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 oral MRL of 0.01 mg/kg/day for acrylamide based on results of fertility testing of male Long-Evans hooded rats administered acrylamide by gavage for 5 days prior to 1-week mating sessions with untreated female rats (Sublet et al. 1989). As discussed in detail in Appendix A, the PBPK model of Sweeney et al. (2010) was used to estimate rat internal dose metrics for blood acrylamide and glycidamide for each of the administered acrylamide dose levels in the principal study. BMD analysis was used to predict the fraction of nonpregnant female rats for each of the PBPK-predicted male rat internal dose metrics for blood acrylamide and glycidamide. The PBPK model was then used to predict the HED associated with the best-fitting BMD result. The resulting HED of 0.31 mg/kg/day was divided by an uncertainty factor of 30 (3 for interspecies extrapolation using a PBPK model and 10 for human variability). See Appendix A for a more detailed description of the acute-duration oral MRL derivation for acrylamide.

ATSDR has derived an intermediate-duration oral MRL of 0.001 mg/kg/day for acrylamide based on a NOAEL of 0.2 mg/kg/day and a LOAEL of 1 mg/kg/day for ultrastructural changes in peripheral nerve fibers in male F344 rats receiving acrylamide from the drinking water for up to 93 days (Burek et al. 1980). As discussed in detail in Appendix A, the PBPK model of Sweeney et al. (2010) was used to estimate rat internal dose metrics for blood acrylamide and glycidamide at the NOAEL of 0.2 mg/kg/day and for estimating the corresponding HED. The resulting HED of 0.038 mg/kg/day was divided by an uncertainty factor of 30 (3 for interspecies extrapolation using a PBPK model and 10 for human variability). See Appendix A for a more detailed description of the intermediate-duration oral MRL derivation for acrylamide.

ATSDR has derived a chronic-duration oral MRL of 0.001 mg/kg/day for acrylamide based on degenerative changes in sciatic nerves from male F344 rats receiving acrylamide from the drinking water for up to 2 years, as detected by light microscopy (Friedman et al. 1995). As discussed in detail in Appendix A, the PBPK model of Sweeney et al. (2010) was used to estimate rat internal dose metrics for blood acrylamide and glycidamide for each of the administered acrylamide dose levels in the principal study (Friedman et al. 1995). BMD analysis was used to predict degenerative peripheral nerve incidence

for each of the PBPK-predicted male rat internal dose metrics for blood acrylamide and glycidamide. The PBPK model was then used to predict the HED associated with the best-fitting BMD result. The resulting HED of 0.042 mg/kg/day was divided by an uncertainty factor of 30 (3 for interspecies extrapolation using PBPK modeling and 10 for human variability). See Appendix A for a more detailed description of the chronic-duration oral MRL derivation for acrylamide.

EPA has established an oral reference dose (RfD) of 0.002 mg/kg/day for acrylamide (EPA 2010; IRIS 2012) based on a $BMDL_{05}$ of 0.27 mg/kg/day for degenerative nerve changes in male F344 rats exposed to acrylamide in the drinking water for up to 2 years (Johnson et al. 1986). The rat $BMDL_{05}$ was converted to a human equivalent dose (HED_{BMDL05}) of 0.053 mg/kg/day using acrylamide AUC and glycidamide AUC to estimate the internal dose in rats, extrapolate that dose to the internal dose in humans, and then to estimate the daily human intake of acrylamide needed to produce the human internal dose comparable to that of the rat at the rat $_{BMDL05}$. The HED_{BMDL05} of 0.053 mg/kg/day was divided by an uncertainty factor of 30 (3 to account for interspecies toxicodynamic differences and 10 for human variability).

EPA has established an inhalation reference concentration (RfC) of 0.006 mg/m^3 for acrylamide (EPA 2010; IRIS 2012) based on route-to-route extrapolation using the $BMDL_{05}$ of 0.27 mg/kg/day for degenerative nerve changes in male F344 rats exposed to acrylamide in the drinking water for up to 2 years (Johnson et al. 1986) as the point of departure. The rat $BMDL_{05}$ was converted to a human equivalent dose (HED_{BMDL05}) of 0.053 mg/kg/day using acrylamide AUC and glycidamide AUC to estimate the internal dose in rats, extrapolate that dose to the internal dose in humans, and then to estimate the daily human intake of acrylamide needed to produce the human internal dose comparable to that of the rat at the rat $BMDL_{05}$. The HED_{BMDL05} of 0.053 mg/kg/day was converted to a human equivalent concentration (HEC_{BMDL05}) of 0.18 mg/m^3 based on a 70-kg person who breathes 20 m^3 of air daily. The HEC_{BMDL05} of 0.18 mg/m^3 was divided by an uncertainty factor of 30 (3 to account for interspecies toxicodynamic differences and 10 for human variability).

The International Agency for Research on Cancer (IARC) has classified acrylamide as a Group 2A carcinogen (probably carcinogenic to humans) (IARC 2011). The National Toxicology Program (NTP) has determined that acrylamide is reasonably anticipated to be a human carcinogen (NTP 2011a). EPA has characterized acrylamide as "likely to be carcinogenic to humans" (EPA 2010; IRIS 2012). The American Conference of Governmental Industrial Hygienists (ACGIH) has classified acrylamide as an A3 carcinogen (confirmed animal carcinogen with unknown relevance to humans) (ACGIH 2011).

OSHA has required employers of workers who are occupationally exposed to acrylamide to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PELs). The employer must use engineering and work practice controls to reduce exposures to not exceed 0.3 mg/m^3 for acrylamide at any time (OSHA 2010).

EPA has designated acrylamide as a hazardous air pollutant (HAP) under the Clean Air Act (CAA) (EPA 2011a). Acrylamide is on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" and has been assigned a reportable quantity (RQ) limit of 5,000 pounds (EPA 2011b). Acrylamide is also considered to be an extremely hazardous substance (EPA 2011c). The RQ represents the amount of a designated hazardous substance which, when released to the environment, must be reported to the appropriate authority.

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

Table 8-1. Regulations and Guidelines Applicable to Acrylamide

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 2A[a]	IARC 2011
WHO	Air quality guidelines	No	WHO 2000
	Drinking water quality guidelines	0.0005 mg/L[b]	WHO 2008
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)[c,d]	0.03 mg/m^3	ACGIH 2011
	TLV-basis (critical effect)	Central nervous system impairment	
AIHA	ERPG values	No	AIHA 2009
EPA	Hazardous air pollutant	Yes	EPA 2009a 42 USC 7412
	Second AEGL Chemical Priority List	Yes[e]	EPA 2008
NIOSH	REL (10-hour TWA)[f]	0.03 mg/m^3	NIOSH 2011
	IDLH	60 mg/m^3	
	Potential occupational carcinogen	Yes	
	Target organs	Eyes, skin, central nervous system, peripheral nervous system, and reproductive system	
OSHA	PEL (8-hour TWA) for general industry[f]	0.3 mg/m^3	OSHA 2010 29 CFR 1910.1000, Table Z-1
b. Water			
EPA	Drinking water standards and health advisories		EPA 2011a
	1-day health advisory for a 10-kg child	1.5 mg/L	
	10-day health advisory for a 10-kg child	0.3 mg/L	
	RfD	0.002 mg/kg/day	
	DWEL	0.07 mg/L	
	Lifetime	No data	
	10^{-4} Cancer risk	No data[g]	

Table 8-1. Regulations and Guidelines Applicable to Acrylamide

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	National primary drinking water standards		EPA 2003
	Treatment technique	Yes[h]	
	Potential health effects from exposure above the MCL	Nervous system or blood problems	
	Common sources of acrylamide in drinking water	Added to water during sewage/waste water treatment; increased risk of cancer treatment	
	Public health goal	Zero	
	National recommended water quality criteria	No	EPA 2006
c. Food			
FDA	EAFUS[i]	No	FDA 2008
d. Other			
ACGIH	Carcinogenicity classification	A3[j]	ACGIH 2011
EPA	Carcinogenicity classification	Likely to be carcinogenic to humans[k]	EPA 2010; IRIS 2012
	RfC	0.006 mg/m^3	
	RfD	0.002 mg/kg/day	
	Inhalation unit risk	1x10^{-4} per µg/m^3	
	Oral slope factor	0.5 per mg/kg/day	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance	Yes[l]	EPA 2011b 40 CFR 302.4
	Reportable quantity	5,000 pounds	
	Effective date of toxic chemical release reporting	01/01/1987	EPA 2011d 40 CFR 372.65
	Extremely hazardous substances and its threshold planning quantity	1,000/10,000 pounds	EPA 2011c 40 CFR 355, Appendix A
	TSCA health and safety data reporting		EPA 2011e 40 CFR 716.120
	Effective date	10/04/1982	
	Sunset date	10/04/1992	

Table 8-1. Regulations and Guidelines Applicable to Acrylamide

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
NTP	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen	NTP 2011a

[a]Group 2A: probably carcinogenic to humans
[b]For substances that are considered to be carcinogenic, the guideline value is the concentration in drinking-water associated with an upper-bound excess lifetime cancer risk of 10^{-5} (one additional cancer per 100,000 of the population ingesting drinking-water containing the substance at the guideline value for 70 years) (WHO 2006).
[c]TWA: inhalable fraction and vapor. Material exerts sufficient vapor pressure such that it may be present in both particle and vapor phases.
[d]Skin: refers to the potential significant contribution to the overall exposure by the cutaneous route.
[e]Acrylamide is included on the list of 371 priority chemicals that are acutely toxic and represent the selection of chemicals for AEGL development by the NAC/AEGL committee during the next several years.
[f]Carcinogen; skin designation
[g]Likely to be carcinogenic to humans
[h]Each water system must certify, in writing, to the state (using third-party or manufacturers certification) that when it uses acrylamide to treat water, the combination (or product) of dose and monomer level does not exceed 0.05% of acrylamide dosed at 1 mg/L (or equivalent).
[i]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[j]A3: confirmed animal carcinogen with unknown relevance to humans.
[k]Based on sufficient evidence of carcinogenicity in animals.
[l]Designated CERCLA hazardous substance pursuant to Section 112 of the Clean Air Act and Section 3001 of the Resource Conservation and Recovery Act.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; 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; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; NAC = National Advisory Committee; 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; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization