8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates, which are intended to serve as screening levels 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 2 ppm for 1,4-dioxane based on a NOAEL of 20 ppm for sensory irritation and pulmonary function in humans (Ernstgård et al. 2006). An uncertainty factor of 10 was used for human variability.

ATSDR has derived an intermediate-duration inhalation MRL of 0.2 ppm for 1,4-dioxane based on an increased incidence of nasal lesions in rats exposed to 1,4-dioxane 6 hours/day, 5 days/week for 13 weeks (Kasai et al. 2008). The MRL was derived using BMD modeling of incidence data for nasal lesions in rats. The predicted exposure concentration associated with a 10% extra risk for nasal lesions (BMC_{10}) for nasal lesions in female rats was 40.39 ppm; the lower 95% confidence limit on this concentration ($BMCL_{10}$) was 27.99 ppm. An uncertainty factor of 30 was used (3 for using dosimetric adjustments and 10 for human variability).

ATSDR has derived a chronic-duration inhalation MRL of 0.03 ppm for 1,4-dioxane based on a LOAEL of 50 ppm for increased incidence of nasal lesions in male rats exposed to 1,4-dioxane 6 hours/day, 5 days/week for 2 years (Kasai et al. 2009). An uncertainty factor of 300 was used (3 for using dosimetric adjustments, 10 for using a LOAEL, and 10 for human variability).

ATSDR has derived an acute-duration oral MRL of 5 mg/kg/day for 1,4-dioxane based on a NOAEL of 516 mg/kg/day for developmental and maternal effects in rats (Giavini et al. 1985). The LOAEL was 1,033 mg/kg/day. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for human variability).

ATSDR has derived an intermediate-duration oral MRL of 0.5 mg/kg/day for 1,4-dioxane based on a NOAEL of 52 mg 1,4-dioxane/kg/day for liver effects in male rats (Kano et al. 2008). The LOAEL was 126 mg/kg/day in males and 185 mg/kg/day in females. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for human variability).

ATSDR has derived a chronic-duration oral MRL of 0.1 mg/kg/day for 1,4-dioxane based on a NOAEL of 9.6 mg 1,4-dioxane/kg/day for liver effects in male rats (Kociba et al. 1974). The LOAEL was 94 mg/kg/day in males and 148 mg/kg/day in females. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for human variability).

The EPA (IRIS 2011) has derived a reference dose (RfD) of 0.03 mg/kg/day for 1,4-dioxane based on a NOAEL of 9.6 mg/kg/day for liver and kidney toxicity in male Sherman rats in a 2-year drinking water study (Kociba et al. 1974). The EPA (IRIS 2011) also derived an oral slope factor of $1x10^{-1}$ $(mg/kg/day)^{-1}$ based on increased incidence of hepatocellular adenoma and carcinoma in female BDF_1 mice in a 2-year drinking water study (Kano et al. 2009).

The National Academy of Sciences (NAS) established a maximum specification of 10 ppm for 1,4-dioxane in the ingredient polysorbate, a food additive (NAS 2003). It is also listed as an indirect food additive [21 CFR 175.105] (FDA 2003). FDA considered the same level, 10 ppm, to be an acceptable limit for 1,4-dioxane, during its consideration of a spermicide, N-9, in a contraceptive sponge product (prior to at least 1997) (FDA 1997). FDA also set a limit on 1,4-dioxane at 10 ppm in approving glycerides and polyglycerides for use as excipients in products such as dietary supplements (FDA 2006). (This regulation is located at 21 CFR 172.736.)

The international and national regulations, advisories, and guidelines regarding 1,4-dioxane in air, water, and other media are summarized in Table 8-1.

Table 8-1. Regulations, Advisories, and Guidelines Applicable to 1,4-Dioxane

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 2B[a]	IARC 1999
WHO	Air quality guidelines	No data	WHO 2000
	Water quality guidelines	No data	WHO 2004
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	20 ppm[b]	ACGIH 2011
NIOSH	REL (30-minute ceiling TWA)	1 ppm[c]	NIOSH 2004
	IDLH	500 ppm	
EPA	Hazardous air pollutant		EPA 2004d 42 USC 7412
OSHA	PEL (8-hour TWA) for general industry	100 ppm[b]	OSHA 2004c 29 CFR 1910.1000, Table Z-1
	PEL (8-hour TWA) for construction industry	100 ppm[b]	OSHA 2004b 29 CFR 1926.55, Appendix A
	PEL (8-hour TWA) for shipyard industry	100 ppm[b]	OSHA 2004a 29 CFR 1915.1000, Table Z
b. Water			
EPA	Drinking water standards and health advisories		EPA 2004b
	1-Day HA for a 10-kg child	4.0 mg/L	
	10-Day HA for a 10-kg child	0.4 mg/L	
	10^{-4} cancer risk	0.3 mg/L	
c. Food			
FDA	Indirect food additive for use only as a component of adhesives		FDA 2003 21 CFR 175.105
d. Other			
ACGIH	Carcinogenicity classification	Group A3[d]	ACGIH 2011
EPA	Carcinogenicity classification	Likely to be carcinogenic to humans	IRIS 2011
		No data	
	RfC	0.03 mg/kg/day	
	RfD		
	Oral slope factor	$1x10^{-1}$ $(mg/kg/day)^{-1}$	
	Drinking water unit risk	$2.9x10^{-6}$ $(\mu g/L)^{-1}$	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to 1,4-Dioxane

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
	Community right-to-know; toxic chemical release reporting; effective date	01/01/1987	EPA 2004e 40 CFR 372.65
EPA	Superfund, Emergency Planning, and Community Right-To-Know Programs; designated as a hazardous substance pursuant to Section 112 of the Clean Air Act and Section 3001 of RCRA		EPA 2004a 40 CFR 302.4
	Reportable quantity	100 pounds	
	Hazardous waste identification	U108	EPA 2004c 40 CFR 261, Appendix VIII
NTP	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen	NTP 2011
STATE			
a. Air			
No data			
b. Water			
California	Drinking water guidelines	3 µg/L	HSDB 2010
Florida	Drinking water guidelines	5 µg/L	
Maine	Drinking water guidelines	32 µg/L	
Massachusetts	Drinking water guidelines	50 µg/L	
c. Food			
No data			
d. Other			
No data			

[a]Group 2B: Possibly carcinogenic to humans.
[b]Skin designation: Potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, either by contact with vapors, or of probable greater significance, by direct skin contact with the substance.
[c]Potential occupational carcinogen.
[d]Group A3: Confirmed animal carcinogen with unknown relevance to humans.

ACGIH = American Conference of Governmental Industrial Hygienists; CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HA = Health Advisory; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; RfC = reference concentration; RfD = reference dose; TLV = threshold limit values; TWA = time-weighted average; USC = United States Codes; WHO = World Health Organization