APPENDIX A

TOXICOLOGICAL AND CHEMICAL-SPECIFIC VALUES, SSSLs, AND TOXICOLOGICAL PROFILE FOR PERCHLORATE

Table A-1

Toxicity Values*
Fort McClellan, Calhoun County, Alabama

Chemical	Oral Reference Dose (mg/kg-day)	Inhalation Reference Dose (mg/kg-day)	Dermal Reference Dose (mg/kg-day)	Oral Slope Factor (mg/kg-day)-1	Inhalation Slope Factor (mg/kg-day)-1	Dermal Slope Factor (mg/kg-day)-1	GAF
Perchlorate	9.00E-04	ND	ND	ND	ND	ND	ND

mg/kg-day = Milligram per kilogram-day
GAF = Gastrointestinal absorption factor
ND = No data
NA = Not applicable
*See Toxicological Profile for references

Table A-2

Chemical-Specific Values*
Fort McClellan, Calhoun County, Alabama

Chemical	BCF (L-water/kg-Fish)	Bp (unitless)	Bb (days/kg)	Bv (mg soil/g venison)	ABS (unitless)	BSAF (unitless)	Df (unitless)	log Kow	PC (cm/hour)	Molecular Weight (g/mole)
Perchlorate	ND	NA	NA	NA	NA	ND	ND	NA	NA	

NA = Not applicable or not available
ND = No data
BCF = Bioconcentration factor
Bp = Soil to plant biotransfer factor
Bb = Plant to beef biotransfer factor
Bv = Soil to venison biotransfer factor
ABS = Dermal absorption factor
BSAF = Ratio of the concentration in fish lipid to the concentration in sediment organic carbon
Df = Ratio of the concentration of contaminant in fish to the concentration of contaminant in sediment
Kow = Octanol-water partitioning coefficient
PC = Permeability coefficient
MW = Molecular weight
g/mole = Grams per mole

References:
*Please see Toxicological Profile and/or *Final Installation-Wide Work Plan (IWWP)*, Fort McClellan, Alabama (IT, 1998a) for all references.

Table A-3

General Variable Names*
Fort McClellan, Calhoun County, Alabama

Pathways	Parameter		Units	Resident		Recreational Site User		Groundskeeper	
General	Body weight (child)	BW	kg	15	BWrc	45	BWrec	70	BWg
	Body weight (adult)	BW	kg	70	BWra	NA		NA	
	Exposure frequency	EF	days/yr	350	EFr	104	EFrec	250	EFg
	Exposure duration (child)	ED	years	6	EDrc	10	EDrec	NA	
	Exposure duration (adult)	ED	years	24	EDra	NA		25	EDg
	Noncancer averaging time (child)	ATn	days	2190	ATnrc	3650	ATnrec	NA	
	Noncancer averaging time (adult)	ATn	days	8760	ATnra	NA		9125	ATng
	Cancer averaging time	ATc	days	25550	ATc	25550	ATc	25550	ATc
	Conversion factor	CF1	mg/kg	1.00E+06	CFa	1.00E+06	CFa	1.00E+06	CFa
	Target risk	TR	unitless	1.00E-06	TR	1.00E-06	TR	1.00E-06	TR
	Target hazard index	THI	unitless	1.00E-01	THI	1.00E-01	THI	1.00E-01	THI
Surface Water Ingestion	Surface water ingestion rate	IRsw	Liters/day	1		1	IRswrec	NA	
	Fraction exposed to contaminated media	FIsw	unitless	1		1	FIswrec	NA	
Surface Water Dermal	Fraction exposed to contaminated media	FIsw	unitless	1		1	FIswrec	NA	
	Body surface area exposed to surface water	SAsw	cm^2	4000		4000	SAswrec	NA	
	Exposure time	ETsw	hour/day	2		2	ETswrec	NA	
Groundwater Dermal	Exposure (bathing) time	ETgw	hours/day	0.2	ETgwr	NA		1	ETgwg
	Fraction of exposure	FIgw	unitless	1	FIgwr	NA		1	FIgwg
	Skin surface area (child)	SAgw	cm^2/day	7300	SAgwrc	NA		NA	
	Skin surface area (adult)	SAgw	cm^2/day	18150	SAgwra	NA		4100	SAgwg
	Age-adjusted body surface area-gw factor	SAWadj	cm^2-yrs/kg-day	9140	SAWadjr	NA		NA	
Groundwater Ingestion	Drinking water ingestion rate (child)	IRgw	L/day	1	DWgwrc	NA		NA	
	Drinking water ingestion rate (adult)	IRgw	L/day	2	DWgwra	NA		1	DWgwg
	Fraction of exposure	FIgw	unitless	1	FIgwr	NA		1	FIgwg
	Age-adjusted drinking water ingestion factor	DWFadj	L-years/kg-day	1.09	DWFadjr	NA		NA	
Groundwater Inhalation	Age-adjusted groundwater inhalation factor	GWIFadj	L-years/kg-day	0.7	GWIFadjr	NA		NA	
Soil Ingestion	Ingestion rate	IRso	mg/day	200	IRsor	100	IRsorec	100	IRsog
	Fraction of exposure	FIso	unitless	1	FIsor	0.25	FIsorec	1	FIsog
	Age-adjusted soil ingestion	IFadj	mg-yrs/kg-day	114	IFadjr	NA		NA	

Table A-3

General Variable Names*
Fort McClellan, Calhoun County, Alabama

Pathways	Parameter		Units	Resident		Recreational Site User		Groundskeeper	
Soil Inhalation	Inhalation rate	IRa	m^3/day	NA		NA		20	IRag
	Fraction of exposure	FIso	unitless	NA		NA		1	FIsog
	Particulate emission factor	PEF	m^3/mg	NA		NA		10	PEFg
Soil Dermal	Skin surface area (child)	SAso	cm^2/day	1800	SAsor	5250	SAsorec	NA	
	Skin surface area (adult)	SAso	cm^2/day	NA		NA		5250	SAsog
	Fraction of exposure	FIso	unitless	1	FIsor	0.25	FIsorec	1	FIsog
	Age-adjusted body surface area-soil factor	SASadj	cm^2-yrs/kg-day	2520	SASadjr	NA		NA	
	Soil to skin adherence factor	AFso	mg/cm^2	0.07	AFsor	0.04	AFsorec	0.01	AFsog
Sediment Ingestion	Ingestion rate	IRsd	mg/day	100		100	IRsdrec	NA	
	Fraction of exposure	FIsd	unitless	0.13		0.13	FIsdrec	NA	
Sediment Dermal	Skin surface area	SAsd	cm^2/day	5250		5250	SAsdrec	NA	
	Fraction of exposure	FIsd	unitless	0.13		0.13	FIsdrec	NA	
	Sediment to skin adherence factor	AFsd	mg/cm^2	0.29		0.29	AFsdrec	NA	
Fish Consumption	Age-adjusted fish consumption rate	FCadj	g-yrs/kg-day	17.8	FCadjr	17.8		NA	
	Fish consumption	FC	g/day	12	FCr	12		NA	
	Exposure duration	ED	years	6	Edfcr	6		NA	
	Body weight	BW	kg	15	BWfcr	15		NA	
	Averaging time (noncancer)	ATn	days	2190	ATnfcr	2190		NA	
Venison Ingestion	Fraction exposed to contaminated media	FIso	unitless	1	FIso	1		NA	
	Venison consumption rate	VC	g/day	30	VCr	30		NA	
	Averaging time (noncancer)	ATn	days	3650	ATnvc	3650		NA	
	Exposure duration	ED	years	30	EDvc	30		NA	
	Body weight	BW	kg	45	BWvr	45		NA	

*See *Final Human Health and Ecological Screening Values and PAH Background Summary Report* (IT, 2000) for description and documentation of variables

Table A-3

General Variable Names*
Fort McClellan, Calhoun County, Alabama

Pathways	Parameter		Units	Construction Worker		Highway Worker	
General	Body weight (child)	BW	kg	70	BWcw	70	BWhw
	Body weight (adult)	BW	kg	NA		NA	
	Exposure frequency	EF	days/yr	250	EFcw	15	EFhw
	Exposure duration (child)	ED	years	NA		NA	
	Exposure duration (adult)	ED	years	1	EDcw	0.74	EDhw
	Noncancer averaging time (child)	ATn	days	NA		NA	
	Noncancer averaging time (adult)	ATn	days	365	ATncw	270	ATnchw
	Cancer averaging time	ATc	days	25550	ATc	25550	ATc
	Conversion factor	CF1	mg/kg	1.00E+06	CFa	1.00E+06	CFa
	Target risk	TR	unitless	1.00E-06	TR	1.00E-06	TR
	Target hazard index	THI	unitless	1.00E-01	THI	1.00E-01	THI
Surface Water Ingestion	Surface water ingestion rate	IRsw	Liters/day	NA		NA	
	Fraction exposed to contaminated media	FIsw	unitless	NA		NA	
Surface Water Dermal	Fraction exposed to contaminated media	FIsw	unitless	NA		NA	
	Body surface area exposed to surface water	SAsw	cm^2	NA		NA	
	Exposure time	ETsw	hour/day	NA		NA	
Groundwater Dermal	Exposure (bathing) time	ETgw	hours/day	1	ETgwcw	NA	
	Fraction of exposure	FIgw	unitless	1	FIgwcw	NA	
	Skin surface area (child)	SAgw	cm^2/day	NA		NA	
	Skin surface area (adult)	SAgw	cm^2/day	4100	SAgwcw	NA	
	Age-adjusted body surface area-gw factor	SAWadj	cm^2-yrs/kg-day	NA		NA	
Groundwater Ingestion	Drinking water ingestion rate (child)	IRgw	L/day	NA		NA	
	Drinking water ingestion rate (adult)	IRgw	L/day	1	DWgwcw	NA	
	Fraction of exposure	FIgw	unitless	1	FIgwcw	NA	
	Age-adjusted drinking water ingestion factor	DWFadj	L-years/kg-day	NA		NA	
Groundwater Inhalation	Age-adjusted groundwater inhalation factor	GWIFadj	L-years/kg-day	NA		NA	
Soil Ingestion	Ingestion rate	IRso	mg/day	200	IRsocw	100	IRsohw
	Fraction of exposure	FIso	unitless	1	FIsocw	1	FIsohw
	Age-adjusted soil ingestion	IFadj	mg-yrs/kg-day	NA		NA	

Table A-3

General Variable Names*
Fort McClellan, Calhoun County, Alabama

Pathways	Parameter		Units	Construction Worker		Highway Worker	
Soil Inhalation	Inhalation rate	IRa	m^3/day	20	IRacw	20	IRahw
	Fraction of exposure	FIso	unitless	1	FIsocw	1	FIsohw
	Particulate emission factor	PEF	m^3/mg	5	PEFcw	5	PEFhw
Soil Dermal	Skin surface area (child)	SAso	cm^2/day	NA		NA	
	Skin surface area (adult)	SAso	cm^2/day	5250	SAsocw	5250	SAsohw
	Fraction of exposure	FIso	unitless	1	FIsocw	1	FIsohw
	Age-adjusted body surface area-soil factor	SASadj	cm^2-yrs/kg-day	NA		NA	
	Soil to skin adherence factor	AFso	mg/cm^2	0.1	AFsocw	0.12	AFsohw
Sediment Ingestion	Ingestion rate	IRsd	mg/day	NA		NA	
	Fraction of exposure	FIsd	unitless	NA		NA	
Sediment Dermal	Skin surface area	SAsd	cm^2/day	NA		NA	
	Fraction of exposure	FIsd	unitless	NA		NA	
	Sediment to skin adherence factor	AFsd	mg/cm^2	NA		NA	
Fish Consumption	Age-adjusted fish consumption rate	FCadj	g-yrs/kg-day	NA		NA	
	Fish consumption	FC	g/day	NA		NA	
	Exposure duration	ED	years	NA		NA	
	Body weight	BW	kg	NA		NA	
	Averaging time (noncancer)	ATn	days	NA		NA	
Venison Ingestion	Fraction exposed to contaminated media	FIso	unitless	NA		NA	
	Venison consumption rate	VC	g/day	NA		NA	
	Averaging time (noncancer)	ATn	days	NA		NA	
	Exposure duration	ED	years	NA		NA	
	Body weight	BW	kg	NA		NA	

*See *Final Human Health and Ecological Screening Values and PAH Background Summary Report* (IT, 2000) for description and documentation of variables

Table A-4

Soil-Residential SSSLs
Fort McClellan, Calhoun County, Alabama

	Noncancer				Cancer			
Chemical	Numerator	Oral	Dermal	SSSL (mg/kg)	Numerator	Oral	Dermal	SSSL (mg/kg)
Perchlorate	1.56E+06	2.22E+05	NA	7.04E+00	7.30E+01	NA	NA	NA

SSSL = Site-Specific Screening Level
mg/kg = Milligrams per kilogram
NA = Not applicable

Table A-5

Soil- Groundskeeper SSSLs
Fort McClellan, Calhoun County, Alabama

	Noncancer					Cancer				
Chemical	Numerator	Oral	Dermal	Inhalation	SSSL (mg/kg)	Numerator	Oral	Dermal	Inhalation	SSSL (mg/kg)
Perchlorate	1.02E+07	1.11E+05	NA	NA	9.20E+01	2.86E+02	NA	NA	NA	NA

SSSL = Site-specific screening level
mg/kg = Milligrams per kilogram
NA = Not applicable

Table A-6

Soil - Recreational Site User SSSLs
Fort McClellan, Calhoun County, Alabama

	Noncancer				Cancer			
Chemical	Numerator	Oral	Dermal	SSSL (mg/kg)	Numerator	Oral	Dermal	SSSL (mg/kg)
Perchlorate	6.32E+07	1.11E+05	NA	5.69E+02	4.42E+03	NA	NA	NA

SSSL = Site-specific screening level
mg/kg = Milligrams per kilogram
NA = Not applicable

Table A-7

Soil - Construction Worker SSSLs
Fort McClellan, Calhoun County, Alabama

	Noncancer					Cancer				
Chemical	Numerator	Oral	Dermal	Inhalation	SSSL (mg/kg)	Numerator	Oral	Dermal	Inhalation	SSSL (mg/kg)
Perchlorate	1.02E+07	2.22E+05	NA	NA	4.60E+01	7.15E+03	NA	NA	NA	NA

SSSL = Site-specific screening level
mg/kg = Milligrams per kilogram
NA = Not applicable

Table A-8

Soil - Highway Worker SSSLs
Fort McClellan, Calhoun County, Alabama

	Noncancer					Cancer				
Chemical	Numerator	Oral	Dermal	Inhalation	SSSL (mg/kg)	Numerator	Oral	Dermal	Inhalation	SSSL (mg/kg)
Perchlorate	1.70E+08	1.11E+05	NA	NA	1.53E+03	1.61E+05	NA	NA	NA	NA

SSSL = Site-specific screening level
mg/kg = Milligrams per kilogram
NA = Not applicable

Table A-9

Soil - Recreational Site User
Venison SSSLs
Fort McClellan, Calhoun County, Alabama

	Noncancer			Cancer		
Chemical	Numerator	Oral	SSSL (mg/kg)	Numerator	Oral	SSSL (mg/kg)
Perchlorate	1.56E+06	NA	NA	1.10E+02	NA	NA

SSSL = Site-specific screening level
mg/kg = Milligrams per kilogram
NA = Not applicable

Table A-10

Groundwater - Residential SSSLs
Fort McClellan, Calhoun County, Alabama

	Noncancer Child					Noncancer Adult				Final Noncancer	Cancer				
Chemical	Numerator	Oral	Dermal	Inhalation	SSSL (mg/L)	Numerator	Oral	Inhalation	SSSL (mg/L)	SSSL (mg/L)	Numerator	Oral	Dermal	Inhalation	SSSL (mg/L)
Perchlorate	1.56E+00	1.11E+03	---	---	1.41E-03	---	---	---	---	1.41E-03	7.30E-05	NA	---	---	NA

SSSL = Site-specific screening level
mg/L = Milligrams per liter
NA = Not applicable

Table A-11

Groundwater - Groundskeeper SSSLs
Fort McClellan, Calhoun County, Alabama

	Noncancer				Cancer			
Chemical	Numerator	Oral	Dermal	SSSL (mg/L)	Numerator	Oral	Dermal	SSSL (mg/L)
Perchlorate	1.02E+01	1.11E+03	NA	9.20E-03	2.86E-04	NA	NA	NA

SSSL = Site-specific screening level
mg/L = Milligrams per liter
NA = Not applicable

Table A-12

Groundwater - Construction Worker SSSLs
Fort McClellan, Calhoun County, Alabama

	Noncancer				Cancer			
Chemical	Numerator	Oral	Dermal	SSSL (mg/L)	Numerator	Oral	Dermal	SSSL (mg/L)
Perchlorate	1.02E+01	1.11E+03	NA	9.20E-03	7.15E-03	NA	NA	NA

Table A-13

Surface Water Recreational Site User SSSLs
Fort McClellan, Calhoun County, Alabama

	Noncancer				Cancer			
Chemical	Numerator	Oral	Dermal	SSSL (mg/L)	Numerator	Oral	Dermal	SSSL (mg/L)
Perchlorate	1.58E+01	1.11E+03	NA	1.42E-02	1.11E-03	NA	NA	NA

SSSL = Site-Specific Screening Level
mg/L = Milligrams per liter
NA = Not applicable

Table A-14

Surface Water - Recreational Site User Fish Consumption SSSLs
Fort McClellan, Calhoun County, Alabama

	Noncancer			Cancer		
Chemical	Numerator	Oral	SSSL (mg/L)	Numerator	Oral	SSSL (mg/L)
Perchlorate	1.56E+03	NA	NA	7.30E-02	NA	NA

SSSL = Site-specific screening level
mg/L = Milligrams per liter
NA = Not applicable

Table A-15

Sediment - Recreational Site User SSSLs
Fort McClellan, Calhoun County, Alabama

	Noncancer				Cancer			
Chemical	Numerator	Oral (mg/kg)	Dermal (mg/kg)	SSSL (mg/kg)	Numerator	Oral (mg/kg)	Dermal (mg/kg)	SSSL (mg/kg)
Perchlorate	1.21E+08	1.11E+05	NA	1.09E+03	8.50E+03	NA	NA	NA

SSSL = Site-specific screening level
mg/kg = Milligrams per kilogram
NA = Not applicable

Table A-16

Sediment - Recreational Site User Fish Consumption SSSLs
Fort McClellan, Calhoun County, Alabama

	Noncancer			Cancer		
Chemical	Numerator	Oral	SSSL (mg/kg)	Numerator	Oral	SSSL (mg/kg)
Perchlorate	1.56E+03	NA	NA	7.30E-02	NA	NA

SSSL = Site-specific screening level
mg/kg = Milligrams per kilogram
NA = Not applicable

TOXICOLOGICAL PROFILE

Perchlorate

Commonly used perchlorate salts include ammonium perchlorate (7790-98-9), magnesium perchlorate (10034-81-8), potassium perchlorate (7778-74-7), and sodium perchlorate (7601-89-0). All are colorless or white crystalline **inorganic** substances (HSDB, 2001; Lewis, 1997). Generally, the anionic (perchlorate) moiety rather than the cation is analyzed in environmental investigations. The ammonium salt is the form generally associated with military establishments. However, it makes little difference which perchlorate salt was released or found in the environment because all commonly encountered forms are highly soluble, which dictates their behavior in environmental media.

Ammonium perchlorate is used as a high explosive in pyrotechnics, rocket and jet propellant (HSDB, 2001; Lewis, 1997). It is also used as an etching and engraving agent, and as an animal fattening agent because of its thyroid-active properties. Magnesium perchlorate is used as a regenerable drying agent for gases and as an isolating adsorbent in certain instruments. Potassium perchlorate is used in explosives, photography, pyrotechnics and flares, as an oxidizer in solid rocket propellants, and as an inflating agent in automobile safety air bags. Sodium perchlorate is used in explosives, jet fuel and in the production of other perchlorates. The perchlorates are a strong oxidizing agents and are commonly used as laboratory reagents. Relevant physical properties are compiled below:

MW (g/mole)	log K_{ow} (unitless)	H (atm-m^3/mole)	K_d (L/kg)	D_a (cm^2/s)	D_w (cm^2/s)	VP (atm)	S (mg/L)
--	ND	ND	ND	ND	ND	ND	2.0E+5 to 2E+6[a]

-- = depends on the particular perchlorate salt under consideration; ND = no data.
[a]Hazardous Substance Data Bank (HSDB), 2001, National Library of Medicine, on line.

The perchlorates, ammonium perchlorate in particular, may be released during manufacture, use or disposal (EPA, 1998). Widespread release is expected to result from its use as a rocket and jet propellant.

Empirical data regarding the fate and transport of perchlorate in the environment were not located. Transport, however, is expected to be dominated by its very high solubility in water. Therefore, the perchlorates are expected to be removed from the atmosphere efficiently by wet deposition and to leach rapidly from soil to groundwater (ATSDR, 2001), where it has been observed in several public drinking water supplies (EPA, 1998). Although perchlorates are strong oxidizing agents, natural reduction is not expected to be a significant fate process; therefore, perchlorate may persist for decades under natural groundwater and surface water conditions (EPA, 1998).

Empirical data regarding the biotransfer of ammonium perchlorate were not located. Pharmacokinetic studies in laboratory mammals suggest that the thyroid may actively sequester low doses of perchlorate; however, the substance is generally rapidly excreted via the kidney, suggesting that the potential for bioconcentration or bioaccumulation is low (EPA, 1998).

Perchlorate is readily absorbed from the GI tract (EPA, 1998). However, as noted below, its potential for causing toxicity via dermal exposure is expected to be low; therefore, a gastrointestinal absorption factor is not estimated and dermal toxicity values are not derived.

Empirical data regarding the dermal absorption of ammonium perchlorate were not located. Perchlorate in environmental media exists as a highly charged anion that is not expected to be readily absorbed by the skin (EPA, 1998). Therefore, dermal exposure is expected to be toxicologically insignificant and is not evaluated further.

Perchlorate compounds, particularly potassium perchlorate (approximately 71.8 percent perchlorate by mass), have been used to control goiter and hyperthyroidism in Graves' disease (EPA, 1998). Graves' disease is an autoimmune disorder in which the body produces immunoglobulins that stimulate the thyroid to hypertrophy and hypersecretion of iodine-containing thyroid hormones. Perchlorate acts by inhibiting iodide uptake by the thyroid and by causing an efflux of iodide from the gland, thereby reducing the iodide available for synthesis of thyroid hormones.

Most of the data from humans are clinical reports that focus on thyroid effects. Pharmacological dose rates, expressed as perchlorate (rather than potassium perchlorate), range from 0.042 mg per kg body weight per day (mg/kg-day) to 20.8 mg/kg-day. The low end of the range produces a minimal but measurable effect on iodide efflux from the thyroid. A single 0.14 mg/kg dose was associated with approximately 50 percent release of accumulated iodine from the thyroid of Graves' disease patients. Adverse effects on other systems, e.g., nausea and gastrointestinal problems, skin rash, sore throat, hematological effects and lymphadenopathy, were reported at dose rates exceeding 4.3 mg/kg-day. One infant born to a mother treated with approximately 6 to 10 mg/kg-day for an unknown duration, but probably for less than 8 weeks, exhibited very slightly enlarged thyroid, which returned to normal size within 6 weeks of birth. These data suggest that effects on the thyroid, particularly efflux of iodine or reduction in release of thyroid hormones, are the critical effects of short-term oral exposure to perchlorate.

Far fewer data are available from healthy humans (EPA, 1998). The data suggest that dose rates of 9.2 to 9.7 mg/kg-day for 8 days to 4 weeks block iodine uptake and increase iodine efflux by the thyroid, and alter circulating levels of thyroid hormones. The data were insufficient to identify the threshold for thyroid effects in normal humans.

The use of perchlorate to treat Graves' disease fell from favor in the 1960s due to the occurrence of severe hematological effects, including aplastic anemia (fatal in some cases), leukopenia and agranulocytosis (EPA, 1998). The dose rates associated with these effects range from 4.3 to 10 mg/kg-day for approximately 3 to 8 months. In all cases, the dose rate was reduced in response to the appearance of (unspecified) side effects. The hematological effects appear to be mediated through an immune phenomenon. EPA (1998) concluded that Graves' disease patients are likely to be more sensitive to hematologic effects than normal humans because of their underlying immune dysfunction.

A large body of data from animal toxicity testing is available. No attempt is made here to review all available animal studies with perchlorates. The studies reviewed herein are intentionally limited to those of acceptable quality from which thresholds for effects can be identified with

reasonable confidence. For example, foreign studies that are not published in peer-reviewed scientific journals, and studies that used high dose rates from which thresholds for effects cannot be identified, are not included in this evaluation. The reader is referred to EPA (1998) for a comprehensive bibliography and an evaluation of the more relevant high-dose studies.

It should be noted that the information presented herein is taken entirely from EPA (1998), which must be considered as a secondary source because no attempt was made to obtain the original studies. EPA (1998), however, invested considerable time and energy in evaluating the original studies, in several instances requesting additional information from the study authors and conferring with experts in certain specialties (e.g., neurotoxicology). The EPA (1998) evaluation is currently the most thorough and thoughtful analysis and synthesis of the data regarding the toxicity of perchlorate.

Serum levels of thyroid stimulating hormone (TSH) and 2 thyroid hormones (designated T3 and T4) were measured by radioimmunoassay in groups of 5 to 6 male rats given potassium perchlorate in their drinking water at levels that provided doses of perchlorate of 0, 1.1, 5.5, 11.0 or 54.8 mg/kg-day, respectively, for 4 days (EPA, 1998). Perchlorate induced increases in circulating levels of TSH and decreases in circulating levels of T3 and T4. All three hormone levels were statistically significantly altered in rats in the two highest dose groups. Both T3 and T4 were statistically significantly decreased in the 5.5 mg/kg-day group; a slight increase in TSH levels in this dose group was not statistically significant. Circulating levels of hormones in the 1.1 mg/kg-day group were not different from controls. The study defines a(NOAEL of 1.1 mg/kg-day and a LOAEL of 5.5 mg/kg-day.

Caldwell et al. (1995) administered ammonium perchlorate (approximately 84.6 percent perchlorate) in drinking water to groups of 6 male and 6 female rats at levels that provided doses of perchlorate of 0, 0.093, 0.37, 0.94, 1.9, 3.7, 9.7, or 19 mg/kg-day to the males, and 0, 0.10, 0.40, 1.0, 2.6, 4.2, 9.7 or 21 mg/kg-day to the females for 14 days. Thyroids were weighed and subjected to histopathological examination, and TSH, T3, T4, hTG and rT3 (produced largely in extrathyroidal tissues) circulating levels were measured by radioimmunoassay. The synopsis provided herein reflects the EPA (1998) reevaluation of the results of the histopathology and hormone level measurements.

Relative thyroid weights (thyroid weight divided by body weight) were statistically significantly increased in male and female rats in the two highest dose groups. Three histopathological parameters were evaluated: thyroid follicular epithelial cell hypertrophy, follicular lumen size determined by standard histopathological techniques, and follicular lumen size as determined by computerized morphometry. Epithelial cell hypertrophy appears to be the most sensitive of the histological parameters; the dose rates of 0.093 mg/kg-day in males and 0.10 mg/kg-day in females was the LOAEL for this effect. The study did not identify a NOAEL for histopathological alteration of the thyroid.

The EPA (1998) reevaluation of circulating hormone levels indicates that perchlorate-induced reduction of T3 levels is slightly greater in females, the induced increase in TSH levels is slightly greater in males, and the induced reduction in T4 and increase in hTG and rT3 levels is independent of gender. Circulating levels of rT3 and TSH appear to be less sensitive to treatment than levels of hTG, T3 and T4. The lowest dose rate (0.093 mg/kg-day for the males, 0.10

mg/kg-day in the females) was a LOAEL for reduction in hTG and T4 levels. The lowest dose rate was a LOAEL for T3 reduction in females and a NOAEL for T3 reduction in males.

An interim sacrifice of 10 rats per sex per dose group was performed at 14 days in a 90-day well controlled drinking water study with ammonium perchlorate (EPA, 1998). The 14-day sacrifice was an attempt to replicate the results of the Caldwell et al. (1995) study. The purity and stability of the ammonium perchlorate concentrations in drinking water were monitored throughout the study (and in all other studies reviewed below) and were found to be satisfactory. Concentrations in drinking water were adjusted to provided dose rates of ammonium perchlorate of 0, 0.01, 0.05, 0.2, 1 or 10 mg/kg-day to rats of both sexes throughout the study. These correspond to perchlorate dose rates of 0, 0.0085, 0.042, 0.17, 0.85 and 8.5 mg/kg-day. Parameters evaluated after 14 and 90 days of treatment, and after an additional 30-day recovery period during which no treatment was administered, included clinical observations, body and organ weights, food and water consumption, hematology, clinical chemistry, ophthalmology and gross necropsy. Histopathological evaluation was performed on all tissues from the control and high-dose groups, but was limited to the liver, kidneys, lungs, thyroid and parathyroids, and gross lesions from the intermediate-dose groups. Hormone circulating levels (TSH, T3, T4) were measured. In addition, reproductive parameters; e.g., estrous cyclicity, and sperm motility and morphology, were evaluated after 90 days of exposure and after the recovery period.

Treatment had no effect on clinical observations, body weight, food or water consumption, ophthalmology, hematology, clinical chemistry or sperm parameters. Thyroid weights were increased significantly in the high-dose males at 14 and 90 days, and in high-dose females only at 90 days. Treatment-related lesions were limited to the thyroid. The incidence of follicular hyperplasia was increased over controls in both sexes only in the high-dose group at both the 14- and 90-day sacrifices. The thyroid lesions reported in this study are not exactly the same as those reported by Caldwell et al. (1995). Treatment also appeared to alter estrous cyclicity at 0.042 mg/kg-day, but the shape of the dose-response curve is confusing, confounding interpretation of this observation.

The EPA (1998) reevaluation of circulating hormone levels indicated that the lowest dose rate was a LOAEL for T3 reduction in males at 14 and 90 days, and in females at 90 days. T3 levels in treated females at 14 days did not appear to differ from controls, but this impression may arise from unusually low T3 levels in control females at 14 days compared with 90 days. Gender did not appear to be significant in the results observed for T4. The highest dose rate was a LOAEL for T4 reduction at 14 days; the lowest dose rate was a LOAEL for T4 reduction at 90 days. Gender appeared to significantly affect TSH results at 14 days but not at 90 days. LOAELs for the 14-day sacrifice were 0.17 mg/kg-day for males and 0.0085 mg/kg-day for females. At 90 days, 0.17 mg/kg-day was a LOAEL for both genders. The reason for the apparent greater sensitivity of females at the 14-day sacrifice is unclear; however, TSH levels in control females appear to be unusually low.

The effects on thyroid weight and the histopathological lesions in the thyroid were fully reversible during the recovery period. Effects on estrous cyclicity and thyroid hormone levels in high-dose rats were not yet fully reversed at the end of the 30-day recovery period.

Interpretation of the biological significance of minor changes in circulating levels of thyroid hormones is fraught with difficulty because of the large natural variation in circulating levels and

the limitations of analytical technology (EPA, 1998). There is considerable variation in circulating levels even within individuals, due in part to diurnal changes. Pregnancy and other physiological states also alter hormonal levels. T4 is produced in readily measurable levels by the thyroid, but circulating levels of T3 are much lower, and most of the circulating T3 arises from deiodination of T4 at the target tissues. Overall, changes in circulating hormone levels without histological evidence of early changes in the thyroid are judged to be of minor biological significance.

EPA (1998) reviewed reproductive studies that used large dose rates in rats, guinea pigs and rabbits. Thyroid enlargement was observed in both the dams and offspring, with at least one study suggesting that the offspring are more sensitive than the adults. None of the studies suggested that perchlorate interfered with reproductive performance. One study reported that nursing rats given drinking water containing 1 percent potassium perchlorate (7180 mg perchlorate/L) had a reduced incidence of pregnancy, compared with controls. However, there was no difference in the number of implantation sites in the dams that became pregnant, and the authors concluded that there was no significant effect on reproductive performance.

EPA (1998) evaluated a neurodevelopmental toxicity study in which groups of 25 female rats were given drinking water containing ammonium perchlorate that provided dose rates of 0, 0.1, 1.0, 3.0 or 10 mg/kg-day from gestation day 0 until scheduled sacrifice. Offspring were maintained on the same treatment regimen as their dams. The ammonium perchlorate dose rates are equivalent to perchlorate dose rates of 0, 0.085, 0.85, 2.5 and 8.5 mg/kg-day. Parameters evaluated included clinical appearance, body weight, food and water consumption, histopathological appearance of the thyroid, and circulating levels of pituitary and thyroid hormones. The female offspring were also evaluated for rate of sexual maturation (vaginal opening). Offspring were divided into four subsets for the following examinations:

- Subset 1: scheduled sacrifice (postpartum day [PD] 12) for brain weights and neurohistological examination.

- Subset 2: avoidance testing, water maze testing, scheduled sacrifice (PD 90 to 92) and blood collection for circulating hormone levels.

- Subset 3: motor activity, auditory startle habituation, scheduled sacrifice (PD 67 to 69).

- Subset 4: scheduled sacrifice (PD 80 to 86) for neurohistological examination and regional brain weights.

There were no effects on body weight, clinical appearance, food or water consumption, or necropsy observations, in the parental generation or the offspring. Treatment had no effects on the outcome of pregnancy or on the rate of sexual maturation in female offspring. The remainder of the discussion of effects is limited to the offspring. Neurohistological examination suggested that the corpus callosum of the brain was enlarged, with 2.5 mg/kg-day being the NOAEL and 8.5 mg/kg-day being the LOAEL. Interpretation of thyroid histopathology is more difficult because judgement plays a large role in identification and classification of thyroid morphology. Follicular height was found to be a more sensitive endpoint than other thyroid histological indicators. EPA (1998) determined the low dose rate to be a LOAEL for follicular epithelial cell

hypertrophy. Morphometric analysis of follicular lumen size did not show a significant decrease until the dose rate reached 2.5 mg/kg-day. Both T3 and T4 were reduced and TSH was increased in the offspring, which is consistent with the observations of the other experiments. NOAELs for altered T3, T4 and TSH levels were 0.085, 0.85 and 2.5 mg/kg-day, respectively. Performance in the behavioral tests was unaffected by treatment with the possible exception of motor activity, which was evaluated at PD 14, 18, 22 and 59. A dose-dependent increase was seen in both the number of movements and the time spent in movements in male rats tested on PD 14, but not when tested on PD 18, 22 or 59. Although the differences were not statistically significant, EPA (1998) concluded that the effect was biologically significant at the higher dose rates.

EPA (1998) evaluated the results of the first part (i.e., data from the parental generation and the F1 generation up to weaning) of a two-generation reproduction study in which rats were given drinking water that provided ammonium perchlorate at dose rates of 0, 0.3, 3 and 30 mg/kg-day. These dose rates of ammonium perchlorate are equivalent to dose rates of perchlorate of 0, 0.25, 2.5 and 25 mg/kg-day. Thyroid weights were significantly increased in male rats in the 2.5 and 25 mg/kg-day groups and in females in the 25 mg/kg-day group. There were no significant effects on reproductive parameters. Thyroid histopathology, pituitary and thyroid hormone circulating levels, and reproductive performance of the F1 generation have not yet been completely evaluated.

A developmental toxicity study was performed in which pregnant rabbits were given drinking water that provided ammonium perchlorate at dose rates of 0, 0.1, 1.0, 10, 30 or 100 mg/kg-day on gestation day 6 to 28 (EPA, 1998). These dose rates of ammonium perchlorate are equivalent to dose rates of perchlorate of 0, 0.085, 0.85, 8.5, 25 and 85 mg/kg-day. There were no effects on the dams except for effects on the thyroid. Hypertrophy of the follicular epithelium of the thyroid was observed; the NOAEL for this effect was 0.85 mg/kg-day and the LOAEL was 8.5 mg/kg-day. T4 was significantly depressed in does in the 0.85 mg/kg-day group (LOAEL), but not in does in the 0.085 mg/kg-day group (NOAEL). There were no treatment related effects on the outcome of pregnancy or on any developmental parameters.

A battery of 14- and 90-day immunotoxicity tests were performed (or are in progress) in which female mice were given ammonium perchlorate in drinking water that provided dose rates of 0, 0.1, 1.0, 3.0 or 30 mg/kg-day (EPA, 1998). These are equivalent to perchlorate dose rates of 0, 0.085, 0.85, 2.5 and 25 mg/kg-day, respectively. Some mice were permitted a 30-day recovery period. There were no consistent treatment-related effects on parameters of general toxicity, organ weights or cellularity. The results of thyroid histopathology are pending. T4 was significantly depressed after 14 and 90 days of treatment, but had returned to control levels by the end of a recovery period. The NOAEL for this effect was 0.085 mg/kg-day; 0.85 mg/kg-day was the LOAEL.

Interpretation of the results and the biological significance of the many indicators of altered immune function is confounded by large amounts of variation, laboratory technical errors, and inconsistent results between study replications (EPA, 1998). Generally, it appears that there were no clear treatment related effects on immune function. However, the data suggest that the phagocytic capacity of peritoneal macrophages was reduced in the 2.5 and 25 mg/kg-day groups, and there may be a trend toward increased resistance to challenge with live *L. monocytogenes*.

An earlier provisional oral reference dose (RfD) for chronic exposure was based on a single dose of 0.14 mg/kg, which was associated with approximately 50 percent release of accumulated iodine from the thyroid of Graves' disease patients (EPA, 1998). The dose rate of 0.14 mg/kg was designated a NOAEL. The current provisional oral RfD is based on a much larger set of animal studies. Although all studies are not yet complete, they identify effects on the thyroid as the critical effects of exposure to perchlorate. Rats appear to be slightly more sensitive than either rabbits or mice to the thyroid effects, but the species differences are not large. There are indications that chronic exposure to perchlorate may also have effects on fetal regional brain weights, behavioral development and immune function, but the data suggest that these effects do not occur at dose rates lower than those associated with thyroid effects.

EPA (1998) proposed a dose-response continuum for perchlorate that begins with perturbations of thyroid function (reduced uptake and accumulation of iodide) manifested as reduction in circulating levels of thyroid hormones (T3, T4), followed by a compensatory increase in circulating levels of pituitary hormone (TSH). Compensatory changes in the histology of the thyroid appear at the same or slightly higher dose rates. Effects on neurological development and immune function may arise secondarily from the effects on thyroid. For that reason the neurological and immunological changes are expected to occur at somewhat higher levels than those associated with measurable changes in circulating levels of thyroid hormone. Further support for this conclusion arises from the fact that the NOAEL for effects on thyroid hormone levels has not been identified; i.e., is below the NOAEL for the secondary effects.

EPA (1998) noted that data in both rats and rabbits suggest that the fetal thyroid may be more sensitive than the maternal thyroid. This is supported by observation of the LOAEL for perchlorate of 0.085 mg/kg-day for thyroid histopathology in the offspring of treated rats in the neurodevelopmental study. The same (or slightly higher) dose level was a NOAEL for thyroid histopathology in adult rats and rabbits.

EPA (1998) selected the LOAEL for follicular epithelial hyperplasia of the thyroid in offspring from the neurodevelopmental study in rats of 0.1 mg ammonium perchlorate/kg-day, equivalent to 0.085 mg perchlorate/kg-day, as the basis for the new provisional oral RfD for chronic exposure. This dose rate was designated a minimal LOAEL because the associated histopathological effects and hormonal changes are mild. EPA (1998) noted that the histopathological effects in the offspring occurred at or below dose rates associated with similar effects in adults exposed for longer durations. Therefore, the LOAEL in rat pups from the developmental study is the appropriate endpoint for derivation of an RfD for chronic exposure.

An uncertainty factor (UF) of 100 (rounded to one significant figure) was chosen; factors of 3 for incomplete data base (all the results from developmental, reproductive and immunological studies are not yet available), 3 to estimate a NOAEL from a minimal LOAEL, 3 to account for interspecies variability, and 3 to account for intraspecies variability. EPA (1998) noted that the mechanism of toxicity suggests that there is little reason to expect significant differences between subchronic and chronic exposure at a given dose rate. Therefore, an additional UF to expand from short term exposure in the developmental study to chronic exposure is unnecessary. This conclusion is supported by the human data, which associate effects on the thyroid with a single 0.14 mg/kg dose, and by the 90-day drinking water study in rats, which shows no significant differences in rats exposed for 14 days compared with rats exposed for 90 days.

Application of the UF of 100 to the LOAEL of 0.1 mg ammonium perchlorate/kg-day, equivalent to 0.085 mg perchlorate/kg-day, yields provisional oral RfDs of 1E-3 mg/kg-day for ammonium perchlorate, equivalent to 8.5E-4 mg/kg-day for perchlorate. The RfD of 8.5E-4 mg/kg-day for perchlorate is rounded to 9E-4 mg/kg-day for use in risk assessment. The thyroid gland is considered to be the target organ for oral exposure to perchlorate. Inhibition of iodine uptake by the thyroid is the mechanism of toxicity. The very young, the elderly, and those with abnormal thyroid function may be unusually sensitive to the effects of perchlorate. Confidence in the provisional oral RfD is judged to be medium. Ongoing reproductive, immunotoxicity, and perchlorate kinetics and iodine inhibition studies may necessitate a reevaluation of the provisional RfD (EPA, 1998). Revision of the value would probably be downward because sources of uncertainty will be removed but the dose-response model discussed above is unlikely to change.

Data regarding inhalation exposure to perchlorate were not located in the available literature. EPA (1998) noted that perchlorate is unlikely to volatilize from environmental media because of its very high solubility in water, which reduces considerably the potential for inhalation exposure. Perchlorate is unlikely to persist in soil and be available for suspension in air as dust because of its very high mobility in this medium. EPA (1998) made no attempt to estimate a reference concentration for inhalation exposure to ammonium perchlorate because of the low potential for inhalation exposure.

EPA (1998) noted that orally administered ammonium perchlorate is associated with an increased incidence of thyroid tumors in rats. However, tumors develop only at high doses that are associated with severe histopathological disruption of the gland. EPA concluded that the provisional oral RfD based on noncancer effects is sufficiently protective for carcinogenicity as well as noncancer effects. Therefore, no perchlorate compound nor the perchlorate moiety were assigned to a cancer weight-of-evidence group, and no attempt was made to develop a cancer slope factor.

EPA Region 9 has developed preliminary remediation goals (PRG) that are useful for screening chemical concentrations in environmental media (EPA, 2000). The Region 9 PRGs are based on standard default exposure assumptions, and are often adapted for the risk-based screening step for selecting chemicals of potential concern for human health risk assessments.

PRGs are available for nearly 600 chemicals for soil for residential use, for soil for industrial use, for ambient air, and for tap water (EPA, 2000). Exposure routes addressed by PRGs for soil include incidental ingestion, dermal contact, and inhalation of volatiles or dust; exposure routes addressed by PRGs for tap water include drinking water ingestion and inhalation of volatiles. EPA (2000) provides the methodology and standard exposure default assumptions with which to estimate PRGs for chemicals not included in the tables. Generally, PRGs are developed for both cancer risk and noncancer hazard, and the smaller of the two estimates is chosen. As noted above, the oral RfD of 9E-4 mg/kg-day is considered to be sufficiently protective against carcinogenicity as well as noncancer effects. Therefore, only PRGs based on noncancer effects are developed for perchlorate.

PRGs are not available for perchlorate presumably because EPA-verified toxicity values are not available. The provisional oral RfD value described above, however, may be applied to the equations developed by EPA (2000) to estimate PRGs for perchlorate. However, the EPA

(2000) equations are modified to remove the dermal and inhalation exposure component because these exposure routes are unlikely to be significant for the reasons mentioned above. PRGs estimated for perchlorate follow:

Chemical	Provisional Oral RfD (mg/kg-day)	PRG[a]		
		Residential Soil (mg/kg)	Industrial Soil (mg/kg)	Tap Water (µg/L)
Perchlorate Anion	9E-4	70.3929 (7.0E+1)	1839.6 (1.8E+3)	32.85 (3.3E+1)
[a]Values in parentheses are rounded to two significant figures.				

The PRGs are based on a target hazard index of 1.

References for Ammonium Perchlorate

Agency for Toxic Substances and Disease Registry (ATSDR), 2001, ***Public Health Assessment Guidance Manual***, on line www.atsdr.cdc.gov.

Caldwell, D.J., J.H. King, Jr., E.R. Kinkead, et al., 1995, "Results of a Fourteen Day Oral-Dosing Toxicity Study of Ammonium Perchlorate," In: ***Proceedings of the 1995 JANNAF Safety and Environmental Protection Subcommittee Meeting: Volume 1***, December, Tampa, FL, Columbia, MD: Chemical Propulsion Information Agency; Joint Army, Navy, NASA, Air Force (JANNAF) Interagency Propulsion Committee Publication 634 (as cited in EPA, 1998).

Hazardous Substance Data Bank (HSDB), 2001, National Library of Medicine, on line.

Lewis, R.J., Sr., 1997, ***Hawley's Condensed Chemical Dictionary***, Thirteenth Edition, John Wiley & Sons, Inc., New York, pp. 65, 692, 920, 1024.

U.S. Environmental Protection Agency (EPA), 1998, ***Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization Based on Emerging Information***, External Review Draft, National Center for Environmental Assessment, Office of Research and Development, Washington, DC, NCEA-1-0503, 31 December.

U.S. Environmental Protection Agency (EPA), 2000, ***Region 9 Preliminary Remediation Goals (PRGs) 2000 Update***, online, 1 November.