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IRIS Assessment Plan
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IRIS Assessment Plan for Ethylbenzene

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1. INTRODUCTION

The Integrated Risk Information System (IRIS) Program is undertaking a reassessment of the health effects of ethylbenzene. EPA included ethylbenzene on the December 2015 multiyear agenda for the IRIS program (https://www.epa.gov/iris/iris-agenda) as an ongoing agency priority for assessment development because of interest by multiple program or regional offices.

IRIS assessments provide high quality, publicly available information on the toxicity of chemicals to which the public might be exposed. These assessments are not regulations, but provide a critical part of the scientific foundation for decisions made in EPA program and regional offices to protect public health.

Before beginning an assessment, the IRIS Program consults with EPA program and regional offices to define the scope of the assessment, including the nature of the hazard characterization needed, identification of the most important exposure pathways, and level of detail needed to inform program and regional office decisions. Based on the scope defined by EPA, the IRIS Program undertakes problem formulation activities to frame the scientific questions that will be the focus of the assessment, which is conducted using systematic review methodology.

This document presents the draft assessment plan for ethylbenzene, including a summary of the IRIS Program's scoping and initial problem formulation conclusions, objectives and specific aims of the assessment, draft PECO (Populations, Exposures, Comparators, and Outcomes) framework that outlines the evidence considered most pertinent to the assessment, assessment approach, and identification of key areas of scientific complexity. Brief background information on uses and potential for human exposure is provided for context.

2. SCOPING AND INITIAL PROBLEM FORMULATION

2.1. BACKGROUND

Ethylbenzene, also known as phenylethane, is an aromatic hydrocarbon present in crude petroleum and gasoline. It is used in the production of styrene monomer (IPCS, 1996), primarily as a chemical intermediate. Ethylbenzene also is used as an industrial solvent and a diluent in the paint industry and in the manufacture of synthetic rubber, acetophenone, and cellulose acetate (Cal/EPA, 1997). It is present in naphtha and asphalt and as an impurity in xylene solvents (Cal/EPA, 1997).

Individuals that may be exposed are those living near manufacturing and processing facilities, petroleum refineries, and hazardous waste sites where ethylbenzene has been detected or those using well water downgradient from leaking underground storage tanks (ATSDR, 2010).

An assessment of ethylbenzene is available on the IRIS website https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=51 (U.S. EPA, 1991). An oral RfD of 1 x 10^{-1} mg/kg-day was posted in 1987 based on hepatic and renal toxicity. An inhalation RfC of 1 mg/m^3 was posted in 1991 based on developmental toxicity. In 1988 the cancer weight of evidence for ethylbenzene was categorized as "Group D," that is, not classified concerning its potential to cause cancer in humans, due to a lack of animal and human data. Since then, several relevant studies on ethylbenzene toxicity have been completed and new data have become available.

2.2. SCOPING SUMMARY

During scoping, the IRIS Program met with EPA program and regional offices that had interest in an updated IRIS assessment for ethylbenzene to discuss specific assessment needs. Table 1 provides a summary of input from this outreach.

Table 1. EPA program or regional office interest in an updated ethylbenzene assessment

Program or regional office[a]	Oral	Inhalation	Statutes/ Regulations	Description of authority/Regulation	Anticipated uses/Interest
OLEM	✓	✓	Comprehensive Environmental Response, Compensation	Authorizes EPA to promulgate regulations designating as hazardous substances those substances which, when released	Ethylbenzene is a hazardous substance under CERCLA. Releases of
EPA Regions	✓	✓			

Program or regional office[a]	Oral	Inhalation	Statutes/ Regulations	Description of authority/Regulation	Anticipated uses/Interest
			and Liability Act (CERCLA)– Sections 102 and 103	into the environment, may present substantial danger to public health or welfare or the environment. EPA must also promulgate regulations establishing the quantity of any hazardous substance the release of which must be reported under Section 103.	ethylbenzene in excess of 1000 pounds must be reported (40 CFR 302.4).
OAR		✓	Clean Air Act (CAA) – Section 112	Section 112 (b) defines the original list of 189 hazardous air pollutants (HAP). Under 112(c) of the CAA, EPA must identify and list source categories that emit HAP and then set emission standards for those listed source categories under CAA section 112(d). Section 112(d) states that the EPA must establish NESHAPs for each category or subcategory of major sources and area sources of HAPs [listed pursuant to Section 112(c)]. The standards must require the maximum degree of emission reduction that the EPA determines to be achievable by each particular source category. Different criteria for maximum achievable control technology (MACT) apply for new and existing sources. Less stringent standards, known as generally available control technology (GACT) standards, are allowed at the Administrator's discretion for area sources.	Ethylbenzene is listed as a HAP under Section 112 (42 U.S.C. § 7412) of the CAA. There are a number of source-specific NESHAPs that are applicable to ethylbenzene including: - Organic Liquids Distribution (40 CFR Part 63, Subpart EEEE) - Shipbuilding and Ship Repair (Surface Coating; 40 CFR Part 63 Subpart II) - Municipal Solid Waste Landfills (40 CFR Part 63 Subpart AAAA).
OW	✓		Clean Water Act (CWA) – Sections 304/307	EPA is required to develop and revise list of toxic pollutants or combination of pollutants. From time to time, EPA may revise taking into account toxicity of the pollutant, its persistence, degradability, the usual or potential presence of the affected organisms in any waters,	Ethylbenzene is identified on the list of toxic pollutants under section 307 of the Clean Water Act.

Program or regional office[a]	Oral	Inhalation	Statutes/ Regulations	Description of authority/Regulation	Anticipated uses/Interest
				the importance of the affected organisms, and the nature and extent of the effect of the toxic pollutant on such organisms.	
OCSPP	✓	✓	Toxic Substances Control Act (TSCA) – Section 6(b)	EPA is directed to identify and begin risk evaluations on 10 substances drawn from the 2014 update of the TSCA Work Plan for Chemical Assessments.	Ethylbenzene was identified on the 2014 update of the TSCA Work Plan for Chemical Assessments, and may be among the next chemicals to be evaluated.

[a]OLEM (Office of Land and Emergency Management); OW (Office of Water); OAR (Office of Air and Radiation); OCSPP (Office of Chemical Safety and Pollution Prevention)

2.3. PROBLEM FORMULATION

A public science meeting on the scoping and problem formulation activities for ethylbenzene was held on September 3–4, 2014 (U.S. EPA, 2014). Although an ATSDR Toxicological Profile was published on ethylbenzene in 2010 (ATSDR, 2010), the discussion from the public meeting indicated that a comprehensive assessment of ethylbenzene was warranted based on such considerations as the size of the new evidence base and the time since EPA conducted an assessment.

Following the initial literature search and screening, identified studies were reviewed and sorted into bins according to the type(s) of health outcomes and/or health effects reported. This was done to appropriately direct the study reports to subject matter experts for the next stages in the IRIS Assessment Development Process, namely study evaluation, data extraction, evidence synthesis and integration, and dose-response analysis. The initial results of the binning process are shown below. Heat maps indicating the number of studies for each endpoint/health outcome category are shown for the 36 studies in humans (Table 2), and separately for the 47 studies in animals (Table 3).

Many studies report on more than one health effect/outcome category; therefore, there is not a one-to-one correspondence between the total number of studies across all endpoints and the total number of studies identified in the screening process. The upper set of values in each row in both Table 2 and Table 3 indicate the number of studies that examined the endpoint while the lower set of values indicate number of studies reporting response measurements from ethylbenzene exposure. Blanks indicate that no studies were identified in the systematic literature search and screening for that specific effect category. When studies were identified that examined

the effect (upper values) but no effects were observed, zeroes were shown in the lower set of values to indicate the lack of an ethylbenzene-specific, exposure-related effect.

Table 2. Heat map of ethylbenzene (EB) human database

	Cardiovascular	Dermal	Developmental	Endocrine/ Exocrine	Gastrointestinal	Hematological	Hepatic	Immunological	Musculoskeletal	Nasal	Neurological	Pulmonary	Renal	Reproductive	Ocular	Other effects[a]
Human studies – inhalation exposure																
Occupational Epidemiological Studies						1 0	1 0				1 1					
General Population Epidemiological Studies	1 1	2 0	5 2		1 0		1 0	9 7		2 0	2 0	4 2			2 1	2 2
Controlled Exposure Studies								1 0		7 6					5 4	2 2
Case Reports and Case Series Reports																
Human studies – oral exposure																
Occupational Epidemiological Studies																
General Population Epidemiological Studies																
Controlled Exposure Studies																
Case Reports and Case Series Reports																
Human studies – dermal/multiple routes or unknown (biomarker) exposure																
Occupational Epidemiological Studies						1 0	1 0									1 0
General Population Epidemiological Studies	1 1						1 0	1 1				2 1				1 0
Controlled Exposure Studies																
Case Reports and Case Series Reports											1 0					

Heat map key

Number of studies that examined the endpoint

0	1	2	3	4	5 - 9	10 - 14	15+

Number of studies reporting response measurements from ethylbenzene exposure.

0	1	2	3	4	5 - 9	10 - 14	15+

[a]Other includes body weight, clinical signs, and other observations (not organ specific).

Table 3. Heat map of ethylbenzene (EB) animal database

	Cardiovascular	Dermal	Developmental	Endocrine/ Exocrine	Gastrointestinal	Hematological	Hepatic	Immunological	Musculoskeletal	Nasal	Neurological	Pulmonary	Renal	Reproductive	Ocular	Other effects[a]
Animal studies - inhalation exposure																
Chronic	6	2		6	2	6	7	6	2	2	2	6	6	6	2	7
	0	0		1	0	0	5	0	0	0	0	1	2	3	0	4
Subchronic	3	1		3	3	3	6	3	2	3	4	3	7	3	3	7
	0	0		0	0	0	6	1	0	0	1	1	6	0	0	1
Short-term	9	4	1	8	6	7	17	9	6	9	18	13	16	10	7	23
	0	0	0	1	0	2	10	0	0	0	9	2	5	0	0	8
Acute										1	4	3			1	2
										1	4	3			1	2
Multigenerational			3				3						3	3		3
			1				2						2	1		1
Gestational	2		12	2			6	5			2	5	6	12		11
	0		10	0			4	3			0	0	3	3		4
Animal studies - oral exposure																
Chronic	2			2	1	1	2	2	1	1	1	2	2	2		2
	0			0	0	0	1	0	0	1	0	0	1	0	0	1
Subchronic	1	1		1	1	1	2	1	2	1	2	1	2	1	2	2
	0	0		0	0	1	2	1	0	0	0	0	2	0	0	2
Short-term	1			1		1	2	1			1		1	2		2
	0			0		0	1	0			0		1	1		2
Acute					1		1					1				1
					1		1					1				1
Multigenerational																
Gestational																

Heat map key

Number of studies that examined endpoint

0	1	2	3	4	5 to 9	10 to 14	15+

Number of studies reporting response measurements from ethylbenzene exposure.

0	1	2	3	4	5 to 9	10 to 14	15+

[a]Other includes body weight, clinical signs, and other observations.

3. OVERALL OBJECTIVE, SPECIFIC AIMS AND DRAFT POPULATIONS, EXPOSURES, COMPARATORS, AND OUTCOMES (PECO) FRAMEWORK

The overall objective of this assessment is to identify adverse health effects and characterize exposure-response relationships for these effects of ethylbenzene to support development of toxicity values. This assessment will use systematic review methods to evaluate the epidemiological and toxicological literature, including consideration of relevant mechanistic evidence. The evaluations conducted in this assessment will be consistent with relevant EPA guidance.[a] The systematic review protocol will be disseminated after review of the draft assessment plan and will reflect changes made to the specific aims and the PECO framework in response to public input.

3.1. SPECIFIC AIMS

- Identify epidemiological (i.e., human) and toxicological (i.e., experimental animal) literature reporting effects of exposure to ethylbenzene as outlined in the PECO framework.

- Use an iterative approach to determine which mechanistic studies are most important to summarize, based on factors such as robustness of the evidence in humans and animals, likelihood to influence evidence synthesis conclusions for human health, and directness or relevance of the model systems for understanding potential human health hazards. When summarizing individual mechanistic studies is not critical, this information will generally be summarized by relying on other published authoritative sources, such as public health agency reports and expert review articles.

- Conduct study evaluations (risk of bias and sensitivity) for individual epidemiological and toxicological studies. Studies with critical deficiencies will be considered uninformative and not considered further.

- Extract data on relevant health outcomes from epidemiological and toxicological studies included based on the study evaluation

- Synthesize the evidence across studies assessing similar health outcomes using a narrative approach or meta-analysis (if appropriate).

[a]EPA guidance documents: http://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance/.

- For each health outcome, express confidence in conclusions from across studies (or subsets of studies) within human and animal evidence streams, evaluating each evidence stream separately.

- For each health outcome, integrate results across evidence streams (human and animal) to conclude whether a substance is hazardous to humans. Identify and discuss issues concerning potentially susceptible populations and life stages. Biological support from mechanistic studies and nonmammalian model systems will be considered based on the iterative prioritization approach outlined in the PECO framework.

- Derive toxicity values as supported by the available data.

- Characterize uncertainties and identify key data gaps and research needs such as limitations of the evidence base, limitations of the systematic review, and consideration of dose relevance and pharmacokinetic differences when extrapolating findings from higher-dose animal studies to lower levels of human exposure.

3.2. DRAFT PECO FRAMEWORK

A PECO framework is used as an aid to focus the research question(s), search terms, and inclusion/exclusion criteria in a systematic review. The draft PECO framework for ethylbenzene (Table 4) was based on (1) nomination of the chemical for assessment, (2) discussions with scientists in EPA program and regional offices to determine the scope of the assessment that will best meet Agency needs, and (3) preliminary review of the health effects literature for ethylbenzene to identify the major health hazards associated with exposure and key areas of scientific complexity.

Table 4. Draft PECO framework for the ethylbenzene assessment

PECO Element	Evidence
Populations	**Human:** All populations and life stages (e.g., children, general population, occupational, or high exposure from an environmental source). The following study designs will be considered most informative: controlled exposure, cohort, case-control, cross-sectional, and ecological. Note: Case reports and case series will be tracked during study screening but are not the primary focus of this assessment. They may be retrieved for full-text review and subsequent evidence synthesis if no or few more informative study designs are available. Case reports also can be used as supportive information to establish biologic plausibility for some target organs and health outcomes.
	Animal: Non-human mammalian animal species (whole organism) of any life stage (including preconception, in utero, lactation, peripubertal and adult stages).

	Nonmammalian model systems/in vitro/in silico: Non-mammalian model systems (e.g., fish, amphibians, birds, *Caenorhabditis elegans*, etc.); human or animal cells, tissues, or biochemical reactions (e.g., ligand-binding assays) with in vitro exposure regimens; bioinformatics pathways of disease analysis; or high-throughput screening data. These studies are tagged during title and abstract screening and an iterative approach is used to prioritize their inclusion for full-text retrieval and evidence synthesis based on likelihood to impact evidence synthesis conclusions for human health[a]
Exposures	**Human:** Exposure to ethylbenzene (CASRN 100-41-4), including occupational exposures, alone or as a mixture by any route.
	Animal: Exposure to ethylbenzene (CASRN 100-41-4) alone by any route. Studies employing chronic exposures will be considered the most informative. Studies involving exposures to mixtures will be included only if they include an arm with exposure to ethylbenzene alone.
	Nonmammalian model systems/in vitro/in silico: Exposure to ethylbenzene via growth or assay medium.
Comparators	**Human:** Any comparison or reference group exposed to; lower levels of ethylbenzene, no exposure to ethylbenzene, or to ethylbenzene for shorter periods of time.
	Animal: Quantitative exposure versus lower or no exposure with concurrent vehicle control group.
	Non-mammalian model systems / in vitro / in silico: Quantitative exposure versus lower or no exposure with concurrent vehicle control group.
Outcomes	All health outcomes (both cancer and noncancer). In general, endpoints related to clinical diagnostic criteria, disease outcomes, histopathological examination, or other apical/phenotypic outcomes will be prioritized for evidence synthesis over outcomes such as biochemical measures.

[a]**Note:** An iterative approach is used to prioritize evidence from nonmammalian model systems (e.g., fish, amphibians, birds, *C elegans*), in vitro, in silico, and other types of mechanistic studies based on likelihood to impact evidence synthesis conclusions for human health. Evidence from these studies will be tagged preliminarily during title/abstract screening as "Other Informative Studies" or "Supporting Information" according to hazard categories or types of mechanistic outcomes/pathways. These studies are prioritized for full-text retrieval and evidence synthesis to focus on those studies most important to summarize, based on factors such as robustness of the evidence in humans and animals, directness or relevance of the model systems, and concentrations tested. For example, if robust epidemiological or nonhuman mammalian evidence is available, the need to conduct a thorough assessment of individual non-mammalian and mechanistic studies could be diminished unless controversial issues need to be resolved, e.g., issues related to applicability of animal evidence to humans or the shape of the dose-response curve at low exposure levels.

3.3. ASSESSMENT APPROACH

This assessment will use a modular approach. Toxicity values not requiring advanced quantitative methods (e.g., physiologically based pharmacokinetic [PBPK] modeling) will be derived first. When more complex modeling approaches will be required to develop a toxicity value, progress on developing those values shall be handled once the models have been developed and evaluated by EPA. Based on the ample database for inhalation studies, EPA anticipates an RfC for ethylbenzene can be derived without the need for PBPK modeling. The very limited database

for oral studies, however, might necessitate use of PBPK modeling to develop an RfD. Dermal toxicity values will not be derived based on the survey of needs (see Table 1). Evaluation of cancer endpoints could be complex and, therefore, might require more time to assess than noncancer endpoints. For this reason, a cancer assessment might be developed separately from RfC or RfD toxicity values.

3.4. KEY SCIENCE ISSUES

Based on the preliminary literature survey, the following key scientific issues and potential mode-of-action hypotheses were identified that warrant evaluation in the assessment.

- Toxicokinetics of ethylbenzene.
- Human relevance for cancer and noncancer hazards observed in experimental systems (e.g., rat renal toxicity and tumors, mouse lung toxicity and tumors).
- Mechanisms of neurotoxicity including ototoxicity.
    - Reversibility, persistence, or potential for progression of the neurobehavioral or ototoxic effects after humans are removed from ethylbenzene exposure.
    - The relevance of ototoxicity to humans at lower exposure levels.

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