

8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

ATSDR has derived an acute-duration inhalation MRL of 5 ppm for ethylbenzene based on a BMCL for auditory threshold shifts observed in rats exposed to ethylbenzene 8 hours/day for 5 days (Cappaert et al. 2000). The BMCL was estimated using an internal dose metric to simulate time averaged arterial blood concentration of ethylbenzene; a human equivalent concentration (HEC) of the BMCL was estimated using a human PBPK model. This $BMCL_{HEC}$ of 154.26 ppm was divided by an uncertainty factor of 30 (3 for animal to human extrapolation with dosimetric adjustment and 10 for human variability).

ATSDR has derived an intermediate-duration inhalation MRL of 2 ppm for ethylbenzene based on a BMCL for auditory threshold shifts observed in rats exposed to ethylbenzene 6 hours/day, 6 days/week for 4–13 weeks (Gagnaire et al. 2007). The BMCL was estimated using an internal dose metric to simulate time averaged arterial blood concentration of ethylbenzene; a HEC of the BMCL was estimated using a human PBPK model. This $BMCL_{HEC}$ of 63.64 ppm divided by an uncertainty factor of 30 (3 for animal to human extrapolation with dosimetric adjustment and 10 for human variability).

ATSDR has derived a chronic-duration inhalation MRL of 0.06 ppm for ethylbenzene based on a LOAEL for a significant increase in the severity of nephropathy in female rats exposed to ethylbenzene by inhalation for 6 hours/day, 5 days/week for 104 weeks (NTP 1999). Using a PBPK model, an internal dose metric (time averaged arterial blood concentration of ethylbenzene, MCA) of the LOAEL of 75 ppm was simulated. The HEC of this $LOAEL_{MCA}$ (17.45 ppm) was divided an uncertainty factor of 300 (10 for use of a LOAEL, 3 for animal to human extrapolation with dosimetric adjustment, and 10 for human variability).

The EPA inhalation reference concentration (RfC) (verified in 1991) for ethylbenzene is 1 mg/m^3 (equivalent to 0.23 ppm), based on developmental toxicity seen in rats and rabbits exposed to $4,340 \text{ mg/m}^3$ (Hardin et al. 1981; IRIS 2007; NIOSH 1981).

ATSDR has derived an intermediate-duration oral MRL of 0.4 mg/kg/day for ethylbenzene based on a BMDL for hepatotoxicity (centrilobular hepatocyte hypertrophy) in male rats exposed to ethylbenzene by

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gavage for 13 weeks (Mellert et al. 2007). The BMDL was estimated using an internal dose metric to simulate time averaged liver concentrations of ethylbenzene; a HED of the BMDL was estimated using a human PBPK model. This BMDL_{HED} of 10.68 mg/kg/day was divided by an uncertainty factor of 30 (3 for animal to human extrapolation with dosimetric adjustment and 10 for human variability).

The EPA oral reference dose (RfD) for ethylbenzene is 0.1 mg/kg/day, based on the LOAEL for liver and kidney toxicity in rats administered 291 mg/kg/day ethylbenzene via gavage 5 days/week for 182 days (Wolf et al. 1956). The RfD was calculated by dividing the NOAEL of 97 mg/kg/day by an uncertainty factor of 1,000 (10 for use of a subchronic study, 10 for interspecies extrapolation, and 10 for intraspecies variability).

The international and national regulations, advisories, and guidelines regarding ethylbenzene in air, water, and other media are summarized in Table 8-1.

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Table 8-1. Regulations, Advisories, and Guidelines Applicable to Ethylbenzene

Agency	Description	Information	Reference
<u>INTERNATIONAL</u>			
Guidelines:			
IARC	Carcinogenicity classification	Group 2B ^a	IARC 2006
WHO	Air quality guidelines	No data	WHO 2000
	Drinking water quality guidelines	0.3 mg/L ^b	WHO 2004
<u>NATIONAL</u>			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	100 ppm	ACGIH 2006
	STEL (15-minute TWA)	125 ppm	
EPA	AEGL-1, -2, -3	No data	EPA 2007a
	Hazardous air pollutant	Yes	EPA 2007c 42 USC 7412
NIOSH	REL (10-hour TWA)	100 ppm	NIOSH 2005
	STEL (15-minute TWA)	125 ppm	
	IDLH	800 ppm	
OSHA	PEL (8-hour TWA) for general industry	100 ppm	OSHA 2006c 29 CFR 1910.1000
	PEL (8-hour TWA) for shipyard industry	100 ppm	OSHA 2006a 29 CFR 1915.1000
	PEL (8-hour TWA) for construction industry	100 ppm	OSHA 2006b 29 CFR 1926.55, Appendix A
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	Yes	EPA 2007b 40 CFR 116.4
	Designated as a toxic pollutant pursuant to Section 307(a)(1) of the Clean Water Act	Yes	EPA 2007g 40 CFR 401.15
	Drinking water standards and health advisories		EPA 2006a
	1-Day health advisory for a 10-kg child	30 mg/L	
	10-Day health advisory for a 10-kg child	3 mg/L	
	DWEL	3 mg/L	
	Lifetime 10 ⁻⁴ Cancer risk	0.7 mg/L No data	

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Agency	Description	Information	Reference
NATIONAL (cont.)			
EPA	National primary drinking water standards		EPA 2003
	MCLG	0.7 mg/L	
	MCL	0.7 mg/L ^c	
	Public health goal	0.7 mg/L	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	1,000 pounds	EPA 2007d 40 CFR 117.3
	Water quality criteria for human health consumption of:		EPA 2006b
	Water + organism	0.53 mg/L	
	Organism only	2.1 mg/L	
c. Food			
EPA	Inert pesticide ingredients in pesticide products	List 2 ^d	EPA 2004
FDA	Bottled water requirement	0.7 mg/L	FDA 2006a 21 CFR 165.110
	EAFUS	No data	FDA 2007b
d. Other			
ACGIH	Carcinogenicity classification	A3 ^e	ACGIH 2006
	Biological exposure indices (end of shift at end of workweek); sum of mandelic acid and phenyl glyoxylic acid in urine	1.5 g/g creatinine ^f	
EPA	Carcinogenicity classification	Class D ^g	IRIS 2007
	Oral slope factor	No data	
	Inhalation unit risk	No data	
	RfC	1 mg/m ³	
	RfD	0.1 mg/kg/day	
	Master Testing List	Yes ^h	EPA 2007j
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance	Yes ⁱ	EPA 2007e 40 CFR 302.4
	Reportable quantity	1,000 pounds	
	Effective date of toxic chemical release reporting	01/01/87	EPA 2007f 40 CFR 372.65
	TSCA health and safety data reporting requirements	Yes	EPA 2007h 40 CFR 716.120

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NATIONAL (cont.)			
NTP	Carcinogenicity classification	No data	NTP 2005

^aGroup 2B: possibly carcinogenic to humans

^bConcentrations of the substance at or below the health based guideline value may affect the appearance, taste, or odor of the water, leading to consumer complaints.

^cPotential health effects from exposure above the MCL include liver or kidneys problems; and the common sources of contaminant in drinking water is from the discharge from petroleum refineries.

^dList 2: potentially toxic other ingredients and high priority for testing inerts

^eA3: confirmed animal carcinogen with unknown relevance to humans

^fACGIH (2006) has submitted notice of intended changes for ethylbenzene in which the BEI will be lowered to 0.7 g/g creatinine.

^gClass D: not classifiable as to human carcinogenicity

^hEthylbenzene was recommended to the Master Testing List (MTL) by the U.S. EPA's Office of Pollution Prevention and Toxics on the basis of the Screening Information Data Sets (SIDS). Styrene was added to the MTL in 1993 and the chemical testing program is currently underway by way of a VTA. The testing needs include health effects, environmental effects, and environmental fate and exposure. The Office of Air and Radiation recommended ethylbenzene to the MTL in 1995 on the basis that ethylbenzene is a hazardous air pollutant. EPA is in the process of determining the testing needs for the following: acute toxicity, neurotoxicity, developmental toxicity, reproductive, and immunotoxicity

ⁱDesignated CERCLA hazardous substance pursuant to Section 311(b)(2) and Section 307(a) of the Clean Water and Section 112 of the Clean Air Act.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = Acute Exposure Guideline Levels; BEI = biological exposure indices; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term exposure limit; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization