SIRC Styrene Information & Research Center

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October 2, 2017

Oregon Department of Environmental Quality
Attn: Sue MacMillan
700 NE Multnomah Street, Suite 600
Portland, OR 97232

RE: Proposed Ambient Air Toxics Benchmark for Styrene

Dear Dr. MacMillan:

The Styrene Information and Research Center (SIRC)[1] appreciates the opportunity to provide comments on the Department of Environmental Quality's (DEQ's) proposed changes to OAR 340, division number 246, that will add a new Ambient Benchmark Concentration (ABC) for styrene. The recommended ABC for styrene is 1,000 µg/m^3, based on the U.S. EPA IRIS reference concentration.

SIRC wishes to bring to the DEQ's attention several issues pertinent to finalizing a styrene ABC, in particular:

1. Limitations of recent styrene carcinogen listings that DEQ may review, including the National Toxicology Program (NTP) Report on Carcinogens and the California EPA's Office of Environmental Health Hazard Assessment (OEHHA) listing of styrene under Proposition 65;
2. Recent animal data on styrene mode of action that show that mouse lung tumors seen in styrene inhalation studies are not relevant to humans, and;
3. A current, comprehensive, systematic styrene risk assessment project being conducted by SIRC.

[1] In North America, the Styrene Information & Research Center, Inc. (SIRC) serves as a resource for industry, federal and state governments, and international agencies on issues related to the potential impact of exposure to styrene on human health and the environment. Headquartered in Washington, D.C., 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's charter also addresses the interests of ethylbenzene producers.

More detailed information on these issues are provided as follows:

Limitations of the NTP and OEHHA styrene assessments

SIRC closely followed the process that the NTP used leading to the 2011 listing of styrene as "reasonably anticipated" to be a human carcinogen in its *12th Report on Carcinogens (RoC)*, and upon which was based California's listing of styrene as "known to the state" to be a carcinogen under Proposition 65.

SIRC submitted to NTP large amounts of peer-reviewed, published data on the carcinogenic potential of styrene. Contrary to the NTP's determination, a thorough, inclusive and balanced assessment of the data at that time would not have supported a conclusion that styrene could be considered a significant concern as a potential human carcinogen. Additional research since then has provided substantive additional data that styrene should not be characterized as carcinogenic to humans under any normal exposure scenarios, including worker exposure, but most certainly not for general population exposures.

The collective epidemiology data in highly exposed workers do not indicate an increase in cancer from styrene exposure. Studies in rats showed no tumor formation after two-year exposures up to 1,000 ppm. In mice – a tumor susceptible species – a SIRC-sponsored chronic inhalation study showed tumor effects only in the lung, and only in the late stages of life. Subsequent to that finding, SIRC has invested many years and significant funding to understand if the mode of action of the mouse lung tumors is relevant to a human carcinogenic potential. As outlined in a following section of these comments, it now is clear that the tumor effects in mice are species-specific, and therefore not indicative of a human cancer concern.

In justifying its determination that there were "sufficient" animal data for a styrene cancer determination, NTP had to cite tumor findings in two strains of one species (mice). Supporting this, NTP cited the SIRC-sponsored study, ignoring the mode of action data that showed mouse lung tumors were not relevant. NTP then cited a NCI study in which the authors concluded there was "at best suggestive evidence." But NTP, in a public meeting attended by SIRC, substituted different historical control data for the study that enabled them to find an effect not found in the actual original data, or by the original authors. NTP ignored SIRC's comments that NTP staff was directly defying NTP's own guidance that prohibits such substitution of historical control data.

Likewise, when reviewing the human data, NTP characterized cancer studies in humans as showing "limited" evidence, but the epidemiology studies show no consistent increased incidence of, or mortality from, any type of cancer. Thus, NTO's causal association of human cancer and styrene exposure was invalid. Subsequent updates of

several styrene epidemiology studies have further supported a lack of cancer in styrene exposed workers, the highest exposed population.

Given the serious flaws in the NTP's *RoC* conclusions, SIRC vigorously opposed, and filed comments on, OEHHA's citation of the NTP classification in supporting the listing of styrene as a Proposition 65 carcinogen. We likewise provided data to OEHHA showing that a non-cancer based NSRL for styrene would be exponentially higher. Here, too, OEHHA ignored both comments and proceeded to list styrene absent a full vetting of the available data.

Mouse lung tumor mode of action conclusions are now even stronger

The NTP and OEHHA had available to them mode of action data that already provided persuasive evidence that mouse lung tumors should not be considered a predictor of possible human carcinogenic concern, yet chose to ignore those data.

Since those decisions, a two-year inhalation study in mice has been completed, and the data published in the journal *Toxicological Sciences*.[2] The Abstract states:

> Styrene is a mouse-specific lung carcinogen, and short-term mode of action studies have demonstrated that cytotoxicity and/or cell proliferation, and genomic changes are dependent on CYP2F2 metabolism. The current study examined histopathology, cell proliferation, and genomic changes in CD-1, C57BL/6 (WT), CYP2F2(−/−) (KO), and CYP2F2(−/−) (CYP2F1, 2B6, 2A13-transgene) (TG; humanized) mice following exposure for up to 104 weeks to 0- or 120-ppm styrene vapor. Five mice per treatment group were sacrificed at 1, 26, 52, and 78 weeks. Additional 50 mice per treatment group were followed until death or 104 weeks of exposure. Cytotoxicity was present in the terminal bronchioles of some CD-1 and WT mice exposed to styrene, but not in KO or TG mice. Hyperplasia in the terminal bronchioles was present in CD-1 and WT mice exposed to styrene, but not in KO or TG mice. Increased cell proliferation, measured by KI-67 staining, occurred in CD-1 and WT mice exposed to styrene for 1 week, but not after 26, 52, or 78 weeks, nor in KO or TG mice. Styrene increased the incidence of bronchioloalveolar adenomas and carcinomas in CD-1 mice. No increase in lung tumors was found in WT despite clear evidence of lung toxicity, or, KO or TG mice. The absence of preneoplastic lesions and tumorigenicity in KO and TG mice indicates that mouse-specific CYP2F2 metabolism is responsible for both the short-term and chronic toxicity and

[2] Cruzan, G., et al., Complete Attenuation of Mouse Lung Cell Proliferation and Tumorigenicity in CYP2F2 Knockout and CYP2F1 Humanized Mice Exposed to Inhaled Styrene for up to 2 Years Supports a Lack of Human Relevance, Toxicological Sciences, Vol. 159, 1 October 2017, pages 413–421, https://doi.org/10.1093/toxsci/kfx141

> tumorigenicity of styrene, and activation of styrene by CYP2F2 is a rodent MOA that is neither quantitatively or qualitatively relevant to humans.

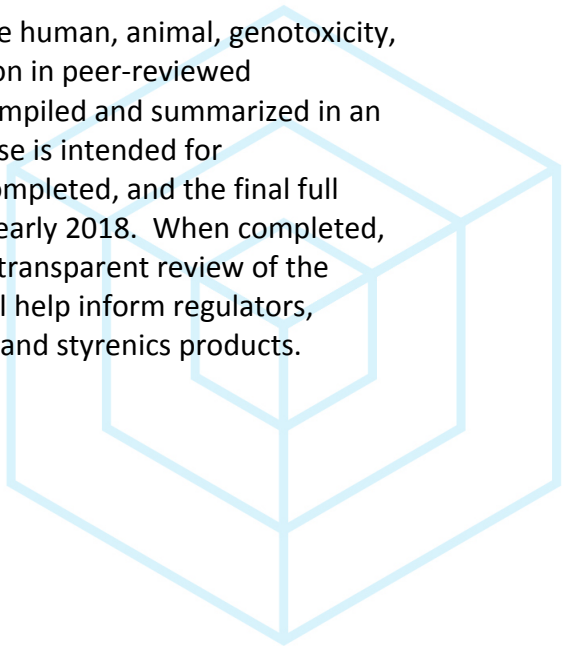
Simply stated, analysis of the mode of action data indicates that unique metabolism of styrene in the mouse lung produce metabolites that are cytotoxic to club cells in the terminal bronchioles. This metabolism does not take place to any meaningful extent in human lungs. These MOA data indicate that mouse lung tumors from styrene exposure are not relevant to human risk.

SIRC is conducting a comprehensive styrene risk assessment that could inform the DEQ's ABC process

In late 2015, as SIRC's 30-year styrene research program began to reach completion, SIRC recognized the need for a current, comprehensive, systematic risk assessment of all aspects of potential styrene health effect data. This project would bring together the collective body of SIRC-sponsored research, as well as other quality, independent, peer-reviewed literature on styrene. SIRC members look upon this project as a capstone to the over $20 million invested over the years in state-of-the-art research to better understand the potential human health effects of styrene.

SIRC's risk assessment project commenced in mid-2016, and to date has made significant progress, with the completion of most components of the project anticipated by the end of 2017. For most areas of data assessment — e.g. epidemiology data, animal data, genotoxicity data, neurotoxicity data, exposure assessment, etc. — SIRC has engaged independent, expert scientists to conduct the reviews, to ensure the highest degree of impartiality. The risk assessment is being conducted under the most current best practices for systematic review, including a Phase 1 stage, developing a project scope and protocol for each sub-focus, and identifying/evaluating the literature, and Phase 2 in which the studies are assessed and evaluated using a weight of evidence approach.

Given their complexity, the individual assessments on the human, animal, genotoxicity, etc., data may be submitted independently for publication in peer-reviewed journals. However, the collective assessments will be compiled and summarized in an overall styrene risk assessment manuscript, which likewise is intended for publication. SIRC hopes that the entire project will be completed, and the final full assessment report ready for submission to a journal, by early 2018. When completed, the assessment should represent the most rigorous and transparent review of the styrene data to date, and SIRC hopes that the project will help inform regulators, industry, and the public alike, as to the safety of styrene and styrenics products.



Conclusion

In summary, SIRC respectfully urges that DEQ briefly postpone finalization of a styrene ABC until completion of the above referenced styrene risk assessment, which will provide a thorough and current assessment of any styrene health effect issues.

Arguably, the IRIS RfC value may be acceptable for general population exposures, but separate exposure values have been set by OSHA and others for safe workplace exposure levels. In 1997, the industry signed an agreement with OSHA to encourage compliance with an 8-hour workplace limit of 50 ppm, in recognition of data showing that OSHA's official PEL of 100 ppm may not be sufficiently protective. SIRC more recently recommended a 20 ppm 8-hour exposure limit based on data demonstrating very mild hearing loss at some frequencies following long-term occupational exposure at 30 ppm and above. SIRC's 20 ppm recommendation is consistent with both European and Japanese workplace limits. It is critical that any styrene ABC be distinguished from appropriate workplace exposure limits. Likewise, use of the California NSRL also is not appropriate in characterizing workplace exposures.

While the SIRC risk assessment will serve as the most timely compendium of the styrene data, we would be happy to provide any references in the interim that might be of interest to DEQ staff. I would be pleased to answer any questions or provide additional details on these comments, as well as making available any SIRC resources.

Very truly yours,

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http://www.oregon.gov/deq/Regulations/rulemaking/Pages/Catbr2017.aspx