



Styrene Information and Research Center (SIRC)

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Director

National Institute of Environmental Health Sciences / National Toxicology Program

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RE: Finalization of NTP Report on Carcinogens Review of Styrene

Dear Linda:

We are writing to you today as representatives of the Science and Technology Task Group of the Styrene Information and Research Center¹ (SIRC), to express our professional concerns as fellow scientists with the ongoing assessment, and proposed classification, of styrene for the 12th *Report on Carcinogens (RoC)*.

Both of us provided oral comment at the February 24 NTP Board of Scientific Counselors (BSC) meeting, and observed the proceedings. Although only a few of the BSC members offered comments on the Draft Substance Profile of Styrene, we found some of the statements supported SIRC's past comments on the NTP's assessment of the styrene data, and are thus disappointed that the written comments of the BSC members are not available to the public.

Our overall observation of the meeting was that the BSC *did not* offer a ringing scientific endorsement of the styrene Draft Substance Profile, but did not feel they had a meaningful way to disagree with the document.

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>.

A major disappointment to us was the general sense that the BSC reviewers did not truly appear to believe that styrene met the criteria for “reasonably anticipated to be a human carcinogen,” but were concerned that recommending against listing would mean either that no further research would be conducted on styrene, or that it would be seen as giving styrene a clean bill of health. It was not the intent of Congress that classification in the RoC serve as a means to prompt additional research on a substance; intimating that a substance should be classified as a means to promoting research is not a valid reason to list a substance in the RoC. Nor do we believe that it was Congress’ intent that NTP attempt to justify the listing of substances when the available data do not validly meet the threshold for “reasonably anticipated.”

Importantly, during the course of the BSC meeting, we heard BSC members who were specifically asked to comment on the styrene data offering opinions that *the styrene data do not justify a classification of “reasonably anticipated:”*

- Two reviewers commented on the animal data. Dr. Pino said the animal data were *less than sufficient*; that there was only *suggestive* evidence by oral exposure, not sufficient because the new historical control was problematic and the O20 study was questionable. Dr. Hines said that mouse lung tumors *should not be used as a basis for listing* in the RoC. Thus, the experts in animal carcinogenicity *did not support the Draft Substance Profile conclusions* regarding animal studies.
- Drs. Eastmond and Friedman-Jimenez commented on the human data that there were *no strong data indicating a carcinogenic effect of styrene in humans* and that a decision that the human data provided limited evidence was a judgment call, *which hinged primarily on NTP’s interpretation of the word “credible.”* It was pointed out by Dr. Friedman-Jimenez that the dictionary indicates that credible means “reliable, trustworthy, believable,” and that a causal association between styrene exposure and increased cancer in humans was not “reliable, trustworthy or believable.” Further, it was pointed out during the BSC review that *the Draft Substance Profile overemphasized potential associations between styrene and cancer in humans* and did not provide any of the contrary data or elaborate on the controversies.
- The argument that seemed to carry the most weight with the BSC members was that styrene should be classified because it is structurally related to a chemical that is already classified in the RoC, namely, styrene-7,8-oxide (SO). This argument is based on the assumption that structurally similar chemicals will share the same mode of action. Dr. Hines indicated that the human data did not justify classification and the animal carcinogenicity data did not justify classification, but since SO was already classified by NTP, they had to classify styrene. This is a false analogy. While styrene and SO are structurally and metabolically related, they present very different toxicologic and tumorigenic profiles. SIRC has provided NTP with data supporting this fact in several previous comment submissions, most recently in our letter February 6, 2009,

commenting on the Draft Substance Profile in advance of the BSC meeting. SO is positive in a number of *in vitro* genotoxicity assays, especially when epoxide hydrolase is inhibited in the system, while styrene is generally negative in these assays. SO by gavage caused forestomach necrosis and tumors, while styrene did not. Styrene caused increased lung tumors in mice, while SO did not, even though the lung level of SO was the same from gavage administration of SO as from metabolically generated from the inhalation of styrene. The argument that styrene should be classified because SO is classified is NOT justified in that the above evidence indicates styrene and SO do not share common key event(s) driving the modes of action for their respective tumorigenic outcomes. Thus the classification of styrene because it is related to an already classified material (SO) is not appropriate.

With due respect to NTP's efforts to revise the RoC review process, as scientists who have devoted extensive effort to understanding the true nature of styrene's carcinogenic potential, we found it to be profoundly frustrating that the BSC was not required to engage in discussion, or reach a consensus, when such comments that called into question the accuracy of NTP's proposal to list styrene had been put forward by BSC members.

The one clear consensus opinion during the BSC meeting, which was acknowledged by you, was on the fundamental limitations of the RoC classification scheme itself. Clearly, the styrene data cannot *objectively* be seen as providing "sufficient evidence" in animals or "limited evidence" in humans. The fact that the only formal classification options for the RoC are "reasonably anticipated" or "known" thus has placed substances with inconclusive or suggestive databases in jeopardy of being pigeon-holed into an inappropriately higher classification. Apart from being scientifically inaccurate and inappropriate, this scenario defeats the intention of the RoC to provide information to the public on *valid* carcinogenic concerns. From the perspective of sound science, as well as sound public policy, there is a *serious* difference between a substance that provides only "suggestive" evidence of carcinogenicity versus one that is "reasonably anticipated" to be a carcinogen. This is certainly the case from the public's perception. Given that BSC member Dr. Eastman stated at the meeting that the data *may not even support a "suggestive evidence" listing*, proceeding to list as "reasonably anticipated" does a disservice to all parties which look to the RoC as an authoritative reference.

We believe that you, as Director, have the administrative ability to ensure that the characterizations of substances slated for listing in the 12th RoC are scientifically accurate and substantiated. We further believe that a thorough reading of the legislative history of the statutory language authorizing the *Report on Carcinogens* provides you the flexibility of including styrene without listing it as "reasonably anticipated," but instead accurately indicating that the database is reflective of a substance that might be characterized as providing "suggestive" or "possible" evidence of human carcinogenicity. Such an action could go beyond the appendix approach of the past, and

would actually serve to strengthen the boundaries of the two categories which prompt actual listing in the *RoC*. This approach would in no way diminish the significant efforts of the NTP staff, the Expert Panel, or the BSC, but fundamentally enhances the accuracy and scientific fairness of the *RoC* itself.

As you proceed to the final Substance Profile and a final decision on whether to list styrene in the 12th *Report on Carcinogens*, we urge that you carefully consider the data on styrene – and in particular the comments of the BSC members we have highlighted – and consider characterizing the analysis of styrene as reflecting a substance that might be considered a “suggestive evidence” or “possible” carcinogen. From our monitoring of the BSC meeting, we feel that – had they had this option, and had been asked to reach a consensus – the BSC reviewers would have concurred with this approach.

As with prior communications from SIRC to NTP on the *RoC* process, we ask that this letter be added to the 12th *Report on Carcinogens* public docket for styrene.

Sincerely,

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Cc: Dr. Ruth Lunn, NTP