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Re: Comments of the Styrene Information and Research Center on the State of Maine Department of Environmental Protection Toxic Chemicals in Food Packaging – Food Contact Chemicals of High Concern Criteria Documentation. Draft Posted for Public Comment February 9, 2021.

Dear Ms. Malinowski:

The Styrene Information and Research Center, Inc. (SIRC)[1] appreciates the opportunity to comment on the Maine Department of Environmental Protection's (DEP) Draft Food Contact Chemicals of High Concern Criteria Documentation posted for public comment February 8, 2021.

Maine's 2019 Toxic Chemicals In Food Packaging legislation amended the Act To Protect the Environment and Public Health by Further Reducing Toxic Chemicals in Packaging (32MRSA §§1731-1747). The amendments require the DEP to publish a list of no more than 10 food contact chemicals of high concern in order to gather information on their use in food packaging available in Maine (32 MRSA §1742). Importantly, the Department must determine that there is "strong credible scientific evidence" that the chemical is a reproductive or developmental toxicant, endocrine disruptor or human carcinogen and meets other criteria.

[1] Since 1987, The Styrene Information & Research Center (SIRC), a nonprofit organization, has served 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 and is the principal focal point for public information and research on styrene. In 2012, SIRC's scope was expanded to include ethylbenzene, the key chemical precursor for styrene. SIRC consists of voting member companies involved in the manufacturing or processing of styrene, associate member companies that fabricate styrene-based products, and an international partner group. Collectively, SIRC's membership represents the majority of the North American styrene industry.

The draft describes the basis for the proposed listing (at page 9) as:

> Styrene is commonly used as a monomer for various types of plastic material, including some that may become food packaging. Listed as one of Maine's Chemicals of High Concern, styrene is classified as a Category 1 Endocrine Disruptor by the European Union. More recently, styrene has been classified by the International Agency for Research on Cancer as a Group 2A Carcinogen. (Page 9 footnotes omitted.)

Regarding styrene's endocrine disruptor status, the draft mistakenly cites an outdated European Union reference. Styrene is not classified as a Category 1 endocrine disruptor by the European Union.

Regarding styrene's potential carcinogenicity, IARC has erroneously concluded in 2018 that styrene was a Group 2A carcinogen. A review of the scientific literature does not provide "strong credible scientific evidence" that styrene is a carcinogen.

For the reasons detailed below, styrene should not be added to the list of food contact chemicals of high concern designated for information gathering in Maine.

A. Styrene is not classified as a Category 1 endocrine disruptor by the European Union.

The cited reference of a report regarding endocrine disruptors by the European Commission DG Environment from 2000 is outdated and the information identified in this report is mis-interpreted. The 2000 DG Environment report that identified substances including styrene was an early activity in the European Union's endocrine property evaluation strategy, the substances listed were not intended as final and unchangeable. As this report does not provide an objective assessment of the current state of the science on endocrine disruption for the identified substances, it should not be used as the basis for concluding these substances to be endocrine disruptors.

Subsequent to this European Commission report, styrene was the subject of a comprehensive European Union scientific risk assessment for potential human health hazards including endocrine disruption and this assessment did not identify any evidence that styrene possesses significant endocrine disruption activity (United Kingdom Competent Authority, 2008; European Union, 2008).

The potential for endocrine disruptor activity for styrene was also critically examined and found styrene was not associated with (anti)estrogenic, (anti)androgenic, or thyroid-modulating activity or with an endocrine activity that may be relevant for the environment (Gelbke et al., 2015). There are studies in exposed workers that have suggested elevations in hormone prolactin levels, however this finding is not supported by an underlying neuroendocrine mechanism from a large number of animal mechanistic studies and rather may have been related to workplace-stress (Gelbke et al., 2015).

Presently the most recent status of endocrine disruption classification in the European Union is an identified "Endocrine Disruptor Assessment List" that is located on the European Chemical Agency (ECHA) website (https://echa.europa.eu/nl/ed-assessment). This list identifies substances undergoing an endocrine disruptor assessment under REACH or the Biocidal Products regulations and that have been brought forth for discussion to the ECHA's Endocrine Disruptor Expert Group. Styrene is not identified on this list.

B. IARC erroneously classified styrene as a Group 2A carcinogen and the classification does not warrant listing.

IARC's 2018 decision to reclassify styrene as a Group 2A "probable" carcinogen was due, in part, to changes that IARC has made since its 2002 assessment of styrene to the technical guidelines IARC uses to assess data. These changes however fall well short of meeting current scientific standards of transparency and objectivity, and instead foster ad hoc procedures for evaluating and integrating mechanistic evidence.

IARC classified styrene as probably carcinogenic to humans based on their conclusions of sufficient evidence in experimental animals but limited evidence in humans. The animal evidence comes from a large database of rat and mouse cancer studies conducted from the late 1970s through 2001 that found evidence of increases in lung tumors in mice but not in rats. IARC's previous review of these data yielded a conclusion of limited animal evidence, whereas with their change in technical guidance, these same data were concluded by IARC in 2018 as now sufficient evidence. Their conclusion is not supported by new scientific evidence.

IARC's review of the mechanistic information on mouse lung tumors concluded that styrene induced mouse lung tumors are human relevant primarily due to shared metabolism of styrene to styrene oxide in rodents and humans. The IARC review simplistically dismissed an extensive body of published mode of action evidence collected over several decades of research that consistently demonstrate that the mode of action of styrene mouse tumors is mediated through mouse lung specific metabolism to ring-oxidized metabolite(s) and is not specific to styrene oxide formation, and that the quantitative or possibly qualitative absence of such metabolism in humans indicates this mode of action does not function in humans (Cruzan et al., 2018).

According to IARC, the epidemiology studies provide some "evidence that exposure to styrene causes lymphohematopoietic malignancies in humans, but confounding, bias, or chance cannot be ruled out." The overall evaluation of the epidemiology studies is that the evidence of carcinogenicity from styrene exposure is inconsistent. While some studies find an association between lymphohematopoietic malignancies and styrene exposures, other studies do not. The IARC assessment of the epidemiology data considers these data limited and reaches this conclusion based upon the strength of the evidence approach. However, using a more appropriate weight of the evidence approach, there is no coherent evidence that

styrene exposure increases risk from cancers of lymphohematopoietic tissue, lung, or pancreas. Using the strength of the evidence allows IARC to focus more attention on the possibility of increased risk of lymphohematopoietic malignancies than is deserved. Considering all the studies in a weight of the evidence approach, a more balanced evaluation of the data would conclude that there is no consistent evidence for carcinogenicity of styrene in the epidemiology studies and these studies do not establish that styrene causes any form of cancer in humans.

While SIRC's comments focus on the scientific literature demonstrating that styrene should not be listed, we note that the U.S. Environmental Protection Agency has taken a similar position regarding IARC's classification of styrene. When conducting a risk and technology review under Section 112 of the Clean Air Act for potential risks from industrial emission of styrene, EPA did not treat styrene as a carcinogen in light of IARC's March 2018 classification of styrene to Groups 2A. National Emission Standards for Hazardous Air Pollutants: Boat Manufacturing and Reinforced Plastic Composites Production Residual Risk and Technology Review. 84 Fed. Reg. 22642, 22651 (May 17, 2019)(proposed rule) and 85 Fed. Reg. 15960 (March 20, 2020)(final rule).

In the Preamble to the Monograph series, IARC carefully conscribes the scope of the Monographs' cancer hazard conclusions.

> The *Monographs* represent the first step in carcinogen risk assessment, which involves examination of all relevant information in order to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans….
>
> A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The Monographs are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the Monographs identify cancer hazards even when risks are very low at current exposure levels . . .[2]

Thus, EPA was correct that the IARC classification does not provide a basis for regulatory action or a conclusion that styrene presents a carcinogen risk. Indeed, IARC notes that its evaluations "represent only one part of the body of information on which public health decisions may be based." And, "[t]herefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations."[3]

[2] Preamble, p. 2.
[3] Preamble, p. 3.

Therefore overall, the available information for styrene carcinogenicity does not support the conclusion that styrene is a probable human carcinogen. **There are no strong or consistent indications that styrene causes any form of cancer in humans. Although some studies suggest that styrene-exposed workers may be at increased cancer risk, the human evidence for styrene carcinogenicity is inconclusive. Studies of general population environmental and consumer styrene exposure and cancer are less informative than the worker studies, but the available evidence does not suggest these low exposures are a concern. Extensive studies on mouse lung tumors show these are of low relevance to human cancer risk.**

C. Styrene presents a low risk to consumers from food packaging exposure

Styrene is a low concern to human health from the low-level exposures that may be associated with migration from polystyrene food packaging into food. A comprehensive review of the extensive toxicological and exposure information available for styrene has found potential risks to consumers to be well within acceptable exposures and hence safe (Banton et al., 2019).

Additional information on the potential human health and environmental effects of styrene to supplement these comments and aid in Maine DEP's assessment of styrene may be found at http://www.styrene.org and http://www.youknowstyrene.org.

Thank you for considering these comments. SIRC would be happy to answer any questions Maine DEP may have or provide additional information.

Sincerely,

Ray Ehrlich

Ray Ehrlich
Executive Director

References

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Gelbke H., Banton M, Leibold E, Pemberton M, and Samson SL. (2015). A critical review finds styrene lacks direct endocrine disruptor activity. Crit. Rev. Toxicol. 45:727–64. doi:10.3109/10408444.2015.1064091.

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