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February 13, 2011

Agency for Toxic Substances and Disease Registry
CDC/ATSDR
Attn: MASO, MS-E11
1600 Clifton Road, N.E.
Atlanta, GA 30333
InfoQuality@cdc.gov

Re: Request for Correction of Information under the Information Quality Act of Statements Regarding Styrene in the ATSDR *Toxicological Profile for Styrene* (November 2010)

Dear Sir/Madam:

This Request for Correction (RFC) of information is submitted by the Styrene Information and Research Center, Inc. (SIRC) under the Information Quality Act (IQA)[1] and implementing guidelines issued by the Office of Management and Budget (OMB),[2] the U.S. Department of Health and Human Services (HHS),[3] and the Agency for Toxic Substances and Disease Registry (ATSDR).[4] SIRC is an association of leading styrene producers and users who are dedicated to

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

[2] Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies, 67 Fed. Reg. 8,452 (Feb. 22, 2002).

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

[4] HHS, Guidelines for Ensuring the Quality of Information Disseminated to the Public. Part II, Subpart D, "Centers for Disease Control and Prevention and Agency for Toxic Substances and Disease Registry," Section V.A, available at http://aspe.hhs.gov/infoquality/Guidelines/cdcinfo2.shtml.

promoting the responsible use and benefits of styrene and ensuring its accurate scientific evaluation. [5]

SIRC appreciates the care and effort that ATSDR expended in drafting the November 2010, Toxicological Profile for Styrene (Styrene Profile). In particular, we support ATSDR's approach of examining studies for deficiencies and expressing the limitations of the reviewed studies. We are nonetheless compelled to request that ATSDR revise the Styrene Profile to reference several highly relevant publications that were not cited in the Styrene Profile, although they were in print prior to ATSDR finalizing the Styrene Profile.

Collectively, these scientific publications support the conclusion that styrene is not expected to be carcinogenic to humans at any anticipated exposure levels. This obviously conflicts with ATSDR's characterization of styrene as a "weak carcinogen." Thus, some information in the Styrene Profile is not supported by the scientific literature and does not meet ATSDR's information quality assurance of "objectivity" because it is not "presented in an accurate, clear, complete and unbiased manner."[6]

I. IQA BACKGROUND AND APPLICABILITY TO THE STYRENE PROFILE

A. Overview

Congress enacted the IQA to "ensur[e] and maximiz[e] the quality, objectivity, utility and integrity of information . . . disseminated by Federal agencies" like the ATSDR. To do so, it required the OMB to issue government-wide implementing guidance.[7] It also instructed each agency to issue its own guidelines, which have two functions:

> (i) to apply the OMB Guidelines to the agency's particular circumstances, and
>
> (ii) to "establish administrative mechanisms allowing affected persons to seek *and obtain* correction of information . . . disseminated by the agency that does not comply with the [OMB] guidelines . . . ."[8]

OMB issued its final guidelines in February 2002. HHS issued department-wide guidelines,[9] and ATSDR issued its own agency-specific guidelines.[10]

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[5] SIRC was formed in 1987 as the principal focal point for public information and research on styrene. SIRC is a non-profit organization consisting of voting member companies involved in the manufacturing or processing of styrene, and associate member companies that fabricate styrene-based products. Collectively, SIRC's membership represents approximately 95% of the North American styrene industry. SIRC is headquartered in Arlington, Virginia. For more information, visit: http://styrene.org/.

[6] See note 4, *supra*.

[7] See note 2, *supra*.

[8] Pub. L. No. 106-554, note 1, *supra*, § 515(b)(2)(B) (emphasis added).

[9] *See* note 3, *supra*.

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OMB's Guidelines require that all disseminations meet "a basic standard of quality . . . appropriate to the nature and timeliness of the information . . . ."[11] They define "quality" in terms of objectivity, utility and integrity.[12] "Objectivity" is centrally relevant in cases of scientific health assessments. As discussed below, objectivity has significant consequences both for the substance of such information and the way it is presented. "Utility" also is important in this case, as it refers to the usefulness of the information to its intended users, including the public.[13]

B. Objectivity — Substance

From a substantive perspective, "objectivity" means that information must be *accurate, reliable* and *unbiased*.[14] Scientific information must be generated using sound statistical and research methods.[15] Additionally, "influential" scientific information must be sufficiently transparent to be reproduced, subject to several caveats.[16] This means, with respect to analytical results, that agencies must provide "sufficient transparency about data and methods that an independent reanalysis could be undertaken by a qualified member of the public."[17]

Influential information regarding risks to health, safety or the environment must be based on "the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices; and . . . data collected by accepted methods or best available methods . . . ."[18]

C. Objectivity — Presentation

From the perspective of presentation, "objectivity" means that information must be presented in an accurate, clear, complete and unbiased manner, which includes presentation in the proper context.[19] The sources of the information must be disclosed, subject to confidentiality and privacy limits, and where appropriate, data should have full, accurate and transparent documentation, with sources of error identified.[20] Scientific, financial and statistical

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[10] *See* note 4, *supra*.

[11] 67 Fed. Reg. at 8,458.

[12] *Id*. at 8,459; *cf*. 44 U.S.C. § 3504(e)(1)(B).

[13] *Id.*

[14] 67 Fed. Reg. at 8,549 (emphasis added).

[15] *Id*.

[16] *Id*. at 8,460.

[17] *Id.* at 8,460.

[18] *Id*.; *see also* 42 U.S.C. § 300g-1(b)(3)(A).

[19] *Id*. at 8,459.

[20] *Id*.

information must be accompanied by supporting data and models.[21] Influential information regarding risks to health, safety or the environment must be comprehensive, informative and understandable, and must specify, among other things, (i) each significant uncertainty and studies that would assist in resolving the same, and (ii) peer-reviewed studies that support, are directly relevant to or fail to support estimates and methodologies used to reconcile inconsistencies in data.[22]

D. The Styrene Profile Must Have Utility

The OMB IQA guidelines define "utility" in terms of:

> [T]he usefulness of the information to its intended users, including the public. In assessing the usefulness of information that the agency disseminates to the public, the agency needs to consider the uses of the information not only from the perspective of the agency but also from the perspective of the public.[23]

This often-underestimated requirement is important because it goes to the heart of why an agency is disseminating information in the first place. To the extent that a Styrene Profile misstates or overstates the carcinogenicity of a substance, for example, the report and documents based on it are not useful to other federal or state agencies whose regulatory or policy resources will now be misdirected. It also is not useful to the public, who will be misled as to the potential impact or prevalence of carcinogens in their environment, which may lead to unnecessary actions to protect themselves from substances that are not, in fact, hazardous as characterized.

II. DISCUSSION OF IQA DEFICIENCIES AND REQUIRED CORRECTIONS

A. Boffetta, et al. (2009)

In November 2009, a blue ribbon panel of internationally renowned epidemiologists, including Dr. Hans Olov Adami and Dr. Dimitrios Trichopoulos, both of the Harvard School of Public Health, and Dr. Paolo Boffetta, formerly the lead epidemiologist with the International Agency for Research on Cancer, concluded that "[t]he available epidemiologic evidence does not support a causal relationship between styrene exposure and any type of human cancer."[24] Boffetta, Paolo MD, MPH; Adami, Hans Olov MD, PhD; Cole, Philip MD, DrPH; Trichopoulos, Dimitrios MD, PhD; Mandel, Jack S. PhD, MPH, *Epidemiologic Studies of Styrene and Cancer: A*

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[21] *Id.* at 8,460.

[22] *Id.*; *see also* 42 U.S.C. § 300g-1(b)(3)(B).

[23] *Id.*

[24] The report was published in the November 2009 issue of the peer reviewed Journal of Occupational and Environmental Medicine, available at http://journals.lww.com/joem/Abstract/2009/11000/Epidemiologic_Studies_of_Styrene_and_Cancer__A.5.aspx.

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Review of the Literature, Journal of Occupational & Environmental Medicine: November 2009 - Volume 51 - Issue 11, pp 1275-1287.

In light of the timeliness and relevance of this review, as well as the prestige of the review panel, Boffetta, et al. (2009) should be referenced and discussed in the ATSDR Toxicological Profile for Styrene.

B. Cruzan et al. (2009)

In this article, the authors propose that metabolism of several structurally-related chemicals by CYP2F isoforms of the cytochromes P450 family results in a cytotoxicity-driven mode of action in organs high in CYP2F; namely, CYP2F2 in nasal and lung tissue in mice and CYP2F4 in nasal tissues in rats. Importantly, the CYP2F1 isozyme expressed in humans appears to have a low capacity to metabolize these compounds. In mice, the resultant cytotoxicity and subsequent regenerative hyperplasia is hypothesized to drive an increase in lung tumors that are mostly benign and are not life shortening. Although a complete picture of the mode of action has not been developed in any one model compound, data from the individual compounds can be combined to synthesize and reinforce confidence in the CYP2F toxicity hypothesis.

For coumarin, naphthalene, and styrene, inhibition of toxicity with inhibition of CYP2F2 has been demonstrated. Rat CYP2F4 appears to be equally active in metabolizing these chemicals; however, CYP2F4 occurs to a much lower extent in rat Clara cells, and levels of metabolites produced are not sufficient to cause lung cytotoxicity. Human lungs contain far fewer of Clara cells than rats or mice, and human lung microsomes fail to, or only marginally, metabolize these compounds.

In addition, the human lung differs markedly from the mouse lung in the morphology of its Clara cells, which make humans much less sensitive than mice to toxicity due to reactive metabolites. The absence of a role for CYP2E1-generated metabolites (primarily alkyl oxidation vs. ring-oxidation) in mouse pulmonary effects was demonstrated by the lack of protection from styrene toxicity by CYP2E1 inhibitor, or reduction of toxicity in CYP2E1-knockout mice, and lack of lung toxicity of the primary metabolite of ethylbenzene. The chemicals used as examples of this mode of action generally are negative in standard genotoxicity assays. Apart from increased sister chromatid exchange (SCE), no consistent pattern in genotoxicity results was found among these chemicals. Thus, while lung tumors from bronchiolar cell cytotoxicity are theoretically possible in humans, it is unlikely that metabolism by CYP2F1 would produce levels of cytotoxic metabolites in human lungs sufficient to result in lung cytotoxic responses and thus tumors. Therefore, it is unlikely several chemicals that cause mouse lung tumors via CYP2F2 metabolism will cause lung tumors in humans.

George Cruzan, James Bus, Marcy Banton, Ralph Gingell, Gary Carlson, *Mouse specific lung tumors from CYP2F2-mediated cytotoxic metabolism: An endpoint/toxic response where data*

from multiple chemicals converge to support a mode of action, Regulatory Toxicology and Pharmacology, Volume 55, Issue 2, November 2009, Pages 205-218.[25]

Cruzan, et al. (2009) should be referenced and discussed in the ATSDR Toxicological Profile for Styrene.

C. Carlson

The Styrene Profile cites Carlson (2000)[26], but fails to cite and discuss several subsequent works by the same author that further elucidated the metabolism of styrene. These include:

> Carlson GP. 1997. Effects of inducers and inhibitors on the microsomal metabolism of styrene to styrene oxide in mice. J Toxicol Environ Health 51(5): 477-488.
>
> Carlson GP, Hynes DE, Mantick NA. 1998. Effects of inhibitors of CYP1A and CYP2B on styrene metabolism in mouse liver and lung microsomes. Toxicol Lett 98(3): 131-7.
>
> Carlson GP, Perez Rivera AA, Mantick NA. 2001. Metabolism of the styrene metabolite 4-vinylphenol by rat and mouse liver and lung. J Toxicol Environ Health A 63(7): 541-551.
>
> Carlson GP. 2002. Effect of the inhibition of the metabolism of 4-vinylphenol on its hepatotoxicity and pneumotoxicity in rats and mice. Toxicology 179(1-2): 129-136.
>
> Carlson GP. 2004a. Comparison of the susceptibility of wild-type and CYP2E1 knockout mice to the hepatotoxic and pneumotoxic effects of styrene and styrene oxide. Toxicol Lett 150(3): 335-339.
>
> Carlson G. 2004b. Influence of selected inhibitors on the metabolism of the styrene metabolite 4-vinylphenol in wild-type and CYP2E1 knockout mice. J Toxicol Environ Health A 67(12): 905-9.
>
> Carlson, G.P., Turner, M., Mantick, N.A., (2006) Effects of Styrene and Styrene Oxide on Glutathione-related Antioxidant Enzymes, Toxicology. 2006 Oct 29;227(3):217-26. Epub 2006 Aug 12.

As a series, these studies further support the conclusion that styrene is not a human carcinogen. In Carlson (2004b) the author observes that:

> 4-Vinylphenol (4-VP), a minor metabolite of styrene, is a more potent hepato- and pneumotoxicant than either styrene or styrene oxide. In CD-1 mice 4-VP is metabolized

[25] This study is available at, http://www.sciencedirect.com/science/article/B6WPT-4WPJ64J-2/2/d314a60890d360acef2cd8fe95b12cd8.

[26] Carlson GP, Mantick NA, Powley MW. 2000. Metabolism of styrene by human liver and lung. J Toxicol Environ Health A 59(8): 591-5.

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> primarily by cytochrome P-450 (CYP) 2E1 and CYP2F2. However, there is no difference in the rate of metabolism of 4-VP between wild-type and CYP2E1 knockout mice, indicating that other cytochromes P-450 play an important role. To understand the role of various cytochromes P-450, the in vitro metabolism of 4-VP was measured in the presence of selected inhibitors. Chemical inhibitors used to ascertain the contributions made by various cytochromes P450 were imipramine for CYP2C, alpha-methylbenzylaminobenzotriazole (MBA) for CYP2B, alpha-naphthoflavone (ANF) for CYP1A, 5-phenyl-1-pentyne (5P1P) for CYP2F2, and diethyldithiocarbamate (DTTC) for CYP2E1. Imipramine, MBA, and ANF produced significant inhibition in both the wild-type and CYP2E1 knockout mouse liver with minimal effects in lung. 5P1P significantly inhibited enzymic activity in both tissues, but to a greater extent in lung. The greatest inhibition was observed with DDTC even in the knockout mice, suggesting that it must also inhibit cytochromes P-450 in addition to CYP2E1. The results show little difference between the wild-type and knockout mice with respect to the contributions made by the cytochromes P-450 in the metabolism of 4-VP.

In Carlson, et al. (2006), the authors state:

> Styrene is both hepatotoxic and pneumotoxic in mice. Its mode of action is not clear, but it may be related to oxidative stress including a very large decrease in reduced glutathione (GSH). The current studies evaluated if: (1) the more toxic R-styrene oxide had a greater effect on reduced GSH levels than the less toxic S-styrene oxide, (2) the ratio of reduced to oxidized forms of glutathione was altered by styrene or styrene oxide, (3) other enzymes involved in the oxidant status of the cell, namely glutathione reductase, glutathione peroxidase and γ-glutamylcysteine synthetase were altered, and (4) lipid peroxidation, as measured by the determination of malondialdehyde, increased. R-Styrene oxide (300 mg/kg, ip) caused greater decreases in mouse liver and lung GSH than did S-styrene oxide (300 mg/kg, ip). Styrene (600 mg/kg, ip) caused decreases in both GSH and GSSG in both liver and lung. Styrene and styrene oxide did not cause significant increases in lipid peroxidation in either liver or lung. Styrene and styrene oxide had minimal effects on glutathione reductase and glutathione peroxidase in liver and lung. Styrene increased γ-glutamylcysteine synthetase activity. The results suggest that while styrene and its metabolite styrene oxide cause significant decreases in GSH levels, they have little effect on the enzymes glutathione reductase and glutathione peroxidase and that in response to decreased glutathione levels there is an increase in its synthesis via induction of γ-glutamylcysteine synthetase activity.

Professor Carlson's full body of work concerning the metabolism of styrene should be referenced and discussed in the ATSDR Toxicological Profile for Styrene.

D. EU Risk Assessment

In June 2008, the United Kingdom published the draft European Union (EU) Risk Assessment Report on Styrene. The Report had been peer-reviewed during its preparation in accordance with the EU's process.[27] The Dossier rejected any connection between styrene exposure and lung cancer and concluded that "pointing to a possible carcinogenic potential of styrene in other organs is highly speculative."[28] In rejecting any connection between styrene and lung cancer, the Report states:

> There is no evidence from extensive epidemiological investigations that long term exposure to styrene has produced lung damage or lung cancer in humans.
>
> Hence, overall, the weight of evidence appears to indicate that the consequences of long term exposure to styrene in mouse lung cannot be replicated in the human situation at relevant levels of exposure.

Because the Styrene Profile cites a very dated American Conference of Industrial Hygienists (ACGIH) statement, IQA considerations of balance warrant both a reference to and discussion of the conclusion by an EU authoritative body, based on a significantly broader and more current database than was available to the ACGIH.

III. IMPACT OF THE DOCUMENT ON SIRC AND ITS MEMBERS

A. ATSDR is a Recognized and Influential Authority on Health Effects

Consistent with its mission, ATSDR is a recognized authority on information that people and communities use to protect their health through health promotion, health education, prevention of disease, and preparedness. Toxicology descriptions by ATSDR are highly influential and assumed to be based on the best scientific evidence available. The

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[27] The Annex XV Transitional Dossier was submitted by the UK Competent Authority to the European Chemicals Agency (ECHA) on 28 November 2008. As the document explains, it was prepared according to the provisions of article 136(3) "transitional measures regarding existing substances" of REACH (Regulation (EC) 1907/2006). The hazards and risks associated with styrene have been evaluated and agreed under the Existing Substances Regulations (ESR) (793/93/EEC). The human health risk assessment report (RAR) was agreed by the Technical Committee for New and Existing Substances (TCNES) in 2008 and underwent independent peer review by the Scientific Committee on Health and Environmental Risks (SCHER) at its meeting of 6 May 2008. The document is available at: http://echa.europa.eu/chem_data/transit_measures/annex_xv_trans_reports_en.asp

[28] European Union Risk Assessment Report, Styrene, p. 273. In rejecting any connection between styrene and lung cancer, the Report states:

> There is no evidence from extensive epidemiological investigations that long term exposure to styrene has produced lung damage or lung cancer in humans.
>
> Hence, overall, the weight of evidence appears to indicate that the consequences of long term exposure to styrene in mouse lung cannot be replicated in the human situation at relevant levels of exposure.

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dissemination of incorrect or misleading information on styrene is currently having an adverse impact on SIRC and its member companies. Health effects information from ATSDR is used as a basis for action by federal, state, and local governments as well private interests ranging from builders to home owners. If information from ATSDR does not meet IQA requirements, direct and substantial economic and reputational damage to the industry that SIRC represents will result. It is thus important that the Styrene Profile and other pronouncements by ATSDR be accurate, reliable, unbiased, clear, complete and transparent in substance and presentation. The report in its present form does not meet these criteria.

B. Adverse Effects of the Styrene Profile

As noted above, SIRC is a nonprofit trade association that represents the leading producers and users of styrene in the United States who are dedicated to promoting the responsible use of styrene. SIRC is committed to advancing the state of scientific understanding on potential toxicological, epidemiological, and environmental effects related to styrene, as well as providing accurate technical and scientific information relating to potential exposures, uses and effects of styrene or styrene-based products.

ATSDR Toxicological Profiles are widely recognized as highly influential and significant. The dissemination of incorrect or misleading information on styrene in connection with the Styrene Profile can have an adverse impact on SIRC and its member companies. Moreover, deselection of products derived from styrene would harm not only those SIRC members who produce and use styrene-based packaging, but also the environment and consumers if substitute products have inferior performance, environmental, or public health attributes. It is thus of the utmost importance that ATSDR revise the Styrene Profile and other related pronouncements to ensure accuracy, reliability, non-bias, clarity, completion, and transparency in both substance and presentation.

IV. CONCLUSION

For the above-stated reasons, the Information Quality Act requires that ATSDR correct the Toxicological Profile for Styrene of November 2010, by referencing and discussing the scientific literature listed in this request for correction. In SIRC's view, the evaluation of this additional information does not support ATSDR's characterization of styrene as a human carcinogen, and that determination should also be revised. Any subsequent ATSDR documents based on the flawed Styrene Profile should be withdrawn and, if reissued, be revised consistent with the corrected Styrene Profile.

Thank you for considering SIRC's RFC. We trust the information provided is helpful. We are available to discuss the issues raised or to provide further supporting information upon request.

Very truly yours,

/S/

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cc: Peter de la Cruz, Keller & Heckman