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.

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

ATSDR has derived an intermediate-duration oral MRL of 0.6 mg/kg/day for TCEP based on an increased incidence of brain lesions in female Fischer-344 rats dosed by gavage 5 days/week for 16 weeks (NTP 1991a). The MRL was derived using benchmark modeling of incidence data for brain lesions in female rats. The predicted dose associated with a 10% extra risk (BMD_{10}) for brain lesions was 143.41 mg/kg/day; the lower 95% confidence limit on this dose ($BMDL_{10}$) was 85.07 mg/kg/day. 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 0.2 mg/kg/day for TCEP based on an increased incidence of renal tubule epithelial hyperplasia in female Fischer-344 rats dosed by gavage 5 days/week for 2 years (NTP 1991a). The MRL was derived using benchmark modeling of incidence data for renal lesions in female rats. The BMD_{10} for renal lesions was 48.00 mg/kg/day; the $BMDL_{10}$ was 32.82 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 acute-duration oral MRL of 1.1 mg/kg/day for TnBP based on decreased body weight gain in Wistar rats during pregnancy (Noda et al. 1994). The MRL was derived using benchmark modeling of the decrease in body weight gain. The BMD_{1SD} was 130.32 mg/kg/day; the corresponding $BMDL_{1SD}$ was 111.47 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 0.08 mg/kg/day for TnBP based on an increased incidence of urinary bladder hyperplasia in male Sprague-Dawley rats dosed via the diet for 10 weeks (Arnold et al. 1997). The MRL was derived using benchmark modeling of incidence data for urinary bladder lesions in male rats. The BMD_{10} for urinary bladder lesions was 19.74 mg/kg/day; the

Table 8-1. Regulations, Advisories, and Guidelines Phosphate Ester Flame Retardants

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 3[a]	IARC 2009
	Tris-(2-chloroethyl)-phosphate		
WHO	Air quality guidelines	No	WHO 2000
	Drinking water quality guidelines	No	WHO 2006
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)		ACGIH 2008
	Tributyl phosphate	2.5 mg/m^3 (0.19 ppm)	
	Triphenyl phosphate	3.0 mg/m^3 (0.22 ppm)	
	TLV Basis		
	Tributyl phosphate	Nausea, headache, eye and upper respiratory irritation	
	Triphenyl phosphate	Cholinesterase inhibitor	
AIHA	ERPG values	No	AIHA 2008
EPA	AEGL values	No	EPA 2009a
	Hazardous air pollutant	No	EPA 2009b 42 USC 7412
NIOSH	REL (10-hour TWA)		NIOSH 2005b
	Tributyl phosphate	2.5 mg/m^3 (0.19 ppm)	
	Triphenyl phosphate	3.0 mg/m^3 (0.22 ppm)	
	IDLH		
	Tributyl phosphate	327 mg/m^3 (30 ppm)	
	Triphenyl phosphate	1,000 mg/m^3 (75 ppm)	
	Target organs		
	Tributyl phosphate	Eyes, skin, and respiratory system	
	Triphenyl phosphate	Blood and peripheral nervous system	
OSHA	PEL (8-hour TWA) for general industry		OSHA 2009 29 CFR 1910.1000, Table Z-1
	Tributyl phosphate	5.0 mg/m^3 (0.46 ppm)	
	Triphenyl phosphate	3.0 mg/m^3 (0.22 ppm)	

Table 8-1. Regulations, Advisories, and Guidelines Phosphate Ester Flame Retardants

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
b. Water			
EPA	Drinking water standards and health advisories	No	EPA 2006a
	National primary drinking water standards	No	EPA 2003
	National recommended water quality criteria	No	EPA 2006b
c. Food			
FDA	EAFUS[b]	No	FDA 2008
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2008
	Tributyl phosphate	No	
	Triphenyl phosphate	A4[c]	
EPA	Inert ingredients are permitted for use in nonfood use pesticide products		EPA 2009c
	Tributyl phosphate, tributoxyethyl phosphate, and triphenyl phosphate	Yes	
	Inert ingredients are no longer permitted for use in nonfood use pesticide products		EPA 1998b 63 FR 34834
	Tricresyl phosphate	Yes	
	Carcinogenicity classification	No	IRIS 2009
	RfC	No	
	RfD	No	
	MTL		EPA 2009
	Triphenyl phosphate	Yes[d]	
	Tricresyl phosphate	Yes[d]	
	Tri-(2-chloroisopropyl) phosphate	Yes[e]	
	Tris-(2-chloroethyl)-phosphate	Yes[e]	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance	No	EPA 2009d 40 CFR 302.4
	Effective date of toxic chemical release reporting	No	EPA 2009e 40 CFR 372.65

Table 8-1. Regulations, Advisories, and Guidelines Phosphate Ester Flame Retardants

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	TSCA chemical lists and reporting periods		EPA 2009f 40 CFR 712.30
	Tributyl phosphate, triisobutyl phosphate, and tributoxyethyl phosphate		
	Effective date	10/29/1990	
	Reporting date	12/27/1990	
	TSCA health and safety data reporting		EPA 2009g 40 CFR 716.120
	Tributyl phosphate		
	Effective date	06/18/1986	
	Sunset date	06/18/1996	
	Tricresyl phosphate		EPA 2009g 40 CFR 716.120
	Effective date	10/04/1982	
	Sunset date	10/04/1992	
	Trisobutyl phosphate		
	Effective date	10/29/1990	
	Sunset date	11/09/1993	
	Tributoxyethyl phosphate		
	Effective date	10/29/1990	
	Sunset date	12/19/1995	
	Triphenyl phosphate		
	Effective date	10/04/1982	
	Sunset date	10/04/1992	
	TSCA chemical lists and reporting periods		EPA 2009f 40 CFR 712.30
	Tri-(2-chloroisopropyl) phosphate and tris-(2-chloroethyl)-phosphate		
	Effective date	12/16/1988	
	Sunset date	11/09/1993	
	Tris(1,3-dichloro-2-propyl) phosphate		
	Effective date	12/16/1988	
	Sunset date	12/19/1995	

Table 8-1. Regulations, Advisories, and Guidelines Phosphate Ester Flame Retardants

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
NTP	Carcinogenicity classification	No data	NTP 2005
	Nominated for in-depth toxicological evaluation	Tricresyl phosphate	NTP 2011

[a]Group 3: not classifiable as to carcinogenicity to humans
[b]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.
[c]A4: not classifiable as a human carcinogen
[d]Triphenyl phosphate and tricresyl phosphate were added to the MTL in 1992 and the testing action development is underway. The testing needs include health effects, ecological effects, and chemical fate.
[e]Tri-(2-chloroisopropyl) phosphate and tris-(2-chloroethyl)-phosphate were added to the MTL in 1992 and the chemical testing program is underway.

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; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; 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; MTL = Master Testing List; 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

$BMDL_{10}$ was 8.03 mg/kg/day. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for human variability).

ATSDR has adopted the intermediate-duration oral MRL of 0.08 mg/kg/day for TnBP also as the chronic-duration oral MRL for TnBP. A detailed explanation can be found in Section 2.3.

ATSDR has derived an acute-duration oral MRL of 4.8 mg/kg/day for TBEP based on decreased body weight gain in CD rats during Gd 6–15 (Monsanto Co. 1985b). The MRL was derived using benchmark modeling of the decrease in body weight gain. The BMD_{1SD} was 824.97 mg/kg/day; the corresponding $BMDL_{1SD}$ was 477.25 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 0.09 mg/kg/day for TBEP based on an increased incidence of periportal hepatocyte vacuolization in male Sprague-Dawley rats dosed via the diet for 18 weeks (Reyna and Thake 1987a). The MRL was derived using benchmark modeling of incidence data for hepatocyte vacuolization in male rats. The BMD_{10} for hepatocyte vacuolization was 22.02 mg/kg/day; the $BMDL_{10}$ was 8.88 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 0.05 mg/kg/day for TDCP based on increased absolute kidney weight in male Sprague-Dawley rats dosed via the diet for 12 months (Stauffer Chemical Co. 1981a). The MRL was derived using benchmark modeling of the increase in kidney weight. The BMD_{1SD} was 13.36 mg/kg/day; the corresponding $BMDL_{1SD}$ was 4.69 mg/kg/day. 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 0.02 mg/kg/day for TDCP based on an increased incidence of renal tubular epithelial hyperplasia in male Sprague-Dawley rats dosed via the diet for 2 years (Stauffer Chemical Co. 1981a). The MRL was derived using benchmark modeling of incidence data for renal lesions in male rats. The BMD_{10} for renal tubular hyperplasia was 2.60 mg/kg/day; the lower 95% confidence limit on this dose ($BMDL_{10}$) was 1.94 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 0.04 mg/kg/day for TCP based on an increased incidence of hyperplasia of the interstitial cell in the ovary in female F344/N rats dosed via the diet for

3 months (NTP 1994). The MRL was derived using benchmark modeling of incidence data for ovarian lesions. The BMD_{10} for ovarian lesions was 6.21 mg/kg/day; the lower 95% confidence limit on this dose ($BMDL_{10}$) was 3.72 mg/kg/day. 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 0.02 mg/kg/day for TCP based on an increased incidence of hyperplasia of the interstitial cell in the ovary in female F344/N rats dosed via the diet for 15 months (NTP 1994). The MRL was derived using benchmark modeling of incidence data for ovarian lesions. The BMD_{10} for ovarian lesions was 5.22 mg/kg/day; the lower 95% confidence limit on this dose ($BMDL_{10}$) was 2.12 mg/kg/day. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for human variability).

EPA (IRIS 2009) has not established an oral reference dose (RfD) or inhalation reference concentration (RfC) for phosphate ester flame retardants.

The International Agency for Research on Cancer (IARC) has classified TCEP as a Group 3 carcinogen (*not classifiable as to carcinogenicity to humans*) (IARC 2009). The American Conference of Governmental Industrial Hygienists (ACGIH) has classified TPP as an A4 carcinogen (*not classifiable as a human carcinogen*) (ACGIH 2008). Neither the National Toxicology Program (NTP) nor the EPA has classified the phosphate ester flame retardants discussed in this profile for human carcinogenicity (IRIS 2009; NTP 2005).

OSHA has required employers of workers who are occupationally exposed to TnBP and TPP to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PELs) (OSHA 2009). The employer must use engineering and work practice controls to reduce exposures to not exceed 5 and 3 mg/m^3 at any time for TnBP and TPP, respectively (OSHA 2009).

Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), TnBP, TBPE, and TPP are permitted for use in nonfood pesticide products (EPA 2009c).

All of the phosphate ester flame retardants subject of this profile are required under Section 4(a) of the Toxic Substances Control Act (TSCA) to submit copies of health and safety studies (EPA 2009f). TnBP,

TiBP, and TBEP are required to report production, use, and exposure-related information on chemical substances listed under TSCA (EPA 2009g).