

## 8. REGULATIONS AND ADVISORIES

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

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 a chronic-duration inhalation MRL of 1 ppm for 1,4-dioxane based on a NOAEL of 111 ppm for liver effects in rats (Torkelson et al. 1974). No LOAEL was defined in the study. The MRL was derived using the PBPK model developed by Reitz et al. (1990). An uncertainty factor 30 was used (3 for using dosimetric adjustments and 10 to protect sensitive populations). The chronic-duration inhalation MRL of 1 ppm also has been adopted as the intermediate-duration inhalation MRL.

ATSDR has derived an acute-duration oral MRL of 4 mg/kg/day for 1,4-dioxane based on a NOAEL of 370 mg/kg/day for nasal effects in male rats (JBRC 1998a). The LOAEL was 1,010 mg/kg/day in males and 1,040 mg/kg/day in females. An uncertainty factor of 100 was used (10 for the protection of sensitive populations and 10 for animal to human extrapolation).

ATSDR has derived an intermediate-duration oral MRL of 0.6 mg/kg/day for 1,4-dioxane based on a NOAEL of 60 mg 1,4-dioxane/kg/day for liver effects in male rats (JBRC 1998b). The LOAEL was 150 mg/kg/day in males and 200 mg/kg/day in females. An uncertainty factor of 100 was used (10 for the protection of sensitive populations and 10 for animal to human extrapolation).

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 the protection of sensitive populations and 10 for animal to human extrapolation).

The EPA (IRIS 2004) has not derived a reference dose (RfD) or a reference concentration (RfC) for 1,4-dioxane, but derived an oral slope actor of  $1.1 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$  based on the increased incidence of

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

Agency	Description	Information	Reference
<u>INTERNATIONAL</u>			
Guidelines:			
IARC	Carcinogenicity classification	Group 2B <sup>a</sup>	IARC 1999
WHO	Air quality guidelines	No data	WHO 2000
	Water quality guidelines	No data	WHO 2004
<u>NATIONAL</u>			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	20 ppm <sup>b</sup>	ACGIH 2003
NIOSH	REL (30-minute ceiling TWA)	1 ppm <sup>c</sup>	NIOSH 2004
	IDLH	500 ppm	
EPA	Hazardous air pollutant		EPA 2004d 42 USC 7412
OSHA	PEL (8-hour TWA) for general industry	100 ppm <sup>b</sup>	OSHA 2004c 29 CFR 1910.1000, Table Z-1
	PEL (8-hour TWA) for construction industry	100 ppm <sup>b</sup>	
	PEL (8-hour TWA) for shipyard industry	100 ppm <sup>b</sup>	
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 <sup>-4</sup> 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 <sup>d</sup>	ACGIH 2003
EPA	Carcinogenicity classification	B2 <sup>e</sup>	IRIS 2004
	RfC	No data	
	RfD	No data	
	Oral slope factor	1.1x10 <sup>-2</sup> (mg/kg/day) <sup>-1</sup>	
	Drinking water unit risk	3.1x10 <sup>-7</sup> (µg/L) <sup>-1</sup>	
	Community right-to-know; toxic chemical release reporting; effective date	01/01/1987	

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Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
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 2005
<u>STATE</u>			
a. Air			
No data			
b. Water			
California	Drinking water guidelines	3 µg/L	HSDB 2005
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			

<sup>a</sup>Group 2B: Possibly carcinogenic to humans.

<sup>b</sup>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.

<sup>c</sup>Potential occupational carcinogen.

<sup>d</sup>Group A3: Confirmed animal carcinogen with unknown relevance to humans.

<sup>e</sup>B2: probable human carcinogen.

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

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nasal tumors in male Osborne-Mendel rats (NCI 1978). As part of its systematic prioritization process, the EPA is currently re-evaluating the health assessment for 1,4-dioxane (EPA 2004f).

The National Academy of Sciences (NAS) established a specification of 10 ppm for 1,4-dioxane in the ingredient polysorbate, a food additive. 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 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 and is available on FDA's website at <http://www.cfsan.fda.gov/~lrd/fr060331.html>.) In addition, FDA issued a regulation that the label of foaming detergent bath products, except for those labeled as intended for use exclusively by adults, bear adequate directions for safe use and the following caution: "Use only as directed. Excessive use or prolonged exposure may cause irritation to skin and urinary tract. Discontinue use if rash, redness, or itching occurs. Consult your physician if irritation persists. Keep out of the reach of children." In the case of products intended for children's use, the phrase "except under adult supervision" may be added (FDA 1986).