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Re: Comments of the Styrene Information and Research Center, Inc.
Initiation of Prioritization for Styrene (CASRN: 100-42-5) Under TSCA; Notice of Availability, 89 Fed. Reg. 102,903 (Dec. 18, 2024) Docket No. EPA-HQ-OPPT-2018-0461

Dear Dr. Au:

The Styrene Information and Research Center, Inc. (SIRC) appreciates the opportunity to comment on the U.S. Environmental Protection Agency's (EPA) selection of styrene as a candidate for designation as a High-Priority Substance for risk evaluation under section 6 of the Toxic Substances Control Act (TSCA).[1] SIRC is a non-profit organization consisting of voting member companies involved in manufacturing or processing of styrene and ethylbenzene, and associate member companies that fabricate products based on these chemistries. Collectively, SIRC's styrene monomer manufacturing members represent the vast majority of the North American styrene manufacturing industry. For nearly 40 years, SIRC and its members have sponsored and (in nearly all cases) published peer-reviewed studies regarding the potential hazards, exposures and risks that styrene poses to human health. These include animal toxicology studies, toxicokinetic studies, epidemiology studies, and a comprehensive state of the science review and human health risk assessment.

The enclosed comments reference and summarize the best available, peer-reviewed science concerning the relative hazards of styrene, and information on occupational and consumer exposures to styrene under its conditions of use, all within the context of EPA's prioritization criteria, along with the conclusions of regulatory and public health agencies and recommendations on issues related to risk. The toxicological and epidemiological evidence demonstrates that styrene cannot be considered a known human carcinogen, is an otherwise low potency chemical that presents potential developmental effects and ototoxicity at exposures considerably higher than those documented for consumers and the general public, as well as nearly all occupational scenarios. Respiratory protection is sufficient for the very highest occupational exposure scenarios (see Banton et al., 2019). As such, styrene should be considered a Low Priority Substance. Full

[1] Initiation of Prioritization Under TSCA; Notice of Availability, 89 Fed. Reg. 102,903 (Dec. 18, 2024).

references for the citations in these comments are provided below, together with copies of five previously unpublished styrene exposure reports (Attachments 1-5).

However, as discussed below, given the Agency's current multiyear risk evaluation backlog, TSCA section 6(b)(2)(C) requires the Agency to pause initiating these or any other additional prioritization candidates. Accordingly, the Agency should withdraw each of the five pending prioritization candidate designations (including for styrene and ethylbenzene) at least until the risk evaluation backlog is resolved.

Alternatively, EPA should withdraw the styrene candidate designation and replace it with another chemical to assure the Agency can meet future obligations under TSCA section 6(b)(3)(C). That provision requires EPA to commence a new risk evaluation as soon as an earlier risk evaluation is completed. Based on the information and analysis provided, if the styrene prioritization were completed, styrene would be classified as a Low-Priority for risk evaluation and, in that event, styrene would be unavailable to replace a High-Priority Substance exiting the risk evaluation process as currently planned by the Agency. To avoid a future gap, EPA should withdraw styrene from prioritization now and designate a different substance more likely to be designated High-Priority.

For convenience, following is an outline of SIRC's comments

1. All Pending Prioritization Candidate Designations Should be Withdrawn From Further Consideration as Untimely

Given its current inventory of overdue and pending TSCA section 6 work, EPA currently is unable to complete risk evaluations in the three (or three and a half) years allowed by the statute. Until EPA has worked down its inventory of prioritization, risk evaluation and risk management activity to the point that it is able consistently to complete five three-year risk evaluations each year, it should not initiate prioritization for any additional chemicals. TSCA section 6(b)(2)(C) directs that the Agency "shall … designate priority substances and conduct risk evaluations…at a pace consistent with the ability of the Administrator to complete risk evaluations in accordance with" the three-year deadline in TSCA section 6(b)(4)(G). This instruction overrides any inconsistency with TSCA section 6(b)(3)(C). SIRC submits that the Agency is required by TSCA section 6(b)(2)(C) to immediately withdraw the candidate designations for ethylbenzene, styrene and the other three prioritization candidate chemical substances identified in the December 18, 2024 notice without any further substantive consideration of the prioritization criteria, and to forbear from initiating prioritization for these or any other chemicals until the current risk evaluation backlog

has been resolved and the Agency has a reasonable prospect of being able to complete risk evaluations in period allowed by statute.

TSCA section 6(b)(4)(G) requires EPA to complete risk evaluations for chemicals designated as High-Priority within three years of their designation (with a six-month extension allowed when needed). EPA has been unable to maintain that schedule. Of the 20 chemicals designated as High-Priority in December 2019, EPA has completed risk evaluations for only four. These evaluations took five years to complete and were two years late.[2] The Agency is under agreed court order to complete (i) another six risk evaluation in 2025, which would be a six year evaluation period and three years late, and (ii) complete the final 10 risk evaluations from the 2019 class by December 2026, which, if EPA is able to keep to this schedule, would be a seven year evaluation period and four years late.[3] And the Agency has just commenced risk evaluation for five more chemicals.[4] In addition to risk evaluation work, the Agency has incurred and will continue to incur new risk *management* rule obligations. The completion of a risk evaluation creates a new obligation to complete risk management rules within two years. EPA currently has four proposed risk management rules pending and is obligated to finalize those and propose six more in the next year.

At the same time, the Administrator has announced plans to decrease the Agency's budget by 65%,[5] and plans to initiate further rulemaking in the near future that will reexamine multiple aspects of the current risk evaluation procedural rule for consistency with the law and Administration policy, including reconsideration of the "whole chemical approach," the appropriate consideration of PPE in risk evaluation, and whether EPA may evaluate less than all conditions of use of a chemical at the same time.[6] Finally, each of the four risk management rules that have been finalized are subject to multiple petitions for review and that can be expected to result in multiple judicial decisions in the next two years that may require EPA to go back and reopen the risk evaluations for one or more of those chemicals, the corresponding risk management rules, or both. All this additional work, coupled with the expected loss of staff and contractor

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[2] See EPA, Ongoing and Completed Chemical Risk Evaluations under TSCA, https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/ongoing-and-completed-chemical-risk-evaluations-under (last visited March 17, 2025).

[3] See Consent Decree Regarding High-Priority Risk Evaluation Deadlines, ECF No. 39, Community In-Power and Development Assn. Inc., v. United States Environmental Protection Agency, No. 1:23-cv-02715-DLF (D.D.C. Nov. 22, 2024). See also, Agency's 2025 Annual Plan for Chemical Risk Evaluations Under TSCA, https://www.epa.gov/system/files/documents/2025-01/2025-annual-plan-for-chemical-risk-evaluations-under-tsca.pdf

[4] High-Priority Substance Designations Under the Toxic Substances Control Act (TSCA) and Initiation of Risk Evaluation on High-Priority Substances; Notice of Availability, 89 Fed. Reg. 102,900 (Dec. 18, 2024).

[5] See, e.g., Z. Budryk, White House says EPA will cut 65 percent of spending, not staff, The Hill (Feb. 27, 2025) (available at https://thehill.com/policy/energy-environment/5167068-white-house-epa-65-percent-cuts-staff-spending/).

[6] EPA, Press Release, EPA Announces Path Forward on Chemical Reviews to Protect Public Health, Increase Efficiency and Follow the Law (March 10, 2025) available at https://www.epa.gov/newsreleases/epa-announces-path-forward-chemical-reviews-protect-public-health-increase-efficiency.

resources due to projected budget cuts, make it even more unlikely that the Agency will be able to keep to its current, court-ordered risk evaluation completion schedule.

1.1. Withdrawal of All Current Prioritization Candidate Designations is Required by TSCA § 6(b)(2)(C)

Given this record and the extensive inventory of pending risk evaluation and risk management work, it is undeniable that, even under the most favorable assumptions, it will be several years before EPA will have sufficiently cleared the backlog and settled on final procedural rules sufficient to enable the Agency to complete newly commenced risk evaluations within the three-year statutory time frame. In these circumstances, TSCA instructs the Agency to forbear from initiating the prioritization of any chemical or commencing a new risk evaluation until such time as EPA is able as a practical matter to start and complete a risk evaluation within three years. Specifically, TSCA section 6(b)(2)(C) ("Continuing [prioritization] designations and risk evaluations") directs that:

> [t]he Administrator *shall* continue to designate priority substances and conduct risk evaluations in accordance with this subsection *at a pace consistent with the ability of the Administrator* to complete risk evaluations in accordance with the [three-year] deadlines under paragraph (4)(G). (emphasis added)

Accordingly, it is entirely appropriate, if not required, for EPA to forbear from designating any new prioritization candidates or initiating any new risk evaluations until it has the ability to complete risk evaluations within three years. For this reason, it was inappropriate for EPA to designate styrene, ethylbenzene, or any of the other three substances at issue as candidates for prioritization in December 2024. Consistent with the requirements of TSCA section 6(b)(2)(C), those designations should simply be withdrawn at this time, subject of course to potential candidate designation in the future at such time as EPA has the practical ability, under all of the circumstances, to complete risk evaluations in three years. This approach is consistent with the approach to TSCA risk evaluation announced by the Administrator on March 10, 2025, which includes procedural rule reforms to make it possible to complete individual risk evaluations within the required three-year period.[7]

1.2. Withdrawal of All Current Prioritization Candidate Designations is Not Inconsistent with TSCA § 6(b)(3)(C).

Withdrawing prioritization candidate designations for styrene, ethylbenzene and the other three substances at issue would not be inconsistent with TSCA section 6(b)(3)(C). That provision nominally requires the Agency to designate a new substance as High-Priority (and commence risk evaluation) upon completing a risk evaluation for another substance. First, section 6(b)(3)(C) does not address the *commencement* of prioritization at all; it only addresses the *completion* of prioritization and commencement of risk evaluation. Second, the two provisions were enacted at

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[7] EPA, Press Release, EPA Announces Path Forward on Chemical Reviews to Protect Public Health, Increase Efficiency and Follow the Law (March 10, 2025).

the same time such that Congress intended that the two provisions should be read together in a way that gives them both meaning. As we understand it reading them together, the evergreen risk evaluation process described by section 6(b)(3)(C) represents the baseline, standard practice, but subject to override by the section 6(b)(2)(C) safety valve, which allows EPA to match the risk evaluation flow rate to its then current capacity. Section 6(b)(2)(C) establishes Congress' intent that timely (three-year) completion of risk evaluations once started was more important than keeping an unsustainable high flowrate that might otherwise result from unchecked adherence to section 6(b)(3)(C). If section 6(b)(2)(C) does not override section 6(b)(3)(C) in appropriate circumstances, then it would have no potential function at all and would represent mere surplusage. It is a basic canon of statutory construction that statutes should be construed "so as to avoid rendering superfluous" any statutory language: "A statute should be construed so that effect is given to all its provisions, so that no part will be inoperative or superfluous, void or insignificant....".[8]

1.3. Withdrawal of All Current Prioritization Candidate Designations is Good Policy for Proper Administration of TSCA

Deferring prioritization and any commencement of risk evaluation also would be good policy given the ongoing and continuous change in the rules governing risk evaluation procedures. The procedural rules were first adopted in 2017 and challenged and partially vacated in the U.S. Court of Appeals in 2019. EPA completed risk evaluations for the first 10 chemicals under those rules by early 2021, but then spent the next two years or more completely reworking most of those evaluations using different interpretations of the procedural rules. EPA then rewrote important aspects of those procedural rules in 2023 and 2024 and completed several risk evaluations using the revised procedures. However, now both those revised procedural rules and every chemical-specific risk evaluation and corresponding risk management rule issued by EPA so far is under review in different U.S. courts of appeals as a result of petitions for review filed both by industry and by NGOs. Finally, as noted, EPA recently announced its intent to again revisit and revise the risk evaluation procedural rule in a manner that can be expected to affect the outcomes.

Any changes to current risk evaluation procedures – either arising from court decisions, new agency interpretations or following reevaluation of the 2024 final rule – could lead to reconsideration of ongoing risk evaluations, as well as the process for designating chemicals as High-Priority Substances. The Agency should defer designating any additional chemicals as High-Priority Substances until it is more certain about its path forward.

2. Introduction to Styrene

Styrene (CASRN 100-42-5) is both naturally occurring and manufactured in high volumes, being used primarily as an intermediate in the production of a number of commercially important

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[8] *Hibbs v. Winn*, 542 U.S. 88, 101 (2004) (quoted in *Corley v. United States*, 556 U.S. 303, 314 (2009)); *Astoria Federal Savings & Loan Ass'n v. Solimino*, 501 U.S. 104, 112 (1991); *Sprietsma v. Mercury Marine*, 537 U.S. 51, 63 (2003).

polymers and copolymers that are in turn used to make a wide variety of products of industrial, consumer, and medical importance. These materials include polystyrene (e.g., plastic packaging, building construction and food packaging materials), styrene butadiene rubber (SBR) (the most widely used synthetic rubber in the world, used for primarily for manufacturing tires and other automotive parts), unsaturated polyester resins (e.g., gel-coating and laminating operations in the production of glass-fiber-reinforced plastic products such as boats, bathtubs, and shower stalls), styrene butadiene latexes (e.g., carpet backings and paper coatings), acrylonitrile-butadiene-styrene (e.g., household and office appliances), and styrene-acrylonitrile (e.g., housewares and battery casings). Additionally, since it is manufactured using ethylbenzene, the production and manufacture of these two compounds are inextricably tied together (reviewed in Banton et al., 2019; NTP, 2021).

On September 30, 2024, EPA hosted an informational webinar titled "Prioritization of Chemical Substances Under TSCA – September and October 2024" in which it provided its pre-prioritization criteria for selecting the next five chemicals for prioritization assessment[9]. EPA stated in the 2024 Update that it seeks to identify chemical substances from the 2014 TSCA Work Plan for prioritization that:

- have persistence and bioaccumulation scores of three (high);
- are known human carcinogens; and
- have high acute or chronic toxicity.

In its 2014 TSCA Workplan, EPA gave styrene a score of "one" (low) for persistence and bioaccumulation, while scoring both hazard and exposure criteria with "three" (high). For hazard, EPA indicated that styrene was a "Possible human carcinogen" that could also adversely impact the central nervous system. Regarding exposure, EPA observed that styrene was used in the manufacture of many consumer products while also being detected in human biomonitoring studies and in environmental media.

This submission identifies and summarizes the key studies and literature on the potential hazards of, and exposures to, styrene that are critical for EPA to evaluate as it considers a decision on whether styrene should be prioritized for TSCA risk evaluation. The literature includes several peer-reviewed studies of styrene that have been published since the 2014 TSCA Workplan. As described below, the weight of the scientific evidence does not support styrene either as a "high acute or chronic toxicity" chemical or as a known human carcinogen. Additionally, styrene exposures in the general public (either through diet, consumer product use or via environmental exposures) occur at such low levels that they do not begin to approach potential concern for health impacts. Given these facts, combined with EPA's acknowledgement that styrene is neither persistent nor bioaccumulative, it is clear that styrene does not present an unreasonable risk of

[9] S. Au, EPA, Data Gathering, Management and Policy Division, OPPT, OCSPP, Prioritization Of Chemical Substances Under TSCA, EPA-HQ-OPPT-2023-0606-0011 (Sep. and Oct. 2024), available at https://www.regulations.gov/document/EPA-HQ-OPPT-2023-0606-0011.

injury to health or the environment under its conditions of use, and does not meet the TSCA criteria for prioritization as a High-Priority Substance (40 C.F.R. § 702.3).

3. Hazard Evidence for Styrene

Styrene is one of the most extensively studied chemicals in the literature, with numerous high-quality animal toxicology tests and human peer-reviewed studies available and has been the subject of a number of regulatory and science agency reviews. Styrene has been assessed under EPA's Integrated Risk Information System (IRIS; EPA, 1992) and more recently by ATSDR (2010). At the time of their assessments, both agencies identified effects of the central nervous system (CNS) as the most sensitive health outcomes associated with styrene exposures in humans and derived very similar non-cancer inhalation values protective of chronic exposures based on these effects (EPA RfC = 1 mg/m^3 [0.23 ppm], ATSDR inhalation MRL = 0.9 mg/m^3 [0.2 ppm]). These noncancer toxicity values indicate styrene is a low potency, noncancer chemical hazard and does not meet the TSCA prioritization criteria of a "high chronic toxicity" chemical. Neither EPA nor ATSDR have evaluated the carcinogenic potential of styrene in humans, though the National Toxicology Program (NTP, 2021) and the International Agency for Research on Cancer (IARC, 2019) have developed cancer hazard assessments. For risk assessment purposes, EPA has not derived or adopted any cancer-based toxicity values and only considers styrene noncancer hazard. As described below, the weight of scientific evidence as published in the animal toxicity, human epidemiology and mechanistic literature do not support designating styrene as a known human carcinogen.

Considerably more information on the toxicology and epidemiology of styrene have been published since EPA and ATSDR released their styrene assessments. SIRC recently commissioned a comprehensive review of the potential health risks associated with exposure to styrene (Banton et al., 2019), which provides an extensive and exhaustive analysis of the styrene cancer and noncancer toxicology and epidemiology literature, as well as an overview environmental, occupational and consumer exposure studies. This review was an update of a previous assessment conducted by the Harvard Center for Risk Analysis and published by Cohen et al. (2002), and presents updated, state of the science non-cancer occupational exposure levels as well as inhalation and oral toxicity values protective of the general population. While acknowledging the weight of the evidence does not support styrene as a known human carcinogen, Bus et al. (2024) recently conducted a quantitative cancer risk assessment for styrene conservatively assuming lung tumors in mice were relevant to humans operating through a non-genotoxic mode of action. From their assessment, the authors derived styrene threshold-based cancer occupational exposure levels for workers (6.2 ppm, or 26 mg/m^3) and styrene inhalation reference concentrations RfC values for the general public (0.8 ppm, or 3.4 mg/m^3). Overall, these peer-reviewed, state-of-the-science assessments support the conclusion that styrene is a low concern for human health risk. Additional details on styrene hazards are summarized below.

3.1. The Weight of the Evidence Does Not Support Styrene as a Known Human Carcinogen

Whereas EPA has yet to formally assess the cancer potential of styrene, the International Agency for Research on Cancer (IARC) and Report on Carcinogens (RoC) under the National Toxicology Program (NTP) have conducted cancer hazard assessments. IARC (2019) classified styrene as a Group 2A "probable" human carcinogen, based in part on limited evidence in both humans and animals and in part on its classification of the styrene metabolite SO as a Group 2A carcinogen due to "strong evidence" that SO is genotoxic. Similarly, in the most recent RoC, styrene monomer was listed as "reasonably anticipated to be carcinogenic to humans" while acknowledging that the scientific literature provided "limited evidence of carcinogenicity from studies in humans" (NTP, 2021). However, these assessments are limited by the lack of dose response analysis and do not represent the state of the science regarding the carcinogenic and genotoxic potential of styrene. Key considerations and studies are summarized below.

3.1.1. Styrene is not genotoxic in vivo and not a genotoxic hazard for humans

The potential for styrene to induce genotoxicity as an initial key event in the etiology of carcinogenicity (i.e., tumorigenicity of the lung) has been debated given positive findings reported in some short-term *in vitro* studies (IARC, 2019; Banton et al., 2019). Indeed, there has been an extensive effort to test and characterize the genotoxic potential of styrene over the past several decades, which has been the topic of extensive summary and review by several groups of investigators (Cohen et al., 2002; Speit and Henderson, 2005; Nestmann et al., 2005; Scott and Preston, 1994a,b). However, the vast literature on potential genotoxic activity of styrene is complicated by the fact that test reporting and standards were not always in-line with the state of the science methodologies available today. To address this issue, Moore et al. (2019) critically reviewed the genotoxicity of styrene based on recommendations in the current Organization of Economic Co-operation and Development (OECD) testing guidelines. The review included studies that examined genetic effects, including the Ames test, gene mutation in mammalian cells, chromosome aberrations (CAs) in mammalian cells, micronuclei (MN) in mammalian cells, and *in vivo* rodent studies for chromosomal aberrations (CAs) and MN.

Based on OECD guidelines, many of the styrene studies were technically deficient and considered uninterpretable; those that did report usable data demonstrated that styrene was not mutagenic or clastogenic in test systems lacking metabolic activation capability (Moore et al., 2019). In contrast, *in vitro* test systems with metabolic activation of styrene to styrene 7,8-oxide (SO) reported positive results for mutagenicity. Selected studies also indicate that SO is mutagenic and clastogenic in cultured mammalian cell lines. The evaluation by Moore et al. (2019) also concluded that SO itself is mutagenic and clastogenic when tested in selected assays *in vitro*. At the time of their review, however, there were no *in vivo* studies available that evaluated either styrene or SO mutagenicity, and the available *in vivo* studies that evaluated the potential for styrene/SO clastogenic/aneugenic reported negative responses.

Recently, Gollapudi published a series of genotoxicity studies reporting several high-quality *in vivo* experiments in rodents conducted following OECD testing guidelines (Gollapudi, 2023; 2024; Gollapudi et al., 2025). These studies assayed multiple endpoints in mice and rats, including the

Pig-a gene mutation assay, the erythrocyte micronucleus (MN) assay for cytogenetic effects, and the comet assay for DNA damage. The study designs and results are summarized in **Table 1**.

Table 1. Summary of recent *in vivo* genotoxicity tests in rodents

Study	OECD Test Guideline No.	Species	Route of exposure	Duration	Exposure levels (mg/kg-bw/d)	Positive Controls	Tissue Analyzed	Results
Gollapudi (2023)	470 - Pig-a Gene Mutation Assay	B6C3F1 mice (m)	oral (gavage)	29 days	0, 75, 150, 300	EMS/ENU	Blood (erythrocytes)	STYRENE: No statistically significant response at any dose. No statistically significant trend across dose groups. EMS/ENU: Statistically significant response.
	474 - Erythrocyte Micronucleus Assay	B6C3F1 mice (m)	oral (gavage)	29 days	0, 75, 150, 300	EMS/ENU	Blood (erythrocytes)	STYRENE: No statistically significant response at any dose. No statistically significant trend across dose groups. EMS/ENU: Statistically significant response.
	498 - Alkaline Comet Assay	B6C3F1 mice (m)	oral (gavage)	29 days	0, 75, 150, 300	EMS/ENU	Duodenum, Kidney, Liver, Lung, Glandular Stomach	STYRENE: No statistically significant response at any dose in any tissue. No statistically significant trend across dose groups. EMS/ENU: Statistically significant response.
Gollapudi (2024)	470 - Pig-a Gene Mutation Assay	F344 rats (m)	oral (gavage)	28-29 days	0, 100, 250, 500	EMS/ENU	Blood (erythrocytes)	STYRENE: No statistically significant response at any dose. No statistically significant trend across dose groups. EMS/ENU: Statistically significant response.
	474 - Erythrocyte Micronucleus Assay	F344 rats (m)	oral (gavage)	28-29 days	0, 100, 250, 500	EMS/ENU	Blood (erythrocytes)	STYRENE: No statistically significant response at any dose. No statistically significant trend across dose groups.

Study	OECD Test Guideline No.	Species	Route of exposure	Duration	Exposure levels (mg/kg-bw/d)	Positive Controls	Tissue Analyzed	Results
								EMS/ENU: Statistically significant response.
	498 - Alkaline Comet Assay	F344 rats (m)	oral (gavage)	28-29 days	0, 100, 250, 500	EMS/ENU	Duodenum, Kidney, Liver, Lung, Glandular Stomach	STYRENE: No statistically significant response increases at any dose in Duodenum, Kidney, Lung, or Liver tissue. Low but statistically significant increase in Glandular Stomach attributable to lower-than-normal response in the vehicle control group for this tissue. No statistically significant trend across dose groups. EMS/ENU: Statistically significant response.
Gollapudi et al. (2025)	488 - Transgenic Gene Mutation Assay	B6C3F1 BigBlue® mice (m)	oral (gavage)	28 days	0, 75, 150, 300	ENU	Duodenum, Liver, Lung, Glandular Stomach	STYRENE: No statistically significant response increases at any dose in Duodenum, Lung, or Glandular Stomach. Low but statistically significant increase in Liver, though within historical vehicle control response distribution, and well below positive control results. No statistically significant trend across dose groups. ENU: Statistically significant response.

m, males; EMS, ethyl methanesulfonate; ENU, N-ethyl-N-nitrosourea

The findings from these OECD test guideline genotoxicity studies provide critical evidence that styrene is not mutagenic or clastogenic/aneugenic *in vivo* and does not induce marked DNA damage in the lungs of two species of rodents. The last observation is notable as the lung is the key target organ of concern reported in the styrene carcinogenicity studies in mice (see Section 2.1.2. Animal Cancer Studies).

In addition to animal studies, the genotoxic potential of styrene was also evaluated in two meta-analyses of occupational epidemiology studies that considered the CAs and MN responses in workers exposed to styrene. The meta-analysis published by Collins and Moore (2019) considered 12 occupational studies that reported MN frequency. The meta-analysis showed that the evidence base lacked consistent response, was equivocal regarding exposure-related activity, and did not support an elevation in MN frequency in styrene exposed workers. In a second meta-analysis based on 18 published studies, Collins and Moore (2021) similarly determined there was "insufficient evidence" to support a conclusion that styrene increased CA frequency risk in workers occupationally exposed to styrene. Moreover, the authors found that potential confounders (e.g., age, gender, and smoking) were related to higher exposure-effect levels, highlighting the importance of accounting for such confounding factors when conducting future epidemiology studies.

A new critical review of the genotoxicity literature for styrene and SO has been prepared for publication later this year. This paper will be submitted to the Agency upon acceptance for publication, as it represents an important synthesis of the relevant genotoxicity evidence base that should be considered as a part of the TSCA prioritization process.[10]

Taken together, the peer-reviewed literature does not indicate that styrene or SO are genotoxic *in vivo* in rodents, and do not support the conclusion that styrene is known or anticipated to be genotoxic in humans.

3.1.2. Animal Cancer Studies

There is limited evidence of styrene tumorigenicity in animal toxicity studies, with the literature indicating that styrene-related cancer responses are species and strain specific. As documented and reviewed by Cruzan et al. (2018), the only consistent finding in long-term carcinogenicity animal studies is the induction of lung tumors in B6C3F1 (NCI, 1979) and O20 (Ponomarkov & Tomatis, 1978) mouse strains following oral gavage and in CD-1 mice after inhalation exposure (Cruzan et al., 2001). In contrast, no lung tumors were observed in C57BL6 mice or in rats administered styrene by oral gavage or via inhalation exposure (Conti et al., 1988; Cruzan et al., 1998; NCI, 1979; Ponomarkov & Tomatis, 1978). Cruzan et al. (2018) further noted that styrene animal tumorigenicity lacks multi-site and multi-species activity; the tumors developed late (increase in tumors were only observed after 18 months of exposure) in cancer bioassays; the tumors were

[10] The pre-submission citation is as follows: Pottinger LH, Gollapudi BB. A Critical Review of Styrene and Styrene-7,8-oxide Genotoxicity Literature: An Update. Manuscript under preparation.

mostly benign in nature; and did not result in increased tumor-associated mortality in the animals. This limited tumorigenic response is inconsistent with known genotoxic carcinogens.

Sophisticated mechanistic research on the primary cancer of concern – lung tumors – demonstrate that mouse lung tumors are mouse-specific and of low relevance to human cancer risk. There have been several weight-of-the-evidence MOA analysis studies published for styrene and SO carcinogenicity that demonstrate support for a threshold-based mode of action in animal tumorigenicity. These analyses are based on a collection of 13 robust *in vivo* subchronic animal study data sets collected across a wide range of exposure concentrations and durations (Cruzan et al., 2018).

Cruzan et al. (2018) found that these data sets support the identification of a molecular initiating event directly attributed to the metabolism of styrene via the mouse-specific CYP2F2 enzyme. Metabolism of styrene by this enzyme results in metabolites that activate Nr4a signaling and induce a mitogenic response. Longer-term modifying factors include down-regulation of Nr4a genes and shifts in both circadian clock transcription factors (TFs) and other TFs, linking circadian clock to cellular metabolism. Gene expression changes indicative of cytotoxicity or activation of p53-mediated DNA-damage pathways were identified at various doses and durations of exposure to styrene. In the absence of CYP2F2 metabolism, or CYP2F1 metabolism in transgenic mice, neither styrene nor SO produce cytotoxic or proliferative changes in lung. Studies showing the lack of SO toxicity in both CYP2F2 knock-out mice and CYP2F1 (humanized) transgenic mice support the conclusion that SO is not the proximate metabolite accounting for lung toxicity and tumorigenicity in styrene exposed mice. The evidence of this mode of action is supported by the observations that SO is only formed in humans primarily by CYP2E1 and is not subsequently metabolized by CYP2F1 to ring-oxidized metabolite(s) to a concentration associated with lung toxicity or tumorigenic risk. The role of CYP2F2 metabolism in this mode of action is consistent in rats since 1) rats have less CYP2F (2F4) than mice, and 2) rats produce less ring-oxidized styrene metabolites with no cytotoxic, proliferative, or tumorigenic changes in lungs even with styrene exposures up to 1000 ppm for two years (Cruzan et al., 2018). As such, the mode of action by which styrene results in lung tumors in mice is not relevant to humans.

The mechanistic evidence base also includes whole-genome transcriptomic assessments in mouse strains sensitive (wild-type) or genetically modified (insensitive) mice to styrene-induced lung toxicity (Andersen and Bus, 2020; Andersen et al., 2018; reviewed by Banton et al., 2019 and Bus et al., 2024). These analyses support the non-genotoxic mechanism in which styrene-induced lung tumors in mice result from mitogenic stimulation of Clara cells in mouse lungs via CYP2F2-mediated formation of styrene ring-oxidized metabolites and or ring-oxidized metabolites of SO (Cruzan et al., 2018).

Thus, lung tumors in styrene exposed susceptible mouse models are not relevant to humans due to species differences as demonstrated in sophisticated mechanistic toxicology studies.

3.1.3. Epidemiology Studies

Several epidemiology studies have examined the potential association between occupational styrene exposure and cancer risk in a variety of industries, primarily the fiber-reinforced polymer composites (FRP), styrene/polystyrene production, and synthetic rubber industries. While there are reports of elevated cancers or cancer-related mortality in some of these workplace studies, the observations are not consistent across studies and lack exposure–response relationships (Banton et al., 2019).

A comprehensive systematic review by Collins and Delzell (2018) of available cohort and case-control studies found no strong and consistent indication of a causal association between styrene and non-Hodgkins's lymphoma (NHL) or NHL subtypes, all leukemia or leukemia subtypes, or cancers of the esophagus, pancreas, lung, or kidney. As a part of their analysis, the authors used the well-established Hill criteria for causation (Hill, 1965) to summarize the strengths and limitations of the available studies providing evidence for each type of cancer. As is typical of the epidemiological literature, Collins and Delzell (2018) found that the human evidence for styrene exposure associations with cancer outcomes suffer from methodological limitations such as reliance on mortality data, lack of quantitative exposure estimates, and lack of information on lifestyle factors. Additionally, confounding factors and biases cannot be ruled out in the few studies that suggest a potential association between styrene exposure and cancer outcomes.

New cohort updates for two styrene epidemiology studies have been prepared for publication later this year, together with a further analysis of potential healthy worker survivor bias for one of the cohorts. These will be submitted to the Agency upon acceptance for publication, as they represent important updates to key styrene epidemiology study cohorts that should be considered as a part of the TSCA prioritization process. They are as follows:

- Egnot NS, Fairbanks H, and Leleck OM. Historical Cohort Study of Male Styrene-based Products Manufacturers: A 33-year Mortality Update. Manuscript under preparation.
- Egnot NS, Leleck OM, Fairbanks H, Ramirez R, Hernandez A, and Marsh G. Historical Study of Workers Exposed to Styrene in the US Reinforced Plastics and Composite Industry: Mortality Update. Manuscript under preparation.
- Hernandez A, Egnot NS, Leleck O, Allen H, Ramirez R, Marsh GM. Historical Study of Workers Exposed to Styrene in the US Reinforced Plastics and Composite Industry: Evaluation of Healthy Worker Survivor Bias. Manuscript under preparation.

Overall, the epidemiologic evidence does not suggest a causal association between styrene and any form of cancer in humans and does not provide sufficient exposure response data for deriving plausible health-based toxicity values.

3.1.4. Limitations of IARC's 2019 Styrene Cancer Hazard Assessment

In their most recent monograph of styrene, IARC (2019) upgraded their cancer classification of styrene from a Group 2B "possible" human carcinogen to a Group 2A "probable" human carcinogen. Part of the rationale IARC used to justify the new classification was that the Agency had also classified the styrene metabolite (SO) as a Group 2A carcinogen due to "strong evidence"

that SO's electrophilic character induces DNA adducts *in vitro* and *in vivo* and is genotoxic (IARC, 2019). As discussed above, current state of the science reviews of the genotoxic potential of styrene and SO – in addition to the recent series of high-quality *in vivo* genotoxicity studies – have comprehensively assessed and demonstrated that styrene is not a genotoxic hazard for humans (Moore et al., 2019; Collins and Moore, 2019; Collins and Moore, 2021; Gollapudi, 2023; 2024; Gollapudi et al., 2025).

The most recent genotoxicity reviews and studies cited above were published at the same time or after IARC's 2019 assessment, so the IARC's assessment does not reflect the current state of the science. However, other important data existed at the time of IARC's updated assessment that should have played a role in the decision to ***not*** upgrade the cancer classification. For example, the IARC analysis of SO genotoxicity failed to consider the role that internal SO dosimetry has on the relevance of SO genotoxic potential in carcinogenic outcomes. If SO were the primary driver of styrene carcinogenicity in mice, one would expect a clear relationship between blood SO levels and tumor outcomes, yet the available data show the opposite: the peak blood concentration of SO in mice chronically exposed at the highest styrene tumorigenic exposure concentration (160 ppm) is about 5.5-fold lower than the peak concentration observed in the highest non-carcinogenic exposure level (1000 ppm styrene) in the chronic rat bioassay (Cruzan et al. 1998, 2001).

Furthermore, IARC (2019) failed to take the findings of styrene physiological-based pharmacokinetic (PBPK) modeling to their logical conclusions, which illustrate that internal levels of SO in humans estimated from to styrene metabolism are inadequate to pose a genotoxic threat. While IARC noted that the PBPK analysis by Filser and Gelbke (2016) "predicted the concentrations of styrene and SO in the blood of humans and rats after oral exposure to styrene to predict genotoxic potential", what Filser and Gelbke (2016) actually observed contradicts the IARC position that SO genotoxicity is a key to styrene carcinogenicity. The PBPK analysis showed that styrene metabolism to SO is saturated following inhalation or oral exposure in rats and humans such that the maximum blood concentrations of SO cannot exceed 0.33 μg/ml in rats and 0.036 μg/ml in humans. The evidence from human exposure studies supports this as blood SO levels measured in human volunteers exposed to 50 ppm styrene for 2 hrs only averaged 0.0008 μg/ml (Johanson et al., 2000 as reviewed by Cruzan et al., 2018). Importantly, these blood SO concentrations are several orders of magnitude lower than those necessary to elicit genotoxic effects in human cell assays (reviewed by Cruzan et al., 2018).

Although IARC assessments are limited to hazard classifications, the authors of one of the seminal papers cited in the IARC Preamble (2019) (i.e., The 10 Key Characteristics of Carcinogens; Smith et al., 2016) clearly advocate for the relevance of dose response for determining the role of the key mechanistic events of carcinogenesis:

> *Other considerations include whether multiple mechanisms might contribute to tumor development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals, and whether a unique mechanism might operate in a susceptible group.* (Smith et al., 2016)

As Bus et al. (2024) concluded, "[t]he IARC analysis avoids necessary integration of dosimetry and dose–response considerations that are critical to establishing the plausibility of genotoxicity MOA evaluations." In fact, a very recent risk assessment by the European Food Safety Authority (EFSA) of styrene exposures from food contact materials (EFSA, 2024) considered the IARC 2019 styrene assessment, along with the recent animal study data and species-specific differences in styrene metabolic pathways referenced above and concluded "that there is no scientific evidence that styrene is genotoxic following oral exposure."

Given the very recent toxicological data illustrating the lack of styrene genotoxic potential *in vivo*, and published weight of the evidence assessments discussed above, the current IARC (2019) cancer classification for styrene is of limited use for informing TSCA's styrene prioritization assessment as it does not reflect the best available science.

3.1.5. Alternative Analysis: The proposal of a threshold-based cancer toxicity value for styrene

The weight of the scientific evidence indicates that styrene-induced mouse lung tumors are not driven by a genotoxic mode of action and lack qualitative relevance to human risk (reviewed by Banton et al. 2019; Cruzan et al., 2018). However, if, notwithstanding the clear weight of the scientific evidence, a risk assessor nevertheless was to conservatively assume that the tumor data from animal cancer studies (i.e., mouse lung tumors) were relevant to human health (which SIRC would dispute for the reasons recited here), the mechanistic evidence dictates that the development of a cancer toxicity value should be predicated on a threshold-based mode of action. To this point, Bus et al. (2024) postulated a conservative and health protective approach that further considered the potential human risks of the mouse lung tumors by assuming a non-genotoxic, threshold-based exposure-response relationship for deriving a quantitative carcinogenic toxicity value. This approach is informed by the well-defined non-genotoxic mechanism in which styrene-induced lung tumor in mice result from mitogenic stimulation of Clara cells via CYP2F2-mediated formation of styrene ring-oxidized metabolites and or ring-oxidized metabolites of SO (Cruzan et al., 2018).

For their quantitative tumor analysis, Bus et al. (2024) identified the CD-1 mouse 2-year styrene inhalation study published by Cruzan et al. (2001) as the key study, using the lung tumor incidence data from male and female mouse exposures to 0, 20, 40, 80, and 160 ppm styrene for BMD modeling. Following EPA BMD modeling guidance (EPA, 2012), Bus et al. (2024) identified a BMDL10 value of 4.7 ppm for incidence of pulmonary adenoma in male mice as the most conservative POD for risk assessment of animal tumorigenicity.

Bus et al. (2024) used the BMDL10 of 4.7 ppm as basis of deriving reference concentrations (RfCs) protective of cancer for both occupational and general populations. To derive the cancer RfC protective of workers, the authors made the following adjustments:

- 6hr/8hr - 6hr daily mouse exposures relative to the assumed 8 hr workdays, and

- 70yr/40yr – 70-year lifetime (analogous to mouse study exposure) relative to an assumed 40-year worker career.[11]

The resulting adjusted POD is 6.2 ppm styrene. The authors applied the following Uncertainty Factors:

- UFL = 1 (POD based on BMDL)
- UFS = 1 (POD from a chronic study)
- UFA = 0.1 (2.5 for toxicodynamic species differences, and 0.04 for toxicokinetic species differences where a chemical specific adjust factor of 100 is applied to the default value of 4 given that PBPK modeling demonstrates mouse lung has 100-fold higher oxidative metabolism of styrene compared to human lungs)
- UFH = 10 (default human individual variability)
- UFD = 1 (robust toxicology database for styrene)

Thus, Bus et al. (2024) derived an alternative cancer-based styrene RfC protective of workers equal to 6.2 ppm (26 mg/m^3). By comparison, Banton et al. (2019) proposed a non-cancer-based occupational RfC of 20 ppm based on ototoxicity observed in workers, which approximates the current occupational threshold limit value (TLV) set by ACGIH (TLV = 20 ppm). These occupational exposure levels are all lower than the NIOSH recommended exposure limit (REL = 50 ppm) and OSHA permissible exposure limit (PEL = 100 ppm).

To derive the cancer RfC protective of the general population, Bus et al. (2024) made the following adjustments:

- 6hr/24hr - 6hr daily mouse exposures relative to 24 hr/day continuous exposure, and
- 5d/7d – 5 days/week mouse exposures relative to 7 days/week continuous exposure.[12]

The resulting adjusted POD = 0.8 ppm styrene. Applying the same Uncertainty Factors described above, Bus et al. (2024) determined that the cancer-based styrene RfC for the general population is equal to 0.8 ppm (3.4 mg/m^3). By comparison, Banton et al. (2019) determined the most conservative non-cancer-based RfC for styrene exposure in the general public to be 3.7 ppm (16 mg/m^3) based on developmental effects observed in a two-generation reproductive study in rats (Cruzan et al., 2005). As noted above, the EPA IRIS RfC and ATSDR chronic inhalation MRLs approximate 0.2 ppm (about 1 mg/m^3), though these toxicity values are based on a small cross-sectional worker exposure study (Mutti et al., 1984) and a less reliable health outcome (dyschromatopsia in human studies; Benignus et al., 2005), respectively.

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[11] No days/week frequency adjustment is necessary since mouse study exposure frequency (5 days/week) is analogous to the assumed occupational days/week frequency.

[12] No lifetime adjustment is necessary since the 2-year mouse study exposure duration is analogous to human lifetime.

3.2. Ototoxicity and developmental effects are the most relevant non-cancer health outcomes associated with styrene exposure

Banton et al. (2019) conducted an extensive review and analysis of the animal toxicology and human epidemiology literature and evaluated all relevant non-cancer health outcomes potentially associated with styrene exposure with the goal of identifying the most scientifically robust dose-response data sets for deriving chronic toxicity values protective of occupational exposures and those experienced by the general public. Their overall evaluation of the styrene literature demonstrated that ototoxicity and developmental/ reproductive toxicity are the most sensitive and appropriate endpoints for assessment of human-relevant health risks (Banton et al., 2019).

For occupational exposures, the authors identified ototoxicity observed in exposed workers as the most sensitive noncancer health endpoint to serve as the basis of an occupational exposure level (OEL). Triebig et al. (2009) studied FRP workers and reported high-quality occupational data of appropriate long and short durations. The authors determined that styrene exposures of approximately 39–49 ppm were not associated with ototoxicity, while past exposures exceeding this range resulted in hearing loss. Based on these observations, and following ECETOC guidelines for deriving occupational exposure levels, Banton et al. (2019) proposed an 8-hr Time-Weighted Average (TWA) occupational exposure level of 20 ppm styrene protective of workers.

To determine the most appropriate chronic styrene exposure level protective of the general population, Banton et al. (2019) identified the developmental findings from the two-generation rat study reported by Cruzan et al. (2005) as the most sensitive endpoint on which to base a chronic inhalation exposure value. The most appropriate POD from this study was identified by the U.K. HSE (2008), which determined the overall study NOAEC to be 150 ppm styrene based on minor, but statistically significant body weight loss only in F2 generation pups. Banton et al. (2019) adjusted the POD to 37.5 ppm to convert the 6 hr/day animal exposures to 24 hr continuous exposures in humans, and applied adjustment factor (AF) recommendations of the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC, 2003; 2010) that address uncertainties associated with inter- and intra-species extrapolation, study duration, dose-response, and specific/severity of the response and overall quality of the data supporting the derived value. Thus, Banton et al. (2019) derived an RfC of 3.7 (15.7 mg/m^3) ppm based on developmental effects for the general population.

It should also be noted that extensive research has been invested in the question of whether or not styrene is an endocrine disruptor. This is largely due to its listing as such by the European Commission (BKH 2000), and EPA including styrene on its List 2 for study in the Agency's Endocrine Disruptor Screening Program (EPA, 2014, as referenced by Banton et al., 2019). Gelbke et al. (2015) critically reviewed the styrene literature for evidence of (anti)estrogenic, (anti)androgenic, thyroid, and prolactin activities. The authors included an assessment of study quality and relevance and integrated the available information in a weight of evidence assessment. The experimental evidence did not support styrene as an endocrine disruptor of estrogenic, androgen or thyroid pathways, as demonstrated by a large number of repeated-dose and multigeneration guideline studies (Gelbke et al., 2015).

More recently, Borgert (2023) performed a systematic literature search to identify relevant studies to evaluate the potential for styrene to act as an endocrine disruptor. As a part of this analysis, Borgert (2023) evaluated study quality of the relevant literature, and applied a weight of evidence approach to evaluate the data. Twenty-two developmental and reproductive toxicity studies along with subchronic and chronic toxicity studies were identified as providing relevant data for evaluating the potential for styrene to caused adverse outcomes attributed to perturbations across the estrogen (E), androgen (A), thyroid (T) and steroidogenesis (S) pathways. In these studies, styrene failed to produce responses consistent with disruption of EATS pathways. Borgert (2023) also evaluated high throughput *in vitro* assay data generated as a part of EPA's EDSP21 and ToxCast programs and found that styrene elicited no EATS pathway responses in any of the relevant EDSP21 assays tested. Borgert (2023) concluded that "styrene cannot be deemed an endocrine disruptor, a potential endocrine disruptor, or to exhibit endocrine disruptive properties."

4. Human Exposure to Styrene

4.1. Overview of Human Exposure

Styrene is a well characterized chemical in terms of its physical-chemical properties, fate and transport in the environment and potential sources of exposures for humans. It is extensively regulated across a wide range of environmental programs which serve to minimize the amount of anthropogenic emissions in the U.S. The body of knowledge regarding human exposures to styrene is extensive, and recent data compiled by SIRC-sponsored investigators regarding occupational, consumer, environmental, and food exposure are of high quality and will be informative for USEPA's TSCA Prioritization Assessment and (if necessary) Risk Evaluation. These studies are summarized below and will be submitted with these comments (See Attachments 1-5).

4.2. Occupational Exposures

Occupational exposure to styrene can occur during the manufacturing of the substance as well as the production and processing of resins, polymers, rubbers, and fiberglass-reinforced plastics (Persoons, 2018). In general, the highest occupational exposures likely occur in the FRP industry (ATSDR, 2010).

Morgott (2024) examined personal exposure measurements to styrene from five North American styrene monomer producing companies from 2001 to 2023. This study is significant as it examines a large data set of recent occupational exposure data at styrene monomer producing companies, where the potential for exposure is significant. Personal exposure measurements are considered high on the hierarchy of exposure assessment strategies because they are generally more representative of actual worker exposures in specific workplaces than estimates generated through exposure modeling.

4.2.1. Industrial Hygiene Measurement Data

Morgott (2024) examined personal exposure measurements collected from five North American styrene monomer producing companies from 2001 to 2023. These measurements were taken from workers in six job categories during the production of styrene monomer:

1. Equipment cleaners,
2. Lab personnel,
3. Maintenance,
4. Shipping/receiving,
5. System operators, and
6. Sampling technicians.

This analysis included occupational exposure measurements from long term samples (greater than 15 minutes to less than 480 minutes; N = 778), and short-term samples less than 15 minutes (N = 192). The samples were normalized to 15-min time-weighted average (TWA) and 8-hour TWA results. A majority of short-term (58%) and long-term (81%) samples were below the analytical limit of detection (LOD). Non-detect measurements were conservatively estimated with Regression on Order Statistics (ROS) for lognormal distributions and the LOD divided by the square root of two (1.414) for non-lognormal distributions. The author used USEPA's ProUCL (v 5.1) software to calculate statistics of the results.

Notably, only 3 out of 192 short term styrene measurements exceeded exposure limits at the time of sampling, which resulted in a 1.6% exceedance fraction, which is below the OSHA compliance standard of 5%. Additionally, the mean personal 8-hr TWA exposures did not exceed 0.4 ppm for any job category, which is below the current occupational exposure limits for styrene. The calculated 8-hr TWA exposure concentrations ranged from 0.10-0.40 ppm as the central tendency value and 0.2-0.9 ppm as the 95% upper confidence limit (UCL). The mean 15-minute TWA values ranged from 0.17-19 ppm, and the 95^{th} percentile UCLs were 0.2-31 ppm.

4.2.2. Occupational Exposure Modeling

In addition to the assessment of personal exposure measurements, Morgott (2019) also explored the performance of the ChemSTEER model as a tool for predicting occupational exposures to styrene, and to understand its strengths and limitations. Morgott (2019) used ChemSTEER to predict inhalation and dermal occupational exposures to styrene during the following manufacturing processes:

1. Styrene monomer production,
2. Unsaturated polyester resin formulation, and
3. Open-mold fabrication of fiber-reinforced polymer products.

Model inputs for inhalation included production and use volumes obtained from published literature and online sources (Statistica, 2019; USITC, 2019), fractional amount of styrene in formulation obtained from historical summaries (Forsdyke and Starr, 2022; Dholakiya, 2012), average amount of resin produced by each plant estimated from information from the U.S. Census Bureau (USCB, 2018), emission factors estimated using published emission factors (ACMA, 2019), and consumption of styrene-resins modeled after boat manufacturing facilities (ACMA, 2004). Most ChemSTEER default model assumptions were utilized, except for operating days, which was modified according to EPA's use of ChemSTEER in recent TSCA risk evaluations, and ventilation rate, which was modified for operations taking place outdoors.

Overall, Morgott (2019) concludes that the ChemSTEER model performed well at predicting inhalation exposure levels compared to published measurements from the European Union Risk Assessment Report for styrene (EU, 2008). Notable exceptions were for unsaturated polyester resin formulation, where the model provided higher predictions, and indoor loading of drums and totes, where the model also gave higher estimates because it did not account for vapor capture and control devices.

Model inputs for dermal exposures included default model assumptions from EPA/OPPT's 2-Hand Dermal Contact with Liquid Model, such as skin retention, skin surface area, and styrene weight fraction. The author also used the updated model from the 1-BP TSCA risk evaluation, which included the new variables of skin absorption, body weight, and use of personal protective equipment (PPE). Default assumptions changed in the styrene modeling included body weight and the absorption factor.

For the applied dermal dose, the results were higher than expected when compared to other published estimates for all scenarios. Morgott (2019) determined that these outcomes were likely due to the model variable of skin contact after comparing the ChemSTEER results with a European model (Estimation and Assessment of Substance Exposure Model) (EU, 2008). The applied dose predictions from ChemSTEER were used to calculate an absorbed dermal dose. These results yielded an absorbed central tendency dose ranging from 0.01-0.2 mg/kg/day and high-end values ranging from 0.3-0.6 mg/kg/day when gloves were not utilized.

4.2.3. Overall Quality of the Occupational Data

The occupational styrene exposure analyses (Morgott, 2024; Morgott, 2019) employed sound scientific principles to derive high quality, yet conservative estimates of occupational styrene exposures to workers. The industrial hygiene data was collected using validated methods including (OSHA Method 80, OSHA Method 1014, and NIOSH Method 1501) and detailed information was available for each sample included in the analysis. These analyses followed well-established industrial hygiene practices to ensure that exposures to workers, a sensitive population, are properly characterized. The modeling exercise demonstrated that the ChemSTEER model will generate overestimates of exposure in some circumstances and modeling results may warrant validation before being used as the basis for decision making.

4.3. Consumer Exposures

Styrene may be present intentionally or unintentionally in a wide variety of consumer products, making consumer exposures a relevant condition of use. Morgott (2020a) modeled exposures to both users and bystanders of consumer product applications of styrene. These unpublished modeling studies included a variety of products with higher likelihoods of inhalation exposures to styrene.

4.3.1. Consumer Product Use Exposure Modeling

Morgott (2020a) used the USEPA's Consumer Exposure Model (CEM v.2.1) to estimate peak, 8-hour TWA, and 24-hour TWA styrene exposures to consumers who use five products:

1. Caulk,
2. Gelcoat resin,
3. Putty/filler,
4. Surface primer, and
5. Structural adhesive.

This analysis also considered potential exposures to bystanders, which may include sensitive populations. These five products were identified since it could be confirmed online that they contained 1-40% of styrene monomer, and the product type matched a default CEM category.

This study was not designed to estimate reasonably likely exposures. This study conservatively assumed that all products were used in worst case conditions, where no personal protective equipment or ventilation was utilized. Other conservative assumptions included that the packaging volume was used as the product mass rather than the CEM default value and CEM default parameters were used for each high intensity use scenario. Additionally, it was assumed that the consumer started using the product in the morning and stayed at home all day. Furthermore, adjustments to the CEM input and reporting parameters were adopted from the TSCA-related consumer exposure assessment for N-methyl pyrrolidone (NMP) conducted by the USEPA.

The modeled airborne concentrations included peak exposure concentrations ranging from 1.5-16 ppm, 8-hour TWA concentrations ranging from 0.5-1.8 ppm, and the 24-hour TWA concentrations ranging from 0.2-0.6 ppm. Furthermore, the acute and chronic dermal dose rates ranged from 10-447 mg/kg-day 0.07-2.45 mg/kg-day, respectively. The highest peak exposure was for the spray application of the surface primer (16 ppm) and the highest dermal dose was for the gelcoat resin. The dermal dose rate could not be calculated for the surface primer because skin absorption is not predicted by CEM for spray applications.

Morgott (2020a) noted that the model provided reasonable worst-case estimates of styrene exposures, however the estimates are skewed high compared to published measurements, as the CEM model does not consider the reactivity of styrene, and the amounts removed during the curing process. Despite the conservative nature of the exposure estimates, the worst case 24-hr TWA

concentrations are still lower than the state-of-the-science chronic cancer (0.8 ppm) and noncancer (3.7 ppm) RfC values for the general public (Bus et al., 2024; Banton et al., 2019). Morgott (2020a) explains that future modeling efforts should include an experimental determination of the emission rate for more accurate exposure estimates.

4.3.2. Indoor Air Concentrations

As reviewed by Banton et al. (2019), styrene in residential indoor air is associated with carpets, rubber, and adhesive, though outdoor sources (e.g., long-range transport of compounds associated with traffic emissions and other combustion sources) contribute to the majority (approximately 58%) of indoor styrene air levels. Morgott (2021) performed exposure modeling for indoor levels of styrene following the installation or use of three home products during a home renovation in a bedroom or kitchen of a standard-sized home:

1. Carpeting,
2. Vinyl flooring, and
3. Latex paint.

Morgott (2021) used environmental chamber assay data published by Hodgson (1999) to estimate peak, 8-hour and 24-hour inhalation TWA exposures using the Multi-Chamber Concentration and Exposure Model (MCCEM). The author noted that although MCCEM is an older and less supported Tier 1 mass-balance model as it can only be used on the Windows XP operating system, it is nevertheless reliable and has been used in several previous TSCA-related risk evaluations.

This MCCEM modeling predicted that during the summer with lower ventilation rates, the 24-hr TWA would range from 12 to 15 $\mu g/m^3$ and maximum concentrations ranged from 15-19 ug/m^3. These results are consistent with published literature for home use of styrene-based products and seasonal variability in exposures. For example, Gallon et al. (2020) reported styrene levels of 15.1 $\mu g/m^3$ and greater than 22 $\mu g/m^3$ inside the bedrooms following delivery of newly constructed homes. These results are similar to studies that have found background levels of styrene in the apartment and residential buildings up to approximately 10 $\mu g/m^3$ (Kozielska et al., 2020). Morgott (2021) also notes that other factors can contribute to styrene exposures inside of a home, and reports on two studies that review data that demonstrate higher styrene air concentrations in homes of smokers versus non-smokers (Rothberg et al., 1998; Banton et al., 2019).

In addition, toys made of commercial styrene-containing polymers can be sources of consumer exposure. Banton et al. (2019) evaluated the potential exposures in children from mouthing of toys and estimated that daily styrene exposures from this source pathway in children ranged from 0.0000047 to 0.00005 mg/kg-d in children up to 3 years old, or approximately an order of magnitude less than estimates of dietary styrene intake. The combined exposures to styrene from toy mouthing and diet are still orders of magnitude lower than the EPA's conservative styrene reference dose (RfD) of 0.2 mg/kg-d (EPA, 1992), and the state of the science RfD of 2.5 mg/kg-d derived by Banton et al. (2019).

4.3.3. Overall Quality of the Consumer Exposure Data

Both Morgott (2020a) and Morgott (2021) employed sound scientific principles to derive estimates of consumer exposure to styrene from products. However, the estimates from Morgott (2020a) are more conservative due to the inherent nature of the CEM model and physical properties of styrene. These analyses follow well-established industrial hygiene practices to ensure that exposures to consumers and bystanders, a sensitive population, are well-characterized. Additionally, the consumer exposure data summarized by Banton et al. (2019) represents a robust and comprehensive evaluation that complements the modeling results of Morgott (2020a, 2021).

4.4. Environmental Exposures

The TSCA Risk Evaluation process also considers releases to the environment. Styrene is one of a number of VOCs that the EPA tracks through several air monitoring programs it oversees for characterizing the composition and magnitude of air toxics concentrations across the U.S. (e.g., the Urban Air Toxics Monitoring Program (UATMP); National Air Toxics Trends Stations (NATTS) network; the Community-Scale Air Toxics Ambient Monitoring Program (CSATAM); and Air Quality System (AQS) database). In their extensive review, Banton et al. (2019) reported that data collected under the EPA's AQS showed that median levels of styrene declined by 7% per year from 2000–2005, and that national annual average styrene concentrations from 2012–2016 were stable, ranging from 0.17 μg/m^3–0.24 μg/m^3, with an overall 5-year average of 0.21 μg/m^3. In a study of the relative importance of commercial, industrial, and mobile sources on ambient air levels of styrene, Yu et al. (2014) reported significantly higher styrene air concentrations at commercial locations (mean = 0.28 μg/m^3) than at industrial locations (0.16 μg/m^3) and mobile locations (0.17 μg/m^3) locations; the higher styrene levels were associated with solvent emissions from coatings/paints and industrial uses (reviewed by Banton et al., 2019).

To this end, Morgott (2021) presents the results of ambient air modeling to characterize outdoor air concentrations from industrial air emissions and surface water modeling to characterize water concentrations from industrial water releases.

4.4.1. Ambient Air Modeling

Morgott (2021) performed SCREEN3 modeling to estimate the outdoor air concentrations of styrene at the nearest residential location from manufacturing sites. EPA's SCREEN3 model is part of the General Population and Ecological Exposure from Industrial Releases module within EPA's E-FAST 2014 program.

This analysis was conducted to characterize potential inhalation styrene exposures to the general population (nearest residential location) from manufacturing sites' emissions. The nearest residential location was selected to be indicative of a potentially sensitive population. Point and area source emission rate data from the Toxic Release Inventory (TRI) database was utilized to determine stack and fugitive releases of styrene. This study conservatively assumed that facilities were operating 300 days a year in a rural location. SCREEN3 model default assumptions were utilized except for distance from residence.

The modeled maximum 24-hr outdoor average concentration of styrene associated with the top 20 annual TRI stack emitters in 2015-2019 ranged from 1 to 6 mg/m^3. For the top 20 sites with fugitive releases, the 24-hr outdoor average concentration of styrene ranges from 3 to 50 mg/m^3. The author notes that these results were higher than observed measurements reported in various studies (Mukerjee et al., 2018; Knighton et al., 2012), so a more advanced screening modeling, such as AERSCREEN, or a robust higher tier dispersion model should be utilized. The author reports that AERSCREEN was not used initially due to SCREEN3's easy to use platform and general acceptance by regulatory authorities. However, this information appears to be dated as AERSCREEN is now the primary screening air dispersion model promoted by EPA (EPA, 2024).

Another way to evaluate the relative styrene exposure levels in ambient air is to consider the EPA Regional Screening Level (RSL) tables[13] and annual AirToxScreen risk assessments of hazardous air pollutants (HAPs). The EPA derived a highly conservative air screening level of 1 mg/m^3 (based on the EPA IRIS RfC) for styrene exposures to the general public in residential areas across the country. According to conservative inhalation exposure estimates from EPA's most recent completed AirToxScreen assessment[14], the U.S. population is exposed to very low levels of styrene in outdoor air, with average and 95th percentile inhalation exposure level estimates of 0.00089 and 0.0033 mg/m^3, which are more than 1,000 and 300 times lower, respectively, than EPA's conservative styrene RSL for the general public. Banton et al. (2019) calculated a similar central tendency and upper bound styrene inhalation exposure estimates for the general population of 0.0008 to 0.0024 mg/m^3 (Table 11). Again, these exposure estimates are well below the highly conservative health-based exposure screening level derived by EPA.

4.4.2. Surface Water Modeling

Morgott (2020b) performed E-FAST modeling to predict surface water styrene concentrations resulting from industrial and commercial operations in the United States. The predicted concentrations were compared to surface water measurements from the Water Quality Portal (WQP).

Modeled waterways included those for 20 National Pollutant Discharge Elimination System (NPDES) permit numbers associated with the highest annual release amounts listed in the 2015-2019 Toxic Release Inventory (TRI). The facilities identified were generally associated with using styrene as a starting material for manufacturing of foam and resin products. The resulting estimates were then compared with historical surface water measurements (2019-2023) from the Water Quality Portal (WQP). It was conservatively assumed that facilities were operating under USEPA default estimates for release days and historical flow rates for waterways.

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[13] EPA, Regional Screening Levels (RSLs) - Generic Tables (last updated Nov. 24, 2024), available at https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables.

[14] EPA, 2019 AirToxScreen: Assessment Results (last updated Aug. 27, 2024), available at https://www.epa.gov/AirToxScreen/2019-airtoxscreen-assessment-results.

Using TRI reporting, the modeled surface water levels ranged from 0.5 ng/L to 650 ug/L under low flow conditions. A review of EPA databases found these surface water levels to be higher than expected, as the 90th and 95th percentiles of measured concentrations ranged from 0.5-1.1 ug/L. The author notes that these discrepancies are likely because E-FAST does not consider fate and transport processes that result in the removal of styrene from surface water. This is supported by the fact that most styrene released to water volatilizes to the atmosphere, with half-lives ranging from less than 1 hour to 51 days depending on various factors (e.g., depth, degree of turbulence, and environmental conditions; reviewed by Banton et al., 2019).

4.4.3. Overall Quality of Environmental Exposure Data

Both Morgott (2020b) and Morgott (2021) employed sound scientific principles to derive estimates of general population and environmental exposure to styrene. However, both papers reveal over-conservatism with the employed models, so it is recommended that higher tier modeling be conducted to better characterize representative environmental styrene concentrations and general population exposure estimates.

4.5. Food Exposures

Most styrene exposures occur through inhalation. However, styrene also can be found in food, although it is a minor contributor to overall intake. Styrene can be a natural component of foods, but the presence of styrene in food is primarily a result of migration from styrenic food contact materials (FCM) (ATSDR, 2010). Many studies have measured the migration of styrene from FCM, and safe exposure levels (SEL) have been determined. For example, Gelbke (2014) reviewed toxicology and human biomonitoring studies to derive a safe exposure level for ingestion of styrene from food packaging. Conservative assumptions included the potential consumer exposure to styrene (1 kg food/day for adults), determination of the point of departure (ototoxicity endpoint from worker biomonitoring studies), and various assessment/safety factors. The proposed safe exposure level was set to 95.6 mg/person/day, which is an order of magnitude higher than expected consumer exposures.

Gelbke (2014) employed sound scientific principles to derive a safe exposure level for ingestion of styrene from food packaging. Many conservative estimates were built into the model as well as consideration of sensitive populations, such as children and pregnant women. Additionally, the derived safe exposure level derived is higher than conservative consumer exposure estimates.

4.6. Biomonitoring

Biomonitoring data is useful tool in understanding population exposures since it measures aggregated human exposure from all sources of exposure and exposure routes. Biomonitoring studies of occupationally exposed workers compared to a control population can help determine occupational exposures to a chemical as well as background exposures of the same chemical to the general population. With styrene specifically, biomonitoring can help determine general population exposures to non-industrial styrene sources, such as cigarette smoking or exposures through food. It should be noted that both metabolites typically measured for styrene exposure, mandelic acid (MA) and phenylglyoxylic acid (PGA), are also the major urinary metabolites for ethylbenzene exposure (Capella et al., 2019). There is another metabolite that is specific to styrene

exposure, 4-vinylphenol, but is not typically measured as it is excreted in small amounts compared to other metabolites and thus is not informative in determining low level background exposures (Manini et al., 2003).

One of the studies that Gelbke (2014) reviewed to determine the proposed SEL was a biomonitoring study by Triebeg et al in 2009. Triebig et al. (2009) conducted a biomonitoring study evaluating styrene exposures to laminators from a boat building plant in comparison to matched controls from the same plant. The biomonitoring data was converted to equivalent airborne concentrations of styrene, and the airborne concentration was used to categorize workers for comparison. Workers in the high and chronic duration exposure group demonstrated a notable increase in hearing loss. The authors concluded that this hearing loss was likely due to historically high styrene exposure concentrations of about 50 ppm on average, not the current styrene exposure levels at the boat building plant.

5. Existing EPA Regulations of Styrene

Styrene is extensively regulated by EPA across a wide range of environmental programs including the Clean Air Act, the Clean Water Act, the Comprehensive Environmental Response, Compensation, and Liability Act, and the Resource Conservation and Recovery Act. SIRC is preparing additional information on the current regulation of potential styrene exposures and environmental releases as applicable to styrene's conditions of use, together with additional information on workplace engineering, and administrative controls, and use of PPE, as applicable.

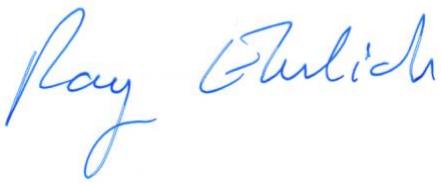
6. Conclusion

SIRC and its member companies appreciate the opportunity to provide EPA with the most current scientific information characterizing potential hazards and exposures to styrene under its conditions of use. However, given the current multiyear risk evaluation backlog, TSCA section 6(b)(2)(C) requires the Agency to pause initiating additional prioritization candidates. Accordingly, the Agency should withdraw each of the five pending prioritization candidate designations (including for styrene and ethylbenzene) at least until the risk evaluation backlog is resolved.

Alternatively, EPA should withdraw the styrene candidate designation and replace it with another chemical to assure the Agency can meet future obligations under TSCA section 6(b)(3)(C). That provision requires EPA to commence a new risk evaluation as soon as an earlier risk evaluation is completed. Based on the information and analysis provided, if the styrene prioritization were completed, it would be classified as a Low Priority for risk evaluation and, in that event, styrene would be unavailable to replace a High-Priority Substance exiting the risk evaluation process as currently planned by the Agency. To avoid a future gap, EPA should withdraw styrene from prioritization now and designate a different substance more likely to be designated High-Priority.

SIRC would be pleased to discuss further the several issues raised in the comments.

Very truly yours,



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