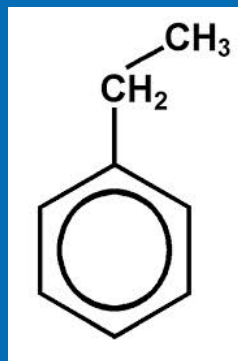


Problem Formulation for the IRIS Assessment of Ethylbenzene

*Paul Reinhart and George Woodall,
Assessment Managers*





Production and Uses

Production

- High production volume chemical

Uses

- As a chemical intermediate in the production of styrene
- Industrial solvent
- Diluent for paints and other coating products
- Manufacture of synthetic rubber, acetophenone and cellulose acetate
- Fuel component / additive

Environmental Interest

- Clean Water Act (**CWA**)
- Federal Insecticide, Fungicide and Rodenticide Act (**FIFRA**)
- Clean Air Act (**CAA**)
- Safe Drinking Water Act (**SDWA**)
- Emergency Planning and Community Right-to-Know Act (**EPCRA**)
- Toxic Substances Control Act (**TSCA**)
- Resource Conservation and Recovery Act (**RCRA**)
- Comprehensive Environmental Response, Compensation, and Liability Act (**CERCLA**)



Timeline for Ethylbenzene Events

- 1991** **Ethylbenzene assessment posted to IRIS database**
 - Included RfD and RfC
 - Not classifiable as to human carcinogenicity

- 1999** **NTP 2 year inhalation study in mice and rats**

- 2010** **ATSDR Ethylbenzene Toxicological Profile**

- 2014** **EPA Workshop on mouse lung tumors**
(Jan)

- 2014** **Release of ethylbenzene Scoping and Problem**
(July) **Formulation materials**

Health Outcomes Identified by the Preliminary Literature Survey

	Human Studies		Animal Studies		In Vitro Studies
	Oral	Inhalation	Oral	Inhalation	
Health Outcomes					
Body Weight Effects				✓ (Subchronic)	
Cancer		✓ (Occupational)	✓ (Chronic)	✓ (Chronic)	
Cardiovascular			✓ (Subchronic)	✓ (Subchronic, Chronic)	
Dermal				✓ (Chronic)	
Developmental				✓ (Subchronic)	
Endocrine				✓ (Subchronic, Chronic)	
Gastrointestinal				✓ (Subchronic, Chronic)	
Hematological		✓ (Occupational)	✓ (Subchronic)	✓ (Subchronic, Chronic)	
Hepatic			✓ (Subchronic)	✓ (Subchronic, Chronic)	

Health Outcomes Identified by the Preliminary Literature Survey

	Human Studies		Animal Studies		In Vitro Studies
	Oral	Inhalation	Oral	Inhalation	
Health Outcomes					
Immunological				✓ (Subchronic)	
Metabolic disease					
Musculoskeletal				✓ (Subchronic, Chronic)	
Neurological and Sensory		✓ (Occupational)	✓ (Subchronic)	✓ (Subchronic)	✓
Renal			✓ (Subchronic)	✓ (Subchronic, Chronic)	
Reproductive			✓ (Subchronic)	✓ (Subchronic)	
Respiratory		✓ (Community)	✓ (Subchronic)	✓ (Subchronic, Chronic)	
Other Data and Analyses					
ADME ¹		✓	✓	✓	
Toxicokinetic models ²					✓
Mode-of-action hypotheses					✓
Susceptibility data		✓ ³			
Genotoxicity		✓	✓	✓	✓
Other mechanistic data					✓ ⁴

¹ Absorption, distribution, metabolism and excretion (ADME) data also exists for dermal exposure for human and animals

² Inhalation PBPKs included

³ Individuals that may be more susceptible to toxic effects include those with pre-existing hearing loss and diseases of the respiratory system, liver, kidney, or skin; fetuses; young children; pregnant women; and those taking certain medications, such as hepatotoxic medications or drugs (ATSDR 2010).

⁴ Adverse outcome models of carcinogenesis and benchmark dose



Key Science Issues

1. Health Outcomes
2. Relating Health Outcomes to Mode of Action (MOA)
 - a. Toxicokinetics
 - b. Tumor formation – lung and kidney, **separately**
 - c. Non-cancer toxicity
3. Ethylbenzene (EB) as a mixture component (e.g., petroleum)
4. Data gaps, new studies, and research in progress



Health outcomes identified in the preliminary literature survey:

Cancer

Developmental

Hematological

Hepatic

Neurological

Sensory

Renal

Reproductive

Respiratory

- Additional health outcomes?
- Any inter-relationships among the outcomes?

Science Issue 2a: MOA and Toxicokinetics

Ethylbenzene mainly metabolized via hydroxylation and subsequent conjugations.

Qualitative and quantitative metabolic differences exist between humans and laboratory animals. Toxicokinetic issues include:

- What is the chemical form responsible for the various toxicities?
- What are the relevant inter- and/or intra-species differences in toxicokinetics of ethylbenzene?
- Are there reliable PBPK models for interspecies or route-to-route extrapolation?

Science Issue 2b: MOA for Tumor Formation

Are there newer data (since MLTW) that would be useful in understanding:

- Metabolism:
 - Role of CYP450 enzymes?
 - Other enzymes or cofactors involved?
- Induction of tumors by metabolites?
- Mechanisms inducing tumors?
 - Genotoxicity
 - Cytotoxicity and regenerative cell proliferation



Science Issue 2c: Non-cancer Toxicity

Have all effects from EB exposure been identified?

Common mechanisms across affected organs?

Effects common to EB and related chemicals (xylene, styrene, etc.)?

Effects unique to EB (not seen in related chemicals)?

Science Issue 3: EB as a Mixture Component

Most IRIS assessments are for single chemicals.

- Is there scientific value in performing a mixtures assessment?
- What are the scientific issues for assessing EB as part of a mixture?
- Which mixtures are most important?
 - Petroleum, paints, tobacco smoke, others?
- What data are available for assessing a mixture?



Science Issue 4: Data Gaps, New Studies, and Research in Progress

Anything missing?

Any new studies?

Any new research coming?