

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.

MRLs of 4 mg nitrate/kg/day have been derived for acute-, intermediate, and chronic-duration oral exposure (≤ 14 days) to nitrate. The MRLs are based on a no-adverse-effect concentration (NOAEC) of 10 mg nitrate-nitrogen/L (44 mg nitrate/L) in drinking water used to prepare formula for infants < 6 months of age (Walton 1951). A NOAEL of 4.33 mg nitrate/kg/day at the NOAEC of 44 mg nitrate/L was calculated based on estimates of 0.525 L/day for water intake (Kahn and Stralka 2009) and 5.33 kg for body weight (EPA 2008) of an infant from birth to < 3 months of age. A total uncertainty factor of 1 was applied because the point of departure is a NOAEL for nitrate-induced effects on methemoglobin in a sensitive human subpopulation (i.e., < 3 -month-old infants, which in many cases may have been at increased risk of methemoglobinemia due to microbial contamination and associated gastrointestinal infection). Following ingestion of relatively large amounts of nitrate by healthy normal individuals, blood methemoglobin levels increase rapidly, followed by a return to normal within several hours following intake. Repeated ingestion for intermediate- or chronic-duration time periods would be expected to result in changes in methemoglobin levels similar to those elicited from a single exposure. Therefore, the acute-, intermediate- and chronic-duration oral MRL values are equivalent. Refer to Appendix A for additional information regarding derivation of oral MRLs for nitrate.

MRLs of 0.1 mg nitrite/kg/day have been derived for acute-, intermediate, and chronic-duration oral exposure (≤ 14 days) to nitrite. The ingestion of nitrate results in the formation of nitrite, which is the moiety responsible for methemoglobinemia. In adults, approximately 5% of an oral dose of nitrate is reduced to nitrite in the saliva, most of which is absorbed into the blood in the small intestine. Based on the assumption of 100% absorption of ingested nitrite, an oral dose of 0.2 mg nitrite/kg/day by an adult would be expected to result in a nitrite blood level similar to that achieved following ingestion of nitrate at the oral MRL dose of 4 mg nitrate/kg/day (i.e., 0.2 mg nitrite/kg/day is 5% of an oral dose of nitrate at the MRL of 4 mg nitrate/kg/day). A modifying factor of 2 was applied to the point of departure (0.2 mg nitrite/kg/day $\div 2 = 0.1$ mg nitrite/kg/day) because young infants exhibit increased susceptibility to methemoglobinemia following nitrate ingestion; the modifying factor assumes that the effective methemoglobin level from a given intake of nitrate by an infant is up to twice that of an adult. Following ingestion of relatively large amounts of nitrate by healthy normal individuals, blood methemoglobin

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levels increase rapidly, followed by a return to normal within several hours following intake. Repeated ingestion for intermediate- or chronic-duration time periods would be expected to result in changes in methemoglobin levels similar to those elicited from a single exposure. Therefore, the acute-, intermediate-, and chronic-duration oral MRL values are equivalent. Refer to Appendix A for additional information regarding derivation of oral MRLs for nitrite.

EPA (IRIS 2002) derived an oral reference dose (RfD) of 1.6 mg nitrate-nitrogen/kg/day (i.e., 1.6 mg nitrogen from nitrate; ~7 mg nitrate/kg/day) based on a NOAEL of 1.6 mg nitrate-nitrogen/kg/day and a LOAEL of 1.8–3.2 mg nitrate-nitrogen/kg/day (7.92–14.08 mg nitrate/kg/day) for early clinical signs of methemoglobinemia in excess of 10% among formula-fed infants 0–3 months of age (Bosch et al. 1950; Walton 1951). An uncertainty factor of 1 was employed because available data defined the NOAEL for the critical effect in the most sensitive human subpopulation.

EPA (IRIS 2002) derived an RfD of 0.1 mg nitrite-nitrogen/kg/day (~0.33 mg nitrite/kg/day) based on a NOAEL of 10 mg nitrate-nitrogen/L and a LOAEL of 11–20 mg nitrate-nitrogen/L for early clinical signs of methemoglobinemia in excess of 10% (Walton 1951). The NOAEL of 10 mg nitrate-nitrogen/L was converted to an estimated dose of 1 mg nitrate-nitrogen/kg/day based assumptions that a 10-kg child would ingest 1 L of water/day. EPA applied a modifying factor of 10 to the NOAEL of 1 mg nitrate-nitrogen/kg/day from the Walton (1951) study to account for the direct toxicity of nitrite, resulting in an RfD of 0.1 mg nitrite-nitrogen/kg/day. As described in a Drinking Water Criteria Document for Nitrate/Nitrite (EPA 1990a), the modifying factor of 10 was used to account for an estimated rate of 10% conversion of ingested nitrate to nitrite in infants compared to an estimated rate of 5% conversion in adults.

Based on available human data, IARC (2010) determined that there is *inadequate evidence* for the carcinogenicity of nitrate in food or drinking water and *limited evidence* for the carcinogenicity of nitrite in food (based on association with increased incidence of stomach cancer). Evaluation of available animal data by IARC (2010) resulted in the determination that there is *inadequate evidence* for the carcinogenicity of nitrate, *limited evidence* for the carcinogenicity of nitrite *per se*, and *sufficient evidence* for the carcinogenicity of nitrite in combination with amines or amides. The overall conclusions of IARC (2010) were that “ingested nitrate and nitrite under conditions that result in endogenous nitrosation is *probably carcinogenic to humans (Group 2A)*.” IARC (2010) noted that: (1) the endogenous nitrogen cycle in humans includes interconversion of nitrate and nitrite; (2) nitrite-derived nitrosating agents produced in the acid stomach environment can react with nitrosating compounds such as secondary

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amines and amides to generate N-nitroso compounds; (3) nitrosating conditions are enhanced upon ingestion of additional nitrate, nitrite, or nitrosatable compounds; and (4) some N-nitroso compounds are known carcinogens.

Neither nitrate nor nitrite have been classified as to their carcinogenicity by the U.S. EPA Integrated Risk Information System (IRIS 2002), the National Toxicology Program (NTP, 2011), or the American Conference of Governmental Industrial Hygienists (ACGIH 2013).

The EPA lists maximum contaminant levels (MCL) and maximum contaminant level goals (MCLG) of 10 mg/L for nitrate (as nitrate-nitrogen; ~44 mg nitrate/L) and 1 mg/L for nitrite (as nitrite nitrogen; ~3.3 mg nitrite/L) in the 2012 Edition of the Drinking Water Standards and Health Advisories (EPA 2012b).

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

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Table 8-1. Regulations, Advisories, and Guidelines Applicable to Nitrate and Nitrite

Agency	Description	Information	Reference
<u>INTERNATIONAL</u>			
Guidelines:			
IARC	Carcinogenicity classification Nitrate or nitrite (ingested) under conditions that result in endogenous nitrosation	Group 2A ^a	IARC 2014
WHO	Air quality guidelines	No data	WHO 2010
	Drinking water quality guidelines		WHO 2011a
	Nitrate (as NO ₃ ⁻)	50 mg/L ^b	
	Nitrite (as NO ₂ ⁻)	3 mg/L ^c	
	Combined nitrate plus nitrite	The sum of the ratios of the concentrations as reported or detected in the sample of each to its guideline value should not exceed 1	
<u>NATIONAL</u>			
Regulations and guidelines:			
a. Air			
ACGIH	TLV-TWA	No data	ACGIH 2013
AIHA	ERPGs	No data	AIHA 2013
DOE	Nitrate(s)		DOE 2012
	PAC-1 ^d	30 mg/m ³	
	PAC-2	330 mg/m ³	
	PAC-3	2,000 mg/m ³	
	Ammonium nitrate		
	PAC-1 ^d	6.7 mg/m ³	
	PAC-2	73 mg/m ³	
	PAC-3	440 mg/m ³	
	Potassium nitrate		
	PAC-1 ^d	0.074 mg/m ³	
	PAC-2	0.82 mg/m ³	
	PAC-3	600 mg/m ³	
	Sodium nitrate		
	PAC-1 ^d	12 mg/m ³	
	PAC-2	130 mg/m ³	
PAC-3	250 mg/m ³		

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Agency	Description	Information	Reference
NATIONAL (cont.)			
EPA	Sodium nitrite		
	PAC-1 ^d	2.3 mg/m ³	
	PAC-2	26 mg/m ³	
EPA	PAC-3	280 mg/m ³	
	AEGLs	No data	EPA 2013a
	Hazardous air pollutant	No data	EPA 2014a 42 USC 7412
NIOSH	NAAQS	No data	EPA 2014d
	REL	No data	NIOSH 2014
	STEL	No data	
OSHA	IDLH	No data	
	PEL (8-hour TWA) for general industry	No data	OSHA 2013b 29 CFR 1910.1000, Table Z-2
	Highly hazardous chemicals	No data	OSHA 2013a 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	No data	EPA 2013b 40 CFR 116.4
	Drinking water contaminant candidate list	No data	EPA 2009b 74 FR 51850
	Drinking water standards and health advisories		EPA 2012b
	Nitrate		
	MCL	10 mg nitrogen/L (~44 mg nitrate/L) ^e	
	MCLG	10 mg nitrogen/L (~44 mg nitrate/L) ^f	
	Health advisory for 1 day for 10-kg child	100 mg nitrogen/L (~440 mg nitrate/L) ^e	
Health advisory for 10 days for 10-kg child	100 mg nitrogen/L (~440 mg nitrate/L) ^e		
DWEL	No data		

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Agency	Description	Information	Reference
NATIONAL (cont.)			
EPA	Nitrite		
	MCL	1 mg nitrogen/L (~3.3 mg nitrite/L) ^f	
	MCLG	1 mg nitrogen/L (~3.3 mg nitrite/L) ^f	
	Health advisory for 1 day for 10-kg child	10 mg nitrogen/L (~33 mg nitrite/L) ^f	
	Health advisory for 10 days for 10-kg child	10 mg nitrogen/L (~33 mg nitrite/L) ^f	
	DWEL	No data	
	Nitrate + nitrite (both as nitrogen)		
	MCL	10 mg/L	
	MCLG	10 mg/L	
	National primary drinking water standards		EPA 2009c
	Nitrate		
	MCL	10 mg nitrogen/L (~44 mg nitrate/L) ^e	
	Potential health effects from long-term exposure above the MCL	Serious illness; symptoms include shortness of breath and blue-baby syndrome ⁹	
	Common sources of contaminant in drinking water	Runoff from fertilizer use; leaching from septic tanks, sewage; erosion of natural deposits	
	Public Health Goal	10 mg nitrogen/L (~44 mg nitrate/L) ^e	
Nitrite			
MCL	1 mg nitrogen/L (~3.3 mg nitrite/L) ^f		
Potential health effects from long-term exposure above the MCL	Serious illness; symptoms include shortness of breath and blue-baby syndrome ⁹		
Common sources of contaminant in drinking water	Runoff from fertilizer use; leaching from septic tanks, sewage; erosion of natural deposits		
Public Health Goal	1 mg nitrogen/L (~3.3 mg nitrite/L) ^f		

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Agency	Description	Information	Reference
NATIONAL (cont.)			
EPA	National recommended water quality criteria: human health for the consumption of (at 10 ⁻⁴ risk)		EPA 2014e
	Nitrates		
	Water + organism	10,000 µg nitrogen/L	
	Organism only	No data	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act		EPA 2013d 40 CFR 117.3
	Sodium nitrite	100 pounds	
c. Food			
FDA	Bottled water (allowable limits)		FDA 2013 21 CFR 165.110
	Nitrate	10 mg nitrogen/L (~44 mg nitrate/L) ^e	
	Nitrite	1 mg nitrogen/L (~3.3 mg nitrite/L) ^f	
	Total nitrate and nitrite (as nitrogen)	10 mg/L	
	EAFUS ^h		FDA 2014
	Potassium nitrate, sodium nitrate, potassium nitrite, and sodium nitrite	Yes	
d. Other			
ACGIH	Carcinogenicity classification	No data	ACGIH 2013
EPA	Nitrate		EPA 1990a; IRIS 2002
	Carcinogenicity classification	No data	
	RfC	No data	
	RfD	1.6 mg nitrogen/kg/day (~7 mg nitrate/kg/day) ^e	
	Nitrite		
	Carcinogenicity classification	No data	
	RfC	No data	
	RfD	0.1 mg nitrogen/kg/day (~0.33 mg nitrite/kg/day) ^f	
	Identification and listing of hazardous waste	No data	EPA 2013c 40 CFR 261, Appendix VIII

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Agency	Description	Information	Reference
NATIONAL (cont.)			
EPA	Inert pesticide ingredients in pesticide products approved for nonfood use only		EPA 2014b
	Ammonium nitrate, potassium nitrate, sodium nitrate, potassium nitrite, and sodium nitrite	Yes	
	Master Testing List	No data	EPA 2014c
	RCRA waste minimization PBT priority chemical list	No data	EPA 1998 63 FR 60332
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list	No data	EPA 2013e 40 CFR 264, Appendix IX
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance and reportable quantity pursuant to Section 311(b)(2) of the Clean Water Act		EPA 2013f 40 CFR 302.4
	Sodium nitrite	100 pounds	
	Nitrate compounds (water dissociable; reportable only when in aqueous solution); sodium nitrite	Effective date of toxic chemical release reporting; 01/01/1995	EPA 2013h 40 CFR 372.65
	Superfund, emergency planning, and community right-to-know		
	Extremely hazardous substances and its threshold planning quantity	No data	EPA 2013g 40 CFR 355, Appendix A
	TSCA chemical lists and reporting periods	No data	EPA 2013i 40 CFR 712.30
	TSCA health and safety data reporting	No data	EPA 2013j 40 CFR 716.120

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Agency	Description	Information	Reference
NATIONAL (<i>cont.</i>)			
NTP	Carcinogenicity classification	No data	NTP 2011

^aGroup 2A: probably carcinogenic to humans.

^bAs nitrate ion (or 11 mg/L as nitrate-nitrogen) to protect against methemoglobinemia in bottle-fed infants (short-term exposure).

^cAs nitrite ion (or 0.9 mg/L as nitrite-nitrogen) to protect against methemoglobinemia in bottle-fed infants (short-term exposure).

^dPAC-1: mild, transient health effects; PAC-2: irreversible or other serious health effects that could impair the ability to take protective action; PAC-3: life-threatening health effects (DOE 2012).

^e1 mg nitrate-nitrogen/L (i.e., nitrogen from nitrate) ~4.4 mg nitrate/L

^f1 mg nitrite-nitrogen/L (i.e., nitrogen from nitrite) ~3.3 mg nitrite/L

^gInfants below the age of 6 months who drink water containing nitrate and/or nitrite in excess of the MCL could become seriously ill and, if untreated, may die (EPA 2009b).

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

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline level; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DOE = Department of Energy; 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; 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; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; 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; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term exposure limit; TLV = threshold limit value; TSCA = Toxic Substances Control Act; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization