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October 18, 2017

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U.S. Environmental Protection Agency
EPA Docket Center (ORD Docket)
Mail Code: 28221T
1200 Pennsylvania Avenue N.W.
Washington, D.C. 20460

Submitted electronically to docket EPA-HQ-ORD-2017-0497-0001

Re: **Integrated Risk Information System (IRIS) Draft Assessment Plan for Ethylbenzene**

Dear Ms. Ross:

The Styrene Information and Research Center[1] (SIRC) is pleased to submit these comments to the U.S. Environmental Protection Agency (EPA) on the draft IRIS Assessment Plan for Ethylbenzene.[2] These comments supplement SIRC's comments at the EPA Science Advisory Board's Chemical Assessment Advisory Committee meeting on September 28, 2017, and the information SIRC submitted in 2014 in response to EPA's problem formulation materials related to ethylbenzene.[3] SIRC appreciates EPA's consideration of all the information now available on

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

[2] *Availability of Integrated Risk Information System (IRIS) Assessment Plans for Nitrate/Nitrite, Chloroform, and Ethylbenzene*. 82 Fed. Reg. 43,539 (Sep. 18, 2017). SIRC serves as a resource for industry, federal and state governments, and international agencies on issues related to the potential impact of exposure to styrene on human health and the environment. Headquartered in Washington, D.C., SIRC was formed in 1987 and is the principal focal point for the public information and research on styrene and ethylbenzene. SIRC is a non-profit organization consisting of voting member companies involved in the manufacture or processing of ethylbenzene and styrene, and associate member companies that fabricate styrene-based products. Collectively, SIRC's membership represents approximately 95% of the North American styrene industry. SIRC's charter also addresses the interests of ethylbenzene producers, and its use in the production of styrene monomer.

[3] 82 Fed. Reg. 42,095 (Sep. 6, 2017) (notice of SAB CAAC Meeting). SIRC submitted the following data on ethylbenzene to EPA in 2014: a discussion paper presenting technical factors that are relevant to whether or not risk managers may prefer an assessment on mixtures containing ethylbenzene rather than an assessment focused on pure ethylbenzene, EPA-HQ-ORD-2014-0526-0005; a discussion paper discussing

ethylbenzene exposure, toxicology and risk, and the agency's proposed approaches to conducting IRIS reviews.

EPA asserts that an IRIS review is warranted because it is of "interest by multiple program or regional offices."[4] Table 1 of the draft assessment plans list these offices and the statutory or regulatory basis of interest. This is not a surprise because ethylbenzene is subject to numerous regulations.[5] Multiple program and regional offices have a continuing interest in ethylbenzene.

The question that the National Center for Environmental Assessment (NCEA) should be considering is not whether another office has an interest in an updated IRIS assessment. The threshold question is whether the listed IRIS values continue to be protective of human health and the environment. This is the question other agency offices should ask NCEA. It is then NCEA's task to address the question.

If the existing values are protective, expending agency resources on a new assessment are unjustified. Based on a review of exposure, toxicology, and regulatory information summarized in these comments, all of which has been available to the agency, the agency's current IRIS reference values remain protective for both cancer and noncancer endpoints. Thus, ethylbenzene is an inappropriate candidate for IRIS review.

Given current budget constraints, a preliminary review of information by the IRIS program staff must be sufficient to support the conclusion that NCEA resources can be better used elsewhere. If such a review is not considered sufficient, this would demonstrate institutional or programmatic problems.

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the human relevance of data from studies in which test animals are dosed at levels above metabolic saturation, EPA-HQ-ORD-2014-0526-0005; a letter from Dr. Ken Olden, EPA-HQ-ORD-2014-0526-0010; a letter to EPA highlighting key points about the scoping process that SIRC believes need to be addressed by NCEA, if EPA is to progress towards Step 1 activity for ethylbenzene, EPA-HQ-ORD-2014-0526-0009; issue papers on the following four topics Genetic Toxicity and Carcinogenicity of Ethylbenzene, Mode of Action for Kidney Carcinogenicity of Ethylbenzene, Developmental and Reproductive Effects of Ethylbenzene, Neurotoxicity and Ototoxicity of Ethylbenzene, EPA-HQ-ORD-2014-0526-0003; a copy of the 2007 assessment conducted by ethylbenzene producers whom SIRC represented for EPA's Voluntary Children's Chemical Evaluation Program for Ethylbenzene, and a copy of the 2005 assessment conducted by the American Chemistry Council for EPA's Voluntary Children's Chemical Evaluation Program for Xylenes, EPA-HQ-ORD-2014-0526-0002; draft slides for a presentation on on-going research related to ethylbenzene, a redacted version of the protocol for a chronic study, a redacted version of the protocol for an ethylbenzene Mode of Action study, and a list of references related to the mouse lung tumor mode of action for ethylbenzene, EPA-HQ-ORD-2014-0526-0004.

[4] U.S. EPA. IRIS Assessment Plan for Ethylbenzene (Scoping and Problem Formulation Materials). U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-17/332, p. 1 (2017).

[5] A list of regulations appears in EPA's Substance Registry Services (SRS) profile on ethylbenzene, https://iaspub.epa.gov/sor_internet/registry/substreg/searchandretrieve/substancesearch/search.do?details=displayDetails&selectedSubstanceId=94770.

Highlights from the comments follow.

1. Given its high volatility, air exposures are the only reasonable exposure of concern.
    a. Measured human exposures to ethylbenzene in North America are low (generally < 10 ppb), which is well below toxic effects of concern (750 ppm tumors).
    b. Emissions of ethylbenzene have been declining.
    c. 99% of ethylbenzene is manufactured and used in a closed-system, consumptive process to produce styrene and accounts for 1% of ethylbenzene exposure.
2. The agency's oral RfD is 0.1 µg/kg bwt/day and the RfC is 0.1 µg/m^3 (0.2 ppm).
    a. As discussed in Sweeney et al. (2015),[6] a review of the toxicological data for ethylbenzene supported a cancer reference value of 0.48 ppm (lower bound; central tendency = 0.80 ppm; and upper bound = 2.0 ppm) based on an uncertainty factor of 300 applied to the points of departure for mouse lung tumors and applying a conservative estimate of human lung metabolism using EPA methodology.
    b. The same authors also derived an RfC of 0.3 ppm.
    c. The most sensitive endpoint is a noncancer effect.
    d. There is no reasonable basis for concluding that an IRIS review will support lowering reference values, although increases could be anticipated.
3. Recent federal and state actions confirm that existing regulations properly address potential risks from ethylbenzene production and use.
    a. In a 2006 rule sustained on judicial appeal, EPA confirmed that air and wastewater emissions from ethylbenzene production presented no risk requiring reduction.
    b. Federal and state regulatory activity regulating industrial sources of ethylbenzene have and will continue to operate effectively without an updated IRIS review.
4. Ethylbenzene will be subject to an agency review under TSCA.
    a. TSCA was amended in 2016 and includes a robust program to assess potential risks from existing chemicals.
    b. Amended TSCA directs EPA to consider substances on the agency's 2014 TSCA Work Plan.
    c. Ethylbenzene is a 2014 Work Plan Chemical.
    d. The agency is required by statute to consider ethylbenzene and determine whether conditions of use present an unreasonable risk to human health or the environment based on a comprehensive, weight of the evidence review using the best available scientific information.

[6] Sweeney, L.M., Kester, J.E., Kirman, C.R., Gentry, P.R., Banton, M.I., Bus, J.S., Gargas, M.L. (2015). Risk assessments for chronic exposure of children and prospective parents to ethylbenzene (CAS No. 100-41-4). Crit Rev Toxicol 45, 662–726.

e. The IRIS Assessment Plan (Table 1) recognizes that ethylbenzene "may be among the next chemicals to be evaluated."
f. An IRIS review is not a substitute for the TSCA Prioritization and Risk Evaluation processes nor will it replace the required notice and comment rulemaking on the record mandated by TSCA.

There is little, if any, value in the agency spending unnecessary agency resources on an IRIS review of ethylbenzene, and the proposed review should be withdrawn.

A. Exposure and Toxicology

1. Exposure

As described by Sweeney et al. (2015) and the EPA Voluntary Children's Chemical Evaluation Program (VCCEP) Dossier, ethylbenzene has two distinct chains of commerce: the refinery chain associated with petroleum-derived products; and the ethylbenzene/styrene chain associated with the manufacture of ethylbenzene and styrene, and its presence in styrenic products. Thus, there are two main sources of environmental ethylbenzene: commercial synthesis (made and used in closed systems as part of the manufacture of styrene) and products distilled from petroleum crude oil (mostly gasoline and mixed xylenes). Ethylbenzene is present in gasoline at about 2% by weight. Ethylbenzene is a component of hydrocarbon solvents, commercial mixed xylenes, which may contain 6–15% of ethylbenzene by volume. As part of these mixtures, ethylbenzene may be found in diluents in varnishes, paints, and lacquers, including some consumer products, as well as in solvents used in the rubber and chemical manufacturing industries (Agency for Toxic Substances and Disease Registry [ATSDR] 1999). Minor contributors include ethylbenzene naturally present in several foods and in cigarette smoke.

The 1999 National Emission Inventory (NEI) database available at the time of the Tier 1 VCCEP submission indicated that mobile sources contributed the majority of ethylbenzene emissions at nearly 76%, followed by non-point (area) sources at 19%. The smallest contribution in the 1999 NEI database came from major point sources (5%). Industries under Standard Industrial Classification (SIC) code series 2800 (Chemicals and Allied Products) and 3000 (Rubber and Miscellaneous Plastics Products) contributed 12% to total point-source emissions, and less than 1% to total ethylbenzene emissions. On this basis, it was conservatively estimated that 1% of airborne ethylbenzene exposure was derived from the ethylbenzene/styrene chain of commerce.

The physicochemical characteristics and behavior of ethylbenzene in the environment indicate that the most likely route of human exposure is inhalation.

As reported in Sweeney et al. (2015), a number of large studies examining indoor and personal exposures to VOCs in North America, Western Europe, and Australia have been published since 2007, and the CDC has added VOCs to the analytes biomonitored in the general U.S. population in the continuous NHANES. As discussed in the following sections, these studies have provided much high-quality data concerning exposure sources and magnitudes, and confirmed the preferability of personal over environmental—outdoor or indoor—

measurements for ethylbenzene exposure estimation. As noted by Sweeney et al. (2005) (p. 42 and 44), the importance of motor vehicle emissions and human exposure to ethylbenzene are prominent.

> Concentrations of ethylbenzene were higher in urban and suburban than in rural areas, as expected due to its association with automotive fuels and exhaust. While the annual average ethylbenzene concentrations have remained quite consistent in rural areas, data collected in urban and suburban areas demonstrated a decreasing trend (about 5% annually from 1990 to 2005 [McCarthy et al. 2007]). These decreases paralleled the decreasing trend observed in on-road motor vehicle emissions of ethylbenzene over the same decade (Cook et al. 2004, Figure 14). The decreasing trend continued from 2006 to 2014 (Figure 14). In EPA's 2012 Urban Air Toxics Monitoring Program or UATMP (US EPA 2014a), ethylbenzene was detected in 1452 of 1459 valid samples (99.5%) at concentrations ranging from 0.02 to 3.6 micrograms per cubic meter (μg/m^3). The mean, median, and standard deviation of this data set were 0.35 μg/m^3, 0.24 μg/ m^3, and 0.36 μg/m3, respectively (US EPA 2014a). In 2014, the average ethylbenzene concentration in rural areas was 0.05 μg/m^3 compared with 0.16 and 0.31 μg/m^3 at suburban and urban stations, respectively. On-road motor vehicle emissions of ethylbenzene also continued to decline through 2011, the most recent year for which NEI results are currently available (Figure 14).[7]

Sweeney also states that, "Su et al. (2013) reported that home ethylbenzene levels dominated median personal exposures (64–73% of total personal exposure). Their results also confirm the seemingly paradoxical fact that motor vehicles are the primary source of ethylbenzene in indoor air: the outdoor source exposure fraction was 48% versus 15% for indoor sources (Su et al. 2013). Similar results were obtained for other VOCs lacking strong indoor sources (Su et al. 2013)."[8]

Total ethylbenzene releases to air, water and land have decreased 60%, that is, from 13 million pounds in 1994 to less than 4 million pounds per year since 2009. Sweeney et al. (2015) (Figure 10). Environmental exposures are generally less than 10 ppb, although a few environmental monitors report values up to 50 ppb.

2. Toxicology

Ethylbenzene was subjected to a comprehensive battery of toxicology tests as part of the VCCEP program, which included neurotoxicity, immunotoxicity, and reproductive/developmental/ neurodevelopmental toxicity. Studies conducted included acute, subchronic, and chronic studies in rats or mice, and genotoxicity studies. The VCCEP findings were reviewed and updated by Sweeney et al. (2005), and these materials are drawn from that publication.

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[7] Sweeney et al. (2015) p. 42.

[8] *Id*. at 44.

a. Acute Toxicity

Ethylbenzene is not acutely toxic (LD_{50}s are above 3500 mg/kg). As summarized by Sweeney et al. (2015), "The repeated exposure (non-cancer) systemic toxicity of ethylbenzene has been evaluated in laboratory animals in subchronic and chronic inhalation studies and subchronic oral studies (NTP 1992a, 1999, Mellert et al. 2004, 2007, Li et al. 2010). Overall, ethylbenzene is a moderate repeated exposure toxicity hazard with consistent targeted effects to the liver and kidney at concentrations ≥250 ppm or doses ≥250 mg/kg bwt/day."[9]

Sweeney summarizes the neurotoxicity findings:

> Consistent with the known effects of organic solvents which cause a general and non-specific depression of the nervous system, acute exposure to high concentrations of ethylbenzene can induce acute neurological effects. Repeated exposure to ethylbenzene at concentrations up to 500 ppm vapor or oral dosages of up to 500 mg/kg bwt/day, however, do not produce any behavioral or morphological effects in standard neurotoxicity studies that are indicative of a specific, persistent, or progressive action on the nervous system (Barnett 2006, Faber et al. 2007, Li et al. 2010). Specialized investigations of ethylbenzene effects on hearing do indicate that ethylbenzene can cause ototoxicity. Ototoxicity has been reported for other aromatic hydrocarbons and a 13-week study in rats found alterations in brainstem auditory evoked responses and outer hair cell (OHC) morphology in rats at concentrations of 200 ppm and greater ethylbenzene (Gagnaire et al. 2007). Therefore, hearing effects may be a concern for ethylbenzene.[10]

Sweeney goes on to summarize the developmental and reproductive toxicity findings:

> Ethylbenzene is not a teratogen or reproductive toxicant. At doses that produced maternal effects (=/> 1000 ppm) in laboratory animals, as indicated by adverse clinical signs, reductions in bwt, and increases in organ weights, ethylbenzene was fetotoxic causing decreases in fetal bwts and increases in skeletal variations (Andrew et al. 1981, Hardin et al. 1981, Saillenfait et al. 2003, 2006). No fetotoxicity was present in developmental toxicity studies at 500 ppm or lower ethylbenzene concentrations. Ethylbenzene administered at up to 500 ppm to rats also did not adversely affect reproductive performance or offspring development over two generations (Faber et al. 2006)….
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> Developmental neurotoxicity was evaluated in rats as a component of the 2-generation reproductive toxicity study for ethylbenzene (Faber et al. 2007). This study found no exposure-related effects on functional observational battery assessments, locomotor activity, acoustic startle responses, learning and memory evaluations in a Biel water maze task, and neurohistopathology and brain area morphometric measurements at up to 500 ppm of ethylbenzene.[11]

[9] Sweeney et al. (2015) at p.4.

[10] *Id*. at p. 6.

[11] *Id.* at pp.5–6.

With regard to non-cancer effects, Sweeney concluded that, "[e]thylbenzene is negative for genotoxicity in all *in vivo* studies that have been conducted and predominately negative for genotoxicity in *in vitro* studies."[12] Additionally, "[t]here is no evidence that ethylbenzene is harmful to the immune system."[13]

b. Carcinogenicity

Sweeney concludes that, "Information regarding the potential carcinogenicity of ethylbenzene from epidemiology studies is limited and therefore uninformative for human risk."[14]

Ethylbenzene caused increased kidney tumors in male rats at 750 ppm for 2 years by inhalation, but not at 250 or 75 ppm. Following extended pathologic examination of the kidneys, the NTP concluded there was some evidence of kidney tumors in female rats at 750 ppm (NTP 1999).

"Following chronic inhalation exposure to ethylbenzene, the development of renal tumors along with an increased incidence and severity of CPN has been observed in male rats (NTP 1999). Following ethylbenzene exposure, advanced severity of CPN, the location of the lesions in kidneys with the highest severity of CPN, the increased proportion of atypical tubule hyperplasias and adenomas, and the increase in proliferative lesions are all features associated with CPN-induced kidney tumors (Hard 2002). Therefore, it was concluded that kidney tumors were induced through exacerbation of rat CPN (Hard 2002)." [15]Ethylbenzene caused increased lung tumors in male mice exposed by inhalation at 750 ppm for 2 years, but not at 250 or 75 ppm in males or at 75, 250, or 750 ppm in females. The mode of action data indicates that the lung tumors are not likely to happen in humans from exposures to ethylbenzene. First, the primary metabolism of ethylbenzene is to 1-phenylethanol; 1-phenylethanol did not cause increased lung tumors in mice, or any other tumors in rats or mice, in a cancer bioassay (NTP 1990). Second, ethylbenzene is metabolized by CYP2F2 in mouse lung Club cells to 2- and 4-hydroxyethylbenzene (ethylphenol) (Saghir et al. 2006, 2010). Ring-oxidized metabolites produced by CYP2F2 have also been hypothesized as the tumorigenic agent for mouse lung tumors from styrene, naphthalene, and coumarin (Cruzan et al. 2009). Recent studies with styrene have demonstrated:

1. Styrene exposure in C57BL/6 (WT) mice resulted in cytotoxicity and increased cell proliferation from styrene (Cruzan et al. 2012). These were not present in CYP2F2-knockout (KO) mice.
2. Styrene exposure in WT mice caused changes in the expression of genes related to cell-cycle, circadian clock, nuclear receptor factors and sterol synthesis (Andersen et al. 2017). These are not present in CYP2F2-knockout mice.
3. Inhalation of styrene at 120 ppm in CD-1 or WT mice for 104 weeks caused preneoplastic/neoplastic effects in terminal bronchioles beginning at 1 week and

[12] *Id*. at p. 51.

[13] *Id*.

[14] *Id*. at 16.

[15] *Id*. at 18, 20.

continuing throughout the study (Cruzan et al. 2017). These effects were absent in CYP2F2-knockout mice.

4. Insertion of a transgene containing the human CYP2F1 into CYP2F2-knockout mice did not result in responses similar to WT mice; i.e., no cytotoxicity, cell proliferation, gene changes, or preneoplastic effects (Cruzan et al., 2013, 2017, Andersen et al. 2017).

Ethylbenzene metabolism is saturated at about 200 ppm.[16] Toxic effects (ototoxicity, rat kidney tumors, and mouse lung tumors occur only at doses that exceed saturation of metabolism). Ototoxicity was reported in a rat study at 4000-fold higher than human exposures (200,000 ppb versus 50 ppb). Rat kidney tumors and mouse lung tumors were reported at 3.5-fold higher exposure than saturation of metabolism and 12,000-fold higher than human exposures. Further, the modes of action for the kidney and lung tumors are specific for the species tested and are unlikely to occur in humans.

Overall, a review of the toxicological data for ethylbenzene supports a cancer reference value of 0.48 ppm (lower bound; central tendency = 0.80 ppm; and upper bound = 2.0 ppm) based upon an uncertainty factor of 300 applied to the points of departure for mouse lung tumors and applying a conservative estimate of human lung metabolism using EPA methodology. The same authors also derived an RfC of 0.3 ppm, and an RfD of 0.5 mg/k/day. The most sensitive endpoint is a noncancer effect.

B. Government reviews confirm that existing regulations address potential risks

The mere existence of regulations governing ethylbenzene is not a justification for discontinuing an IRIS review. But, the necessity of an IRIS review disappears when those regulations are based on health values that are protective or overly protective, such as the IRIS RfC and RfD values, and when the agency has conducted risk reviews and found the regulations to be protective of human health and the environment.

1. EPA confirmed in 2006 that existing regulations governing ethylbenzene production protect the public from air and wastewater emissions

In 2006, after reviewing the risk presented from ethylbenzene production under existing regulations for hazardous air pollutants, EPA issued a regulation confirming that existing standards were protective and need not be changed.

Since 1990, ethylbenzene has been listed as an air toxic, or hazardous air pollutant, under section 112 of the Clean Air Act (CAA), 42 USC § 7412. This listing has generated several maximum achievable control technology (MACT) standards limiting the emissions of ethylbenzene. An important example is the National Emission Standards for Organic Hazardous Air Pollutants from the Synthetic Organic Chemical Manufacturing Industry (HON), one of many regulations applicable to manufacturers of ethylbenzene used to produce styrene. 40 C.F.R. Part 63, Subpart F.

[16] Available at Regulations.gov, EPA-HQ-ORD-2014-0526-0009.

While the HON rule was issued in 1994, in keeping with its statutory obligations, the agency reviewed the standard and, in 2006, published a rule memorializing the agency's "decision not to impose further controls and not to revise the existing standards based on the residual risk and technology review."[17] The agency's findings were upheld by the U.S. Court of Appeals for the District of Columbia Circuit in *Natural Resources Defense Council v. EPA*, 529 F. 3d 1077, D.C. Cir. (2008).

The introductory note in the agency's 2006 Federal Register notice succinctly provides the context and conclusions.[18]

> In 1994, EPA promulgated national emission standards for hazardous air pollutants (NESHAP) for the synthetic organic chemical manufacturing industry. This rule is commonly known as the hazardous organic NESHAP (HON) and established maximum achievable control technology standards to regulate the emissions of hazardous air pollutants from production processes that are located at major sources.
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> The Clean Air Act directs EPA to assess the risk remaining (residual risk) after the application of the maximum achievable control technology standards and to promulgate additional standards if required to provide an ample margin of safety to protect public health or prevent an adverse environmental effect. The Clean Air Act also requires us to review and revise maximum achievable control technology standards, as necessary, every 8 years, taking into account developments in practices, processes, and control technologies that have occurred during that time.
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> On June 14, 2006, EPA proposed two options regarding whether to amend the current emission standards for synthetic organic chemical manufacturing industry units. This action finalizes one of those options, and reflects our decision not to impose further controls and not to revise the existing standards based on the residual risk and technology review. It also amends the existing regulations in certain aspects.

This agency review took place 15 years after ethylbenzene was determined to be an animal carcinogen. No data or information developed after the 2006 EPA decision suggests that risk has increased, only that early estimates of risk to human health are incorrect or overstated.

Many Clean Air Act standards consider potential emissions to air from wastewater because some substances, including ethylbenzene, volatize from water. These Clean Air Act rules directly address and limit emissions from industrial wastewater discharges.[19]

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[17] 71 Fed. Reg. 76,603 (Dec. 21, 2006).

[18] *Id.*

[19] For ethylbenzene, see, e.g., Subpart G—National Emission Standards for Organic Hazardous Air Pollutants from the Synthetic Organic Chemical Manufacturing Industry for Process Vents, Storage Vessels, Transfer Operations, and Wastewater 40 C.F.R. §§ 63.132-149 and Tables 10-13.

2. OEHHA REL

In 2008, the Office of Environmental Health Hazard Assessment (OEHHA) within the California Environmental Protection Agency developed a chronic Reference Exposure Level (REL) for ethylbenzene of 2,000 μ/m^3. OEHHA determines RELs associated with human systems or organs that could be affected by the non-cancer effects of airborne chemicals. The IRIS RfC is 1,000 μ/m^3, one-half the OEHHA REL.[20] Thus, state regulators reached conclusions consistent with the evaluations in the EPA VCCEP docket and Sweeney et al. (2015).

C. The 2016 TSCA amendments obviate the need for an IRIS review of ethylbenzene

The IRIS Assessment Plan states that "[e]thylbenzene was identified on the 2014 update of the TSCA Work Plan for Chemical Assessments, and may be among the next chemicals to be evaluated."[21] We agree. The agency is required by statute to determine whether conditions of use for ethylbenzene present an unreasonable risk to human health or the environment based on a comprehensive, weight of the evidence review using the best available scientific information. An IRIS review is not a substitute for the TSCA Prioritization and Risk Evaluation processes. Further, an IRIS review will not replace the required notice and comment rulemaking on the record mandated by TSCA program

The Frank R. Lautenberg Chemical Safety for the 21st Century Act,[22] which amended the Toxic Substances Control Act (TSCA), was enacted in June 2016 to provide a more robust chemicals management program in the United States. SIRC was a supporter of TSCA reform and has been actively involved in the implementation of the TSCA amendments. Among the most significant of these amendments were provisions that strengthen EPA's existing chemicals program and procedures for chemical risk evaluations.

On July 20, 2017, EPA published final regulations establishing procedures for chemical prioritization[23] and risk evaluations.[24] These regulations create a comprehensive framework in which chemical substances are selected, screened against certain criteria,[25] prioritized as high or

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[20] https://oehha.ca.gov/air/chemicals/ethylbenzene. OEHHA determines Reference Exposure Levels (RELs) associated with human systems or organs that could be affected (for example, respiratory system) by the noncancer effects of airborne chemicals as part of the requirements of the California Air Toxics Hot Spots Program. RELs can cover acute, recurrent 8-hour, and chronic exposures.

[21] IRIS Assessment Plan, p.4, Table 1.

[22] Pub. L. No. 114-182.

[23] *Procedures for Prioritization of Chemicals for Risk Evaluation Under the Toxic Substances Control Act*, 82 Fed. Reg. 33753 (July 20, 2017).

[24] *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act*, 82 Fed. Reg. 33726 (July 20, 2017).

[25] The hazard and exposure potential of the chemical substance; persistence and bioaccumulation; potentially exposed or susceptible subpopulations; storage near significant sources of drinking water; the conditions of use or significant changes in the conditions of use of the chemical substance; and the

low priority, and reviewed under a rigorous risk evaluation process. Risk evaluation requires the agency to define the conditions of use it seeks to review, consider potentially exposed subpopulations, describe the weight of the scientific evidence for the identified hazards and exposures, and not consider costs or non-risk factors in its review.[26] EPA defined weight of scientific evidence to mean a "systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently, identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance."[27]

As illustrated, the TSCA chemical risk evaluation process has similarities to the IRIS program (*i.e*. defining scope of assessment, systematic review). And, EPA has dedicated more staff and resources to implementing the new TSCA risk evaluation process, and will continue to build upon its resources once the agency promulgates its forthcoming user fee rule,[28] which will require industry to pay for manufacturer-initiated risk evaluations and risk evaluations initiated by EPA under Section 6 of TSCA.[29] It is not as clear that the IRIS Program will have the same resources to perform the assessments done under the TSCA program.

Most significantly, the TSCA amendments implement strict deadlines to ensure EPA is accountable in completing each step of the chemical risk evaluation process expeditiously, and requires EPA to complete an aggressive workload within these time frames. For example, by December 22, 2019, EPA must be conducting risk evaluations on at least 20 high-priority substances, and 20 chemical substances must be designed as low priority.[30] By our projections, this would mean that 10 new substances (besides the 10 substances EPA is undertaking risk assessments on[31]) would be nominated for prioritization by the end of 2018, in just over one year.[32]

To have a pragmatic approach to chemical risk assessment, SIRC recommends that the IRIS Program office defer to the Office of Chemical Safety and Pollution Prevention, and perhaps provide support to the staff implementing risk evaluations under TSCA. Because ethylbenzene is

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volume or significant changes in the volume of the chemical substance manufactured or processed. 40 C.F.R. §702.9.

[26] 40 C.F.R. §702.43.

[27] 40 C.F.R. §702.33.

[28] EPA is authorized under the amended TSCA to promulgate rules requiring fees from manufacturers and processors of a chemical substance that is the subject of a risk evaluation. 15 U.S.C. §2625.

[29] Fees for risk evaluations initiated by EPA are subject to limitations set forth in the statute, 15 U.S.C. § 2625(b)(4).

[30] 15 U.S.C. §2605(b)(2)(B).

[31] *Designation of Ten Chemical Substances for Initial Risk Evaluations Under the Toxic Substances Control Act*, 81 Fed. Reg. 91927 (December 19, 2017).

[32] EPA is required by TSCA to ensure the time required to prioritize a substance be no shorter than nine months and no longer than 12 months. 15 U.S. Code § 2605(b)(1)(C).

on the 2014 TSCA Work Plan, the agency will consider ethylbenzene for prioritization. SIRC recommends that EPA cease an unnecessary IRIS assessment and support the TSCA program to not only save the IRIS program significant time and resources, but ensure chemical reviews are performed efficiently and consistent with the strict standards in the Lautenberg Act.

D. An ethylbenzene review conflicts with IRIS program pledges

The portfolio approach proposed by EPA "offers a nimble, flexible, and efficient way to draw on new data streams, develop a continuum of risk assessment products and better meet the needs of stakeholders and decision makers."[33] Indeed, at the CAAC meeting, the NCEA Director stated that the agency will need to be pragmatic, will not start from scratch, and will take advantage of reviews that did not use systematic review.

Several members of the CAAC commented that the Portfolio Approach was deficient because it did not describe an "off ramp," that is, the circumstances under which the agency would terminate a review as unnecessary. While this would be an appropriate addition to the Portfolio Approach documentation, NCEA has the inherent administrative authority to stop ill-advised reviews or to postpone reviews based on shifting agency priorities.

As noted, measured human exposures of ethylbenzene in North America are low (generally < 10 ppb), which is well below toxic effects of concern (750 ppm tumors), and emissions of ethylbenzene have been declining. Industrial production of ethylbenzene accounts for less than 1% of exposure.

These figures along with the key conclusions previously discussed from the VCCEP and Sweeney et al. (2015) review demonstrate how the exposure, toxicology and risk information point to a single conclusion. EPA must indefinitely postpone, if not end, its IRIS review of ethylbenzene.

E. Conclusion

In summary, low exposure and better understood risks to human health demonstrate that a review is exceptionally unlikely to result in a lower the RfC or RfD for ethylbenzene, and that any cancer exposure value will be higher than the RfC and RfD. Beyond this common-sense basis for discontinuing an IRIS review of ethylbenzene, there are additional reasons that the proposed EPA review should end. First, a review by EPA's Office of Air confirmed that the primary air toxics regulation governing the production of ethylbenzene has reduced risk to a safe or acceptable level. Second, ethylbenzene's status as a TSCA Work Plan Chemical and the agency's statutory obligation to review ethylbenzene for prioritization add to the demonstration that an IRIS review will squander scarce agency resources and burden industry with redundant agency proceedings at the very time it is committed to avoiding both outcomes. Finally, a review would contravene EPA's efficiency and effectiveness aspects of the proposed Portfolio Approach.

[33] Memorandum from the IRIS Program to the EPA Science Advisory Board Chemical Assessment Advisory Committee: Overview of Integrated Risk Information System (IRIS) Assessment Plans (IAPs); Development of a Portfolio Approach (Attachment A).

On this basis, SIRC urges EPA to discontinue an IRIS assessment of ethylbenzene given existing studies on human exposure to ethylbenzene, the regulations that address the hazards of ethylbenzene, and deferment to the TSCA prioritization and risk evaluation process as a more robust and appropriate avenue for review.

We would be pleased to answer questions or provide additional details to support these comments.

Sincerely,

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