus, it is inconsistent to state that doctor's should inquire about children's exposure, limiting smoking to limit children's exposures, and having separate drinking water standards for children.

Response: Although children are likely to have similar effects as adults, there are no data on whether there are differences in sensitivity to a given styrene concentration.

PR19, P14, L10-11: Dr. Leavens noted that more information needs to be given as how 87 ppm was selected as the LOAEL when vestibular effects were noted in workers exposed to 18–36 ppm on lines 19–20.

Response: 87 ppm was the lowest LOAEL for vestibular effects following acute inhalation exposure; the range of 18–36 ppm refers to the LOAELs for vestibular effects following chronic exposure. The chronic exposure data were included in the discussion of the acute inhalation MRL to support the identification of the nervous system as the critical target.

PR19, Section 3.2: Dr. Leavens suggested that the reader should be directed to the User's Guide for the LSE tables and figures before being directed to the tables and figures.

Response: The introductory paragraphs in Section 3.2 discusses levels of significant exposure, identification of NOAELs, less serious LOAELs, and serious LOAELs, and the presentation of levels of significant exposure in tables and figures. The reader is also directed to the User's Guide as an aid for interpreting the LSE tables and figures. As this section comes before LSE tables and figures for inhalation, oral, and dermal are called out, no changes were made to the profile.

PR19, Section 3.2.1.5: Dr. Leavens questioned why the neurological effects such as impaired color vision, slowed reaction time, and impaired vestibular function were not considered serious effects as they could affect job performance and safety.

Response: As defined by ATSDR, serious effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death) and less serious effects are those that are not expected to cause significant dysfunction or death. ATSDR believes that the effects observed in the workers, many of which were subclinical and slightly altered from normal values, should be considered less serious.

PR458, P102-103, L32-35: Dr. Leavens noted that the production data are not needed in this section.

Response: Since this section focuses on future data needs related to the production, import/export, use, release and disposal of styrene, no changes were made to the text.

All other comments provided by Dr. Leavens were addressed as suggested.

Review comments provided by Dr. Jean Rabovsky:

PR28, acute-duration inhalation MRL: Dr. Rabovsky requested a more detailed discussion of the upper respiratory tract effects in mice and humans, which includes dose-response data and a comparison between respiratory and neurological effects.

Response: Some revisions were made to the text; however, mice do not appear to be a good model for human respiratory tract toxicity due to toxicokinetic differences between the species (in particular, the much greater local production of styrene oxide in the mouse nose compared to humans).

PR28, chronic-duration inhalation MRL: Dr. Rabovsky suggested expanding the discussion to include the serious nature of the observed neurological effects in humans.

Response: ATSDR does not consider the observed neurological effects occurring at exposure levels which define the NOAEL/LOAEL boundary to be serious LOAELs (effects that evoke failure in a biological system and can lead to morbidity or mortality); in many cases, the performance test scores were only slightly higher than those of the referent group.

PR29, chronic-duration inhalation MRL: Dr. Rabovsky suggested including a comparison of the MRL with values from other agencies (Federal and state) and a justification of the approach taken by ATSDR.

Response: The guidelines and regulations developed by other agencies are presented in Table 8-1 and the rationale for the selection of the critical effect and principal study is presented in Section 2.3.

PR30, Table 3-1: Dr. Rabovsky noted that all neurological effects are listed as “less serious”, but no objective criteria are given to justify the decision. She suggested that the adverse effects of chronic styrene exposure be considered serious effects unless substantiated by objective criteria.

Response: As defined in the introductory paragraphs in Section 3.2, serious effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). In general, the observed effects did not result in significant dysfunction and in some cases, were within the normal range. Thus, ATSDR categorized them as less serious LOAELs.

PR34, P43-44: Dr. Rabovsky suggested adding a more detail discussion of the varying responses of different toxicity end points to different styrene 7,8-oxide enantiomers.

Response: Considerable research has been conducted on the mode of action for styrene oxide and the role of enantiomer specificity on the increased sensitivity of mice to the induction of lung cancer. Enantiomer

specificity has not been as well investigated for other end points; thus, no additional information was added to the profile.

PR35, regarding genotoxicity: Dr. Rabovsky requested that an explanation of the principles underlying the genotoxicity tests that are discussed in the profile and a discussion of the advantages and disadvantages associated with the *in vitro* and *in vivo* tests be included in the profile.

Response: Typically, genotoxicity data are used to evaluate the potential carcinogenicity of an agent and to elucidate possible carcinogenic mechanisms of action. It is beyond the scope of this summary document on styrene to include a discussion of the principles and underlying advantages/disadvantages of individual genotoxicity tests.

PR35, P51, L27-36, P52, L1-16: Dr. Rabovsky commented that studies performed on cells isolated from the blood of styrene workers and those isolated from unexposed humans should be differentiated.

Response: As discussed in the text, *in vivo* studies were conducted in styrene workers. All of the *in vitro* studies were conducted in cells from unexposed humans; *in vitro* tests cannot be done using cells from exposed individuals.

PR35, P52, L25-30: Dr. Rabovsky noted that the metabolic system under discussion should be specified since styrene can be metabolized via CYP-dependent monoxygenase and non-CYP dependent enzymes.

Response: The metabolic activation used in the *in vitro* studies was not specific to styrene and in most cases was S-9 soluble fraction from rat livers.

PR36, regarding reference list: Dr. Rabovsky noted that Rabovsky et al. (2001) and Moscato et al. (1987) were provided in the reference list, but were not cited in the profile.

Response: These papers were not cited in the profile and will eventually be removed from the reference list for the Final version of the profile.

All other comments provided by Dr. Rabovsky were addressed as suggested.