

8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance-specific estimates that are intended to serve as screening levels. They 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 1×10^{-5} ppm for TDI. The MRL is based on LOAEL of 0.005 ppm for decreases in lung function in healthy volunteers exposed to TDI for 6 hours (Vandenplas et al. 1999). The LOAEL was adjusted to continuous 24-hour exposure (from 6 hours/day) and divided by a total uncertainty factor of 100 (10 for the use of a LOAEL and 10 for human variability). Since there is uncertainty that the MRL would be protective for continuous exposure for 14 days, it is suggested that measured air concentrations should not exceed the MRL of 1×10^{-5} ppm during a 24-hour period.

ATSDR has derived a chronic-duration inhalation MRL of 3×10^{-6} ppm for TDI. The MRL is based on the mean daily exposure level of 0.0012 ppm, which resulted in decreases in lung function in workers at flexible foam producing facilities (Clark et al. 1998). The adverse effect level of 0.0012 ppm was adjusted for intermittent exposure (8 hours/day, 5 days/week) and divided by a total uncertainty factor of 100 (10 for the use of a LOAEL and 10 for human variability).

EPA (IRIS 2003) has derived a chronic-duration reference concentration (RfC) of 7×10^{-5} mg/m³ (1×10^{-5} ppm) based on a NOAEL of 0.0009 ppm and a LOAEL of 0.0019 ppm for decreases in lung function in workers at a TDI manufacturing facility (Diem et al. 1982). The NOAEL was adjusted for intermittent exposure ($[10 \text{ m}^3/\text{day}]/[20 \text{ m}^3/\text{day}]$, 5 days/week) and divided by a total uncertainty factor of 30 (3 to account for both extrapolation from a subchronic study and the lack of developmental toxicity data in a second species and 10 for intrahuman variability).

ATSDR has derived a chronic-duration inhalation MRL of 0.001 mg/m³ for polymeric MDI. The MRL is based on a BMCL₁₀ of 0.48 mg/m³ for basal cell hyperplasia in the nasal cavity observed in rats exposed to polymeric MDI for 2 years (Reuzel et al. 1994). The BMCL₁₀ was adjusted for intermittent exposure (6 hours/day, 5 days/week) and multiplied by a regional deposited dose ratio for extrathoracic effect (RDDR_{ET}) of 0.453 to calculate the human equivalent concentration (BMCL_{HEC}). The BMCL_{HEC} of 0.039 mg/m³ was divided by a total uncertainty factor of 30 (3 to extrapolate from animals to humans

8. REGULATIONS, ADVISORIES, AND GUIDELINES

with dosimetric adjustments and 10 for human variability); EPA notes that “the two UFs of 3 each coalesce to a 10, yielding a total UF of 100.”

EPA (IRIS 2002) has derived a chronic-duration RfC of 0.0006 mg/m³ based on a BMCL_{ADJ} of 0.14 mg/m³ for basal cell hyperplasia in rats exposed to polymeric MDI for 2 years (Reuzel et al. 1994). The BMCL_{HEC} was calculated by multiplying the BMCL_{ADJ} of 0.14 mg/m³ by a RDD_{RET} of 0.453. The BMCL_{HEC} of 0.06 mg/m³ was divided by a total uncertainty factor of 100 (10 for intraindividual variation, 3 for the lack of reproductive data, and 3 for “interspecies variation inasmuch as dosimetric adjustments had been made”).

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

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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

Agency	Description	Information	Reference
<u>International</u>			
Guidelines:			
IARC	Carcinogenicity classification		
	TDI	Group 2B ^a	IARC 1999b
	4,4'-MDI	Group 3 ^b	IARC 1999a
WHO	Air quality guidelines	Not listed	WHO 2010
	Drinking water quality guidelines	Not listed	WHO 2017
<u>National</u>			
Regulations and guidelines:			
a. Air			
ACGIH	TLV-TWA ^{c,d,e}		
	2,4-TDI or 2,6-TDI (or as a mixture)	0.001 ppm ^f	ACGIH 2016a
	Monomeric 4,4'-MDI	0.005 ppm	ACGIH 2001
	STEL		
	2,4-TDI or 2,6-TDI (or as a mixture)	0.005 ppm ^f	ACGIH 2016a
DOE	PAC-1 ^g		DOE 2016b
	TDI, mixed isomers	0.020 ppm	
	2,4-TDI	0.020 ppm	
	2,6-TDI	0.020 ppm	
	Monomeric 4,4'-MDI	0.45 mg/m ³	
	Polymeric 4,4'-MDI	29 mg/m ³	
	PAC-2 ^g		
	TDI, mixed isomers	0.083 ppm	
	2,4-TDI	0.083 ppm	
	2,6-TDI	0.083 ppm	
	Monomeric 4,4'-MDI	5 mg/m ³	
	Polymeric 4,4'-MDI	40 mg/m ³	
	PAC-3 ^g		
	TDI, mixed isomers	0.51 ppm	
	2,4-TDI	0.51 ppm	
2,6-TDI	0.51 ppm		
Monomeric 4,4'-MDI	55 mg/m ³		
Polymeric 4,4'-MDI	240 mg/m ³		

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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Agency	Description	Information	Reference
EPA	2,4-TDI		EPA 2016a
	AEGL-1 ^h		
	10 minutes	0.020 ppm	
	30 minutes	0.020 ppm	
	60 minutes	0.020 ppm	
	4 hours	0.010 ppm	
	8 hours	0.010 ppm	
	AEGL-2 ^h		
	10 minutes	0.24 ppm	
	30 minutes	0.17 ppm	
	60 minutes	0.083 ppm	
	4 hours	0.021 ppm	
	8 hours	0.021 ppm	
	AEGL-3 ^h		
	10 minutes	0.65 ppm	
	30 minutes	0.65 ppm	
	60 minutes	0.51 ppm	
	4 hours	0.32 ppm	
	8 hours	0.16 ppm	
	2,6-TDI		
	AEGL-1 ^h		
	10 minutes	0.020 ppm	
	30 minutes	0.020 ppm	
	60 minutes	0.020 ppm	
	4 hours	0.010 ppm	
	8 hours	0.010 ppm	
	AEGL-2 ^h		
	10 minutes	0.24 ppm	
	30 minutes	0.17 ppm	
	60 minutes	0.083 ppm	
	4 hours	0.021 ppm	
	8 hours	0.021 ppm	
	AEGL-3 ^h		
	10 minutes	0.65 ppm	
	30 minutes	0.65 ppm	
	60 minutes	0.51 ppm	
	4 hours	0.32 ppm	
	8 hours	0.16 ppm	
	Hazardous air pollutant		EPA 2016c 42 USC
	2,4-TDI	Yes	7412
	Monomeric 4,4'-MDI	Yes	

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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Agency	Description	Information	Reference
NIOSH	NAAQS	Not listed	EPA 2018b
	REL		NIOSH 2016a, 2016b
	2,4-TDI	Potential occupational carcinogens	
	Monomeric 4,4'-MDI	0.05 mg/m ³	
	Ceiling limit (10-minute)		
	Monomeric 4,4'-MDI	0.2 mg/m ³	
	IDLH		
OSHA	2,4-TDI	2.5 ppm	
	Monomeric 4,4'-MDI	75 mg/m ³	
	Ceiling limit (15-minute TWA) for general industry		OSHA 2017b 29 CFR 1910.1000, Table Z-2
	2,4-TDI	0.02 ppm	
	Monomeric 4,4'-MDI	0.02 ppm	
	Highly hazardous chemicals	Not listed	OSHA 2017a 29 CFR 1910.119, Appendix A
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	Not listed	EPA 2017b 40 CFR 116.4
	Drinking water contaminant candidate list		EPA 2016b 81 FR 81099
	TDI	Yes	
	Drinking water standards and health advisories	Not listed	EPA 2012
	National primary drinking water standards	Not listed	EPA 2009b
	National recommended water quality criteria: human health for the consumption of (at 10 ⁻⁴ risk)	Not listed	EPA 2018c
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	Not listed	EPA 2017d 40 CFR 117.3
c. Food			
FDA	Bottled water	Not listed	FDA 2017 21 CFR 165.110
	EAFUS ⁱ	Not listed	FDA 2013
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2016a
	2,4-TDI or 2,6-TDI (or as a mixture)	A3 ⁱ	

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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

Agency	Description	Information	Reference	
EPA	Carcinogenicity classification		IRIS 2002, 2003	
	TDI (toluene 2,4- (2,6-) diisocyanate)	No data		
	MDI (monomeric MD) and polymeric MDI)	Group D ^k		
	RfC			
	2,4-/2,6-TDI	7x10 ⁻⁵ mg/m ³		
	MDI (monomeric MDI and polymeric MDI)	6x10 ⁻⁴ mg/m ³		
	RfD			
	2,4-/2,4-TDI (toluene 2,4- (2,6-) diisocyanate)	Not listed		
	MDI (monomeric MDI and polymeric MDI)	Not listed		
	Identification and listing of hazardous waste			EPA 2017c 40 CFR 261, Appendix VIII
	TDI (toluene 2,4- (2,6-) diisocyanate)	U223		
	Master Testing List			EPA 1996
	Monomeric 4,4'-MDI	Yes		
	Polymethylene polyphenyl isocyanate	Yes		
	Polymeric 4,4'-MDI	Yes		
	RCRA waste minimization PBT priority chemical list	Not listed		EPA 1998b 63 FR 60332
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list	Not listed		EPA 2017e 40 CFR 264, Appendix IX
	Superfund, emergency planning, and community right-to-know			
	Designated CERCLA hazardous substance and reportable quantity			EPA 2017f 40 CFR 302.4
	TDI (toluene 2,4- (2,6-) diisocyanate) ^l	100 pounds		
	2,4-TDI ^l	100 pounds		
	2,6-TDI ^l	100 pounds		
	Monomeric 4,4'-MDI ^m	5,000 pounds		
Effective date of toxic chemical release reporting		EPA 2017g 40 CFR 372.65		
TDI (toluene 2,4- (2,6-) diisocyanate)	01/01/1990			
2,4-TDI	01/01/1987			
2,6-TDI	01/01/1987			
Monomeric 4,4'-MDI	01/01/1987			
Diisocyanates category (including MDI and polymeric MDI)	01/01/1995			

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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Agency	Description	Information	Reference
	Extremely hazardous substances and its threshold planning quantity		EPA 2017h 40 CFR 355, Appendix A
	2,4-TDI	500 pounds	
	2,6-TDI	100 pounds	
	TSCA chemical lists and reporting periods		EPA 2017i 40 CFR 712.30
	Monomeric 4,4'-MDI		
	Effective date	10/29/1990	
	Reporting date	12/27/1990	
	Polymeric 4,4'-DMDI		
	Effective date	10/29/1990	
	Reporting date	12/27/1990	
	TSCA health and safety data reporting		EPA 2017j 40 CFR 716.120
	TDI (2,4 and 2,6 mixed isomers); 2,4-TDI; monomeric 4,4'-MDI; polymeric 4,4'-MDI		
	Effective date	06/01/1987	
	Reporting date	06/01/1997	
	2,6-TDI		
	Effective date	06/01/1987	
	Reporting date	12/19/1995	
NTP	Carcinogenicity classification		NTP 2016
	TDI	Reasonably anticipated to be a human carcinogen	

^aGroup 2B: possibly carcinogenic to humans.

^bGroup 3: not classifiable as to its carcinogenicity to humans.

^cSkin notation: refers to potential significant contribution to the overall exposure by the cutaneous route (ACGIH 2016b).

^dDermal sensitization notation: refers to potential for agent to produce dermal sensitization (ACGIH 2016b).

^eRespiratory sensitization notation: refers to potential for agent to produce respiratory sensitization (ACGIH 2016b).

^fInhalable fraction and vapor: material exerts sufficient vapor pressure such that it may be present in both particle and vapor phases, with each contributing a significant portion of the dose at the TLV-TWA concentration (ACGIH 2016b).

^gDefinitions of PAC terminology are available from DOE (2016a).

^hAEGL-1 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure. AEGL-2 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape. AEGL-3 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death (EPA 2018a).

ⁱThe EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.

^jA3: confirmed animal carcinogen with unknown relevance to humans.

^kGroup D: not classifiable as to human carcinogenicity.

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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^lDesignated CERCLA hazardous substance and reportable quantity pursuant to Section 112 of the Clean Air Act and Section 3001 of RCRA.

^mDesignated CERCLA hazardous substance and reportable quantity pursuant to Section 112 of the Clean Air Act.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FR = Federal Register; GRAS = generally recognized as safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MDI = methylenediphenyl diisocyanate; NAAQS = National Ambient Air Quality Standards; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PBT = persistent, bioaccumulative, and toxic; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; SIDS = Screening Information Data Set; STEL = short-term exposure limit; TDI = toluene diisocyanate; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization