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Re: Comments of the Styrene Information and Research Center, Inc.
Initiation of Prioritization for Ethylbenzene (CASRN 100-41-4) Under TSCA; Notice of Availability, 89 Fed. Reg. 102,903 (Dec. 18, 2024) Docket No. EPA-HQ-OPPT-2018-0487

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's) selection of ethylbenzene 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 membership represents the vast majority of the North American styrene and ethylbenzene manufacturing industry. For nearly 40 years, SIRC and its members have sponsored and (in nearly all cases) published peer-reviewed studies regarding the exposures and potential hazards that ethylbenzene poses to human health. These include comprehensive state of the science reviews of ethylbenzene exposures in North America, as well as a critical review of the underlying evidence regarding the potential endocrine disruption properties of ethylbenzene. Full references for the citations in the comments above are provided below.

The enclosed comments reference and summarize the best available, peer-reviewed science concerning the relative hazards of ethylbenzene, information on occupational and consumer exposures to ethylbenzene under its conditions of use. The toxicological and epidemiological evidence is insufficient for designating ethylbenzene as a known human carcinogen. The evidence demonstrates that ethylbenzene is an otherwise low potency chemical that presents ototoxicity at exposures considerably higher than those documented for workers, consumers and the general

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

public (see Sweeney et al., 2015). As such, ethylbenzene should be considered a Low-Priority Substance.

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 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 ethylbenzene 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 ethylbenzene prioritization were completed, ethylbenzene would be classified as a Low-Priority Substance for risk evaluation and, in that event, ethylbenzene 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 ethylbenzene 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 the reconsideration of the "whole chemical approach," the appropriate consideration of PPE in risk evaluation, and whether EPA may evaluate less than all

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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/).

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 chemical, the corresponding risk management rules, or both. All this additional work, coupled with the expected loss of staff and contractor 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 evaluation within the required three-year period.[7]

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[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.

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

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 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 unsustainably 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

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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).

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 Ethylbenzene

Ethylbenzene (CASRN 100-41-4) is an aromatic hydrocarbon synthesized by the alkylation of benzene with ethylene and by other methods. Ethylbenzene is one of the highest production volume chemicals in the United States. It is produced primarily to serve the styrene manufacturing industry. Approximately 98% of manufactured ethylbenzene is used for the manufacture of styrene, or in the coproduction of styrene monomer with propylene oxide (Kester and Morgott, 2023). Ethylbenzene is also a natural component of crude oil and refined petroleum products and some natural gas streams.

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 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 ethylbenzene a score of "one" (low) for persistence and bioaccumulation, while administering scores of "three" (high) for both the hazard and exposure criteria. EPA justified the high score for hazard and exposure by noting ethylbenzene was a "Possible human carcinogen" and noting that ethylbenzene 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, ethylbenzene that are critical for EPA to evaluate as it considers a decision on whether ethylbenzene should be prioritized for TSCA risk evaluation. The literature includes many peer-reviewed studies of ethylbenzene that have been published since the 2014 TSCA Workplan. As described below, the weight of the scientific evidence does not support ethylbenzene either as a "high acute or chronic toxicity" chemical or as a known human carcinogen. Additionally, ethylbenzene 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 ethylbenzene is neither persistent nor bioaccumulative, it is clear that ethylbenzene does not

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[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.

present an unreasonable risk of 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. Confirm that the Prioritization Candidate is Limited to Ethylbenzene Manufactured as a Neat Substance and Excludes Class 2 Substances that May Contain Ethylbenzene but have their own TSCA Inventory Identity.

The notice identifies the candidate chemical designated for prioritization as ethylbenzene, identified as CASRN 100-41-4.[10] As noted, nearly all synthetic ethylbenzene manufactured or produced as ethylbenzene is used as an intermediate for the manufacture of styrene. However, ethylbenzene is also a natural component of crude oil and refined petroleum products and some natural gas streams which are Class 2 unknown or variable composition products or complex reaction products (UVCBs). These products have unique chemical identities and CASRNs, separate from ethylbenzene and have their own listings on the TSCA Chemical Inventory. Examples of TSCA Inventory listings of products that may contain ethylbenzene but are not ethylbenzene (CASRN 100-41-4) include:

CASRN	CA Index name	Chemical Substance Definition
68475-70-7	*Aromatic hydrocarbons, C6-8, naphtha-raffinate pyrolyzate-derived*	A complex combination of hydrocarbons obtained by the fractionation pyrolysis at 816ºC (1500ºF) of naphtha and raffinate. It consists predominantly of aromatic hydrocarbons having carbon numbers predominantly in the range of C6 through C8, including benzene.
68476-45-9	*Hydrocarbons, C5-10 arom. conc., ethylene-manuf.-by-product*	A complex combination of hydrocarbons produced by distillation of products from a cracking process in the ethylene plant. It consists of aromatic hydrocarbons having carbon numbers predominantly in the range of C5 through C10, primarily benzene.
68553-14-0	*Hydrocarbons, C8-11*	n/a
68650-36-2	*Aromatic hydrocarbons, C8, o-xylene-lean*	The complex combination of hydrocarbons obtained from the distillation of aromatic streams. It consists predominantly of aromatic hydrocarbons having a carbon number of C8, with o-xylene present only in trace amounts, and boiling in a range of approximately 136ºC to 139ºC (277ºF to 283ºF).
68920-06-9	*Hydrocarbons, C7-9*	n/a
68921-67-5	*Hydrocarbons, ethylene-manuf.-by-product distn. residues*	The complex combination of hydrocarbons produced by the distillation of products from ethylene manufacturing process.
68989-41-3	*Aromatic hydrocarbons, biphenyl-rich, thermal hydrodealkylation residues*	The complex combination of hydrocarbons obtained from a thermal hydrodealkylation process. It consists predominantly of aromatic hydrocarbons, primarily biphenyl, and boiling approximately above 110ºC (230ºF).

[10] High-Priority Substance Designations Under the Toxic Substances Control Act, 89 Fed. Reg. at 102,907.

CASRN	CA Index name	Chemical Substance Definition
71808-48-5	*Hydrocarbons, C5-8, coal-tar raffinates*	A complex combination of hydrocarbons obtained as the raffinate from the desulfurization extraction of crude coal tar. Composed primarily of benzene, toluene, ethylbenzene, xylenes, cyclohexane, cyclopentane, methylhexane and methylpentane.

We understand that the "ethylbenzene" that is the subject of the candidate designation refers to synthetic ethylbenzene produced primarily for the styrene value chain, or other ethylbenzene identified as CASRN 100-41-4 as manufactured, imported, produced, processed, distributed and used as a separate product.

Correspondingly, EPA should confirm that the candidate designation does not refer to ethylbenzene as a natural component of Class 2 hydrocarbon products, such as crude oil and some refined petroleum products and natural gas streams. This is appropriate because these additional identities were not listed in the designation notice and, if ethylbenzene ultimately is designated as High-Priority, the manufacturers only of one or more of the Class 2 products would not be subject to the risk evaluation fee applicable to EPA initiated risk evaluations. It is also appropriate to treat the styrene-stream and petroleum-stream ethylbenzenes differently for risk assessment purposes given distinct differences in the uses, the manner and extent of exposure, and the unique chemical hazard issues raised by the Class 2 mixed petroleum-stream ethylbenzene. That is, while ethylbenzene in the styrene stream will present as neat ethylbenzene in occupational and commercial exposure contexts, exposure to petroleum-stream ethylbenzene will always be as part of a complex mixture with co-exposures to other, potentially hazardous products in a wide range of proportions (e.g., "BTEX" compounds and mixtures), and in a wide range of industrial, commercial and, potentially, consumer contexts. BTEX compounds and residues are widely distributed in the environment.

SIRC submits that data characterizing any hazards potentially associated with exposure to neat ethylbenzene will not be directly applicable to exposure to BTEX or other complex hydrocarbon mixtures. Likewise, data characterizing any hazards potentially associated with exposure to BTEX or other complex hydrocarbon mixtures cannot be used to describe any hazards associated with exposure to neat ethylbenzene. Although the two streams will share ethylbenzene as a common element, any effects of co-located hydrocarbons in the Class 2 mixtures cannot be disaggregated from any effects of ethylbenzene. It is appropriate to review any risks associated with complex hydrocarbons separate from neat ethylbenzene. The petroleum-stream ethylbenzene and styrene-stream ethylbenzene have very different use patterns, and including consideration of one stream with the other will complicate the analysis.

4. Hazard Potential Evidence for Ethylbenzene

There is limited evidence to support ethylbenzene as a human carcinogen. Ethylbenzene has been shown to induce kidney and testicular tumors in rats and liver and lung tumors in mice exposed via high inhalation exposure concentrations. Ethylbenzene is a non-genotoxic carcinogen that operates to induce these tumors through modes of action (MoAs) in rodents that are either not relevant to humans and/or produce neoplastic lesions in animal models only at dose levels in

excess of the kinetic maximum dose (KMD) as presented by Burgoon et al. (2024). The KMD is the maximal dose at which the kinetics of ethylbenzene is unchanged relative to lower doses; essentially, the highest dose at which kinetic processes are not saturated. In the case of ethylbenzene, this dose (corresponding to an inhalation exposure concentration) is approximately 200 ppm (868.44 mg/m^3). Burgoon et al. (2024) concludes that the cancer endpoints observed in ethylbenzene exposed rodents occurred at concentrations above the estimated KMD range, and as such, are not relevant for use in protecting humans especially considering what we know of ethylbenzene exposure levels in workers and the general population (see Section 5, below). As such ethylbenzene does not pose a cancer risk to humans.

The non-cancer effects of ethylbenzene demonstrate ototoxicity as the most sensitive and relevant outcome for human health. Using a PBPK model, a chronic reference concentration (RfC) of 0.3 ppm (1.3 mg/m^3) has been proposed based on outer hair cell (OHC) loss in the apical region of the cochlea (LOAEL 200 ppm) (Sweeney et al., 2015). This point of departure is highly conservative as OHC losses of up to 50% in this region do not cause measurable hearing loss (Prosen et al., 1990). The LOAEL for audiometric threshold changes was 400 ppm. In other non-cancer effects, there is no evidence that ethylbenzene is an endocrine disruptor, and the most sensitive non-neoplastic lesion, hyperplasia of the pituitary gland (pars distills) results in a less conservative RfC value that derived for ototoxicity and therefore should not drive a human risk assessment.

The ethylbenzene chronic and subchronic animal toxicity studies are described below. The potential modes of action (MOAs) for induction of tumors, their relevance to human risk assessment and reference dose derivation is discussed. However, this discussion should be reviewed in light of the fact that most ethylbenzene exposures in these experimental studies were conducted at levels in excess of the KMD.

4.1. There is Limited Evidence to Support Ethylbenzene as a Human Carcinogen

There is limited evidence that ethylbenzene can elicit the development of tumors through MOAs that are relevant to humans based on the chronic inhalation toxicity and carcinogenicity animal studies conducted by the U.S. National Toxicology Program (NTP, 1999).

NTP concluded that there was clear evidence of carcinogenicity in male rats (renal tubule adenoma or carcinoma, Leydig cell tumors), and some evidence of carcinogenicity in female rats (renal tubule adenoma), male mice (alveolar/bronchiolar adenoma) and female mice (hepatocellular adenoma or carcinoma). However, the lack of consistency in response between species and sexes, coupled with MOA assessments that do not support the human relevance of these lesions, indicates there is limited evidence to support ethylbenzene as a human carcinogen. This is further emphasized by data that indicates the kinetic maximum dose (KMD[11]) ranges from 8 to 17 mg/L venous ethylbenzene in rats and 10 to 18 mg/L venous ethylbenzene in humans which corresponds to an inhalation concentration of approximately 200 ppm ethylbenzene (Burgoon et al., 2024).

[11] KMD is defined as the maximal external dose at which kinetics are unchanged relative to lower doses, e.g., doses at which kinetic processes are not saturated (Burgoon et al., 2024).

NTP conducted their chronic bioassay using concentrations of 75, 250 or 750 ppm. Tumor responses occurred at levels above the KMD (750 ppm) which may therefore be qualitatively different from the response produced at lower doses. This reinforces their lack of relevance to human risk assessment.

4.1.1. *Ethylbenzene is Not Genotoxic*

As summarized herein, there is exhaustive literature – including guideline assays conducted by NTP – to support a weight of the evidence determination that ethylbenzene is not a genotoxic hazard to humans and therefore is not a MOA for the limited tumor observations in animal cancer studies. Ethylbenzene did not elicit genotoxicity responses in several animal (*in vivo*) studies. For example, ethylbenzene was negative for micronuclei formation, and did not induce any signs of clastogenicity in the peripheral blood of male and female B6C3F1 mice that inhaled up to 1000 ppm (4,340 mg/m^3) ethylbenzene for 6 hours/day, 5 days/week for 13 weeks (NTP, 1999). Specifically, the NTP reported that ethylbenzene did not show effects on either micronucleated polychromatic erythrocytes (PCEs) or changes to the PCE to normochromatic erythrocytes (NCE) ratio (NTP, 1999).

Ethylbenzene was consistently non-mutagenic in the Ames assay, having been tested in four *S. typhimurium* strains up to a toxic dose of 1,000 µg/plate in the presence of absence of metabolic activation. It is also reported to be negative in mutagenicity assays conducted in *E. coli* WP2 and WP2uvrA, and in *S. cerevisiae* JD1 with and without activation at dose levels up to 2,000 µg/plate (NTP, 1999 and references reported therein including Dean et al., 1985; Florin et al., 1980; Nestmann et al., 1980; Zeiger et al., 1992). Ethylbenzene was consistently negative in reliable assays of clastogenicity. Chromosome aberration and sister chromatid exchange tests conducted in cultured Chinese hamster ovary cells were both negative at concentrations of up to 125 µg/mL ethylbenzene with and without metabolic activation. At higher dose levels (150 µg/mL) toxicity was observed (NTP, 1999).

Ethylbenzene has produced variable mutagenic responses in L5178Y tk+/- mouse lymphoma cells. In an early study, a positive response was observed at the highest tested nonlethal concentration (80 ug/mL) in the absence of S9 metabolic activation, but this response occurred in the presence of significant cytotoxicity (relative growth was reduced by 34% and 13% of control in 2 trials) (McGregor et al., 1988). In a more recent mouse lymphoma forward mutation assay, conducted according to OECD Test Guideline 476 and US EPA OPPTS 870.5300, ethylbenzene did not show any activity in the absence and presence of metabolic activation at non-toxic concentrations in 3 trials (Seidel et al., 2006).

Overall, ethylbenzene has been extensively tested in a series of genotoxic and mutagenic assays, and the weight of the evidence demonstrates that ethylbenzene is not mutagenic or genotoxic. As such, further evaluation of its genotoxic potential is unnecessary, and it would be inappropriate and scientifically unjustifiable to consider genotoxicity as a potential MOA for the few tumor responses that occur in ethylbenzene animal cancer studies.

4.1.2. Ethylbenzene Induced Kidney Tumors in Rats Are Not Relevant to Human Health

In the NTP chronic ethylbenzene cancer study (NTP, 1999), rats and mice were exposed to concentrations of ethylbenzene of 75, 250 or 750 ppm for two years, renal tubule adenoma or carcinoma were reported in male and female rats, but not mice. Increased mortality in male rats (NOAEL 250 ppm) was considered related to the observed renal effects driven by increased severity of chronic progressive nephropathy (CPN), a rat specific lesion identified to drive the renal tumor response. Considering CPN has no human correlate, ethylbenzene is not likely to be a human carcinogen by this mode of action. Non-cancer effects more relevant to human health were reported by NTP and are more suitable for consideration of toxicity value derivation.

In the NTP 2-year study in rats (NTP, 1999), the key cancer findings were renal tubule adenoma or carcinomas in male and female F344 rats (750 ppm). These tumors occurred in conjunction with an increased incidence of renal tubular hyperplasia at 750 ppm (males and females), increased severity of CPN (750 ppm males and all exposed female groups), and decreased survival of 750 ppm (male rats). Based on these findings, NTP established a NOAEL of 250 ppm (NTP, 1999). The concurrent findings of high severity CPN, increased proliferative lesions, atypical tubule hyperplasia and adenomas are all features associated with CPN-induced kidney tumors (Hard, 2002). Hard (2002) reevaluated the kidneys from the NTP carcinogenicity bioassay and concluded that the increase in renal tumors was strongly associated with an accompanying exacerbation of CPN to advanced grades of severity following exposure to ethylbenzene. It was noted that the mild induction of α2u-globulin nephropathy may have had a minor contributing factor in male rats, but in the highest exposure group, three of seven adenomas in female rats were associated with advanced CPN which was similar in male rats. Hard (2002) concluded that the primary MOA for the increased renal tumor incidence was based on ethylbenzene's ability to exacerbate CPN, a spontaneous age-related lesion in rodents. This is reviewed by Sweeney et al. (2015) who again emphasized that CPN is a common age-related finding in F344 rats for which there is no human correlate and is therefore not relevant to human risk assessment (Hard, 2002). The decreased survival of male rats was considered by NTP to be related to the renal effects described above (NTP, 1999) and therefore, also not relevant to human risk assessment.

In conclusion, the kidney tumor response should not be considered for human risk assessment as it occurred only at high exposure concentrations (750 ppm or ~3,257mg/m^3), in rats only, at concentrations that far exceeded the KMD, and at an order of magnitude higher than expected human exposures (OSHA PEL: 100 ppm, 434 mg/m^3).

4.1.3. *Testicular Tumors in Male Rats Are Not Relevant to Human Health*

Another tumor type observed in the 1999 NTP ethylbenzene chronic carcinogenicity study was the interstitial (Leydig) cell adenoma in the testis, which occurred in male rats but not mice. The evidence indicates that while these tumors are common lesions observed in rats by the end of their lifespan, these tumors do not have a human correlate. As such, the Leydig cell tumors observed in rats chronically exposed to ethylbenzene are not evidence that ethylbenzene is a human carcinogen.

A possible MOA for ethylbenzene and Leydig cell adenomas has not been firmly established, but a genotoxic MOA should be excluded given the weight of the evidence discussed above. All other non-genotoxic MOAs proposed for this tumor response (Rasoulpour et al. 2014) have low or no relevance to human health. Sweeney et al. (2015) identified potential key events in a MOA (increased testosterone metabolism) for ethylbenzene induced Leydig cell adenomas in male rats, but within this framework there are a number of data gaps that lead to the conclusion that there is insufficient data to establish a MOA. However, this tumor response is a common finding in male rats; it occurred at an incidence (88%) in male rats exposed to 750 ppm ethylbenzene which was marginally above the historical control range (54-83%). No carcinomas were observed in these animals; however, a negative correlation was noted between the incidence of Leydig cell hyperplasia and adenomas (Sweeney et al., 2015). This correlation likely arises from the fact that the combined incidence of Leydig cell hyperplasia or adenoma approaches 100% in exposed and unexposed animals. The primary distinction between these two lesions lies in the size of the nodule with adenomas classified when the diameter exceeds one or three seminiferous tubule cross-sections (Clegg et al., 1997). As hyperplasia progresses to adenoma, a decrease in hyperplasia incidence is expected alongside an increase in adenoma occurrence. Therefore, ethylbenzene exposure may slightly enhance Leydig cell hyperplasia. However, rats are one of the most sensitive species for Leydig cell adenoma development, with the incidence nearing 100% (NTP, 1999) that live out their natural life span. By comparison, the occurrence of testicular cancers of any type in humans is low (<0.6%; SEER, 2021).

In summary, the Leydig cell tumor response reported in the 1999 NTP study should not be considered for human risk assessment as it was only observed at high exposure concentrations (750 ppm or ~3,257 mg/m^3), and only occurred in rats at a concentration that far exceeded the KMD and at an order of magnitude higher than expected human exposures (OSHA PEL: 100 ppm, 434 mg/m^3).

4.1.4. *Liver Tumors in Female Mice Are Not Relevant to Human Health*

Hepatocellular adenomas or carcinomas were additional tumors reported in the NTP chronic carcinogenicity study, though their occurrence was limited to female mice, but not male mice or rats of either sex. A potential MOA based on a phenobarbital-type response suggests liver tumors found in female mice are unlikely to occur in humans and do not provide strong evidence that ethylbenzene is a human carcinogen (Sweeney et al., 2015).

The key events in a phenobarbital MOA for the induction of female mouse liver tumors is described by Elcombe et al. (2014). Liver adenomas and carcinomas developed following ethylbenzene exposure (750 ppm) and are proposed to occur through a non-genotoxic MOA similar to phenobarbital involving CAR activation leading to increased cell proliferation, and development of hepatic foci. In female mice, a correlation between the eosinophilic foci incidence and formation of liver tumors was observed which is a characteristic of a phenobarbital-type response. In addition, studies show ethylbenzene can induce CYP2E1, 2B1, and 2B2 from which CAR activation can be inferred (as summarized and reviewed by Sweeney et al., 2015). These observations support the use of the phenobarbital MOA in this assessment (reviewed by Sweeney et al., 2015). Chronic exposure to phenobarbital shows no increased cell proliferation or

development of hepatic foci in human hepatocytes *in vitro* (Elcombe et al., 2014), or in male mice or rats of either sex chronically exposed to ethylbenzene via inhalation exposure (NTP, 1999) and has not been associated with liver tumors in humans (Holsapple et al., 2006). Based on the phenobarbital MOA, the relevance of female mice liver tumors to human risk assessment is limited.

In conclusion, the liver tumor response should not be considered for human risk assessment as it occurred only at the highest concentration tested (750 ppm or ~3,257mg/m^3), only occurred in female mice, was only observed at an exposure concentration that far exceeded the KMD and at an order of magnitude higher than most occupational exposures (OSHA PEL: 100 ppm, 434 mg/m^3).

4.1.5. *Lung Tumors in Mice Are Not Relevant to Humans*

The final tumor type reported in the 1999 NTP chronic carcinogenicity study was the alveolar/bronchiolar adenoma, the incidence of which were observed to be statistically increased only in male mice. A potential MOA based on the toxicity of related chemicals (such as styrene) show marked differences between human and mouse lung in terms of the distribution, expression, and/or activity of CYP2F2, an enzyme critical to the development of lung toxicity in mice (Cruzan et al., 2009). These tumors are likely not relevant to humans based on differences in the metabolism of ethylbenzene in mouse compared to human lung and as such supports that ethylbenzene would not induce lung tumors in humans.

The potential MOA for ethylbenzene induced male mice lung tumors following exposure to 750 ppm is proposed based on an adverse outcome pathway (AOP) for Cyp2F2-mediated effects and existing data for structurally dissimilar chemicals like styrene and naphthalene (Hill and Conolly, 2019). Ethylbenzene is metabolized in mouse lung to produce 4-ethylphenol and 2-ethylphenol which are subsequently metabolized to catechols and hydroquinones that undergo auto-oxidation to reactive, cytotoxic quinone metabolites (2,5-ethylquinone and 3,4-ethylquinone) (Saghir et al., 2006; 2009). At high exposure levels, the production of these metabolites can deplete intracellular GSH, which can ultimately lead to increased cytotoxicity. This cytotoxicity drives chronic cell proliferation, which promotes lung tumor development. CYP2F2 is present at high levels in mouse lung, but at much lower levels in rat or human lungs (Cruzan et al., 2009; 2012). Its activity is linked to club (Clara) cells, which are more abundant in mouse lungs than human lungs (Cruzan et al., 2009). Human cells selectively express CYP2F1, an enzyme associated with lower ring oxidation activity. The key role of CYP2F2 in mouse lung toxicity is clearly demonstrated by studies using CYP2F2 knockout mice, which unlike their wildtype counterparts do not develop lung toxicity (necrosis, club cell exfoliation, and increased uptake of bromodeoxyuridine) when exposed to styrene (Cruzan et al., 2012).

The marked difference between human and mouse lung in terms of the number and morphology of club cells, and the distribution, expression, and/or activity of CYP2F1 vs. CYP2F2 in the respiratory tract, indicate that humans are less sensitive than mice to ethylbenzene-induced lung toxicity due to the production of reactive metabolites. Human lung microsomes contain CYP2F1 but this does not, or only marginally, metabolizes ethylbenzene (Saghir et al., 2006; 2009). Based

on this pathway, the pulmonary effects of ethylbenzene are of little relevance to humans and these data do not provide evidence that ethylbenzene is a human carcinogen.

In conclusion, the lung tumor response is not considered relevant for human risk assessment as they only occurred at high exposure concentrations (750 ppm or ~3,257 mg/m^3), were only observed in male mice, and only occurred at a concentration that far exceeded the KMD and at an order of magnitude higher than most occupational exposures (OSHA PEL: 100 ppm, 434 mg/m^3).

4.2. The Literature on the Non-Cancer Effects of Ethylbenzene Demonstrate Ototoxicity is the Most Sensitive and Most Relevant Outcome for Human Health

4.2.1. *Summary of the Evidence for Ototoxicity*

The primary noncancer endpoint of concern from ethylbenzene exposures is ototoxicity. This should be considered the most sensitive and relevant outcome for human health. A PBPK model was used by Sweeney et al. (2015) to derive an RfC of 0.3 ppm (1.3 mg/m^3) based on outer hair cell (OHC) loss in the apical region of the cochlea (LOAEL 200 ppm). This point of departure is highly conservative as OHC losses of up to 50% in this region do not cause measurable hearing loss (Prosen et al., 1990).

In adult male Sprague-Dawley rats, ototoxicity was the key noncancer finding in a 13-week toxicity study (Gagnaire et at., 2007). Audiometric thresholds at the four frequencies tested (2, 4, 8 and 16 kHz) were increased in rats exposed to 400 ppm ethylbenzene and higher compared to controls ($p<0.05$). Some dose-dependency was observed in hearing loss with 23-27 decibels (dB) in the rats exposed to 400 ppm ethylbenzene and 44-49 dB in both the 600 and 800 ppm ethylbenzene exposed rats. The ethylbenzene points of departure for hearing loss were a NOAEL of 200 ppm and LOAEL of 400 ppm.

An observed loss of third row outer hair cells (OHC3) in the Organ of Corti occurred at all ethylbenzene concentrations tested (200, 400, 600 and 800 ppm) with four of the eight rats exposed to 200 ppm ethylbenzene exhibiting up to 30% OHC3 loss. Based on these findings, no NOAEL could be determined, and a LOAEL of 200 ppm was established. This point of departure can be considered conservative as 30% hair cell loss does not result in a detectable loss of hearing. It should also be noted that the OHC3 loss occurred at the KMD (200 ppm) whereas hearing loss occurred above this threshold.

In a separate mechanistic study by Zhang et al. (2023), neonatal rat cochlear progenitor cells were exposed to ethylbenzene in culture, which produced a significant increase in the percentage of apoptotic cells compared to controls. In addition, the authors reported there was a dose dependent decrease in mRNA expression and protein levels of β-catenin, transcription factor T cell factor/lymphoid enhancer factor 1 (LEF-1), and leucine-rich repeat-containing G-protein coupled receptor 5 (Lgr5) (Zhang et al., 2023). Silencing β-catenin expression using shRNA to block the Wnt/β-catenin signaling pathway in neonatal rat cochlear progenitor cells led to mitochondrial damage, whereas overexpression of β-catenin (via infection of cells with a β-catenin lentivirus overexpression vector) prevented ethylbenzene-induced mitochondrial damage and apoptosis. In a separate experiment, Sprague-Dawley rats microinjected with recombinant β-catenin lentivirus

in the ear and exposed to 200 ppm (867 mg/m^3), 400 ppm (1734 mg/m^3), and 800 ppm (3468 mg/m^3) ethylbenzene for 13 weeks showed significant mitigation of ethylbenzene associated hearing loss with cochlear β-catenin overexpression ($p<0.05$) (Zhang et al., 2023). These studies show evidence that mitochondrial damage triggered by Wnt/β-catenin signaling inactivation can lead to apoptosis of cochlear cells and contribute to ototoxicity characterized by hearing loss.

No developmental neurotoxicity studies specifically designed to evaluate ototoxicity in developing rats have been conducted, but a 2-generation reproductive toxicity study found no exposure-related effects on acoustic startle responses or neurohistopathology outcomes at ethylbenzene exposures up to 500 ppm in F2 Sprague-Dawley rats (postnatal day 20 and 460). The absence of an acoustic startle response suggests the lack of an ototoxic effect at these life stages (Faber et al., 2006; 2007).

Existing non-cancer RfC values from the EPA IRIS assessment (0.2 ppm) was derived in 1991 (EPA, 1991) based on a rat 6-month study administered by oral gavage (Wolf et al., 1956). The findings in the Gagnaire et al. (2007) study represents more recent and robust scientific experimental data. As such, Sweeney et al. (2015) applied an updated PBPK-model to the OHC3 loss dose-response data to derive a state-of-the-science chronic RfC of 0.3 ppm (1.3 mg/m^3) for ethylbenzene.

The ethylbenzene PBPK model used to derive the RfC is summarized as follows:[12]

- A rat model was used per study design for simulations to determine a weekly AUCR when animals reach a pseudo-steady state (to build up ethylbenzene in fat); AUCR at 504 hrs-AUCR at 336hr.
- The BMDL of hair cell loss response (272.8 mg-h ethylbenzene/L of RPT/ wk[13]) was used as the dose after dividing it by the composite uncertainty factor (UF)[14] of 100. This represents the Target Human Internal Dose (AUCR).
- A human ethylbenzene model was run (until pseudo-steady state was achieved) with constant exposure to match the AUCR.

It should be reiterated that this RfC is based on a highly conservative point of departure as OHC losses of up to 50% in the apical region of the cochlea do not cause measurable hearing loss (Sweeney et al., 2015).

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[12] See supplemental data from Sweeney et al. (2015) and ACC (2007).

[13] Lower confidence limit on dose predicted to cause 1.05% loss of OHC3, determined using EPA's Benchmark Dose Software (BMDS). Dose represents the 95% upper confidence limit. RPT, richly perfused tissue.

[14] UF Level extrapolation, effect (1) x UF Subchronic effects (3) x UF Animal to human extrapolation (3) x UF Human populations, sensitive (10) x UF Database sufficiency (1)

4.2.2. *Ethylbenzene Does Not Disrupt Endocrine Pathways*

Ethylbenzene is currently on the second list of chemicals prioritized for Tier 1 screening subject to testing under EPA Endocrine Disruptor Screening Program (EDSP). It is anticipated that manufacturers and importers will submit "other scientifically relevant information" (OSRI), to evaluate the endocrine activity of ethylbenzene to assist EPA irrespective of the regulatory program under which a chemical will be evaluated. A recently published systematic evaluation of the potential endocrine disrupting activity of ethylbenzene determined there was no evidence to show ethylbenzene acts as an endocrine disruptor using OSRI as defined by EPA's EDSP (Borgert, 2025).

Borgert (2025) performed a systematic literature search to identify relevant studies, evaluated study quality, and applied a weight of evidence approach to evaluate the data. Results from high throughput (ToxCast) endocrine assays and EDSP 21 assays were not integrated into the assessment as they cannot be relied on due to ethylbenzene's volatility. In particular, quality control for the chemical showed no detectable ethylbenzene in the assay wells. Developmental and reproductive toxicity studies along with subchronic and chronic toxicity studies provided sufficient data to assess if exposure to ethylbenzene caused adverse outcomes attributed to perturbations across the estrogen (E), androgen (A), thyroid (T) and steroidogenesis (S) pathways. In these studies, ethylbenzene failed to produce responses consistent with disruption of EATS pathways. Any effects in endocrine-sensitive endpoints that were observed occurred only at dose levels above its KMD and as such are not relevant to potential effects at lower dose levels or in humans. Thyroid follicular cell hyperplasia observed in female mice in the 1999 NTP chronic carcinogenicity study was likely the result of non-specific toxicity that leads to hyperplastic changes in many organs and tissues (liver, kidney and pituitary), rather than through a MOA involving the thyroid hormone pathway. It is well established that many non-endocrine MOAs can produce changes in endocrine endpoints (Marty et al., 2018). Therefore, it is highly unlikely that this endpoint response reflects a potential for thyroidal activity of ethylbenzene.

In summary, as changes in endocrine endpoints occurred only at high exposure concentrations (750 ppm or ~3,257 mg/m^3) that far exceeded the KMD and therefore were likely the result on non-endocrine MOAs, there is inadequate evidence to classify ethylbenzene as an endocrine disruptor for human risk assessment.

4.3. Overall Conclusion on the Ethylbenzene Hazard

There is limited evidence to support ethylbenzene as a potential human carcinogen. Ethylbenzene is not mutagenic or genotoxic and tumor responses in the NTP ethylbenzene cancer bioassay occur through MOAs that are not relevant to humans or only occurred at dose levels in excess of the kinetic maximum dose (corresponding to an inhalation concentration of approximately 200 ppm (868.44 mg/m^3).

The non-cancer effects of ethylbenzene demonstrate ototoxicity as the most sensitive and relevant outcome for human health. A chronic RfC of 0.3 ppm (1.3 mg/m^3) ethylbenzene was derived using a PBPK model, as described by Sweeney et al (2015), based on outer hair cell loss in the apical region of the cochlea (LOAEL 200 ppm) (Gagnaire et al., 2007). This point of departure is highly

conservative as OHC losses of up to 50% in this region do not cause measurable hearing loss (Prosen et al., 1990). The LOAEL for audiometric threshold changes was 400 ppm. In other non-cancer effects, the available evidence does not support classifying ethylbenzene as an endocrine disruptor and therefore should not drive a human risk assessment.

5. Human Exposure to Ethylbenzene

5.1. Overview of Human Exposure

Ethylbenzene 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 ethylbenzene 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. The Consortium provides a summary of the ethylbenzene exposure reports below for USEPA's review and consideration and has attached the associated detailed reports this comment document (See Attachments 1-5).

5.2. Occupational Exposures

Styrene production and industrial paint production and application are relevant conditions of use for ethylbenzene, and exposures for workers in these industries have been characterized.[15] Kester and Morgott (2023) present a robust analysis of full-shift ethylbenzene air concentrations that characterize potential long-term exposure to styrene production workers. Additionally, unpublished data for short term air concentrations in the styrene production industry (Morgott, 2022) as well as modeled air concentration estimates for industrial paint production and applications workers (Morgott, 2024a) are also available and described in the sections below.

5.2.1. *Industrial Hygiene Measurement Data*

Morgott (2022) examined personal exposure measurements collected from 10 styrene production facilities from 2000 to 2020. These measurements were taken from workers in six job categories:

1. Supervisors and administrators,
2. System operators,
3. Maintenance mechanics,
4. Equipment cleaners,
5. Sampling technicians, and

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[15] As noted in section 3, above, ethylbenzene may be present as a constituent in other chemicals or mixtures (e.g., mixed xylenes, styrene, and petroleum products). Occupational exposures to ethylbenzene as part of such mixtures may occur in a variety of industries which manufacture or use those substances; however, we understand that any ethylbenzene from those sources is outside the scope of the current prioritization exercise.

6. Laboratory personnel.

This analysis included occupational exposure measurements from long-term samples (greater than 15 minutes to less than 480 minutes; N=527), and short-term samples (less than 15 minutes; N=111). The long-term samples that were greater than 15 minutes, but less than 480 minutes were normalized to 8-hour TWA results. A large majority of long-term (87%) and short-term (94%) samples were below the analytical limit of detection (LOD). Nevertheless, non-detect measurements were conservatively estimated as the LOD divided by the square root of two (1.414). The author used USEPA's ProUCL software to determine the statistics of the results which agreed reasonably well with Sweeney et al. (2015).

The calculated 8-hr TWA exposure concentrations ranged from 0.12-0.30 ppm as the central tendency value and 0.20-0.85 ppm as the 95% upper confidence limit (UCL). The mean 15-minute TWA values were 0.26-0.43 ppm, and the 95th percentile UCLs were 0.45-1.04 ppm.

5.2.2. *Occupational Exposure Modeling*

Although measured airborne ethylbenzene air concentrations were available to characterize potential worker exposures at styrene manufacturing facilities (Morgott 2022), these measurements did not include occupational exposures to workers in the paint formulation and application industries. Additionally, the measurements also did not include dermal exposures. As such, Morgott (2024a) used ChemSTEER, a USEPA model used by the Agency for TSCA -related occupational exposure assessments, to predict inhalation and dermal ethylbenzene exposures to workers in three scenarios:

1. Ethylbenzene chemical manufacturing,
2. Paint formulation, and
3. Industrial paint application (automotive painting in a vehicle assembly plant).

Each of these three scenarios was linked in series using the fractional amount of ethylbenzene passing through each operation. Model inputs were obtained from 2019 production data (Statista, 2023), 2022 import data (Indexbox, 2023), 2016 manufacturing data (EPA, 2016), 2005 worker data (EPA, 2016), and 1985 market data extrapolated to 2023 (IARC, 1985; Statista, 2024). Default assumptions were also used to determine TSCA-related exposure estimates for a variety of jobs related to these three scenarios. The ChemSTEER estimates for chemical manufacturing agreed well with published measurements (Banton and Krishnan, 2006; Kester and Morgott, 2023) for all but one job function (loading and unloading of totes). Modeled estimates also aligned with measured values at paint formulation facilities (Purvis et al., 2001; Ghobakhloo et al., 2023; Hosseinzadeh et al., 2023), but with the same exception. Only the high-end exposure estimates for the loading and unloading of totes were greater than 600 ppm, which were considered an unreliable outlier given the modest air flows assumed at indoor loading/unloading stations and a failure of the model to compensate for the use of vapor capture devices. Several studies reported average measured exposures to automotive paint shop employees that were consistent with the central tendency modeled estimates (Golbabei et al., 2018; Khoshakhlagh et al., 2023; Amin and Nasrabadi, 2024; Castaño et al., 2019; Wang et al., 2013), whereas measurements from two other

studies generally agreed with the high-end modeled values (Farshad et al., 2013; Harati et al., 2017). However, there were no experimental data available for ethylbenzene skin absorption, preventing the ability to verify the dermal exposure modeling in ChemSTEER.

5.2.3. *Overall Quality of the Occupational Data*

The occupational ethylbenzene exposure analyses (Morgott, 2022; Morgott, 2024a) employed sound scientific principles to derive high quality, yet conservative estimates of occupational ethylbenzene exposures to workers. The industrial hygiene data was collected using validated methods including: OSHA Method 7, OSHA Method 1002 and NIOSH Method 1501. 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. In general, worker exposure estimates using the EPA ChemSTEER model were more conservative than the actual measurements in the industrial hygiene exposure study.

5.3. Consumer Exposures

Ethylbenzene may be present intentionally or unintentionally in a wide variety of consumer products. Morgott (2024b,c) modeled exposures to both users and bystanders of consumer product applications. These unpublished modeling studies included a variety of products with higher likelihoods of inhalation exposures to ethylbenzene. Kester and Morgott (2023) examined the larger body of evidence, including personal air measurements, to evaluate typical residential ethylbenzene exposures. These studies are described below.

5.3.1. *Consumer Product Use Exposure Measurements and Modeling*

Morgott (2024b) used the EPA's Consumer Exposure Model (CEM v.2.1) to estimate peak, 8-hour TWA, and 24-hour TWA ethylbenzene exposures to consumers who use five products:

1. Gel stain,
2. Paint spray thinner,
3. Paint stripper,
4. Wood finish coating, and
5. Surface primer.

This analysis also considered potential exposures to bystanders, which may include sensitive populations. The five paint- and coating-related products included in the analysis were selected because a small portion (i.e., 1%) of technical grade ethylbenzene manufactured in the U.S. for styrene production may be present as a residual in paint products. Although the vast majority of ethylbenzene is consumed for the manufacture of styrene and styrene monomer (an intermediate used in various chemicals), a small amount of ethylbenzene may be either intentionally or unintentionally added to paints and coatings which contain styrene-based chemicals (Kester and Morgott, 2023; Morgott, 2024b). In addition, ethylbenzene in paint-related products may be the result of adding mixed xylenes which can also contain ethylbenzene (ACC, 2005; EC, 2007).

This modeling effort relied upon the ethylbenzene composition information provided in safety data sheets (SDSs) for the paint related products, which typically ranged from 5 to 7% ethylbenzene but was reported as high as 29%. These modeled exposure estimates conservatively assumed that personal protective equipment, such as gloves and respirators, were not worn and that enhanced ventilation equipment was not used. Other conservative assumptions included that the entire contents of a 1-gallon container would be used for each product, and CEM default parameters were used for each high-intensity use scenario. 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 4.6 to 118 ppm, 8-hour TWA concentrations ranging from 2.4 to 14.8 ppm, and the 24-hour TWA concentrations ranging from 0.8 to 5.0 ppm. Furthermore, the acute dermal dose rates ranged from non-detect to 94.3 mg/kg-day.

5.3.2. *Indoor Air Concentrations*

Morgott (2024c) performed exposure modeling for indoor levels of ethylbenzene following the installation or use of three home renovation products in a bedroom or kitchen of a standard-sized home:

1. Polyamide carpeting,
2. Vinyl flooring, and
3. Latex paint.

Morgott (2024c) used environmental chamber assay data published in 1987-2020 to estimate 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 ranged 14 to 18 $\mu g/m^3$, and the maximum concentrations ranged from 18 to 23 $\mu g/m^3$.

Kester and Morgott (2023) also provided some important analysis of potential residential inhalation exposures to ethylbenzene using area and personal air measurements reported in literature. This study noted that the literature has reported inhalation to be the dominant exposure route (70-100%) for all studied consumer products containing ethylbenzene. This analysis indicated that residential indoor air concentrations generally have trended downward with the most recent concentrations at 1.1-1.7 $\mu g/m^3$ (50^{th} percentile) or 11.3-11.9 $\mu g/m^3$ (95^{th} percentile). Moreover, Kester and Morgott (2023) noted that ambient air monitoring data are appropriate for broadly assessing exposures of large populations to ethylbenzene in outdoor air, but they do not represent indoor exposures which was the focus of their study.

5.3.3. *Overall Quality of the Consumer Exposure Data*

The modeling conducted by Morgott (2024b,c) used reliable EPA exposure models that incorporate conservative assumptions for the input variables. The modeled data for the indoor air scenarios represent an upper bound of indoor air concentrations following installation of new building materials and align well with the upper-bound concentrations reported by Kester and Morgott (2023).

5.4. Environmental Exposures

Air and surface waters can be affected by releases containing ethylbenzene. Measured data and a modeling analysis demonstrate ethylbenzene is present at low levels in the environment, and the state of the science demonstrates environmental exposures do not pose an unreasonable health risk to the general population.

5.4.1. *Environmental Measurements and Modeling*

There is evidence that ambient air concentrations of ethylbenzene have been decreasing over the past two decades. Konkle et al. (2020) summarized arithmetic mean concentrations in ambient air for 11 VOCs as reported annually by EPA's National Monitoring Program NMP annual reports and reported mean annual air concentrations approximating 0.1 ppb (0.4-0.5 $\mu g/m^3$) for the 2005-2006 datasets, which had dropped by approximately half in the 2011-2012 and 2013 datasets. These air concentrations are below EPA's conservative residential regional screening level (RSL)[16] for ethylbenzene in ambient air (1.1 $\mu g/m^3$). Considering all potential inhalation sources, Kester and Morgott (2023) reported updated personal air concentrations of 1.7 and 11.9 $\mu g/m^3$, respectively, for the general population, which are well below EPA's IRIS Reference Concentration for ethylbenzene (1 mg/m^3). Additionally, the available data consistently indicate low detection frequency and concentrations well below the MCL in both groundwater and surface water used for drinking (ACC, 2007; Rowe et al., 2007; Carter et al., 2008; EPA 2010, as reviewed by Sweeney et al., 2015).

Morgott (2024d) used E-FAST (2014 version) to model estimates of surface water ethylbenzene concentrations resulting from industrial and commercial activities. Modeled waterways included those for 20 National Pollutant Discharge Elimination System (NPDES) permit numbers associated with the highest annual release amounts listed in the 2019-2023 Toxic Release Inventory (TRI). E-FAST modeling also incorporated data from the Discharge Monitoring Reports (DMR). The resulting estimates were then compared with historical surface water measurements (2019-2023) from the Water Quality Portal (WQP). If E-FAST did not recognize a NPDES permit number, a generic SIC code was selected to identify an appropriate nonspecific waterway as a substitute.

Using TRI reporting, E-FAST modeling produced a mean (± SD) surface water concentration of 6.5 ± 15.1 µg/L, with most of the predictions at 50 µg/L or less. However, using DMR reporting,

[16] 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.

E-FAST estimated a mean (± SD) surface water concentration of 110.2 ± 131.4 µg/L. Measured surface water ethylbenzene concentrations from the U.S. National Water Information System (NWIS, from the U.S. Geological Survey) and the Storage and Retrieval (STORET, from the EPA) databases in 2019-2023 (retrieved from the Water Quality Exchange) had a mean of approximately 0.4 µg/L and a 95th percentile of about 0.7 µg/L.

Morgott (2024d) concluded that E-FAST modeling with site-specific simulations based on a recognized NPDES permit number may produce more realistic results than the generic simulations based on SIC code assignments. This an important observation since the USEPA has treated both types of approaches equally in past TSCA-related risk determinations. Moreover, there were statistically significant differences between TRI and DMR release volumes. Therefore, documentation of E-FAST modeling should include the release volumes data source and whether a site-specific or generic estimation was performed in order to appropriately frame the results. Nevertheless, E-FAST (2014 version) model results are highly conservative as fate and removal processes that can affect ethylbenzene concentrations in surface water are not incorporated in the model and thus likely overestimate real world concentrations.

5.4.2. *Overall Quality of the Environmental Modeling*

Ambient air levels of ethylbenzene have been declining over the past two decades and have been measured at concentrations lower than EPA's conservative RSLs. Additionally, measured surface water ethylbenzene concentrations (mean and 95th percentile of approximately 0.4 and 0.7 µg/L, respectively) were more than an order of magnitude lower than modeled concentration estimates using the conservative E-FAST model with high-end release estimates from industrial and commercial sources (Morgott, 2024d). Notably, the modeling analysis demonstrated the importance of using site-specific model inputs as there can be highly unrealistic estimates which rely on generic SIC codes.

5.5. Food Exposures

The vast majority of ethylbenzene exposures occurs through inhalation. However, ethylbenzene can also be found in food, presenting a condition of use that for consideration in a TSCA Risk Evaluation although it is a minor contributor to overall intake. The presence of ethylbenzene in food is primarily a result of migration from styrenic food contact materials or plant uptake from ambient air pollution. Modeling and measurement studies for ethylbenzene in food are discussed below. Note that exposures from drinking water are likely negligible for the general population because of the consistently low detection frequencies and concentrations (Kester and Morgott, 2023).

5.5.1. *Food Exposure Modeling and Measurements*

The presence of ethylbenzene in food is largely from migration from styrenic food-contact materials (Kester and Morgott, 2023). Ethylbenzene occurrence in plants is most likely attributed to uptake from ambient air pollution (Dirinck et al., 1977; Biedermann et al., 1995; Tang et al., 2000). Ethylbenzene in water can also be taken up by plants or ingested by humans, although it is not expected to bioaccumulate in the aquatic or terrestrial food webs (ATSDR, 2010). Therefore,

Kester and Morgott (2023) focused on kinetic modeling results for consuming ethylbenzene that migrates from styrenic food-contact materials (Lickly et al., 1995; PWG, 1997).

This model, which was modified from the US Food and Drug Administration (FDA) protocol, was based on robust migration datasets (ACC, 2007). The total estimated ethylbenzene migration-derived concentration in food was 0.45 µg/kg. Although FDA's Cumulative Estimated Daily Intake (CEDI) database indicates a greater ethylbenzene concentration in food from migration (3 µg/kg), there is no explanation for how the FDA derived the higher value. In addition, the FDA's Total Diet Study through the mid-2000s reported ethylbenzene in infant formulas at 34-50 µg/kg, whereas the 2014 Canadian Total Diet Study (Cao et al., 2016) reported a substantially lower concentration in infant formulas (0.22-0.59 µg/kg). Given the detailed analysis by ACC (2007) based on substantial datasets and an established, peer-reviewed model that agrees with other reported values, the estimation provided by ACC (2007) and Kester and Morgott (2023) are more defensible and representative of contemporary exposures than the higher value in the FDA CEDI database which lacks details about its derivation.

5.5.2. *Overall Quality of the Food Exposure Modeling*

Although the FDA has published estimates of ethylbenzene concentrations in food from migration, Kester and Morgott (2023) explain that modeling by ACC (2007) is more defensible. This is an important observation given the discrepancies between the FDA and Canadian datasets.

5.6. Biomonitoring

Kester and Morgott (2023) discussed ethylbenzene biomonitoring data from blood, urine, and breastmilk. Although ethylbenzene is metabolized and eliminated rapidly, its ubiquity makes it consistently detected in humans. Ethylbenzene also readily partitions from blood into human milk, making breastmilk a potential exposure route for nursing infants. Thus, biomonitoring can provide a useful indication of dose from all sources of ethylbenzene exposure.

Kester and Morgott (2023) reviewed blood and urine data obtained from the National Health and Nutrition Examination Survey (NHANES) cycles from 2003-2016, the Agency for Toxic Substances and Disease Registry (ATSDR) 1993 health and exposure investigation, the 2011-2013 Gulf Long-Term Follow-up (GuLF) Study, and the 2014-2015 Canada Health Measures Survey (CHMS). These blood and urine biomonitoring data were stratified by both smokers and non-smokers. Ethylbenzene concentrations in the blood of non-smokers was a mean of 0.022-0.100 µg/L (0.056-0.104 µg/L 95th percentile), whereas blood in smokers had a considerably higher mean concentration of 0.056-0.170 µg/L (0.199-0.202 µg/L 95th percentile). Urine biomonitoring data showed a similar trend in which the concentrations for smokers were nearly twice greater than those from non-smokers (Kester and Morgott, 2023).

Smoking status was not available for participants in the breastmilk studies, but participants who were occupationally exposed to ethylbenzene had breastmilk concentrations approximately an order of magnitude greater (2.2 µg/L central tendency, 21 µg/L upper bound) than from the general population (0.11 µg/L central tendency, 0.25 µg/L upper bound). These breastmilk concentrations were largely obtained from studies dating back to the early 1980s. However, Kester and Morgott

(2023) explained that because ethylbenzene concentrations in both air and blood have decreased over time, it is likely that the originally reported general population milk concentrations conservatively overestimate current concentrations.

Although inhalation (occupational and consumer products) accounts for 93-95% of ethylbenzene exposures, other potential sources include diet (migration from styrene food contact materials and uptake from air or water pollution) and dermal contact (consumer products). Biomonitoring data have confirmed that smoking is an unequivocal dominant, non-occupational ethylbenzene exposure source and that children tend to have greater ethylbenzene intakes than adults. Further, exposure biomarkers offer a critical means of evaluating trends in exposure levels. Data from NHANES indicate ethylbenzene exposure has trended downwards for all age groups, consistent with decreasing concentrations in air and diet. Therefore, exposure estimates which result in doses that are consistent with relevant biomonitoring data are most representative and scientifically robust. The total estimated ethylbenzene intakes compiled and reported by Kester and Morgott (2023) demonstrates this concordance.

6. Current EPA Regulations of Ethylbenzene

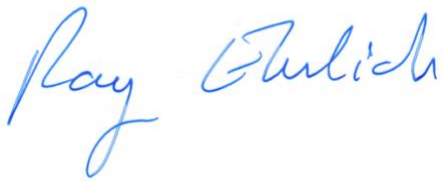
Ethylbenzene is extensively regulated by EPA across a wide range of environmental programs including the Clean Air Act, the Clean Water Act, the Comprehensive Environmental Response, Compensation, And Liability Act, and the Resource Conservation and Recovery Act. SIRC is preparing additional information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

7. Conclusion

SIRC and its member companies appreciate the opportunity to provide EPA with the most current scientific information on the potential hazards and exposures to ethylbenzene under its principal 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 ethylbenzene 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 ethylbenzene prioritization were completed, it would be classified as a Low Priority for risk evaluation and, in that event, ethylbenzene would be unavailable to replace a High-Priority chemical exiting the risk evaluation process as currently planned by the Agency. To avoid a future gap, EPA should withdraw ethylbenzene 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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