3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of perchlorates. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

The perchlorate anion forms salts with a wide variety of cations. There are five perchlorate salts that are manufactured in substantial amounts: magnesium, potassium, ammonium, sodium, and lithium perchlorate (see Section 4.1). The potassium, sodium, and ammonium salts are the ones most commonly encountered in the toxicology literature. Therefore, data on potassium, sodium, ammonium, and other perchlorate salts were considered pertinent to the assessment of the perchlorate anion. Perchloric acid was not included because it is a strong acid and its toxicity is dominated by the irritating effects of the hydrogen cation. In the absence of water, the five commercial perchlorates listed above will exist as a solid. In water, perchlorate salts (perchlorates) will rapidly dissolve and completely dissociate into the perchlorate anion, also referred to as perchlorate, and the corresponding metal cation. Potassium, ammonium, and sodium cations are ubiquitous in the environment and are considered spectator ions. Therefore, the species of concern in this document is the perchlorate anion.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons potentially exposed to perchlorate, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that

evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

No studies were located regarding lethality in humans or animals after inhalation exposure to perchlorate.

3.2.1.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, dermal, or ocular effects in humans or animals after inhalation exposure to perchlorate.

The highest NOAEL values for systemic effects from the two occupational studies available are recorded in Table 3-1 and plotted in Figure 3-1.

Hematological Effects. No hematological effects were found in ammonium perchlorate workers (22–31 high-dose and 18–27 low-dose versus 72–150 controls) exposed for 1–27 years (mean=8.3 years) to average perchlorate concentrations of up to 0.63 mg/m^3 (Gibbs et al. 1998). The researchers estimated an average cumulative lifetime perchlorate absorbed dose of 38 mg/kg in the high-dose workers in this study, which corresponds to a daily dose of 0.01 mg/kg/day based on the approximate average exposure duration of 9 years for high-dose workers. Oral exposure due to deposition in the mouth and throat was also likely to have occurred. The accuracy of dose estimates from this study is questionable; however, because the researchers estimated the fraction absorbed using a study on an unrelated chemical and did not consider the size of the inhaled ammonium particles in their calculations. Particle size (mean and distribution) is an important determinant of inhaled dose for particulates (EPA 1994). A similar study of 37 ammonium perchlorate workers also found no evidence of hematological effects among the workers (Lamm et al. 1999). The workers were assigned to one of three categories of presumptive exposure based on visible dust generated. The average airborne exposure for the high-exposure group was 8.6 mg/day (respirable fraction; particle size 0.1–10 μm) or 59.4 mg/day (total particulate perchlorate). Dividing by the default inhalation volume of 10 m^3/day results in a respirable concentration of 0.86 mg/m^3. The absorbed oral dose per shift was calculated using urinary perchlorate measurements and the assumption that the absorbed dose that is excreted is 95%. In the low-, medium-, and high-exposure categories, the absorbed doses were estimated to be 4, 11, and 34 mg perchlorate/day, respectively. Assuming a body weight of 70 kg, the 34 mg/kg oral dose corresponds to about 0.5 mg perchlorate/kg/day. Measures of cumulative exposure were not considered in this study. It should be noted that workers exposed to perchlorate have an unusual work schedule consisting of three 12-hour day shifts followed by 3 days unexposed.

No studies were located regarding hematological effects in animals after inhalation exposure to perchlorate.

Hepatic Effects. No effects on serum enzymes indicative of liver toxicity were found in the ammonium perchlorate workers studied by Gibbs et al. (1998) or among those studied by Lamm et al. (1999) (see Hematological Effects above for further details on these studies). No further relevant information was located.

Table 3-1 Levels of Significant Exposure to Perchlorates - Inhalation

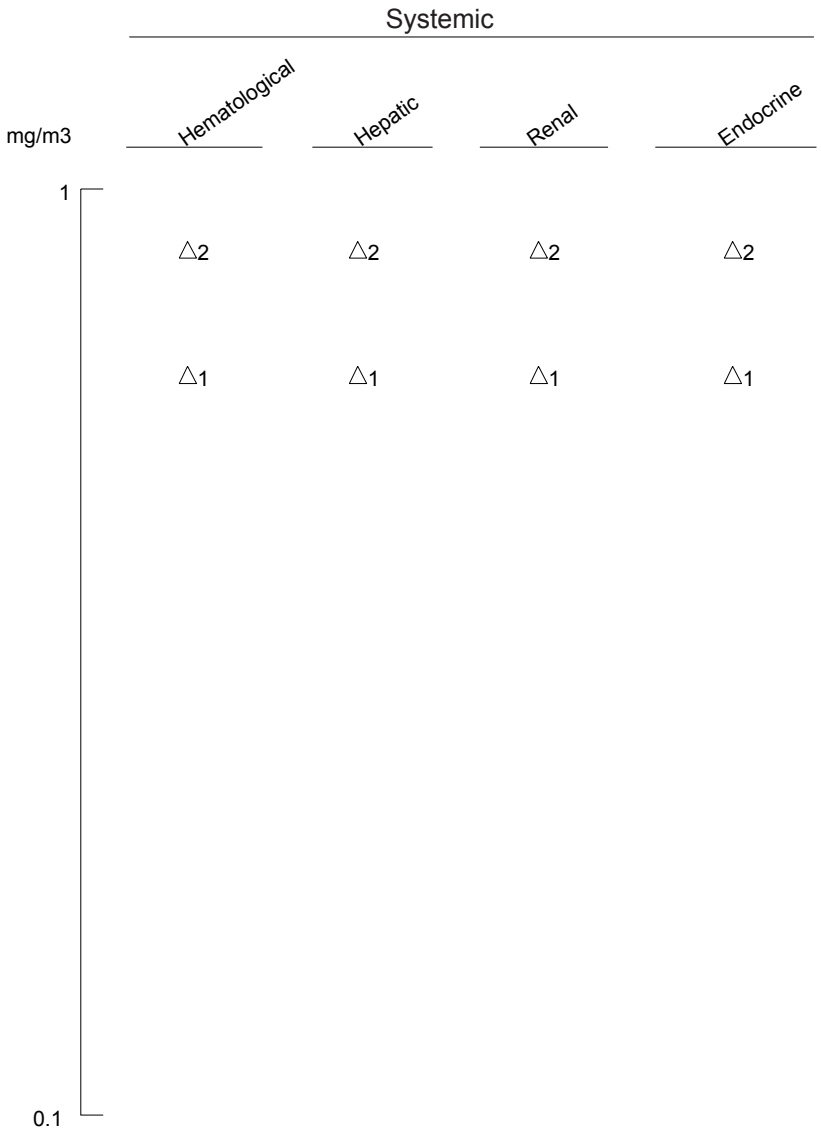
Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Systemic								
1	Human	1-27 yr (avg=8.3 yr) (occup)	Hemato	0.63			Gibbs et al. 1998 NH4ClO4	
			Hepatic	0.63				
			Renal	0.63				
			Endocr	0.63				
2	Human	40% over 5 yr (occup)	Hemato	0.86			Lamm et al. 1999 NH4ClO4	
			Hepatic	0.86				
			Renal	0.86				
			Endocr	0.86				

a The number corresponds to entries in Figure 3-1.

avg = average; Endocr = endocrine; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; occup = occupational; yr = year(s)

Figure 3-1. Levels of Significant Exposure to Perchlorates - Inhalation

Chronic (≤365 days)



c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

No studies were located regarding hepatic effects in animals after inhalation exposure to perchlorate.

Renal Effects. No effects on serum enzymes indicative of kidney toxicity or in serum creatinine and blood urea nitrogen (BUN) were found in the ammonium perchlorate workers evaluated by Gibbs et al. (1998) or Lamm et al. (1999) (see Hematological Effects above for further details on these studies).

No studies were located regarding renal effects in animals after inhalation exposure to perchlorate.

Endocrine Effects. No significant effects on serum levels of TSH, total serum thyroxine (TT4), T3, or free thyroxine index (FTI) were found among the ammonium perchlorate workers studied by Gibbs et al. (1998). The mean airborne concentration of perchlorate to which the workers were exposed ranged from 0.02 to 0.63 mg/m^3. The researchers estimated that exposure to airborne perchlorate provided an average cumulative lifetime absorbed dose of up to 0.01 mg perchlorate/kg/day for high-exposure workers. Comparison of pre- and post-shift serum thyroid hormone measurements for individual workers failed to find any evidence of a transient effect associated with daily exposure. In the occupational-exposure study conducted by Lamm et al. (1999), there were also no significant alterations in serum TSH, T3, T4, FTI, thyroid hormone binding ratio, or thyroid peroxidase antibody concentrations among the workers. In this study, it was estimated that the high-exposure workers, who were exposed to an average of 0.86 mg of respirable airborne perchlorate particles/m^3, absorbed doses of approximately 0.5 mg perchlorate/kg/day (see above under Hematological Effects for further details on these studies). A study conducted in the same manufacturing facility studied by Lamm et al. (1999) found that intermittent, high exposure to perchlorate for many years did not induce goiter or any evidence of hypothyroidism among the workers as judged by no significant alterations in serum TSH or thyroglobulin even though iodine uptakes were decreased during the work shift (Braverman et al. 2005). The median estimated absorbed dose was 0.167 mg/kg/day, equivalent to drinking approximately 2 L of water containing 5 mg perchlorate/L. It should be mentioned that perchlorate workers are exposed during an unusual schedule of three 12-hour shifts followed by 3 days without exposure (long-time, intermittent exposure). Given the relatively short elimination half-life of chlorine in workers of approximately 8 hours (Lamm et al. 1999), perchlorate would not be expected to accumulate to levels that would cause thyroid problems.

No studies were located regarding endocrine effects in animals after inhalation exposure to perchlorate.

No studies were located regarding the following effects in humans or animals after inhalation exposure to perchlorate:

3.2.1.3 Immunological and Lymphoreticular Effects

3.2.1.4 Neurological Effects

3.2.1.5 Reproductive Effects

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

3.2.2 Oral Exposure

NOAEL and LOAEL values in Table 3-2 and Figure 3-2 represent amounts of the perchlorate anion, not of the perchlorate salt.

3.2.2.1 Death

Several cases of human deaths were reported among hyperthyroid patients treated with potassium perchlorate (Barzilai and Sheinfeld 1966; Fawcett and Clarke 1961; Gjemdal 1963; Hobson 1961; Johnson and Moore 1961; Krevans et al. 1962). Deaths were due to aplastic anemia or severe agranulocytosis and were considered to be causally related to potassium perchlorate. The lethal doses in these patients were in the low-to-moderate range of doses employed in thyrotoxicosis therapy: 600–1,000 mg potassium perchlorate/day, or roughly 5–12 mg perchlorate/kg/day. The patients had received treatment for anywhere between 2 and 8 months. All of the deaths were females (Graves' disease, the most common cause of hyperthyroidism, is far more common in women than in men) and their ages ranged from 24 to 82 years.

Gauss (1972) reported an LD_{50} dietary concentration of 3.55% (approximately 3,621 mg perchlorate/kg/day) for potassium perchlorate in mice exposed for up to 30 days. The first deaths occurred within 4 days of the start of treatment. The LD_{50} value for mice is recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Table 3-2 Levels of Significant Exposure to Perchlorates - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Mouse (NMRI)	6 d ad lib (F)				3621 F (LD50)	Gauss 1972 KClO4	
Systemic								
2	Human	14 d (W)	Hemato	0.5			Greer et al. 2002 KClO4	
			Hepatic	0.5				
			Renal	0.5				
			Endocr	0.007[b]	0.1 (42% inhibition of radioiodine uptake by the thyroid)			
3	Human	14 d (W)	Hemato	0.14[c]			Lawrence et al. 2000 KClO4	
			Hepatic	0.14				
			Renal	0.14				
			Endocr	0.14				
4	Human	14 d (W)	Endocr	0.04			Lawrence et al. 2001 KClO4	

Table 3-2 Levels of Significant Exposure to Perchlorates - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
5	Rat (Sprague-Dawley)	14 d ad lib (W)	Endocr		0.1 (increased serum TSH in females, decreased T4 in males and females, and decrease T3 in females)		Caldwell et al. 1995 NH4ClO4	
			Bd Wt	39.9				
			Other	39.9				
6	Rat (Sprague-Dawley)	4 d ad lib (W)	Endocr	1.4 M	7.2 M (approximately 20% decrease in T3 and 37% decrease inT4)		Mannisto et al. 1979 KClO4	

Table 3-2 Levels of Significant Exposure to Perchlorates - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
7	Rat (Sprague-Dawley)	14 d ad lib (W)	Resp	8.5			Siglin et al. 2000 NH4ClO4	
			Cardio	8.5				
			Gastro	8.5				
			Hemato	8.5				
			Musc/skel	8.5				
			Hepatic	8.5				
			Renal	8.5				
			Endocr		0.009 M (approximately 20% decreased serum T3 in males)			
			Dermal	8.5				
			Ocular	8.5				
			Bd Wt	8.5				
			Other	8.5				
8	Rat (Sprague-Dawley)	14 d ad lib (W)	Endocr		0.09 M (increased TSH and decreased serum T3)		Yu et al. 2002 NH4ClO4	
9	Mouse (B6C3F1)	14 d ad lib (W)	Endocr	0.05 F	0.2 F (significant decrease in serum T4 levels; non-significant increase in TSH)		BRT 2000 NH4ClO4	

Table 3-2 Levels of Significant Exposure to Perchlorates - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
10	Mouse (B6C3F1)	14 d ad lib (W)	Hemato	25.5 F			DOD 1999 NH4ClO4	
			Hepatic	25.5 F				
			Renal	25.5 F				
			Endocr		2.6 F (15% decrease serum T4)			
			Bd Wt	25.5 F				
			Other	25.5 F				
Immuno/ Lymphoret								
11	Mouse (B6C3F1)	14 d ad lib (W)			0.05 F (increased response to sensitizer 2,4-dinitrochlorobenzene)		BRT 2000 NH4ClO4	
12	Mouse (B6C3F1)	14 d ad lib (W)		25.5 F			DOD 1999 NH4ClO4	
Neurological								
13	Rat (Sprague-Dawley)	14 d ad lib (W)		8.5			Siglin et al. 2000 NH4ClO4	
Reproductive								
14	Rat (Wistar)	Gd 2-8 ad lib (W)		532 F			Brown-Grant 1966 KClO4	

Table 3-2 Levels of Significant Exposure to Perchlorates - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
15	Rat (Wistar)	Gd 1-13 ad lib (W)		1752 F			Brown-Grant and Sherwood 1971 KClO4	
16	Rat (Sprague-Dawley)	14 d ad lib (W)		8.5			Siglin et al. 2000 NH4ClO4	
INTERMEDIATE EXPOSURE								
Systemic								
17	Human	4 wk (IN)	Endocr		9 M (decreased thyroid I and serum TSH)		Brabant et al. 1992 KClO4	
18	Human	6 mo 1 x/d (C)	Endocr	0.04			Braverman et al. 2006 KClO4	The NOAEL is for thyroid function.
19	Rat (Wistar)	19 wk ad lib (F)	Hepatic	64 M			Hiasa et al. 1987 KClO4	
			Endocr			64 M (thyroid weight doubled; 24% decrease in serum T4; 100% increase in TSH)		
			Bd Wt	64 M				

Table 3-2 Levels of Significant Exposure to Perchlorates - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
20	Rat (Wistar)	6 wk ad lib (W)	Cardio		2327 M (decreased heart weight)		MacDermott 1992 KClO4	
			Musc/skel		2327 M (decreased membrane potential and intracellular K+ activity)			
			Endocr			2327 M (thyroid weight more than doubled; 71% decrease in serum T4)		
			Bd Wt			2327 M (27% reduced weight at 6 weeks)		
21	Rat (Wistar)	25 d ad lib (W)	Endocr			175 M (thyroid weight tripled; undetectable levels of T3 and T4 in serum; 50% increase in TSH)	Ortiz-Caro et al. 1983 KClO4	
			Bd Wt			175 M (40% reduction in weight gain)		
			Metab		175 M (decreased alpha-GPD activity)			
22	Rat (Wistar)	45 d 1 x/d (G)	Metab		359 (decreased glucose and increased urea in serum: increased activity of aldolase, LDH, arginase; decreased G-6-Pase)		Sangan and Motlag 1986 KClO4	

Table 3-2 Levels of Significant Exposure to Perchlorates - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
23	Rat (Wistar)	3 mo ad lib (W)	Hemato			1059 M (decreased hematopoeisis)	Shevtsova et al. 1994 KClO4	
24	Rat (Sprague-Dawley)	90 d ad lib (W)	Resp	8.5			Siglin et al. 2000 NH4ClO4	
			Cardio	8.5				
			Gastro	8.5				
			Hemato	8.5				
			Musc/skel	8.5				
			Hepatic	8.5				
			Renal	8.5				
			Endocr		0.009 (significant decreases in T4 and T3 in both males and females)			
			Dermal	8.5				
			Ocular	8.5				
			Bd Wt	8.5				
			Other	8.5				

Table 3-2 Levels of Significant Exposure to Perchlorates - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
25	Rat (Wistar)	45 d 1 x/d (G)	Metab		406 M (decreased activity of lipase, phospholipase A; decreased free fatty acids; increased cholesterol, triglycerides, phospholipids)		Vijayalakshmi and Motlag 1989a NaClO4	
26	Rat (Sprague-Dawley)	>19 wk ad lib (W)	Endocr	0.26	2.6 (increased absolute and relative thyroid weight in both sexes; hypertrophy and hyperplasia in males; increased TSH)		York et al. 2001a NH4ClO4	
			Bd Wt	25.5				
			Other	25.5				
27	Rat (Sprague-Dawley)	16 wk ad lib (W)	Endocr	0.26	2.6 (hypertrophy/hyperplasia of the thyroid)		York et al. 2001a NH4ClO4	
			Bd Wt	25.5				
			Other		0.26 M (decreased water consumption)			

Table 3-2 Levels of Significant Exposure to Perchlorates - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
28	Rat (Sprague-Dawley)	14 pmd Gd 1-21 pnd 1-10 pnd 1-22 ad lib (W)	Endocr	0.009	0.09 (17% increase in serum TSH)		York et al. 2003 NH4ClO4	
			Bd Wt	25.5				
			Other	25.5				
29	Rat (Sprague-Dawley)	45 d (W)	Endocr		0.009 F (increase serum TSH and decrease T4)		York et al. 2005a NH4ClO4	
			Bd Wt	25.5 F				
30	Mouse (B6C3F1)	90 d ad lib (W)	Endocr	0.02 F	0.05 F (17% increase in serum TSH)		BRT 2000 NH4ClO4	
31	Mouse (B6C3F1)	90 d ad lib (W)	Hemato	25.5 F			DOD 1999 NH4ClO4	
			Hepatic	25.5 F				
			Renal	25.5 F				
			Endocr	0.09 F	0.85 F (significant decrease in serum T4 levels)	25.5 F (colloid depletion; intrafollicular capillary congestion)		
			Bd Wt	25.5 F				
			Other	25.5 F				

Table 3-2 Levels of Significant Exposure to Perchlorates - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
32	Mouse (BALB/c)	3 mo ad lib (W)	Hemato			1750 M (decreased hematopoiesis)	Shevtsova et al. 1994 KClO4	
33	Gn Pig (NS)	30, 60, or 90 d ad lib (W)	Endocr			531 F (thyroid weight almost tripled; thyroid hyperplasia and colloid depletion)	Postel 1957 KClO4	
34	Dog (NS)	3 wk 1 x/d (G)	Gastro		3811 (mucosal irritation)		Selivanova and Vorobieva 1969 NH4ClO4	
			Hemato			3811 (inhibition of hematopoeisis in bone marrrow)		
			Endocr			3811 (inhibited thyroid function)		
Immuno/ Lymphoret								
35	Rat (Sprague-Dawley)	90 d ad lib (W)		8.5			Siglin et al. 2000 NH4ClO4	
36	Mouse (B6C3F1)	90 d ad lib (W)		0.02 F	0.05 F (increased sensitization response to 2,4-dinitrochlorobenzene)		BRT 2000 NH4ClO4	

Table 3-2 Levels of Significant Exposure to Perchlorates - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
37	Mouse (B6C3F1)	90 d ad lib (W)		25.5 F			DOD 1999 NH4ClO4	
Neurological								
38	Rat (Sprague-Dawley)	90 d ad lib (W)		8.5			Siglin et al. 2000 NH4ClO4	
Reproductive								
39	Rat (Sprague-Dawley)	90 d ad lib (W)		8.5			Siglin et al. 2000 NH4ClO4	
40	Rat (Sprague-Dawley)	16 wk ad lib (W)		25.5			York et al. 2001a NH4ClO4	
41	Rat (Sprague-Dawley)	45 d (W)		25.5 F			York et al. 2005a NH4ClO4	The NOAEL is for standard reproductive end points assessed at parturition.
Developmental								
42	Rat (Sprague-Dawley)	2 wk pmd Gd 1-21 pnd 1-10 ad lib (W)		8.5			Bekkedal et al. 2000 NH4ClO4	

Table 3-2 Levels of Significant Exposure to Perchlorates - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
43	Rat (Sprague-Dawley)	31 d Gd 2-21 pnd 1-10 ad lib (W)			1 (increased TSH and decreased T4 in pups exposed via maternal milk)		Mahle et al. 2003 NH4ClO4	
44	Rat (Sprague-Dawley)	16 wk ad lib (W)		0.26	2.6 (thyroid hypertrophy and hyperplasia in F1 females and in F2 males and females)		York et al. 2001a NH4ClO4	
45	Rat (Sprague-Dawley)	15 pmd Gd 1-21 ad lib (W)		0.85	25.5 (delayed sternal and phalanges ossification)		York et al. 2003 NH4ClO4	
46	Rat (Sprague-Dawley)	14 pmd Gd 1-21 pnd 1-10 pnd 1-22 ad lib (W)			0.009 (decreased T3 in fetuses; increased absolute thyroid weight in 10-day-old pups; increased TSH and decreased T4 in 22-day-old pups; increased cerebellum thickness in 22-day-old pups)		York et al. 2003 NH4ClO4	

Table 3-2 Levels of Significant Exposure to Perchlorates - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
47	Rat (Sprague-Dawley)	31 d Gd 1-21 Ld 1-10 ad lib (W)		2.6	8.5	(hypertrophy/hyperplasia of follicular epithelium and decrease in follicle size in pups on pnd 5)			York et al. 2004 NH4ClO4	
48	Rat (Sprague-Dawley)	45 d (W)			0.009	(increased TSH and decreased T4 in pups; decreased T3 in fetuses)			York et al. 2005a NH4ClO4	
49	Rat (Sprague-Dawley)	31-45 d (W)		25.5					York et al. 2005b NH4ClO4	NOAEL is for brain morphometry. A NOAEL of 8.5 mg/kg/day was defined for motor activity (25.5 mg/kg/day not tested).
50	Gn Pig (NS)	Gd 21-48 ad lib (W)					531	(increased weight of fetal thyroid and hyperplasia in fetal thyroid)	Postel 1957 KClO4	
51	Rabbit (NS)	Gd 1-28 ad lib (F)					72	(significantly enlarged fetal thyroid and histological changes in fetal thyroid)	Lampe et al. 1967 KClO4	

Table 3-2 Levels of Significant Exposure to Perchlorates - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
52	Rabbit (New Zealand)	22 d Gd 6-28 ad lib (W)		85			York et al. 2001b NH4ClO4	
Cancer								
53	Rat (Wistar)	12 mo ad lib (W)				928 (CEL: thyroid follicular adenoma)	Florencio Vicente 1990 KClO4	
54	Mouse (NMRI)	160 d ad lib (F)				1020 F (CEL: thyroid adenoma)	Gauss 1972 KClO4	
55	Mouse (BALB/c)	46 wk ad lib (W)				2573 F (CEL: thyroid follicular cell carcinoma in 5/6)	Pajer and Kalisnik 1991 NaClO4	
CHRONIC EXPOSURE								
Systemic								
56	Human	lifetime (W)	Endocr	0.0014 F			Tellez et al. 2005 NH4ClO4	The women's iodide uptake was higher than common in the U.S.
57	Rat (Wistar)	24 mo ad lib (W)	Endocr			956 M (thyroid fibrosis)	Kessler and Kruskemper 1966 KClO4	
			Bd Wt	956 M				

Table 3-2 Levels of Significant Exposure to Perchlorates - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
58	Rat (Wistar)	15 mo ad lib (W)	Endocr			928 (thyroid hypertrophy and hyperplasia)	Toro Guillen 1991 KClO4	
			Bd Wt		928 (unspecified decreased weight gain)			
Developmental								
59	Human	gestational (W)		0.0014			Tellez et al. 2005 NH4ClO4	
Cancer								
60	Rat (Wistar)	24 mo ad lib (W)				956 M (CEL: increased papillary and/or follicular adenomas in thyroid)	Kessler and Kruskemper 1966 KClO4	
61								
	Rat (Wistar)	15 mo ad lib (W)				928 (CEL: follicular and papillary carcinoma of thyroid)	Toro Guillen 1991 KClO4	

a The number corresponds to entries in Figure 3-2.

b ATSDR has adopted the NAS chronic RfD of 0.0007 mg/kg/day for the chronic oral MRL. The RfD was calculated by dividing the NOEL of 0.007 mg/kg/day by an uncertainty factor of 10 (for the protection of sensitive populations).

c Although inhibition of iodide uptake is not considered adverse, this dose is shown to illustrate the dose at which the effect became statistically significant.

ad lib = ad libitum; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = food; F = female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; GPD = glycerophosphate dehydrogenase; (GW) = gavage in water; (IN) = ingestion; Hemato = hematological; Ld = lactation day; LD50 = lethal dose, 50% kill; LDH = lactate dehydrogenase; LOAEL = lowest-observable-adverse-effect level; M = male; Metab = metabolic; mo = month; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; pmd = pre-mating day; pnd = post-natal day; Resp = respiratory; TSH = thyroid-stimulating hormone; (W) = drinking water; wk = week(s); x = times; yr = year(s)

Figure 3-2 Levels of Significant Exposure to Perchlorates - Oral

Acute (≤14 days)

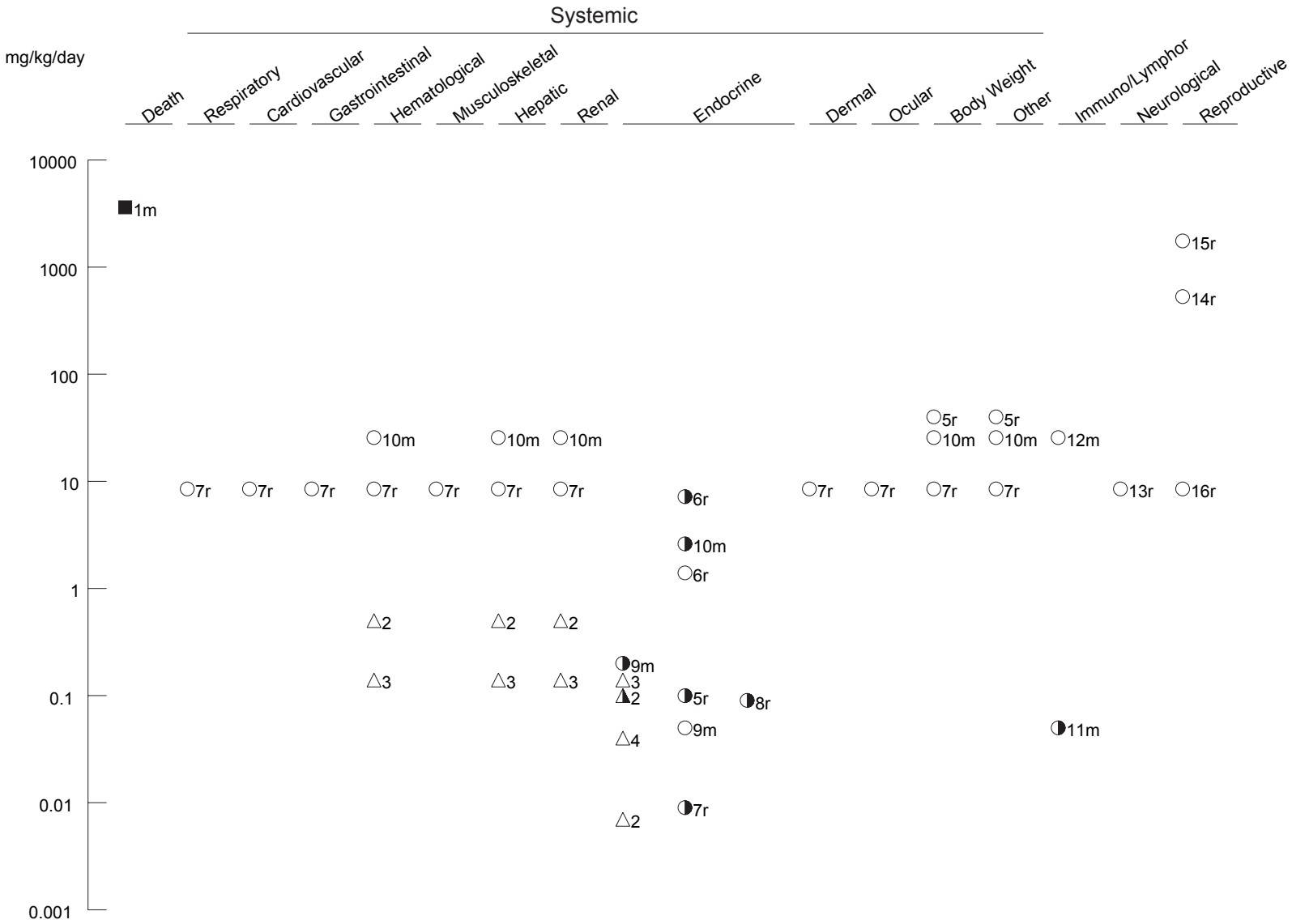


Figure 3-2 Levels of Significant Exposure to Perchlorates - Oral *(Continued)*

Intermediate (15-364 days)

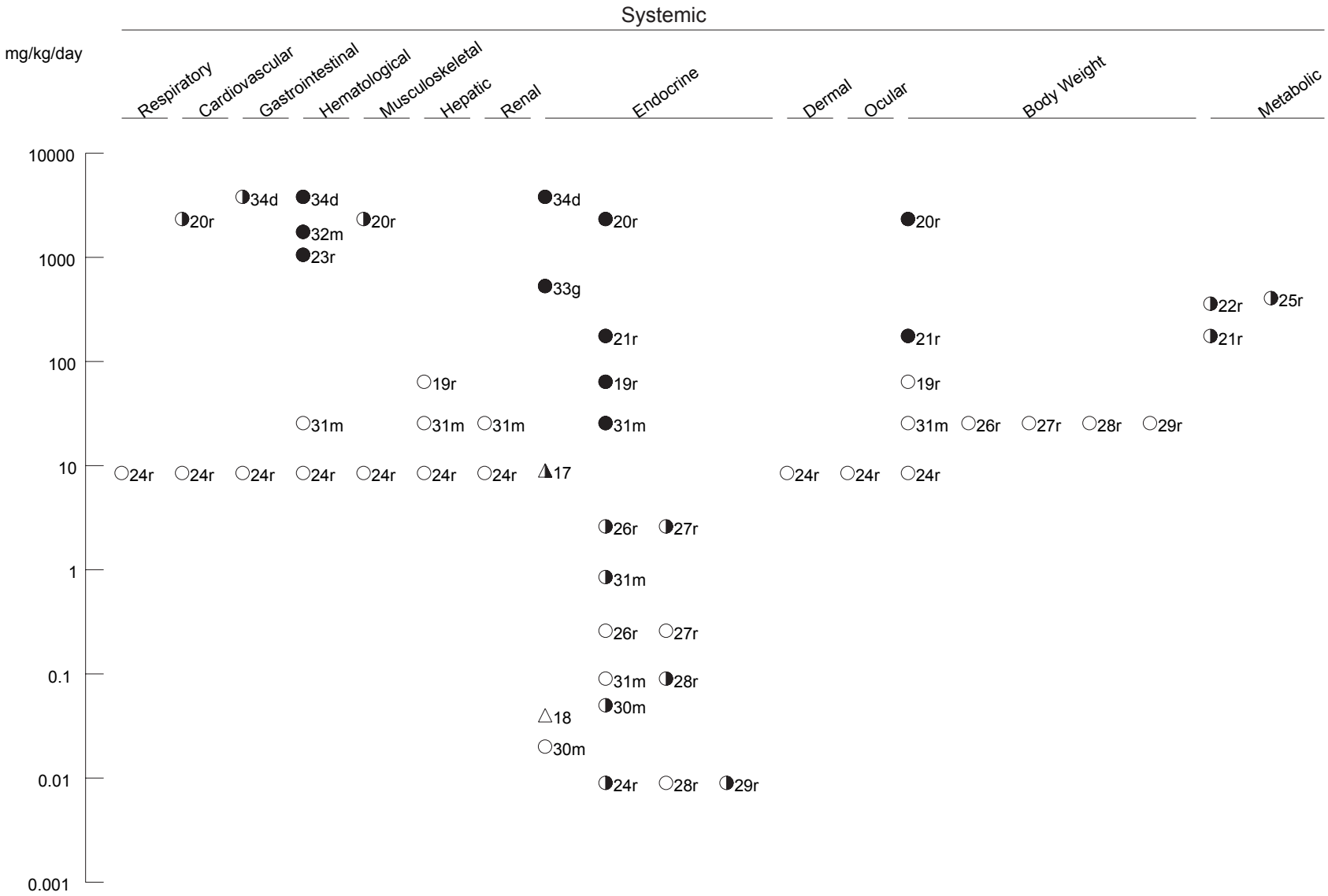
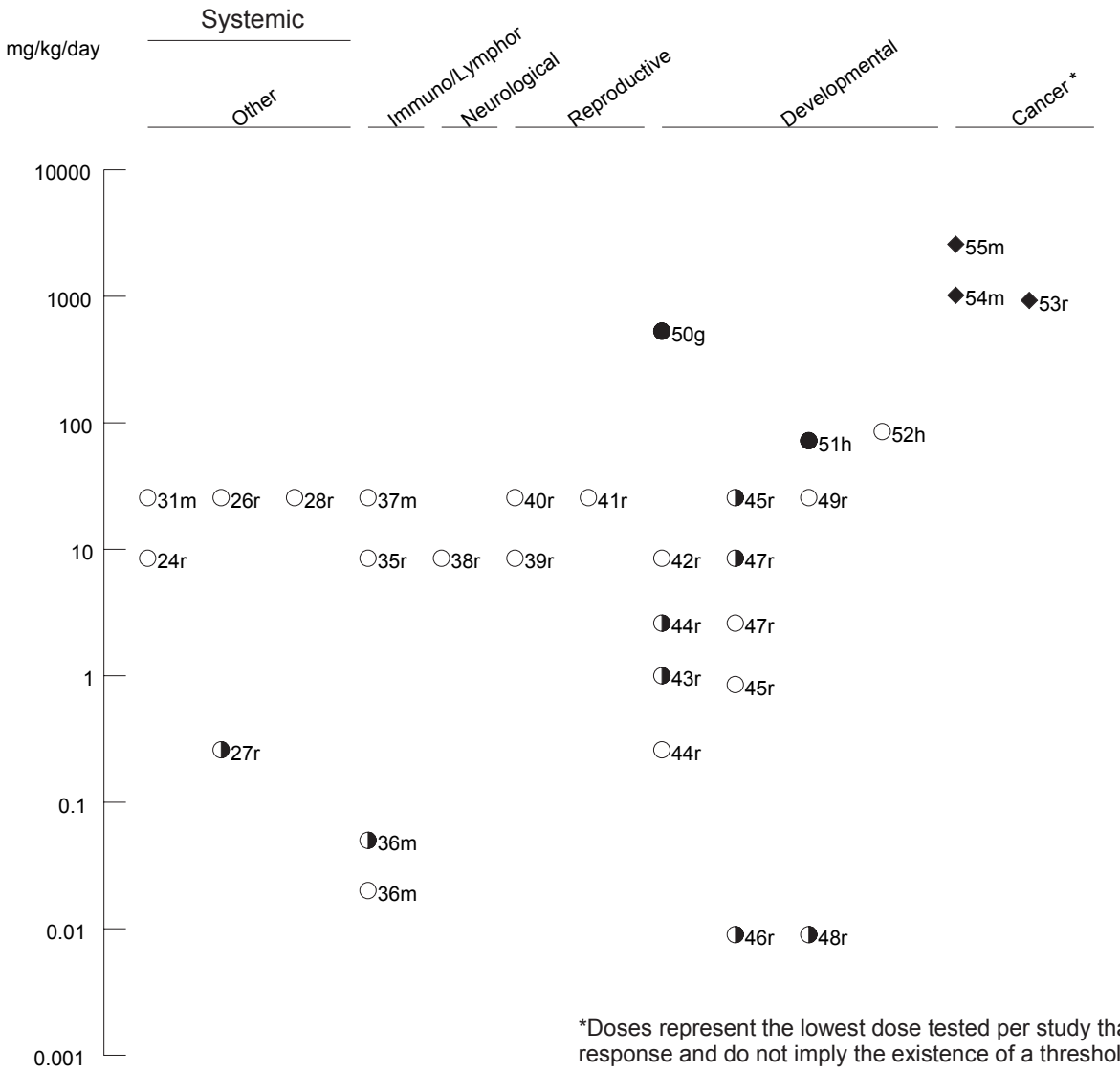


Figure 3-2 Levels of Significant Exposure to Perchlorates - Oral *(Continued)*

Intermediate (15-364 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat -Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

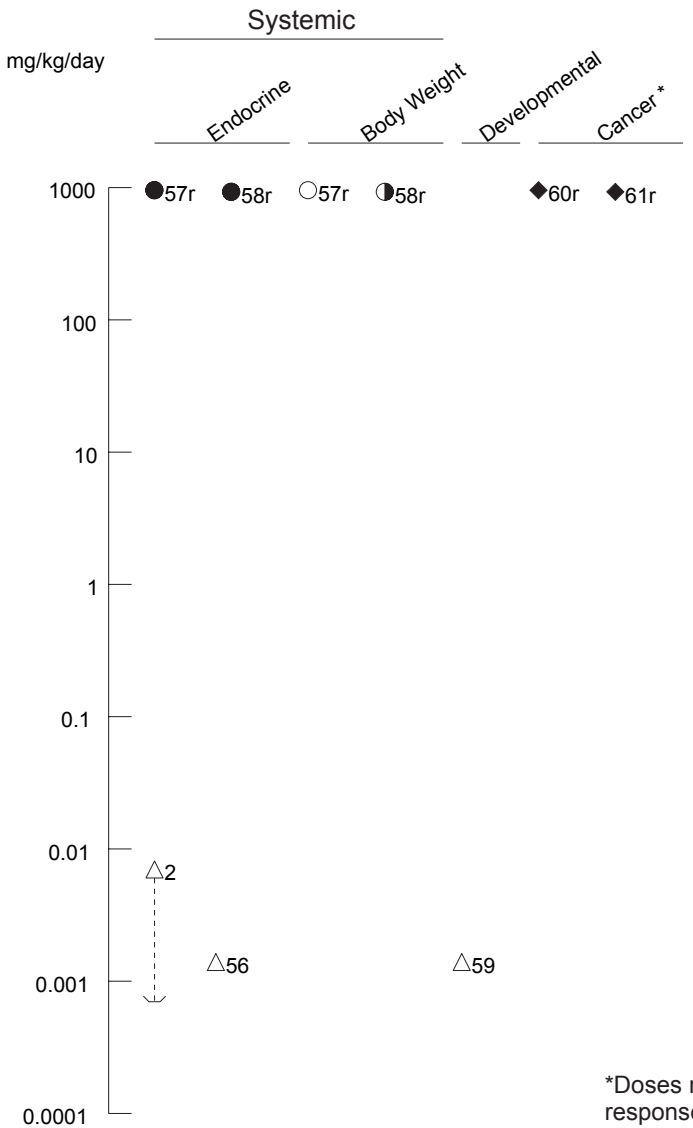
◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Figure 3-2 Levels of Significant Exposure to Perchlorates - Oral *(Continued)*

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to perchlorate. The only relevant information in animals is that from a study by Siglin et al. (2000) in which no significant effects on lung weight and no gross or microscopic alterations were found in the lungs from rats administered up to 8.5 mg perchlorate/kg/day (as ammonium perchlorate) in the drinking water for up to 90 days.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to perchlorate.

Absolute and relative heart weights were significantly decreased in rats treated with 2% potassium perchlorate (approximately 2,327 mg perchlorate/kg/day) in the drinking water for 6 weeks (MacDermott 1992). No gross or microscopical alterations were observed in the heart of rats administered ammonium perchlorate in the drinking water at doses of up to 8.5 mg perchlorate/kg/day for up to 90 days (Siglin et al. 2000); the weight of the heart was also not affected by exposure to perchlorate.

Gastrointestinal Effects. No information was located regarding gastrointestinal effects of perchlorate in healthy humans. Symptoms of gastrointestinal distress, including nausea and vomiting, have been reported in a small percentage of cases of hyperthyroid patients treated with potassium perchlorate (Crooks and Wayne 1960; Godley and Stanbury 1954). In a review of 250 cases, the incidence of nausea was 1.5% (3/200) among patients given 600 or 1,000 mg potassium perchlorate/day (approximately 6 or 10 mg perchlorate/kg/day) and 4% (2/50) among patients given 1,500 or 2,000 mg potassium perchlorate/day (approximately 15 or 20 mg perchlorate/kg/day) (Crooks and Wayne 1960). Although gastrointestinal distress was limited to nausea in most cases, there was one case of a 22-year-old anorectic female Graves' disease patient who experienced burning epigastric discomfort and frequent vomiting within days of starting perchlorate treatment (600 mg potassium perchlorate/day or 6 mg perchlorate/kg/day), and developed a ruptured duodenal ulcer a week later (Godley and Stanbury 1954).

Irritation of the gastric mucosa was reported in dogs given 3,811 mg perchlorate/kg/day as ammonium perchlorate by gavage for 3 weeks (Selivanova and Vorobieva 1969). In rats administered up to 8.5 mg perchlorate/kg/day as ammonium perchlorate in the drinking water for up to 90 days, there was no evidence of gross or histological alterations of any section of the gastrointestinal tract (Siglin et al. 2000).

Hematological Effects. Two recent controlled acute exposure studies in euthyroid volunteers provide information of hematological effects of perchlorate in humans. No alterations in hematological

parameters (complete blood count and routine chemistries) were observed in a group of nine male subjects who consumed once a day for 14 consecutive days a solution of potassium perchlorate that provided 10 mg of perchlorate/day (Lawrence et al. 2000). Blood tests were repeated on days 7 and 14 of dosing and 14 days after perchlorate was discontinued. Assuming a body weight of 70 kg, the perchlorate intake was approximately 0.14 mg/kg/day. Similar lack of hematological alterations was reported among a group of 37 volunteers who ingested up to 0.5 mg of perchlorate/kg/day for 14 days (Greer et al. 2002).

Hematological parameters were evaluated in an epidemiological study of school-age children from three cities with different concentrations of perchlorate in drinking water in northern Chile (Crump et al. 2000). The city with the highest perchlorate concentration was Taltal, 100–120 µg perchlorate/L (ppb); water from the city of Chañaral had 5–7 µg/L. Perchlorate was not detected in water from the city of Antofagasta. Assuming a default consumption of 1–2 L of water/day and a measured body weight of approximately 25 kg, the children in Taltal may have consumed up to 0.004–0.008 mg perchlorate/kg/day via the drinking water only, but the Chilean population also has large dietary sources of perchlorate. The study comprised 162 children 6–8 years of age of which 127 had resided continuously in their respective city since conception. There was nearly an equal number of boys and girls. Analysis of complete blood counts showed no significant differences between the three groups of children whether the analysis included all of the children or only the lifelong residents.

Severe hematological effects were found in several cases of hyperthyroid patients treated with potassium perchlorate. Some patients developed aplastic anemia, characterized by drastic reductions in circulating granulocytes, erythrocytes, and thrombocytes, and a lack of erythropoietic and granulopoietic cells in the bone marrow (Barzilai and Sheinfeld 1966; Fawcett and Clarke 1961; Gjemdal 1963; Hobson 1961; Johnson and Moore 1961; Krevans et al. 1962). Aplastic anemia was the cause of death in most of the documented fatalities associated with potassium perchlorate treatment of thyrotoxicosis. In other patients, the decrease in formed blood elements was limited to the granulocytes (agranulocytosis) and/or thrombocytes (thrombocytopenia). Agranulocytosis was fatal in at least one case (Barzilai and Sheinfeld 1966), although other patients survived this condition (Barzilai and Sheinfeld 1966; Crooks and Wayne 1960; Southwell and Randall 1960; Sunar 1963). The doses in patients who developed agranulocytosis and aplastic anemia were mostly in the low-to-moderate range of doses employed in thyrotoxicosis therapy: 600–1,000 mg potassium perchlorate/day, or roughly 5–12 mg perchlorate/kg/day. Cases of agranulocytosis were found within 14 days to 3 months of the start of potassium perchlorate treatment. Although aplastic anemia was found after 2 months of treatment in one case, in most cases, it was only found after 4–8 months. All of the documented cases of aplastic anemia and agranulocytosis were

females (Graves' disease, the most common cause of hyperthyroidism, is far more common in women than in men), with ages ranging from 24 to 82 years.

Inhibition of hematopoiesis in the bone marrow has also been reported in dogs given 3,811 mg perchlorate/kg/day as ammonium perchlorate by gavage for 3 weeks (Selivanova and Vorobieva 1969), and in rats and mice exposed to 1% potassium perchlorate in the drinking water for 3 months (approximate doses of 1,059 and 1,750 mg perchlorate/kg/day, respectively) (Shevtsova et al. 1994). No significant alterations in hematological parameters were reported following administration of ammonium perchlorate in a drinking water study in mice at doses up to 25.5 mg perchlorate/kg/day for 14 or 90 days (DOD 1999). Similarly, a recent study in rats found no evidence of hematotoxicity after administration of up to 8.5 mg perchlorate/kg/day in the drinking water for 90 days (Siglin et al. 2000). The investigators evaluated routine hematology and clinical chemistry parameters.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to perchlorate.

MacDermott (1992) observed a decrease in membrane potential and in intracellular potassium ion activity in skeletal muscle from rats treated with 2% potassium perchlorate (approximately 2,327 mg perchlorate/kg/day) in the drinking water for 6 weeks. The observed changes are consistent with a decrease in the number of sodium-potassium pump units in the muscle. No alterations in gross or microscopic appearance of skeletal muscle were reported in rats exposed to doses up to 8.5 mg perchlorate/kg/day as ammonium perchlorate in the drinking water for 90 days (Siglin et al. 2000).

Hepatic Effects. No evidence of liver toxicity, as judged by blood chemistry tests, was observed in a group of nine volunteers who ingested approximately 0.14 mg of perchlorate/kg/day as potassium perchlorate for 14 consecutive days (Lawrence et al. 2000). Similar results were reported by Greer et al. (2002) in a study of 37 volunteers who consumed up to 0.5 mg of perchlorate/kg/day also for 14 days. In the study by Crump et al. (2000) of 162 school-age children from three cities in northern Chile with different perchlorate concentration in the drinking water (up to 100–120 μg/L), there were no indications of altered liver function among the children as measured by serum aspartate aminotransferase (AST), alkaline phosphatase (AP), and lactate dehydrogenase (LDH) activities.

Godley and Stanbury (1954) reported no evidence of liver toxicity in a series of 24 hyperthyroid patients treated with potassium perchlorate (600 mg, or approximately 6 mg perchlorate/kg/day) for up to

52 weeks. However, it is not clear what tests were conducted to monitor effects on the liver or how frequently such tests may have been conducted.

A 0.1% concentration of potassium perchlorate in the diet (about 64 mg perchlorate/day) for 19 weeks had no effect on liver weight in rats (Hiasa et al. 1987). A more recent study in rats found that administration of ammonium perchlorate in the drinking water at doses up to 8.5 mg perchlorate/kg/day for up to 90 days caused no significant alterations in liver weight, in the gross or microscopic appearance of the liver, or in serum transaminase activities (Siglin et al. 2000). No effects on liver weight were reported in 14- and 90-day studies in mice administered up to 25.5 mg perchlorate/kg/day in the drinking water as the ammonium salt (DOD 1999).

Renal Effects. Limited information exists regarding renal effects of perchlorate in humans. Two studies in euthyroid volunteers who ingested up to 0.5 mg of perchlorate/kg/day as the potassium salt for 14 days found no evidence of renal effects as judged by standard clinical chemistry tests (Greer et al. 2002; Lawrence et al. 2000). Also, no alterations in BUN or in serum creatinine levels were observed in a group of 60 school-age children from northern Chile exposed to perchlorate in their drinking water at concentrations up to 100–120 μg/L (Crump et al. 2000).

In a case report, a patient with severe hyperthyroidism who was treated with an average of 1,068 mg sodium perchlorate/day (approximately 12 mg perchlorate/kg/day) for 3.5 months developed nephrotic syndrome, as diagnosed by albuminuria, decreased serum albumin, and increased serum cholesterol. The effects subsided after treatment was stopped, and were considered by the researchers to probably have been treatment-related (Weber and Wolf 1969).

There is also limited information on the renal effects of perchlorate in animals. In 14- and 90-day drinking water studies in rats, doses of up to 8.5 mg/kg/day produced no significant alterations in kidney weight or in gross or microscopical appearance of the kidneys (Siglin et al. 2000). In addition, kidney function, monitored by measurements of BUN and serum creatinine, was not affected by exposure to perchlorate (Siglin et al. 2000). A similar study in mice also found no effects of ammonium perchlorate on kidney weight following 14 or 90 days of exposure to up to 25.5 mg perchlorate/kg/day, but kidney function tests were not performed (DOD 1999).

Endocrine Effects. The findings of groundwater contamination with perchlorate in western areas of the United States has triggered considerable research on the effects of this anion on the thyroid gland, its

main target organ, in efforts to describe dose-response relationships at low doses and to define no-effect-level of exposure. For example, Lawrence et al. (2000) evaluated serum TSH, FTI, total serum triiodothyronine (TT3), and RAIU; serum and 24-hour urine perchlorate; and 24-hour urinary iodide excretion in volunteers who ingested approximately 0.14 mg perchlorate/kg/day in drinking water for 14 days. Tests were conducted pre-dosing, on day 7 and 14, and 14 days after perchlorate ingestion was discontinued. The only significant finding was a significant decrease in 4-, 8-, and 24-hour RAIU values by a mean of about 38% relative to baseline on day 14 of dosing. Fourteen days later, RAIU had recovered to a mean of 25% above baseline values. Greer et al. (2002) conducted a similar study in volunteers administered 0.007, 0.02, 0.1, or 0.5 mg perchlorate/kg/day in drinking water for 14 days. RAIU was measured on exposure days 2 and 14, and 15 days after dosing ceased. To estimate daily iodine intake, 24-hour urine samples were collected. As a percentage of baseline RAIU, inhibition in the 0.007, 0.02, 0.1, and 0.5 mg/kg/day dose groups was 1.8, 16.4, 44.7, and 67.1%, respectively. There were no significant differences between the RAIU values measured on day 2 and 14. Fifteen days after perchlorate treatment was discontinued, RAIU values were slightly higher than baseline values. Greer et al. (2002) also found no significant effects of perchlorate treatment on serum TSH, free T4, TT4, and TT3, and on serum antithyroid peroxidase levels; serum antiglobulin levels were below detection levels in all samples tested. The National Academy of Sciences (NAS 2005) recommended a chronic RfD of 0.0007 mg/kg/day for perchlorate based of the findings of Greer et al. (2002). ATSDR has adopted the RfD recommended by NAS for the chronic oral MRL.

A study similar to Greer et al. (2002) was conducted by Braverman et al. (2006) who administered capsules containing potassium perchlorate to 13 volunteers (4 males, 9 females) once a day for 6 months. The estimated doses were 0 (placebo), 0.5, and 3.0 mg perchlorate/day (approximately 0.04 and 0.007 mg perchlorate/kg/day). The outcomes measured were serum thyroid function tests, 24-hour RAIU, serum thyroglobulin (Tg), urinary iodine and perchlorate, and serum perchlorate. RAIU, measured at baseline, 3 and 6 months, and 1 month after termination, was not significantly affected by administration of perchlorate, and there were no significant changes in serum total T3, FTI, TSH, or Tg levels during or after perchlorate exposure compared to baseline values. The small number of subjects per group (4–5), the dosing by capsule rather than intermittent exposure in drinking water, and the lack of information on RAIU during the first 3 months of the study weaken the conclusions of this study.

Other earlier studies in healthy human subjects also showed that perchlorate administered in doses between 7 and 10 mg/kg/day reduced thyroid iodide uptake, increased serum iodide levels, and increased urinary iodide excretion (Brabant et al. 1992; Bürgi et al. 1974; DeGroot and Buhler 1971; Faure and

Dussault 1975). Higher doses of perchlorate were used in the past to treat subjects with hyperactive thyroids. For example, Stanbury and Wyngaarden (1952) found that a single oral dose of 100 mg of potassium perchlorate (approximately 1 mg perchlorate/kg) dramatically reduced uptake of iodide by the thyroid gland in Graves' disease patients. Subsequent to this finding, potassium perchlorate became an accepted treatment for hyperthyroidism, and was widely used for this purpose for several years (Connell 1981; Crooks and Wayne 1960; Godley and Stanbury 1954; Morgans and Trotter 1960). The use of perchlorate for the treatment of hyperthyroidism came to a virtual stop due to the appearance of cases of aplastic anemia (see Hematological Effects).

Epidemiological studies evaluating adults, children, and newborns have also been conducted (studies of children and newborns are summarized in Section 3.2.2.6, Developmental Effects). However, caution should be exercised in the interpretation of the results from the ecological studies due to the ubiquitous nature of perchlorate exposure and because the effects of perchlorate are dependent upon iodine uptake, so that differences in iodine levels will be important.

In a study of the general population, Li et al. (2001) examined the prevalence of thyroid diseases in Nevada Counties with respect to perchlorate in drinking water. The cohort consisted of all users of the Nevada Medicaid program during the period of January 1, 1997 to December 31, 1998. Disease prevalence in residents from Clark County (Las Vegas), whose drinking water had 4–24 μg/L of perchlorate (0.0001–0.0007 mg perchlorate/kg/day), were compared with those from another urban area of similar size (Reno, Washoe County), but with no perchlorate in the water, and also with those from all other counties, also with no perchlorate exposure. Patients were defined as those having one or more of the following diagnoses of thyroid disease: simple and unspecified goiter, nontoxic nodular goiter, thyrotoxicosis with or without goiter, congenital hypothyroidism, acquired hypothyroidism, thyroiditis, other disorders of the thyroid, or malignant neoplasm of the thyroid gland. Analysis of the data showed no statistically significant period-prevalence rate difference between Clark County and Washoe County. For acquired hypothyroidism, the prevalence was lower in Clark County than in other counties (opposite to what would be expected). Li et al. (2001) acknowledged that their analysis was a crude analysis since age- and sex-adjusted prevalence could not be calculated because of lack of information on age and sex distributions of the Medicaid-eligible population in each county.

A study of 184 pregnant women from three cities (Antofagasta, Chañaral, and Taltal) in northern Chile found no significant association between levels of perchlorate in the drinking water and serum levels of TSH, T4, or thyroglobulin measured early (16.1 weeks) or late (32.4 weeks) during pregnancy (Téllez et

al. 2005). The mean concentrations of perchlorate in the drinking water from Chañaral and Taltal were 5.8 and 113.9 µg/L, respectively; drinking water from Antofagasta had 0.46 µg/L of perchlorate. The doses of perchlorate estimated by the investigators for subjects in Antofagasta, Chañaral, and Taltal were 0.42, 6.1, and 93.5 µg perchlorate/day, respectively. Using a mean measured body weight of 66.8 kg, the women from Taltal took doses of approximately 0.0014 mg perchlorate/kg/day. Because of the high iodide intake and high background perchlorate in the Chilean diet, the studied women may not be representative of the U.S. population. Furthermore, such high iodide intake may effectively compete with perchlorate binding sites on the NIS.

A recent study of 2,299 male and female participants in NHANES (2001–2002) found that, for women (n=1,111) but not men, urinary perchlorate was a significant predictor of both serum TT4 and TSH concentrations (Blount et al. 2006). Blood and spot urine samples were collected from the subjects. Separate analysis of women with urinary iodine <100 µg/L showed that urinary perchlorate was a significant negative predictor of TT4 ($p<0.0001$) and a positive predictor of TSH ($p<0.001$). For women with urinary iodine ≥100 µg/L, urinary perchlorate was a significant positive predictor of TSH ($p=0.025$), but not of TT4 ($p=0.550$). These associations of perchlorate exposure with TT4 and TSH are coherent in direction and independent of other variables known to affect thyroid function, but are present at perchlorate exposure levels found in the general population (median estimated dose 0.059 µg/kg bw/day). Covariates included in the analyses were: age, race/ethnicity, body mass index, estrogen use, menopausal status, pregnancy status, premenarche status, serum C-reactive protein, serum albumin, serum cotinine, hours of fasting, urinary thiocyanate, urinary nitrate, and selected medication groups. Of these, several were also predictors of thyroid hormones with various degrees of significance. For example, for women with urinary iodine <100 µg/L, estrogen use, menopause, pregnancy, premenarche, C-reactive protein, and total kilocalorie intake were also predictors of TT4 levels. In the low-iodine group of females, urinary perchlorate accounted for 24% of the variance in serum TT4. Limitations acknowledged by the investigators include those common to cross-sectional analyses, the assumption that urinary perchlorate correlate with levels in the thyroid stroma and tissue, and the measurement of total T4 rather than free T4. In addition, not all variables that may impact thyroid function, such as some dietary factors, were accounted for. Also, the study does not address a logical temporal association or biologic plausibility. The investigators also stated that further research is needed to affirm these findings.

Studies in laboratory animals have described the thyroid effects of perchlorate in great detail. Reported findings have included reduced thyroid iodide uptake, increased levels of iodide in serum, decreased serum T4 and T3, increased serum TSH, increased thyroid size and weight, and hypertrophy and

hyperplasia of thyroid cells, eventually leading to fibrosis and tumor development (see Cancer section), (Fernandez-Rodriguez et al. 1991; Florencio Vicente 1990; Gauss 1972; Hartmann et al. 1971; Hiasa et al. 1987; Kapitola et al. 1971; Kessler and Kruskemper 1966; Logonder-Mlinsek et al. 1985; MacDermott 1992; Mannisto et al. 1979; Matsuzaki and Suzuki 1981; Ortiz-Caro et al. 1983; Pajer and Kalisnik 1991; Postel 1957; Schonbaum et al. 1965; Selivanova and Vorobieva 1969; Spreca and Musy 1974; Tarin-Remohi and Jolin 1972; Toro Guillen 1991; Wyngaarden et al. 1952). In general, many studies conducted in the early 1990s and before used relatively high doses of perchlorate, and/or only one dose level was tested, thus precluding establishing dose-response relationships that defined no-effect dose levels. Perchlorate doses reported to produce the effects mentioned above ranged from 7 to 3,811 mg/kg/day after durations ranging from 1 day to 2 years.

Studies conducted within the past 10 years in adult nonpregnant animals have used much lower doses of perchlorate. For example, Caldwell et al. (1995) conducted a pilot 14-day drinking water study in rats. The animals were exposed to one of seven doses of perchlorate ranging from 0.1 to 39.9 mg perchlorate/kg/day. Perchlorate administration induced dose-related increases in TSH and decreases in T4 and T3 in both males and females, but females appeared to be more sensitive than males. The lowest administered dose, 0.1 mg/kg/day, increased TSH and decreased T4 and T3 in females roughly by 15, 12, and 34%, respectively, relative to controls. An additional 14-day study in rats reported a significant increase in serum TSH and a nonsignificant decrease in T3 at perchlorate doses 0.09 mg/kg/day, the lowest level tested (Yu et al. 2002). A more comprehensive 14-day study in rats was conducted by Siglin et al. (2000). Perchlorate was administered in the drinking water as the ammonium salt in doses of 0, 0.009, 0.04, 0.17, 0.85, or 8.5 mg perchlorate/kg/day. At the end of the exposure period, blood TSH was significantly increased in males at ≥0.17 mg/kg/day (23%) and in females at ≥0.04 mg/kg/day (17%). Blood T4 showed a decreasing trend with increasing perchlorate doses, the differences relative to controls achieved statistical significance in both males (23% decrease) and females (18% decrease) only at the highest dose level. Blood T3 was significantly decreased (dose-related) in all male groups (21% at the lowest dose), but was not significantly affected in any female group. Both absolute and relative thyroid weights were significantly increased in males from the highest dose group, no significant effects were seen in females. Histological alterations in the thyroid were observed only at the high dose ranging in severity classified as minimal, mild, or moderate. Minimal or mild lesions were seen in 7/10 high-dose females and 3/10 high-dose males. Moderate lesions were seen in 7/10 males at 8.5 mg/kg/day and consisted of follicular cell hypertrophy with microfollicle formation and colloid depletion. There was no evidence of focal hyperplasia.

In a 14-day study in mice exposed to 0, 0.09, 0.85, 2.6, or 25.5 mg perchlorate/kg/day, serum T4 was significantly decreased at 2.6 and 25.5 mg/kg/day (14 and 22%, respectively) (DOD 1999). T3 was lower than controls, although not significantly, in all treated groups except the 0.85 mg/kg/day group. There was no clear pattern of change in TSH levels. Morphological evaluation of the thyroid showed colloid depletion, intrafollicular capillary congestion, and mildly hypertrophied follicular epithelium in mice from the highest dose group. An additional 14-day study in mice reported a significant decrease in serum T4 levels at ≥0.2 mg perchlorate/kg/day and a significant increase in TSH at ≥1.7 mg/kg/day; serum T3 was not measured (BRT 2000). Microscopical examination of the thyroid revealed colloid depletion and hypertrophy in 5 out of 5 mice dosed with 42.5 mg/kg/day, but no significant alterations at the next lower dose level, 1.7 mg/kg/day.

A 90-day study was conducted in rats exposed to 0, 0.009, 0.04, 0.17, 0.85, or 8.5 mg perchlorate/kg/day in the drinking water (Siglin et al. 2000). Following the exposure period, the rats were provided uncontaminated drinking water for an additional 30-day period. After the 90 days of exposure to perchlorate, relative to controls TSH was significantly increased in males at ≥0.17 mg/kg/day (17% increase) and in females at 8.5 mg/kg/day (21% increase). Blood T4 was significantly decreased in both males and females from all treated groups (dose-related) (decreases ranged from 14 to 43% in males). The effect of perchlorate on blood T3 was similar to that on T4 (12–35% decrease in males). At 120 days, hormone levels approached control levels except for T4 in males and TSH in females. Both absolute and relative thyroid weights were significantly increased in males and females at 8.5 mg/kg/day at 90 days but returned to near control values at 120 days. Histological alterations in the thyroid ranged in severity from minimal to mild and were seen only at the 8.5 mg/kg/day dose level in both male and female rats. The lesions consisted of follicular cell hypertrophy with microfollicle formation and colloid depletion. There was no evidence of focal hyperplasia. No abnormal pathology was seen in the thyroid after 120 days.

In a 2-generation reproductive study in rats, the F1 generation was exposed directly to perchlorate (0.26, 2.6, or 25.5 mg/kg/day) from weaning to 19 weeks of age, at which time, the animals were killed (York et al. 2001a). In these adult rats, a significant increase in absolute and relative thyroid weight was seen in males at 2.6 and 25.5 mg/kg/day and in all female groups (dose-related). Hypertrophy and hyperplasia of the thyroid also occurred at 2.6 and 25.5 mg/kg/day in males and in high-dose females. TSH increased only in high-dose males and females and T4 decreased in high-dose males (26% decrease); T3 levels were not significantly affected. Hypertrophy and hyperplasia of the thyroid was reported at ≥2.6 mg perchlorate/kg/day in the paternal generation of rats in the 2-generation study mentioned above in which

the rats were exposed for a period that included premating, pregnancy, and lactation (York et al. 2001a); the NOAEL was 0.26 mg/kg/day. The highest dose tested, 25.5 mg/kg/day, induced a significant increase in TSH and a decrease in T4 in males.

In developmental studies in rats in which dosing with ammonium perchlorate at doses of 0, 0.009, 0.09, 0.85, and 25.5 mg perchlorate/kg/day began 14 days premating and continued to gestation day 10 or 21, TSH and T4 were significantly increased and decreased, respectively, in a dose-related manner in all dosed groups of dams (York et al. 2003, 2005a). In an additional developmental study in rats in which exposure started 14 days before mating and continued until postnatal day (PND) 10, treatment with up to 8.5 mg perchlorate/kg/day caused no maternal toxicity as judged by clinical observations, body and thyroid weights, and thyroid histology (York et al. 2004).

BRT (2000) evaluated serum TSH and T4 levels and thyroid histology in mice in a 90-day study. The exposure levels were 0, 0.02, 0.05, 0.2, 1.7, or 42.5 mg perchlorate/kg/day. Treatment with ammonium perchlorate decreased serum T4 levels, and the magnitude of the difference relative to controls achieved statistical significance at the 1.7 mg/kg/day dose level (18% decrease). The decrease in T4 was dose-related at ≥0.2 mg/kg/day and higher. Serum TSH was significantly elevated at ≥0.05 mg/kg/day relative to controls (17% increase at the 0.05 mg/kg/day dose level). Microscopical examination of the thyroid revealed hypertrophy in 3 out of 15 mice at 1.7 mg/kg/day, and in 4 out of 5 high-dose mice. Colloid depletion was present in 5 out of 5 mice dosed with 42.5 mg/kg/day. No significant treatment-related differences were observed between the other groups and controls.

In a developmental study in New Zealand rabbits, exposure to up to 85 mg perchlorate/kg/day on gestation days 6–28 did not significantly alter absolute or relative thyroid weight (York et al. 2001b). However, hypertrophy of the follicular epithelium was seen in the does at ≥8.5 mg/kg/day, and the incidence was dose-related. Neither serum TSH nor T3 levels were significantly affected by treatment with perchlorate. Serum T4 was significantly reduced at 25.5 and 85 mg/kg/day; T4 was also reduced at 0.85 and 8.5 mg/kg/day, but not significantly.

Other endocrine effects reported in perchlorate-treated animals included pituitary hypertrophy and hyperplasia (Pajer and Kalisnik 1991), reduced serum growth hormone levels (Ortiz-Caro et al. 1983), and reduced serum insulin (Tarin-Remohi and Jolin 1972). All of these effects were accompanied by thyroid effects in the same studies. Direct correlation of these diverse animal studies to human endocrine

systems is not provided, reflecting the NAS (2005) recommendation that such animal studies were not indicative or representative of humans.

Dermal Effects. No reports were found of adverse dermal effects of perchlorate in healthy humans. Skin rash was the most frequent side effect of potassium perchlorate therapy in thyrotoxicosis patients, occurring primarily in patients receiving doses at the high end of the therapeutic range. Rash was observed in 10% (5/50) of patients treated with 1,500 or 2,000 mg (approximately 15 or 20 mg perchlorate/kg/day) by Crooks and Wayne (1960), and in 15% (10/67) of patients treated with 1,200 or 1,600 mg (approximately 12 or 16 mg perchlorate/kg/day) by Morgans and Trotter (1960). However, rash was seen in only 0.5% (1/200) patients treated with 600 or 1,000 mg (approximately 6 or 10 mg perchlorate/kg/day) by Crooks and Wayne (1960), and in none of the 24 patients treated with 600 mg (approximately 6 mg perchlorate/kg/day) by Godley and Stanbury (1954). The observed rash was characterized as maculopapular by Crooks and Wayne (1960), and was attributed by these authors to a hypersensitivity reaction. Hemorrhagic skin lesions were frequently noted in cases with severe hematological effects (Barzilai and Sheinfeld 1966; Fawcett and Clarke 1961; Gjemdal 1963; Hobson 1961; Johnson and Moore 1961; Krevans et al. 1962; Southwell and Randall 1960). The lesions, which were described as punctate erythema, hemorrhagic pustulae, purpuric rash, skin hemorrhage, bleeding into the skin, and petecchiae, apparently occurred secondary to the hematological effects.

In rats administered up to 8.5 mg perchlorate/kg/day as ammonium perchlorate in the drinking water for 90 days, no significant gross or microscopical alterations in the skin were found throughout the study (Siglin et al. 2000).

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to perchlorate. Opthalmological examinations on rats dosed with up to 8.5 mg of perchlorate/kg/day for up to 90 days revealed no treatment-related effects (Siglin et al. 2000).

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to perchlorate.

In acute-duration rat studies, reduced growth was reported at an estimated dose of 1,830 mg perchlorate/kg/day (Arieli and Chinet 1985), but not at doses of 1,500 mg perchlorate/kg/day or below (Caldwell et al. 1995; Kapitola et al. 1971; Matsuzaki and Suzuki 1981; Schonbaum et al. 1965; Siglin et al. 2000). In longer-term studies, there are reports of reduced body weight gain in rats at doses of 175 mg

perchlorate/kg/day for 25 days (Ortiz-Caro et al. 1983), 1,362 mg/kg/day for 18 days (Tarin-Remohi and Jolin 1972), 928 mg/kg/day for 12 months (Florencio Vicente 1990), 2,327 mg/kg/day for 6 weeks (MacDermott 1992), and 928 mg/kg/day for 15 months (Toro Guillen 1991). Treatment of rats for 90 days with up to 8.5 mg of perchlorate/kg/day in the drinking water did not result in significant effects on growth (Siglin et al. 2000), nor did treatment with 64 mg/kg/day for 19 weeks (Hiasa et al. 1987). Also, in a 2-generation reproduction study in rats, no significant effects on body weight were seen in F1 animals treated directly with up to 25.5 mg perchlorate/kg/day from weaning to 19 weeks of age in addition to being exposed perinatally (York et al. 2001a); no significant effects on body weight were seen in the paternal generation also in that study. A study in mice also found no alterations in body weight or weight gain following 14 or 90 days of exposure to ammonium perchlorate in the drinking water in doses up to 25.5 mg perchlorate/kg/day (DOD 1999). Where present, reduced growth is considered secondary to hypothyroidism produced by perchlorate.

Metabolic Effects. No studies were located regarding metabolic effects in humans after oral exposure to perchlorate.

Researchers in India conducted a number of studies investigating the metabolic effects of perchlorate in rats given 500 mg/kg/day of potassium, sodium, or ammonium perchlorate by daily gavage for 45 days (Sangan and Motlag 1986, 1987; Vijayalakshmi and Motlag 1989a, 1989b, 1990, 1992). They found that perchlorate increased protein metabolism (increased liver arginase activity and serum urea levels), altered carbohydrate metabolism (decreased serum glucose and increased liver and kidney glycogen levels, reflecting increased activity of aldolase, lactate dehydrogenase, and glycogen synthase, and decreased activity of glucose-6-phosphatase and glycogen phosphorylase), and modified lipid metabolism (increased cholesterol, triglyceride, and phospholipid, and decreased free fatty acid levels, reflecting decreased activity of lipase and phospholipase). They also found that perchlorate reduced the activities of mitochondrial enzymes involved in cellular respiration, apparently due to changes in lipid composition of mitochondrial membranes (increased cholesterol and decreased phospholipid) reducing membrane fluidity.

Other studies reported only a small (11%), nonsignificant decrease in serum glucose levels in rats exposed to potassium perchlorate (1,362 mg perchlorate/kg/day) in the drinking water for 18 days (Tarin-Remohi and Jolin 1972), and no effect on serum glucose in rats exposed to 0.1% potassium perchlorate (approximately 175 mg perchlorate/kg/day) in the drinking water for 25 days (Ortiz-Caro et al. 1983). No

effects were observed on serum glucose levels in rats exposed to up to 8.5 mg of perchlorate/kg/day as ammonium perchlorate in the drinking water for up to 90 days (Siglin et al. 2000).

Ortiz-Caro et al. (1983) observed a significant decrease in the activity of α-glycerophosphate dehydrogenase (α-GPD) in hepatic mitochondria in their study that was considered secondary to hypothyroidism produced by perchlorate. However, Arieli and Chinet (1985) found no effect on cytoplasmic α-GPD in brown fat in rats that received 2% potassium perchlorate (1,830 mg perchlorate/kg/day) in the drinking water for 2 weeks.

Other Systemic Effects. No studies were located regarding other systemic effects in humans after oral exposure to perchlorate.

Eskin et al. (1975) observed reduced iodide uptake, decreased weight, and dysplastic histopathological lesions in the mammary gland of rats treated with 459 mg perchlorate/kg/day as sodium perchlorate in the drinking water for 8 weeks. Mammary gland dysplasia was also seen in ovariectomized rats given estrogen replacement and then dosed with 494 mg perchlorate/kg/day for 8 weeks (Eskin et al. 1976).

Water consumption was not significantly altered in rats administered up to 40 mg of perchlorate/kg/day for 14 days in the drinking water (Caldwell et al. 1995). Neither food or water consumption were affected in rats exposed to perchlorate via drinking water in doses up to 8.5 mg/kg/day for up to 90 days (Siglin et al. 2000). In a 2-generation reproduction study in rats, paternal males exposed for 16 weeks showed a reduction in absolute and relative water consumption at 0.26 and 25.5 mg perchlorate/kg/day, but not at 2.6 mg/kg/day (York et al. 2001a). In that same study, no significant effects were seen on water consumption in the F1 generation exposed directly to up to 25.5 mg perchlorate/kg/day in the drinking water from weaning to 19 weeks of age. No significant effects on water consumption were also reported in 14- and 90-day studies in mice given ammonium perchlorate in the drinking water in doses of up to 25.5 mg perchlorate/kg/day (DOD 1999).

3.2.2.3 Immunological and Lymphoreticular Effects

No reports were found of perchlorate-induced alterations in immune system parameters in healthy humans. Two cases of lymphadenopathy (not further described) were reported among a series of 247 hyperthyroid patients treated with potassium perchlorate (Morgans and Trotter 1960). Both cases

occurred in patients treated with 1,200 or 1,600 mg potassium perchlorate/day (roughly 12 or 16 mg perchlorate/kg/day). Lymphoreticular effects were not reported in other case studies.

Spreca and Musy (1974) found increases in the proportion of degranulated mast cells in the thyroid, skin, liver, and lungs of rats treated with potassium perchlorate (approximately 323 mg perchlorate/kg/day) for 1 day. The effect was greatest in the thyroid (27% decrease) and skin (21% decrease). Degranulation of mast cells is typically associated with exposure to an allergen; degranulation releases pharmacological mediators of immediate hypersensitivity responses (histamine, heparin, etc.), leading to allergy symptoms. Clinical signs of hypersensitivity response were not monitored in this study. There was also an increase in the number of mast cells in the thyroid and small decreases in mast cell numbers in the skin, liver, and lung. The researchers suggested that the increase in the thyroid was associated with hyperplasia in this tissue, and that the decrease in the other tissues may reflect loss of cells by degranulation. An increase in mast cell numbers in the thyroid of mice treated with sodium perchlorate (1.2% in drinking water, or roughly 2,622 mg perchlorate/kg/day) for 64 days was also reported by Logonder-Mlinsek et al. (1985). The extent of mast cell degranulation was not reported in this study.

More recent studies in animals have tested much lower doses of perchlorate and conducted a more complete evaluation of the immune system. For example, 14- and 90-day studies in rats administered ammonium perchlorate in the drinking water in doses up to 8.5 mg perchlorate/kg/day reported no significant effects on spleen weight and no gross or microscopic alterations in lymph nodes, spleen, and thymus; no tests of immunocompetence were conducted in these studies (Siglin et al. 2000). DOD (1999) evaluated a series of immunological end points in 14- and 90-day studies in mice exposed to ammonium perchlorate in the drinking water in doses of 0, 0.09, 0.9, 2.6, and 25.5 mg perchlorate/kg/day. End points evaluated included thymus and spleen weight and cellularity, CD4/CD8 splenocyte and thymocyte subpopulations, stem cell progenitors (90-day), melanoma tumor incidence (90-day), natural killer (NK) cell activity, delayed-type hypersensitivity (DTH), cytotoxic T cell activity, response to challenge with *Listeria monocytogenes* (90-day), peritoneal macrophage phagocytosis and nitrite production, and specific IgM and IgG response to cell dependent sheep red blood cell (SRBC) challenge. Significant findings in the 14-day study included an increase in the percent of CD4-/CD8+ thymic lymphocytes at 0.09 and 0.9 mg/kg/day, decreased macrophage phagocytosis at 0.9 and 25.5 mg/kg/day, and increased DTH response at 25.5 mg/kg/day. In the 90-day study, NK cell activity was increased in the highest-dose group, macrophage phagocytosis was decreased in all treated groups, the DTH response was also increased at 25.5 mg/kg/day, and increased resistance to the challenge with *Listeria* in the high-dose group when challenged only with high immunization levels. Overall, because only a few immunological

parameters were affected and resistance to the challenge with *Listeria* was not decreased, the results of this study do not suggest an immunosuppressive function for perchlorate at the doses tested.

Additional 14- and 90-day drinking water studies exposed mice to 0, 0.02, 0.05, 0.2, 1.7, or 42.5 mg perchlorate/kg/day examined the plaque forming cell (PFC) response following sheep red blood cells (SRBC) immunization and the ability of mice to generate a hypersensitivity response (local lymph node assay [LLNA]) to 2,4-dinitrochlorobenzene (DNCB), a known sensitizing chemical (BRT 2000). No significant effects were seen on the PFC response after 14 days of treatment, but an increased response was seen after 90 days in the 1.7 and 42.5 mg/kg/day dose groups when the results were expressed as number of response per spleen and only at 42.5 mg/kg/day when the responses were expressed per number of spleen cells. In the LLNA assay, perchlorate increased the sensitizing potential of DNCB at all doses except 1.7 mg/kg/day in the 14-day experiment, whereas in the 90-day experiment, perchlorate increased the sensitizing potential of DNCB at 0.05 and 0.2 mg/kg/day, had no effect at 0.02 or 1.7 mg/kg/day, and decreased it at 42.5 mg/kg/day. It should be mentioned, however, that cyclophosphamide, the positive control, did not abolish the sensitizing effect of DNCB alone, calling into question the reliability of the experiment. The physiological relevancy of the enhancement of the LLNA is unclear. Further research in this area is needed to determine whether perchlorate is a contact sensitizer.

NOAEL and LOAEL values for immune system effects from the rodent studies are shown in Table 3-2 and Figure 3-2.

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to perchlorate and limited information is available in animals. No gross or microscopic alterations were observed in the brain from rats treated with ammonium perchlorate in drinking water in doses up to 8.5 mg perchlorate/kg/day for 14 or 90 days (Siglin et al. 2000). Brain weight was also not significantly altered by exposure to perchlorate.

Neurodevelopmental effects resulting from perinatal exposure to perchlorate are discussed in Section 3.2.2.6, Developmental Effects.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to perchlorate.

Exposure to 1% potassium perchlorate (roughly 532 mg perchlorate/kg/day) in the drinking water on days 2 through 8 of gestation had no effect on the number of live litters produced, mean litter size, or duration of pregnancy in rats (Brown-Grant 1966). Nor was there any effect on the number or weight of implantation sites in lactating pregnant female rats that received approximately 1,752 mg perchlorate/kg/day in the drinking water on days 1 through 13 of gestation (Brown-Grant and Sherwood 1971).

A more recent 14-day study in male and female rats administered ammonium perchlorate in the drinking water at doses up to 8.5 mg perchlorate/kg/day found no alterations in absolute weight of the uterus, testes, or ovaries (Siglin et al. 2000). Also, there were no gross or microscopic alterations in the testes, prostate, epididymis, uterus, ovaries, or mammary glands. Examination of these end points following 90 days of exposure to the same doses also revealed no significant effects (Siglin et al. 2000). In addition, the 90-day study showed no significant effects on sperm motility, concentration, count, or morphology.

In a 2-generation reproductive study, male and female rats (P generation) were exposed to ammonium perchlorate in the drinking water at target doses of 0, 0.26, 2.6, or 25.5 mg perchlorate/kg/day for 10 weeks before mating and during pregnancy and lactation (York et al. 2001a). Males were sacrificed after 13 weeks of exposure and females were sacrificed on postpartum day (PPD) 21. Offspring (F1) were dosed from weaning to 19 weeks of age. Mating of F1 generation females and males produced the F2 generation. Male and female mating and fertility parameters were not affected by perchlorate; estrous cycling (before cohabitation) was also not altered by exposure to perchlorate. No significant effects were seen on number of dams delivering litters, duration of gestation, implantations, any litter parameter, lactation index, or sex ratios. In the F1 generation, there were no effects on mating and fertility or in sperm parameters; in F1 females, there were no effects on estrous cycling, fertility, sexual maturation, or in delivery and litter observations. The NOAEL for reproductive effects of perchlorate in this study was 25.5 mg/kg/day. Exposure of female rats to up to 25.5 mg perchlorate/kg/day beginning 2 weeks before cohabitation with untreated males and continuing during gestation did not result in any significant alterations in numbers of corpora lutea and implantations, percent implantation loss, litter size, early or late resorptions, or sex ratio (York et al. 2005a).

The NOAEL values for reproductive effects in these studies are shown in Table 3-2 and Figure 3-2.

3.2.2.6 Developmental Effects

Several developmental studies of perchlorate in humans have focused on the evaluation of neonatal thyroid parameters. Lamm and Doemland (1999) examined rates of congenital hypothyroidism in seven counties of Nevada and California with perchlorate contamination in the drinking water (4–16 μg/L [ppb]) (0.0001–0.0005 mg/kg/day). The investigators analyzed data from the neonatal screening programs of the two states for any increased incidence of congenital hypothyroidism in those counties. The rates for the California births were adjusted for Hispanic ethnicity, which was known to be a risk factor for congenital hypothyroidism. During 1996 and 1997, nearly 700,000 newborns were screened. The risk ratio in the seven counties was 1.0 (95% confidence interval [CI] 0.9–1.2) (249 cases observed/243 expected). The risk ratios for the individual counties relative to statewide expected rates ranged from 0.6 to 1.1. While the results showed no increase in rates of congenital hypothyroidism, it is known that congenital hypothyroidism is caused by developmental events that are not suspected of being affected by perchlorate exposure.

Kelsh et al. (2003) also found no relationship between congenital hypothyroidism and exposure to perchlorate through the drinking water in a study of newborns (n=15,348) whose mothers resided in the community of Redlands, California, during the period 1983 through 1997 and who were screened by the California Newborn Screening Program. Perchlorate was detected in the water system serving the community at a concentration of up to 9 μg/L (mean, <1 μg/L). Two adjacent communities with no detectable perchlorate in their water systems, San Bernardino and Riverside (n=695,967), served as comparison groups. The majority of the newborns had blood collected for TSH assay 18 hours or more after birth. Cases were defined as infants diagnosed with congenital hypothyroidism or whose TSH screening concentrations were >25 μU/mL or sometimes >16 μU/mL. Covariates included in the model were age at specimen collection, sex, race, ethnicity, birth weight, multiple birth status, and calendar year of birth. Analysis of the results showed an adjusted prevalence ratio for congenital hypothyroidism of 0.45 (95% CI, 0.06–1.64) and an odds ratio for elevated TSH of 1.24 (95% CI, 0.89–1.68) among all newborns screened and 0.69 (95% CI, 0.27–1.45) for newborns whose age at screening was ≥18 hours. Limitations of the study include the fact that data from a single year were used to characterize exposures over the entire 15 years of the study.

Li et al. (2000b) compared mean monthly neonatal T4 levels for days 1–4 of life for newborns from the city of Las Vegas and Reno, both in Nevada. Las Vegas has perchlorate in its drinking water, whereas Reno does not. The cohorts consisted of 17,308 newborns in Las Vegas and 5,882 newborns in Reno

evaluated during the period of April 1998 through June 1999; the analysis was restricted to newborns whose birth weights were between 2,500 and 4,000 grams. Perchlorate was detected in the drinking water from Las Vegas during 7 of the 15 months of the study period at levels of 9–15 μg/L (0.0003–0.0004 mg/kg/day). Analyses were performed comparing serum T4 levels of children born during the 7 months in which perchlorate was detected in the drinking water (period A) and children born during the months in which perchlorate was not detected in the drinking water (period B). The mean T4 levels were compared in a univariate analysis both crude and stratified by time period. In a multivariate analysis, T4 was the outcome variable, city and time period were the main effect variables, and gender, birth weight, and age and time of blood collection were the covariates. There was no significant difference in mean T4 level between Las Vegas and Reno in the crude analysis or when data were stratified by time period (period A or B). Gender, birth weight, and age and time of blood collection were significant covariates.

The same group of investigators also evaluated blood TSH levels in newborns in their first month of life from Las Vegas (n=4,070) and Reno (n=133) from December 1998 to October 1999 (Li et al. 2000a). TSH levels were measured on screening samples that were below the 10^{th} percentile of T4 daily measurements in blood samples collected throughout the state. The analysis was restricted to birth weights between 2,500 and 4,500 grams, adjusted for gender and age at screen (days 2–7 vs. 8–30). The mean TSH levels of the two cities did not differ significantly, whether crude or stratified by age or sex. Multiple linear regression analysis showed that the TSH level was significantly affected by age at which the sample was collected (higher at earlier age) and by sex (higher for males), but not by location. These findings suggested that neonatal TSH levels were not affected by living in areas where drinking water contained up to 15 μg/L of perchlorate (0.0004 mg/kg/day).

A similar study of newborn TSH levels was conducted by Brechner et al. (2000). TSH levels were compared between two cities in Arizona, Yuma and Flagstaff, representing areas of exposure and nonexposure, respectively. The study covered a 3-year period between October 1994 and December 1997. Exposure data for the study period were not available. However, measurements done by EPA in 1999 showed perchlorate at 6 μg/L (0.0002 mg/kg/day) in Yuma and nondetectable levels in Flagstaff. Since the water processing facilities had not changed, and perchlorate persists in water for a long time, Brechner et al. (2000) assumed that comparable differences in perchlorate levels existed during the study period. The final analysis comprised 1,099 newborns from Yuma and 443 from Flagstaff. The study controlled for age at screen and Hispanic ethnicity, but not for gender, gestational age, or birth weight. The median first TSH level in Yuma was significantly higher than in Flagstaff (19.9 mU/L vs.

13.4 mU/L); this difference occurred in both non-Hispanics and Hispanics. A residual confounding by age may have persisted in the analysis due to the higher percentage of newborns screened in the first 24 hours (when TSH levels peak) in Yuma (11%) compared with Flagstaff (3.1%). Lamm (2003) reanalyzed the study and compared TSH neonatal values of Yuma and two cities near Yuma, Somerton and San Luis, which get their water from a different source than the city of Yuma. The water from Somerton and San Luis is assumed to have no perchlorate contamination. Lamm's analysis showed no significant difference in TSH values between newborns from Yuma and Somerton/San Luis, suggesting that the results of Brechner et al. (2000) reflected regional differences, possibly related to the difference in altitude (7,000 feet) between Yuma and Flagstaff.

In an additional, unpublished, study of newborns, Schwartz (2001) evaluated T4 and TSH levels for all newborns in California during 1996. All infants were screened for serum T4 and TSH levels, and the samples with a low T4 (≤9 mg/dL and the next lowest 5% of the values in each tray of samples) were further analyzed for TSH levels. Information on the concentration of perchlorate in tap water was not available for this study. Therefore, perchlorate exposure was estimated using the mother's postal zip code, concentration of perchlorate in underground water sources measured between February 1997 and June 2000, water source production, water purchases and sales, and characteristics of the water distribution system. Ultimately, four categories of exposure were made: 0 (n=255,382), 1–2 μg/L (n=127,041), 3–12 μg/L (n=131,483), and ≥13 μg/L (n=1,945). Using default values for daily water consumption and for body weight, a concentration of 13 μg of perchlorate/L would provide doses of approximately 0.0004 mg perchlorate/kg/day. This study used an analysis of the covariance model. After controlling for age at screening, gender, single versus multiple birth, and ethnicity, a statistically significant declining trend for T4 was observed with increasing perchlorate exposure. Infants in the low, medium, and high exposure groups had 0.97, 1.12, and 1.82 μg/dL lower T4 levels, respectively, than unexposed infants. Log transformed TSH values showed a significant increase trend with perchlorate exposure (0.029, 0.03, and 0.128 ln μU/mL, in the low, medium, and high exposure groups, respectively). Although significant associations were found, Schwartz (2001) noted that 90% of the variability in the infants' hormone levels remained unexplained by perchlorate exposure, gender, multiple birth, birth weight, and blood sample age. Schwartz (2001) also noted that no adjustment was made in the study for gestational age and laboratory measurement variability, two strong predictors of T4 and TSH.

As previously mentioned, Crump et al. (2000) conducted a study of school-age children from three cities with different concentrations of perchlorate in drinking water in northern Chile. The city with the highest perchlorate concentration was Taltal, 100–120 μg perchlorate/L (ppb), water from the city of Chañaral

had 5–7 μg/L, and perchlorate was not detected in water from the city of Antofagasta. The study comprised 162 children 6–8 years of age, of which 127 had resided continuously in their respective city since conception. The children underwent examination of the thyroid gland and a blood sample was taken for analysis of TSH, T4, FTI, T3, and antiperoxidase antibody. After adjusting for sex, age, and urinary iodide excretion, the children from Taltal and Chañaral had slightly lower TSH levels than children from Antofagasta (opposite to expected), but the differences were not statistically significant. Serum T4 levels in the city with the highest perchlorate levels were significantly higher than in the city with no perchlorate (opposite to expected). Analysis of all of the children included in the study revealed a small nonsignificant increase risk of goiter in the cities with perchlorate compared with the city without perchlorate, however, there was virtually no difference in risk when only lifelong residents were analyzed. The study also found that lifelong residents of Taltal (high perchlorate) were >5 times more likely to report a family history of thyroid disease compared with lifelong residents of Antofagasta (no perchlorate). Assuming a reference daily consumption of water of 1–2 L and using a body weight for the children of approximately 25 kg (measured in the study), a concentration of perchlorate in the drinking water of 100 μg/L would provide doses of approximately 0.004–0.008 mg perchlorate/kg/day via drinking water alone, but the Chilean population also has large dietary sources of perchlorate.

Crump et al. (2000) also evaluated TSH levels in neonates from the three cities in northern Chile mentioned above. A total of 9,784 neonatal records were analyzed for TSH levels, sex, and date of screening for infants born between February 1996 and January 1999. The study did not control for iodine intake, ethnicity, or birth weight. The rate of congenital hypothyroidism detected in Chile from 1992 to 1999 was 1 per 3,484 cases (based on 773,440 newborns screened). In their study, Crump et al. (2000) detected seven cases of presumptive congenital hypothyroidism corresponding to a rate of 1 per 1,270 newborns. All of these cases originated in the city with no detectable levels of perchlorate. Linear regression comparisons of TSH by city showed a statistically significant decline in TSH with increasing perchlorate concentration in the drinking water, opposite to the known effect of perchlorate. The magnitude of the differences in TSH concentrations did not seem to be clinically significant.

In the Téllez et al. (2005) study of 184 pregnant women in northern Chile mentioned earlier, end points evaluated included neonatal weight, length, head circumference, gestational length, and FT4, T3, thyroglobulin, and perchlorate in cord serum. The evaluation showed no significant differences between the three cities regarding indicators of fetal development or in FT4 or TSH. T3 and thyroglobulin were significantly lower among neonates from Chañaral (low perchlorate, 5.8 μg/L) than in the other two cities.

T3 and thyroglobulin were not significantly different between newborns from Antofagasta (no perchlorate) and Taltal (high perchlorate, 114 μg/L).

A study conducted in Israel evaluated T4 levels (not specified whether TT4 or FT4) in newborns from mothers living in areas with very high (≤340 μg/L, n=97), high (42–94 μg/L, n=216), and low (<3 μg/L, n=843) levels of perchlorate (Amitai et al. 2007). Levels of perchlorate in blood from donors living in the three areas were used as proxy indicators of exposure. Respective blood perchlorate levels in the very high, high, and low exposure proxy groups were 5.99, 1.19, and 0.44 μg/L; these donors had similar blood levels of thiocyanate and nitrate. Blood samples from the newborns collected at the age of 36–48 hours did not reveal significant differences in T4 levels among the three groups. Mean T4 values in the very high, high, and low exposure groups were 13.9, 13.9, and 14.0 μg/L, respectively. In addition, neither birth weight nor gestational age was significantly different among the three groups. Although individual iodine measures were not conducted, the investigators stated that the study was conducted in iodine-sufficient areas.

Chang et al. (2003) evaluated the potential association between exposure to perchlorate via the drinking water and the incidence of attention-deficit-hyperactivity disorder (ADHD) and autism among children less than 18 years of age who were recipients of Medicaid in Nevada. The study included subjects from Clark County, which includes Las Vegas and in which the concentration of perchlorate in the public water supply ranged from undetected to 23.8 μg/L (mean, 10.9 μg/L), as measured in 1997–2001; subjects from Washoe County, which includes Reno, with no detectable perchlorate in the water supply served as an unexposed comparison group, and the remainder of Nevada served as a rural control. No perchlorate was detected in public water supplies from the rural areas. Analysis of the data from the Nevada Medicaid program showed that the rates for ADHD and for autism in the area with perchlorate in the drinking water did not exceed the rates in the areas without perchlorate in the drinking water. Furthermore, there was no difference between the three groups regarding overall fourth-grade school performance. No control was made in the analysis for age, sex, race, or ethnicity.

Studies in laboratory animals have shown that maternal exposure to relatively high doses of perchlorate during pregnancy and/or lactation leads to reduced thyroid function. Pups of rats exposed to 1% sodium perchlorate in the drinking water (about 1,300 mg perchlorate/kg/day) throughout gestation and lactation had reduced growth, increased thyroid weight, drastically decreased serum T4 and T3 levels, and markedly increased serum TSH levels compared with controls (Golstein et al. 1988). These effects are the typical indicators of hypothyroidism in juvenile and adult rats treated with perchlorate directly. In a

study in guinea pigs, near-term fetuses from dams treated with 1% potassium perchlorate (about 531 mg perchlorate/kg/day) in the drinking water during the latter half of gestation had thyroid hyperplasia and a dramatic 15-fold increase in relative thyroid weight compared with controls, while maternal thyroids were unaffected (Postel 1957). This suggests that perchlorate may have entered the fetal circulation and directly affected the fetal thyroid gland. Similar fetal effects were seen in rabbits dosed with 72 mg perchlorate/kg/day in the diet throughout gestation, but in this study, effects on the maternal thyroid, although considerably less intense than in the fetuses, were observed (Lampe et al. 1967). Rat pups exposed to perchlorate only for 10 days during lactation had body weights similar to controls, but significantly increased relative thyroid weights (Brown-Grant and Sherwood 1971). The dams in this study, which were pregnant with a new litter while nursing these pups, had received an approximate dose of 1,752 mg perchlorate/kg/day, and showed an increase in relative thyroid weight of similar magnitude to the pups.

Several developmental studies in animals have focused on the effects of perchlorate on the thyroid and also on neurodevelopmental effects following perinatal exposure to relatively low doses of perchlorate. Information on developmental effects of perchlorate is available in the 2-generation reproduction study in rats by York et al. (2001a) previously described in Section 3.2.2.5, Reproductive Effects. Perchlorate doses were 0, 0.26, 2.6, and 25.5 mg perchlorate/kg/day, and exposure started 10 weeks before mating and continued during pregnancy and lactation. The F1 generation was dosed from weaning (21 days old) to 19 weeks of age, but some pups were sacrificed on PND 21. The second generation (F2) was sacrificed at 3 weeks of age. F1 and F2 generations were exposed *in utero*, via maternal milk, and through maternal water. Exposure to perchlorate had no significant effect on pup weight. High-dose F1 pups killed on PND 21 showed a significant increase in thyroid weight (males and females) and in spleen weight (females). Significant hypertrophy and hyperplasia of the thyroid was seen in high-dose males and females and in mid-dose females. Also, there was a significant reduction in serum T3 in high-dose females, TSH was reduced in low- and mid-dose males, and serum T4 was increased in low-dose females. Thyroid weight from high-dose F2 female pups was significantly increased, and both male and female from the mid- and high-dose group exhibited hyperplasia and hypertrophy of the thyroid. TSH, T3, and T4 levels were not significantly altered in F2 pups, although T3 was somewhat lower in high-dose females. On the basis of morphological alterations in the thyroid observed in mid- and high-dose pups, the 0.26 mg/kg/day dose level is considered a developmental NOAEL. Parental (F0) effects were restricted to the thyroid and consisted mainly in hypertrophy and hyperplasia of the thyroid in the mid- and high-dose groups and significantly increased serum TSH levels in high-dose males.

A subsequent study in rats by York et al. (2003) examined the developmental effects of ammonium perchlorate in doses of 0, 0.009, 0.09, 0.85, and 25.5 mg perchlorate/kg/day. Dosing began 14 days premating and continued to gestation day (GD) 21, at which time, all rats were sacrificed. Satellite groups of rats were treated similarly and were used for collection of blood and thyroid tissues. The rats were observed for clinical signs, abortions, premature deliveries, and deaths. Body weights and food and water consumption were also monitored. At sacrifice, gravid uterine weights were recorded, and the uterus was examined for pregnancy, number and distribution of implantations, live and dead fetuses, and early and late resorptions. In addition, the number of corpora lutea in each ovary was recorded; the placenta was also examined. The fetuses were weighed and examined for gross alterations; one-half was examined for soft tissues alterations and the other half was examined for skeletal alterations and cartilage development. There were no maternal deaths and all clinical observations were considered unrelated to the test material. There were no significant effects on body weights, weight gains, and gravid uterine weights. There were no treatment-related effects on absolute or relative food or water consumption values. Cesarean sectioning and litter parameters were not affected by exposure to perchlorate. Evaluation of the fetuses showed that the average number of ossification sites per litter for sternal centers and for forelimb phalanges was significantly reduced in the 25.5 mg/kg/day exposure group. Examination of the satellite group of pups showed a statistically significant and dose-related decrease in T3 in all dosed groups. No developmental NOAEL is identified in this study and the 0.009 mg/kg/day dose level is a developmental LOAEL. T3 levels also were reduced in pooled serum samples from fetuses exposed through gestation and examined on GD 21 (York et al. 2005a). The lowest dose tested, 0.009 mg/kg/day, induced a 17% decrease in T3 relative to controls, whereas at the highest dose tested, 25.5 mg/kg/day, T3 was decreased by 33%. In this study, perchlorate also induced a dose-related increase in TSH (15% at 0.009 mg/kg/day) and decrease in T4 (16% at 0.009 mg/kg/day) in male pups sacrificed on PND 22.

An additional study was conducted in rats given ammonium perchlorate via the drinking water that provided doses of 0, 0.09, 0.9, 2.6, and 8.5 mg perchlorate/kg/day (York et al. 2004). Exposure began on GD 1 and continued for additional 10 days postpartum. Dams were sacrificed on PND 10 or 22 (12-day recovery period). Four subsets of pups were formed: subset 1 was sacrificed on PND 12 for neurohistological examination; subset 2 was used for neurobehavioral testing (avoidance testing on PND 23–32, water maze on PND 59–70) and sacrificed on PND 90–92, at which time blood was collected for TSH, T4, and T3 determinations; subset 3 was tested for motor activity on PND 14, 18, 22, and 59, and for auditory startle habituation on PND 23 and 60 and sacrificed on PND 67–69; and subset 4 was sacrificed on PND 80–86 and used for thyroid pathology and neurohistological examination and

morphology. In addition, on PND 5, litters were culled to eight pups, blood was collected for hormone analysis, and the thyroid was processed for histopathology.

Treatment with perchlorate caused no maternal toxicity as judged by clinical observations, body and thyroid weights, and thyroid histology. Perchlorate did not significantly affect gestation length, litter size, number of stillborn, gestation index, pup viability index, or pup's weight. In the pups, there were no significant changes in body weight, absolute and relative food consumption, or exposure to perchlorate did not affect the day of vaginal latency or the day of preputial separation. Microscopic examination of the thyroid from pups culled on PND 5 revealed changes restricted mainly to high-dose males consisting of hypertrophy/hyperplasia of the follicular epithelium and decrease in follicle size. TSH was elevated only in pups born to dams treated with 8.5 mg/kg/day, but T3 levels were significantly reduced at 0.9 mg/kg/day and higher doses. T4 was significantly reduced at 2.6 mg/kg/day and higher doses. In pups sacrificed on PND 12 (subset 1), a significant increase in thickness of the corpus callosum was seen in high-dose females; this also was observed in high-dose males but the difference with controls was not statistically significant. Evaluation of the next lower dose group (2.6 mg/kg/day) revealed a significant decrease in the hippocampal gyrus size in males, increase in the anterior to posterior cerebellum size and decrease in the caudate putamen in females, but no significant difference in the corpus callosum. Evaluations of subsets 2 and 3 revealed no behavioral effects in the offspring of dams exposed up to 8.5 mg perchlorate/kg/day (passive avoidance, swimming water maze, motor activity, and auditory startle). Also in subsets 2 and 3, there were no necropsy observations that seemed perchlorate-related, and terminal body weights and absolute and relative thyroid weights were comparable among the groups. In subset 4, there were no necropsy observations related to treatment, no significant effect on final body weight or thyroid weight, and no treatment-related neuropathological changes in the brain. However, morphometry evaluation of eight specific brain areas revealed a significant increase in mean thickness of the frontal cortex, caudate putamen, and corpus callosum from high-dose males. Based on the thyroid effects on pups culled on PND 5, the dose of 0.09 mg/kg/day can be considered a developmental NOAEL. The highest dose tested, 8.5 mg/kg/day is a maternal NOAEL. It should be mentioned that questions and concerns have been raised regarding the brain morphology findings. A more recent refinement of the study from the same group of investigators in which rats were exposed to perchlorate during gestation (0, 0.009, 0.09, 0.9, or 25.5 mg perchlorate/kg/day) and via maternal milk through lactation day 10 showed no treatment-related neuropathological alterations at sacrifice on PND 10 or 22 (York et al. 2005b). The most significant finding was an increased thickness of the corpus callosum in male pups in the 0.09 and 0.9 mg/kg/day dose groups, but not in the 25.5 mg/kg/day dose group. Differences in other brain structures were not statistically significant and/or were present in only one dose group (i.e., thickness of

the right and left frontal cortex, right and left parietal cortex, left striatum, and right hippocampal gyrus were increased only at 0.9 mg/kg/day). Issues that were raised by NAS (2005) include: "(1) apparent systematic differences in the plane of section among treatment groups, (2) lack of a clear and consistent dose-response relationship, (3) doubts about the biological plausibility of the changes that were observed, and (4) concerns that the measures that were used were relatively insensitive and would be unlikely to pick up subtle differences in neurodevelopment."

In a study of similar design, exposure began 2 weeks before mating and was terminated on PND 10 (Bekkedal et al. 2000, 2004). On PND 5, all of the pups were weighed and the litter culled to four males and four females. Tests of motor activity were conducted on one male and one female selected randomly on PND 14, 18, and 22. Nine measures of motor activity were monitored: frequency and time of ambulatory movements, frequency and time of stereotypic movements, frequency of movements in the horizontal plane, distance traveled in the horizontal plane, frequency of rears, total number of horizontal movements made while in rearing position, and time spent resting. Each measure of activity was recorded for 90 consecutive minutes on each test day. Data were divided into nine 10-minute blocks. The results showed that the main effect for perchlorate dose was not significant for any of the nine dependent variables, and there were no reliable interactions for treatment. The highest dose tested, 8.5 mg perchlorate/kg/day, is considered a NOAEL for neurodevelopmental effects in this study. Replication of this study by York et al. (2005b) showed that there were no significant alterations in test results due to consumption of perchlorate relative to controls. However, there was a pattern of response suggesting that exposed pups may have had a lower rate of habituation, and thus maintained a higher level of activity than untreated pups.

Because of EPA's concerns that the changes in motor activity in the rats in the two studies summarized above had biological significance, the results of both studies were re-analyzed (Dunson 2001). Each study was re-analyzed separately and combined using a Bayesian Hierarchical Modeling Approach. According to Dunson (2001), the re-analysis showed evidence of an increasing dose-response trend in motor activity in both studies, though the effect in the York et al. (2004) study was less pronounced. After reviewing the two studies in question and the re-analysis by Dunson, NAS (2005) concluded that: "general motor activity is not necessarily the most relevant or most sensitive aspect of motor function to assess if neonatal hypothyroidism is the suspected mechanism of action".

A cross-fostering study in rats was conducted by Mahle et al. (2003). Pregnant Sprague-Dawley rats were administered ammonium perchlorate in the drinking water at doses of 0 or 1 mg perchlorate/kg/day from

GD 2 to PND 21. Cross-fostering was done on PND 1 such that four groups of pups were formed: never exposed, exposed *in utero* and via maternal milk, exposed only *in utero*, and exposed only via maternal milk. Dams and pups were sacrificed on PND 10. There was no indication of maternal toxicity during the study. However, serum T4 was significantly decreased and TSH was significantly increased in exposed dams that nursed their own pups; TSH was also increased in dams that nursed unexposed pups. The two cross-fostered litters (exposed only *in utero* and exposed only via nursing) had significantly lower weight than control pups and than pups exposed both *in utero* and via milk. T3 was not significantly affected in any pup group (male or female). T4 was significantly reduced in female pups exposed only via milk and in females exposed *in utero* plus via milk; the decrease was more marked in the latter group. T4 was not significantly affected in male pups. TSH was increased significantly in male and female pups (more pronounced in females) from groups that received double exposure and in groups exposed only via milk; there was no significant difference between these two groups. The results suggest that: (1) exposure *in utero* to perchlorate at the dose tested had little or no impact on serum levels of thyroid hormone and TSH measured in pups on PND 10, (2) the changes in serum thyroid hormone and TSH levels seen in PND 10 pups exposed both *in utero* and via maternal milk appear to be completely due to postnatal exposure to perchlorate through lactation, and (3) perchlorate could be acting directly on the pups' thyroid and/or may be limiting the availability of iodide to nursing pups by inhibiting NIS in breast tissue.

The developmental effects of perchlorate were also examined in rabbits administered 0, 0.09, 0.85, 8.5, 25.5, or 85 mg perchlorate/kg/day in the drinking water on GD 6–28 (York et al. 2001b). Sacrifices were conducted on GD 29. There were no deaths attributed to treatment with the test material or chemical-related clinical signs, or effects on body weight or uterine weight. There were no compound-related effects on any of the litter parameters studied including litter averages for corpora lutea, implantations, litter sizes, live and dead fetuses, percent dead or resorbed fetuses, and fetal body weights. All placentae appeared normal. There were no treatment-related increases in gross alterations or in skeletal and soft tissue anomalies. This study defined a maternal NOAEL of 0.85 mg/kg/day (see Endocrine Effects section for summary of maternal effects) and a developmental NOAEL of 85 mg/kg/day.

Developmental NOAEL and LOAEL values from these studies are shown in Table 3-2 and Figure 3-2.

3.2.2.7 Cancer

Limited information was located regarding exposure to perchlorate and cancer in humans. In the ecologic study by Li et al. (2001) described earlier, the prevalence of thyroid cancer was not significantly higher among residents from Clark County (Las Vegas), whose drinking water had 4–24 µg/L of perchlorate (0.0001–0.0007 mg perchlorate/kg/day) than in residents from another urban area of similar size (Reno, Washoe County), but with no perchlorate in the water, or than those from all other counties, also with no perchlorate exposure.

Morgan and Cassady (2002) conducted an ecologic study among residents of 13 contiguous census tracts in Redlands, California, San Bernardino County. Residents had been exposed to various concentrations of trichloroethylene (TCE) and ammonium perchlorate. Testing for TCE began in 1980, whereas, testing for perchlorate began in 1997. The concentration of perchlorate in the wells in 2001 was reported to be in the range 5–98 ppb, with drinking water concentrations not exceeding 18 ppb. The concentration of TCE in the wells initially ranged from 0.09 to 97 ppb, but did not exceed 5 ppb in the drinking water since 1991 after the water underwent treatment or the highly contaminated wells were removed from service. The standardized incidence ratios (SIRs, observed/expected) for all cancers combined or for any specific cancer site was not significantly different than 1.00, except for colon and rectum (SIR, 0.86; 99% CI, 0.74–0.99) and lung and bronchus (SIR, 0.71; 99% CI, 0.61–0.81), which were lower than expected, and melanoma of the skin (SIR, 1.42; 99% CI, 1.13–1.77) and uterine cancer (SIR, 1.35; 99% CI, 1.06–1.70), which were higher than expected. The SIR for thyroid cancer was 1.0 (99% CI, 0.63–1.47) based on 40 observed cases. When the analysis was restricted to children, no cancers were observed more often than expected. NAS (2005) notes that limitations of the study include the fact that timing and duration of exposure to perchlorate is unclear, that there also was exposure to TCE, and that there was no adjustment for other potential confounding variables. NAS (2005) further notes that the expected numbers were derived from the four-county region as a whole, which included the exposed community, not from an unexposed area. The latter could have resulted in an underestimate of the SIR.

Potassium and sodium perchlorates have been shown to produce thyroid tumors (papillary and/or follicular adenomas and/or carcinomas) in rats and mice with long-term exposure (1–24 months) to 1–1.2% concentrations in the feed or drinking water (Fernandez-Rodriguez et al. 1991; Florencio Vicente 1990; Gauss 1972; Kessler and Kruskemper 1966; Pajer and Kalisnik 1991; Toro Guillen 1991). Estimated doses in these studies ranged from 928 to 2,573 mg perchlorate/kg/day. The cancer effect levels from these studies are shown in Table 3-2 and Figure 3-2. In a related study in rats, Fernández-

Santos et al. (2004) determined the incidence of Ki-ras oncogene mutations in follicular cell carcinomas of the thyroid induced by administration of radioactive iodine and potassium perchlorate (1% in drinking water) for up to 18 months. Direct sequencing showed no mutations in the amplified gene segment of any of the induced thyroid tumors. The results suggested that Ki-ras activation via mutations at codons 12 and 13 is neither a constant event nor an early event in the development of rat thyroid follicular cell carcinoma. An additional study found that low level exposure to potassium perchlorate (0.1% in the feed, corresponding to a dose of 64 mg perchlorate/kg/day) for 19 weeks promoted the development of thyroid tumors initiated by N-bis(2-hydroxypropyl)nitrosamine (Hiasa et al. 1987).

NAS (2005) noted that: "on the basis of the understanding of the biology of human and rodent thyroid tumors, it is unlikely that perchlorate poses a risk of thyroid cancer in humans". The EPA has concluded that perchlorate is not likely to pose a risk of thyroid cancer in humans, at least at doses below those necessary to alter thyroid hormone homeostasis, based on the hormonally-mediated mode of action in rodent studies and species differences in thyroid function (IRIS 2007).

3.2.3 Dermal Exposure

No studies were located regarding the following effects in humans or animals after dermal exposure to perchlorate:

3.2.3.1 Death
3.2.3.2 Systemic Effects
3.2.3.3 Immunological and Lymphoreticular Effects
3.2.3.4 Neurological Effects
3.2.3.5 Reproductive Effects
3.2.3.6 Developmental Effects
3.2.3.7 Cancer

3.3 GENOTOXICITY

No studies were located regarding genotoxic effects in humans after inhalation, oral, or dermal exposure to perchlorates. Limited information is available from studies in animals. Siglin et al. (2000) found no evidence of bone marrow erythrocyte micronucleus formation in male and female rats as a result of exposure to 8.5 mg perchlorate/kg/day as ammonium perchlorate in the drinking water for 90 days. Zeiger et al. (1998b) also reported no increase in micronucleus formation in bone marrow from mice

injected intraperitoneally with 500 mg of ammonium perchlorate/kg/day for 3 consecutive days; higher doses were lethal to the mice. Cyclophosphamide was used as positive control in both studies.

Magnesium perchlorate was negative in a test for SOS-inducing activity in *Salmonella typhimurium* strain 1535 (Nakamura and Kosaka 1989) and in a test for production of deoxyribonucleic acid (DNA)-protein cross links in cultured human lymphocytes (Costa et al. 1996). Zeiger et al. (1998a) found no evidence of mutagenicity for ammonium perchlorate with or without metabolic activation in six different *Salmonella* strains. Ammonium perchlorate was not mutagenic in the mouse lymphoma assay with or without metabolic activation (San and Clarke 1999).

The available data suggest that perchlorate is not a mutagenic or clastogenic agent.

3.4 TOXICOKINETICS

Overview. Short-term studies on humans and animals demonstrate that perchlorate appears to be readily absorbed by the digestive system after oral exposure. Maximum blood levels appear within a few hours after ingestion. Perchlorate is rapidly taken up into the thyroid gland, by an active transport mechanism, and reaches a maximum level in the thyroid in approximately 4 hours in rats. Elimination of perchlorate from the thyroid is also rapid; half-lives of 10–20 hours have been estimated in rats. Perchlorate does not appear to be modified in the body, either by degradation or covalent binding. Perchlorate is rapidly eliminated from the body in the urine with half-lives of approximately 8–12 hours in humans and 10–20 hours in rats. No studies on the kinetics of long-term administration of perchlorate in humans or animals have been reported.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No studies were found regarding quantitative absorption of perchlorate after inhalation exposure. Occupational studies have measured urinary perchlorate in workers, suggesting that pulmonary absorption may occur (Lamm et al. 1999), although swallowing of particles may have also occurred. Under normal ambient temperatures, the vapor pressure of a perchlorate salt solution is expected to be low, which would reduce the likelihood of exposure to perchlorate fumes or vapors from that source. However, if perchlorate particles were suspended in air, absorption by inhalation would be possible, depending on the particle size. It is also possible that a portion of perchlorate particles suspended in the air could be

swallowed and absorbed orally. Given the aqueous solubility of perchlorate salts, it is likely that small particles reaching the alveoli would dissolve and readily enter the systemic circulation.

3.4.1.2 Oral Exposure

Perchlorate has been shown, in both human and animal studies, to be readily absorbed after oral exposure. In human subjects who ingested 10 mg/day perchlorate as potassium perchlorate in drinking water for 14 days (0.14 mg/kg/day), urinary excretion rate of perchlorate was 77% of the dose/day, after 7 days of exposure, indicating that at least 77% of the ingested dosage had been absorbed (Lawrence et al. 2000). Evidence for rapid absorption in humans is provided by studies of elimination patterns. Anbar et al. (1959) detected potassium perchlorate in urine samples collected from four subjects 3 hours after ingestion of 200 mg perchlorate. Durand (1938) gave sodium perchlorate in a single oral dose (784 mg perchlorate per person) to two individuals and found perchlorate in the urine as early as 10 minutes after ingestion. Approximately 30% of the ingested dose had been eliminated in the urine within 3 hours after the dose, and 95% was eliminated within 48 hours. In a study of 13 subjects given 0.5 or 3 mg perchlorate/day for 6 months, serum perchlorate increased from undetected at baseline to an average of 24.5 µg/L in the low-dose group and 77.9 µg/L in the high-dose group over the 6 months (Braverman et al. 2006). The investigators estimated that approximately 65–70% of the daily dose was excreted during a 24-hour period. These results suggest rapid and near complete absorption of perchlorate through the digestive system.

Selivanova et al. (1986) examined the absorption of ammonium perchlorate in rats, rabbits, and calves after a single oral dose (2, 20, 200, or 600 mg perchlorate/kg). In rats, a maximum concentration of perchlorate in blood was noted between 30 and 60 minutes after administration (suggesting entrance into the systemic circulation before 30 minutes); in cattle, the maximum blood concentration of perchlorate occurred at 5 hours. In this study, only 8.5% of the administered dose was excreted in feces, and the rest was excreted in the urine, suggesting that >90% of the administered oral dose was absorbed.

3.4.1.3 Dermal Exposure

No studies were found regarding absorption of perchlorate after dermal exposure. As a general rule, electrolytes applied from aqueous solutions do not readily penetrate the skin (Scheuplein and Bronaugh 1983). On this basis, dermal absorption of perchlorate is expected to be low.

3.4.2 Distribution

Perchlorate binds to bovine and human serum albumin (Carr 1952; Scatchard and Black 1949). Perchlorate binds only weakly to either of the two binding sites of transferrin (association constants 7 and 35 M) (Harris et al. 1998).

Studies conducted in rabbits and rats indicate that perchlorate concentrations in most soft tissues (e.g., kidney, liver, skeletal muscle) are similar to the serum concentrations; tissue:serum concentration ratios >1 have been found in thyroid (5–10) and skin (1–2) (Durand 1938; Yu et al. 2002). Accumulation of perchlorate in the thyroid occurs by a saturable, active transport process (see Section 3.5.1). As a result, thyroid serum concentrations and the amount of perchlorate in the thyroid as a fraction of the absorbed dose decrease with increasing dose (Chow and Woodbury 1970). Elimination of perchlorate from the thyroid gland is relatively rapid, with half-times in rats estimated to be approximately 10–20 hours (Fisher et al. 2000; Goldman and Stanbury 1973; Yu et al. 2002).

Studies conducted in rats administered intravenous injections of perchlorate indicate that perchlorate is secreted into the gastric lumen (Yu et al. 2002). Perchlorate secreted into the gastric lumen may be absorbed in the small intestine.

3.4.2.1 Inhalation Exposure

No studies were found in humans or in animals regarding distribution of perchlorate after inhalation exposure.

3.4.2.2 Oral Exposure

In a survey of 36 healthy lactating volunteers, perchlorate was detected in breast milk at a mean concentration of 10.5 µg/L (range, 0.6–92. µg/L) (Kirk et al. 2005). Exposure of the lactating women was presumed to have occurred mainly from perchlorate in food and drinking water. No correlation was apparent between the concentration of perchlorate in the breast milk and the water that the respective mothers consumed. Serial collection of breast milk from 10 lactating women over a 3-day period revealed that the concentrations of perchlorate, iodide, and thiocyanate varied significantly over time (Kirk et al. 2007). For perchlorate, the range, mean and median in 147 samples were 0.5–39.5, 5.8, and 4.0 µg/L, respectively. A study of women from three different cities in Chile also detected perchlorate in breast milk at mean concentrations ranging from 17.7 to 95.6 µg/L (Téllez et al. 2005). This study also

found no significant correlations between breast milk perchlorate and either urine perchlorate or breast milk iodine concentrations. A study of 57 lactating women in Boston reported a median concentration of perchlorate in milk of 9.1 µg/L (range 1.3–411 µg/L) (Pearce et al. 2007).

Perchlorate also has been detected in dairy milk. A survey of 12 U.S. states showed a mean milk perchlorate level of 5.81 µg/L in 125 samples (FDA 2007a, 2007b), which was lower than a reported mean of 9.39 µg/L for Japanese samples (Dyke et al. 2007). The recent Total Diet Study (TDS) study conducted by the FDA reported a mean concentration of perchlorate of 7 µg/L in eight samples of milk (Murray et al. 2008).

Studies conducted in rabbits and rats indicate that perchlorate concentrations in most soft tissues (e.g., kidney, liver, skeletal muscle) are similar to the serum concentrations; tissue:serum concentration ratios >1 have been found in thyroid (5–10) and skin (1–2) (Durand 1938; Yu et al. 2002). Accumulation of perchlorate in the thyroid occurs by a saturable, active transport process (see Section 3.5.1).

Perchlorate has been shown to cross the placenta of rats. In rats exposed to perchlorate in drinking water, fetal:maternal serum concentration ratios were approximately 1 when the maternal dosage was 1 mg/kg/day or lower, and were <1 when the maternal dosage was 10 mg/kg/day, suggesting the possibility of a dose-dependent limitation in the capacity of transplacental transfer (Clewell et al. 2003a).

3.4.2.3 Dermal Exposure

No studies were found regarding distribution of perchlorate after dermal exposure.

3.4.2.4 Other Routes of Exposure

Several studies have examined the distribution of perchlorate in animals after intravenous, intramuscular, or peritoneal injection (Anbar et al. 1959; Chow and Woodbury 1970; Chow et al. 1969; Durand 1938; Goldman and Stanbury 1973; Yu et al. 2002). These studies have shown that absorbed perchlorate, regardless of the route of exposure, will distribute to soft tissues, including adrenal, brain, kidney, liver, mammary gland, skeletal muscle, spleen, testes, and thyroid. The highest concentrations occur in the thyroid, where tissue:serum concentration ratios of 5–10 have been observed (Chow and Woodbury 1970). The elimination half-time for the thyroid was estimated in rats to be approximately 10–20 hours (Fisher et al. 2000; Goldman and Stanbury 1973; Yu et al. 2002).

Other tissues that appear to concentrate perchlorate are the salivary gland and skin, although not to the same degree as the thyroid (Anbar et al. 1959; Lazarus et al. 1974; Yu et al. 2002). Tissue:blood concentration ratios of 1.5–2 have been observed for the salivary gland (Anbar et al. 1959) and 1–2 for the skin (Yu et al. 2002).

3.4.3 Metabolism

There is no evidence that perchlorate is metabolized in the body. Anbar et al. (1959) assayed for potential metabolites of potassium perchlorate (radiolabeled with ^{36}Cl and $^{18}O_4$) in the urine of patients 3 hours after a single oral dose (200 mg perchlorate per person). They did not detect any isotopic exchange of the oxygen atoms in excreted perchlorate; furthermore, although they found that 1–3% of the excreted ^{36}Cl was chloride ion, this value was within experimental error. They concluded that the perchlorate excreted after 3 hours was unmodified. There has been no investigation as to whether perchlorate that is eliminated at later time points would exhibit the same isotopic pattern.

Goldman and Stanbury (1973) found that perchlorate reached a maximum concentration (>3% of the administered dose/g tissue) in the thyroid gland of rats 4 hours after an intraperitoneal injection of radiolabeled potassium perchlorate ($K\ ^{36}ClO_4$; 18 or 24 mg perchlorate/kg). However, trichloroacetic acid precipitates of thyroid homogenates contained only background levels of radioactivity, indicating that perchlorate is not covalently bound to thyroid protein.

3.4.4 Elimination and Excretion

The few studies of the elimination and excretion of perchlorate, described in the sections that follow, suggest that it is rapidly eliminated from the body through the urinary tract. Similar results have been obtained after oral exposure or after intravenous or intraperitoneal injection; the specific cation appears not to influence the pattern of excretion.

3.4.4.1 Inhalation Exposure

A study in two workers occupationally exposed to perchlorate found that the urinary perchlorate concentration increased over 3 days of perchlorate exposure, but there was a decrease between the 12-hour work shifts (Lamm et al. 1999). Excretion after the last exposure appeared to follow a first-order kinetics pattern, particularly when the urinary perchlorate concentration was between 0.1 and 10 mg/L.

The average elimination half-life for the two workers was approximately 8 hours. No information was located regarding excretion of perchlorate in animals following inhalation exposure.

3.4.4.2 Oral Exposure

In adult human subjects who ingested potassium perchlorate in drinking water (0.14 mg/kg/day) for 14 days, urinary excretion rate of perchlorate was 77% of the dose/day after 7 days of exposure, indicating that urine is the main excretory pathway for absorbed perchlorate (Lawrence et al. 2000). The urinary excretion rate of perchlorate returned to control levels (<0.5 mg/day) within 14 days after exposure to perchlorate was terminated (Lawrence et al. 2000). Perchlorate was detected in the urine of two adults at 10 minutes after a single oral dose of sodium perchlorate (784 mg perchlorate per person); urinary excretion as a percentage of the dose was 30% at 3 hours, 50% in at 5 hours, 85% at 24 hours, and 95% at 48 hours (Durand 1938). This suggests an excretion half-time of approximately 12 hours. The latter estimate is consistent with the elimination kinetics of perchlorate from serum. The elimination half-time for perchlorate in serum was estimated to be approximately 8 hours in adult human subjects who ingested potassium perchlorate in drinking water (0.5 mg/kg/day) for 14 days (Greer et al. 2002). In another study in adult humans, it was estimated that approximately 65–70% of a daily dose of 0.5–3 mg perchlorate/day was excreted over a 24-hour period (Braverman et al. 2006). Thus, in humans, perchlorate is rapidly eliminated and would not be expected to accumulate in the body with prolonged exposure. Based on an elimination half-time of approximately 8–12 hours, a steady state would be achieved within 3–4 days of continuous exposure. The detection of perchlorate in breast milk from lactating women (Kirk et al. 2005; Pearce et al. 2007; Téllez et al. 2005) also indicates breast milk as an excretion route in humans.

Studies conducted in a variety of experimental animals, including rats, rabbits, and calves, have shown that absorbed perchlorate is rapidly and nearly completely excreted in the urine (Fisher et al. 2000; Selivanova et al. 1986; Yu et al. 2002).

Studies conducted in rats have shown that perchlorate is excreted in mammary milk (Clewell et al. 2003b). Perchlorate has also been detected in dairy milk (Howard et al. 1996; Kirk et al. 2005).

3.4.4.3 Dermal Exposure

No studies were found regarding elimination or excretion of perchlorates after dermal exposure.

3.4.4.4 Other Routes of Exposure

Studies in which rats received intravenous or intraperitoneal injections of perchlorate provide additional support for the rapid excretion of perchlorate in urine. Rats that received a single intravenous injection of 0.01, 0.1, 1.0, or 3.0 mg/kg perchlorate (as ammonium perchlorate) excreted 85, 86, 80, or 79% of the administered dose, respectively, in urine (Fisher et al. 2000). The elimination half-time for intravenously injected perchlorate (approximately 0.04 mg, 0.18–0.25 mg/kg, as potassium perchlorate) from serum, and the urinary excretion half-time were estimated in rats to be approximately 20 hours (Goldman and Stanbury 1973). Similarly, rats injected with sodium perchlorate (2, 8, or 49 mg perchlorate/kg) excreted 50% of the administered dose in urine during the first 6 hours and had excreted 93–97% of the dose by 60 hours (Eichler and Hackenthal 1962); in this study, higher doses of perchlorate were eliminated at a faster rate than lower doses. Similar results were obtained in rats that received a single intravenous dose of 3.3 mg/kg perchlorate as ammonium perchlorate; urinary excretion of perchlorate was essentially complete within 12 hours (Yu et al. 2002). Possible contributors to the relatively longer elimination half-life of perchlorate in rats than in humans include differences in serum protein binding or perhaps the NIS protein in the gastrointestinal tract may sequester perchlorate temporarily to a greater degree in the rat than human.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of

PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

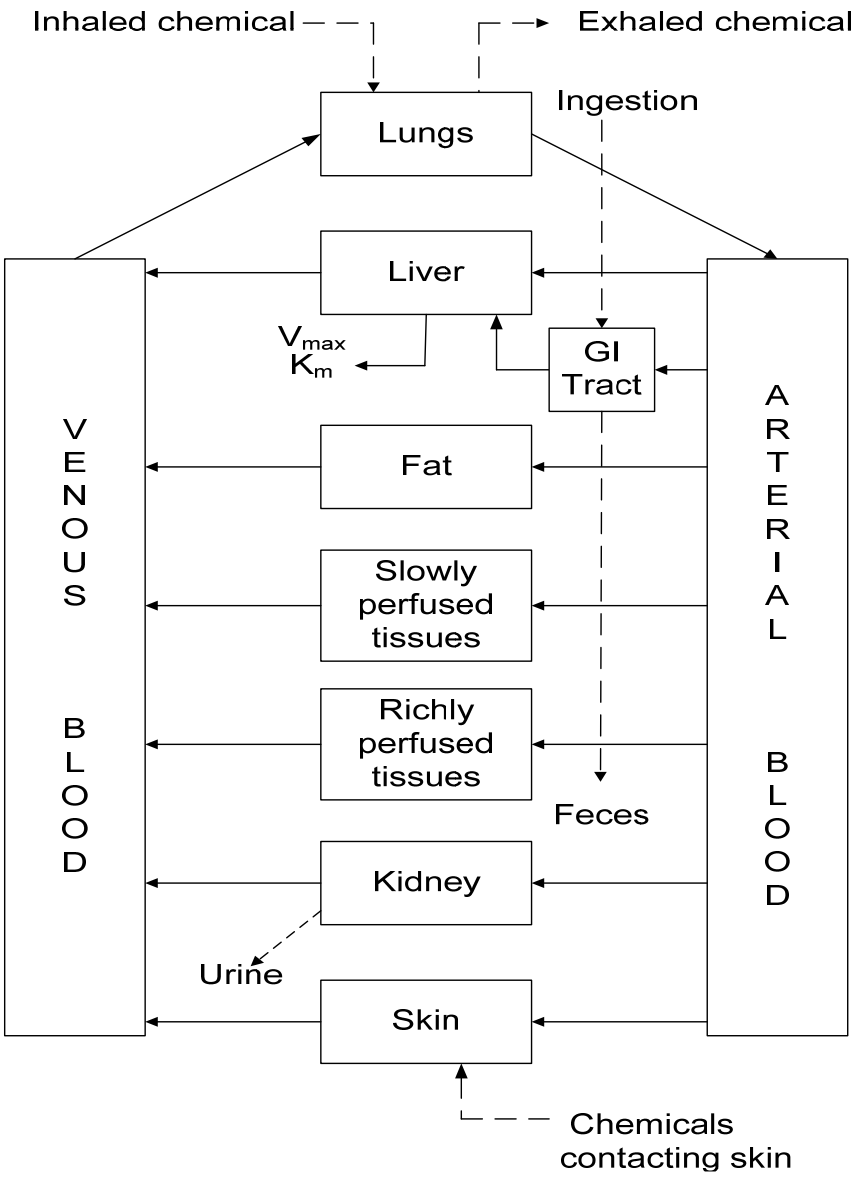
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

If PBPK models for perchlorates exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in urine, feces, or by exhalation.

Source: adapted from Krishnan and Andersen 1994

Perchlorate PBPK Models

Description of the models. PBPK models of the kinetics of ingested or injected perchlorate in rats and humans have been developed (Fisher et al. 2000; Merrill et al. 2003, 2005). The models were developed simultaneously with models of radioiodide biokinetics. When combined, the perchlorate and radioiodide models simulate the competitive inhibition of radioiodide transport by perchlorate in thyroid and other tissues that have NIS activity. The adult rat model was extended to include pregnancy and maternal-fetal transfer of perchlorate, and lactation and maternal-pup perchlorate transfer through milk (Clewell et al. 2003a, 2003b). Corresponding human models of pregnancy, maternal-fetal transfer, and maternal-infant transfer of perchlorate were developed (Clewell et al. 2007).

The adult rat and human models have the same structure and differ only in values for physiological and some of perchlorate parameters (Table 3-3, Figure 3-4). Both models simulate nine tissue compartments: blood, kidney, liver, skin, stomach, thyroid, fat, other slowly perfused tissues, and other richly perfused tissues. Uptakes from blood into the tissue vascular compartments are simulated as flow-limited processes. Distributions within blood, skin, stomach, and thyroid are simulated as diffusion limited processes with first-order clearance terms. Excretion is described with a first-order clearance term for transfer of perchlorate from the kidney into urine. Uptake of perchlorate into tissues that have NIS activity are simulated using a Michaelis-Menten approach with tissue- and species-specific maximum velocities and affinity constants that are conserved across tissues and species. This includes uptake of perchlorate into thyroid follicle cells. Secretion of perchlorate into the follicle lumen, thought to be mediated by the pendrin anion transporter, is simulated using a Michaelis-Menten approach. Upregulation of NIS (i.e., induction in response to TSH) is simulated by fitting increased maximum velocities of perchlorate and radioiodide transport into the thyroid gland. The model does not explicitly include TSH-dependence of NIS levels or other aspects of the metabolism of iodide within the thyroid (e.g., hormone production and secretion), and does not simulate changes in TSH levels resulting from NIS inhibition. Active transport of perchlorate into the stomach lumen and in skin is also simulated in the models.

Extensions of the adult models to simulate perchlorate (and radioiodide) kinetics during pregnancy in rats and humans include the addition of two additional compartments representing the mammary gland and placenta (Clewell et al. 2003a, 2003b, 2007). The structure of the human pregnancy and lactation models for perchlorate (which are identical to the corresponding rat models) are shown in Figure 3-5. Parameter

Table 3-3. Perchlorate and Radioiodide Parameter Values for the Adult Male Rat and Human PBPK Models

Parameter	Male rat		Human	
	Perchlorate	Radioiodide	Perchlorate	Radioiodide
Partition coefficients (unitless)				
Slowly perfused/plasma	0.31	0.21	0.31	0.21
Richly perfused/plasma	0.56	0.40	0.56	0.40
Fat/plasma	0.05	0.05	0.05	0.05
Kidney/plasma	0.99	1.00	0.99	1.09
Liver/plasma	0.56	0.44	0.56	0.44
Gastric tissue/gastric blood	0.70	1.0	1.80	0.50
Gastric juice/gastric tissue	1.70	3.50	2.30	3.50
Skin tissue/skin blood	1.0	0.70	1.15	0.70
Thyroid follicle/thyroid stroma	0.15	0.15	0.13	0.15
Thyroid lumen/thyroid follicle	8.00	8.00	7.00	7.00
Red blood cells/plasma	0.73	1.00	0.80	1.00
Max capacity (ng/hour/kg)				
Thyroid follicle	1.0×10^{3}	5.4×10^{4}	5.0×10^{5}	$\sim 1.5 \times 10^{5} \pm 8.2 \times 10^{4}$
Thyroid lumen	2.0×10^{4}	4.0×10^{6}	2.5×10^{4}	7.0×10^{7}
Skin	5.0×10^{5}	5.0×10^{5}	1.0×10^{6}	6.0×10^{5}
Gastric	2.0×10^{4}	2.0×10^{6}	1.0×10^{5}	9.0×10^{5}
Plasma binding	3.4×10^{3}	1.0×10^{2}	5.0×10^{2}	2.0×10^{2}
Affinity constants (ng/L)				
Thyroid lumen	1.0×10^{8}	1.0×10^{9}	1.0×10^{8}	1.0×10^{9}
Thyroid follicle	1.8×10^{5}	4.0×10^{6}	1.6×10^{5}	4.0×10^{6}
Skin	1.8×10^{5}	4.0×10^{6}	2.0×10^{5}	4.0×10^{6}
Gastric	1.7×10^{5}	4.0×10^{6}	2.0×10^{5}	4.0×10^{6}
Plasma binding	1.1×10^{4}	NA	1.8×10^{4}	7.8×10^{5}
Permeability area cross products (L/hour/kg)				
Gastric blood to gastric tissue	1.00	1.00	0.6	0.2
Gastric tissue to gastric juice	0.80	0.10	0.8	2.0
Skin blood to skin tissue	0.80	0.10	1.0	0.01
Plasma to red blood cells	1.00	1.00	1.0	1.0
Thyroid follicle to thyroid stroma	6.0×10^{-5}	1.0×10^{-4}	1.0×10^{-4}	6.0×10^{-4}
Thyroid lumen to thyroid follicle	0.01	4.0×10^{-7}	0.01	1.0×10^{-4}

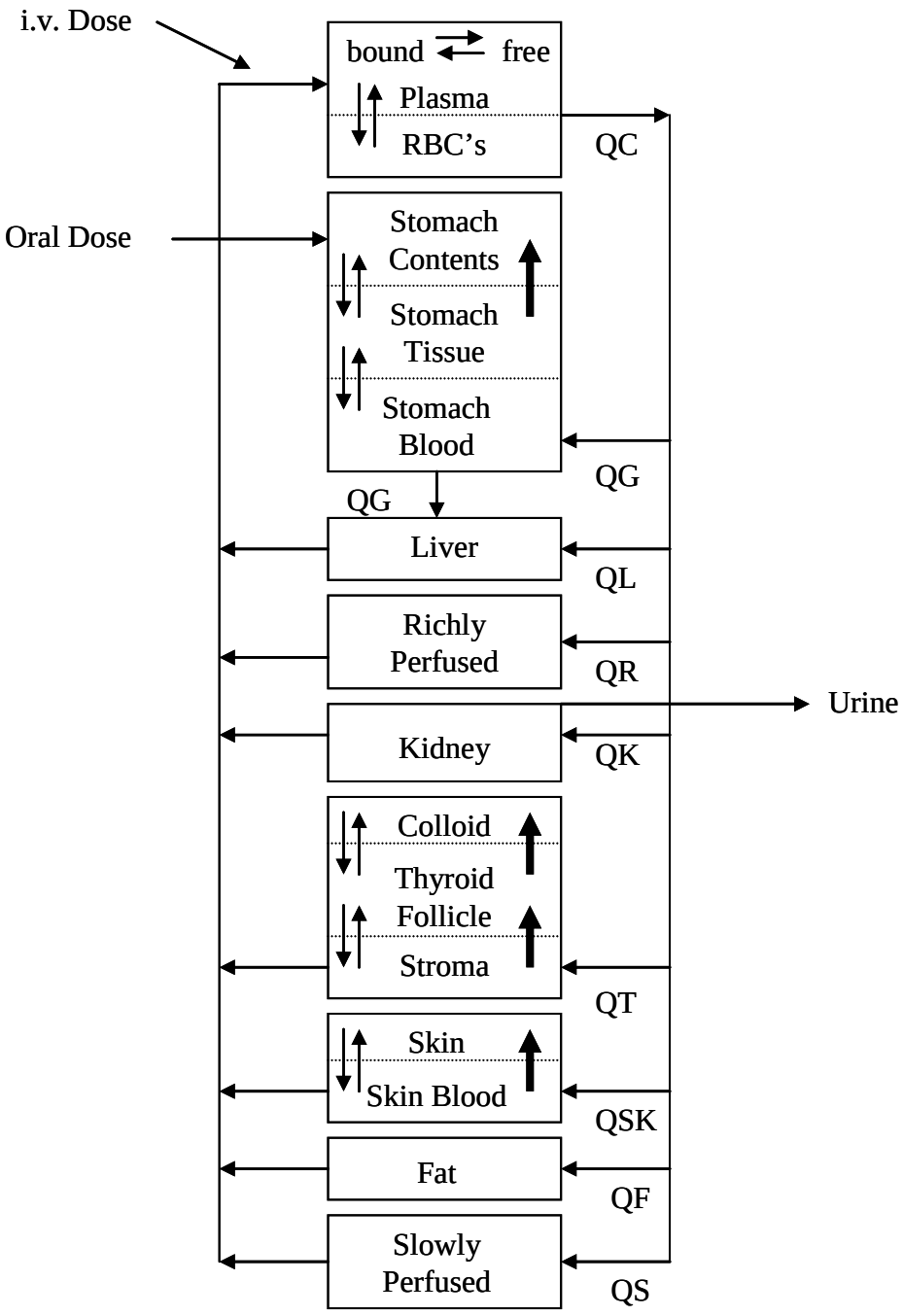
Table 3-3. Perchlorate and Radioiodide Parameter Values for the Adult Male Rat and Human PBPK Models

Parameter	Male rat		Human	
	Perchlorate	Radioiodide	Perchlorate	Radioiodide
Clearance values (L/hour/kg)				
Urinary excretion	0.07	0.05	0.13±0.05	0.11
Plasma unbinding	0.032	NA	0.025	No data
Hormone production	NA	0.10	NA	0.01
Hormone secretion	NA	$1.2x10^{-6}$	NA	$1.2x10^{-6}$
Hormone deiodination	NA	NA	NA	$9.0x10^{-4}$

NA = not applicable; PBPK = physiologically based pharmacokinetic

Sources: Merrill et al. 2003, 2005

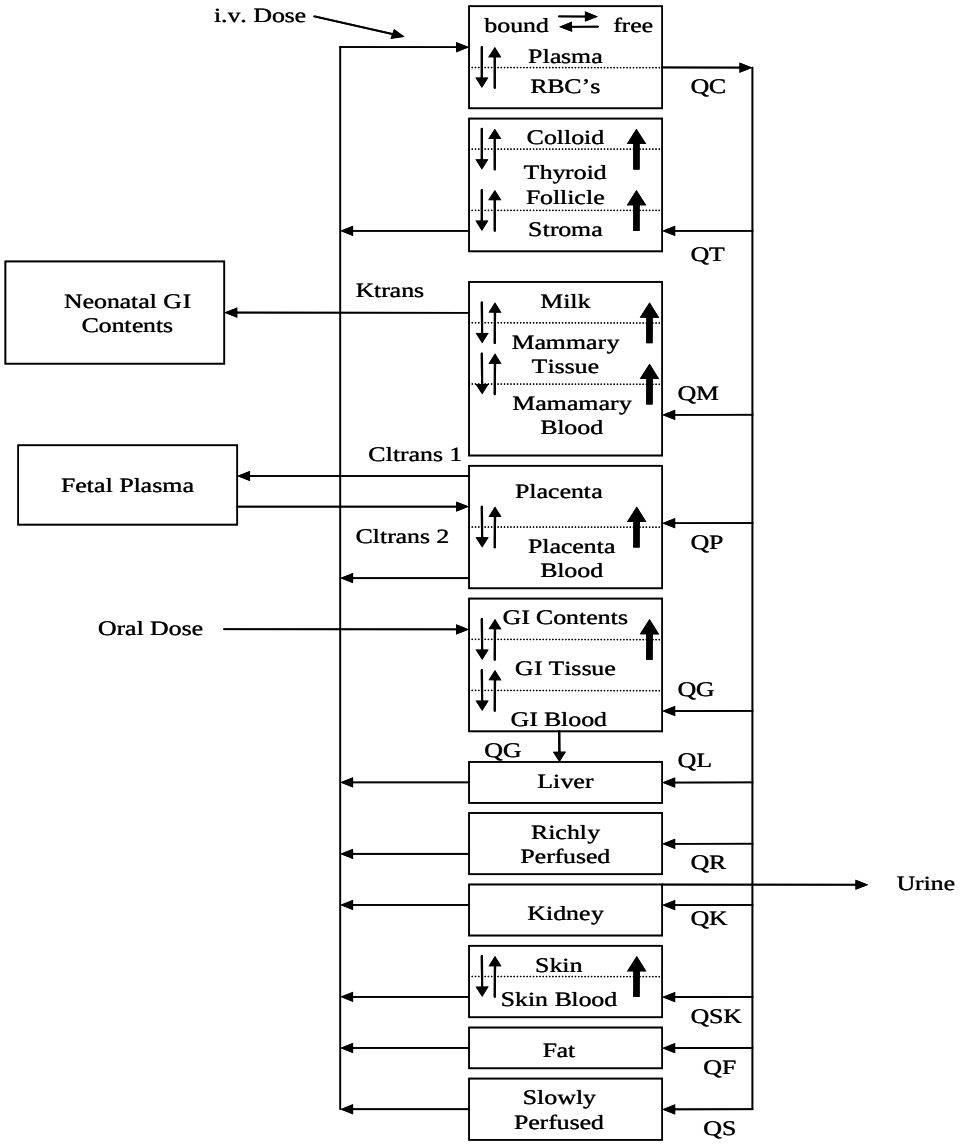
Figure 3-4. Structure of PBPK Model of Perchlorate in Typical Adult Humans and Male Rats*



*Bold arrows within tissue compartments indicate active transport (i.e., Michaelis-Menten), thin arrows represent first-order rate transfers, and double arrows represent passive diffusion. Q indicates blood flow.

PBPK = physiologically based pharmacokinetic

Figure 3-5. Structure of PBPK Models of Perchlorate in the Pregnant and Lactating Woman



Differences between fetal, neonatal, and adult models are described in the text. Bold arrows within tissue compartments indicate active transport (i.e., Michaelis-Menten), thin arrows represent first-order rate transfers, and double arrows represent passive diffusion. Q indicates blood flow. A PBPK model for radioiodide has the same structure with addition of radioiodide incorporation into thyroid hormones within the thyroid and subsequent secretion into the plasma and further estimate for whole-body deiodination (release of iodide from thyroid hormones). Parameter values for the perchlorate and radioiodide models are presented in Tables 3-4 and 3-5.

Source: Clewell et al. 2007

values for the perchlorate and radioiodide human models are presented in Tables 3-4 and 3-5, respectively. Corresponding rat model parameter values are presented in Tables 3-6 and 3-7.

Uptake of perchlorate into the mammary gland tissue from the mammary tissue vascular space is simulated as a capacity-limited transport process, representing the activities of NIS and pendrin in this tissue. Uptake of perchlorate into the placenta from blood into placental blood is simulated as a diffusion-limited process with capacity-limited transport from placenta blood to placental tissue via NIS. Exchanges of perchlorate between the placenta and fetus are simulated with first-order clearance terms. The fetal model is identical in structure to the adult (nonpregnant) model, with adjustments in the physiological and perchlorate parameters to reflect the fetus, and the following exceptions: (1) fetal exposure is described as a first-order transfer from the placenta to the serum of the fetus; (2) clearance in the fetus is described as first-order loss from the fetal serum to the placenta; and (3) binding of iodine is not represented in the fetal thyroid and plasma.

The lactating rat and human models include a milk compartment in mammary tissue and a first-order clearance term for describing secretion of perchlorate from mammary tissue into milk (Clewell et al. 2003b, 2007). Transfer of perchlorate from milk to the neonate is simulated as a first-order clearance process. The neonate model is identical in structure to the adult (nonpregnant) model, with adjustments to the physiological and perchlorate parameter values to reflect the neonate (Clewell et al. 2003a). Parameter values for perchlorate and radioiodide in children were allometrically scaled from adult values.

Validation of the models. The rat adult perchlorate model has been evaluated for predicting kidney, serum, gastric lumen, tissue (including thyroid), and urine perchlorate concentrations in adult rats that received acute intravenous injection of radiolabeled perchlorate ($^{36}ClO_4^-$), (Merrill et al. 2003; Yu et al. 2002). In general, model predictions were within 1–2 standard deviations of observed values. When the same parameter values were used to predict perchlorate concentrations in the thyroid in rats that were exposed to repeated doses of perchlorate in drinking water for 14 days, the model predicted lower levels of perchlorate in thyroid than were observed for dosages ≥3 mg/kg/day. At doses of perchlorate >1 mg/kg/day, only slight inhibition of thyroid radioiodide uptake was observed (Yu et al. 2002); presumably, a result of upregulation of NIS by TSH, whereas the model predicted greater inhibition. However, good correspondence with observations was achieved by adjusting the parameters for maximum velocity of transport of perchlorate and radioiodide into the thyroid gland. This adjustment mimics induction of NIS that occurs in response to elevations in serum TSH, which was observed in the rats exposed to perchlorate in drinking water (Uyttersprot et al. 1997; Yu et al. 2002). TSH stimulates

Table 3-4. Perchlorate Chemical-specific Parameters for Human Gestation and Lactation Models

Parameters	Gestation		Lactation	
	Woman	Fetus	Woman	Neonate
Gastric tissue/gastric blood *PG*	1.29[a]	1.79[a]	4.6[a]	8.25[a]
Gastric juice/gastric tissue *PGJ*	1.76[a]	2.3[a]	3.1[a]	7.63[a]
Skin tissue/skin blood *PSk*	1.32[a]	1.32[a]	1.32[a]	1.32[a]
Mammary tissue/mammary blood *PM*	0.66[b]	NA	0.66[b]	NA
Mammary/milk *PMk*	NA	NA	2.39[b]	NA
Placenta/placental blood	0.56[b]	NA	NA	NA
Maximum capacity (ng/hour/kg)				
Thyroid follicle *VmaxcTF*	$6.0x10^{3}$[a]	0–$2x10^{5}$[e]	$9.0x10^{3}$[a]	0.6–$2.4x10^{5}$[e]/$6x10^{3}$[c]
Thyroid colloid (luman)*VmaxcTL*	$1.7x10^{4}$[a]	$1.7x10^{4}$[a]	$8.4x10^{3}$[a]	$1.7x10^{4}$[a]
Skin *VmaxcS*	$1.2x10^{6}$[a]	$8.0x10^{5}$[a]	$1.6x10^{6}$[a]	$1.6x10^{6}$[a]
Gastrointestinal *VmaxcG*	$3.2x10^{7}$[a]	$4.0x10^{6}$[a]	$5.0x10^{6}$[a]	$5.0x10^{6}$[a]
Mammary *VmaxcM*	$2.2x10^{4}$[b]	NA	$2.0x10^{4}$[b]	NA
Milk *VmaxcMk*	NA	NA	$2.0x10^{4}$[b]	NA
Placenta *VmaxcP*	$6.0x10^{4}$[b]	NA	NA	NA
Affinity constants (ng/L)				
Mammary *KmM*	$2.0x10^{5}$[c]	NA	$2.0x10^{5}$[c]	NA
Milk *KmMk*	NA	NA	$1.0x10^{6}$[b]	N A
Placenta *KmP*	$2.0x10^{5}$[c]	NA	NA	NA
Permeability area cross products (L/hour/kg)				
Gastric blood to gastric tissue *PAGc*	0.6[a]	0.6	0.6	0.6[a]
Gastric tissue to gastric juice *PAGJc*	1.0[a]	1.0	1.0	1.0[a]
Thyroid stroma to thyroid follicle *PATFc*	$1.0x10^{-4}$[a]	$1.0x10^{-2}$[f]	$6.7x10^{-5}$	$6.7x10^{-5}$[a]
Thyroid follicle to thyroid colloid (lumen) *PATLc*	0.01[a]	0.01[a]	0.01	0.01[a]
Skin blood to skin tissue *PASkc*	1.25[a]	1.25[a]	0.63	1.25[a]
Mammary blood to mammary tissue *PAMc*	0.04[a]	NA	0.01	NA
Mammary tissue to milk *PAMkc*	NA	NA	0.1	NA
Placenta blood to placenta *PAPCc*	0.1[b]	NA	NA	NA
Clearance values (L/hour/kg)				
Urinary excretion *CLUc*	0.05[d]	NA	0.05[d]	0.13[c]
Placenta to fetal blood *Cltrans1c*		0.12[f]	NA	NA
Fetal blood to placenta *Cltrans2c*		0.12[b]	NA	NA

Table 3-4. Perchlorate Chemical-specific Parameters for Human Gestation and Lactation Models

Parameters	Gestation		Lactation	
	Woman	Fetus	Woman	Neonate
Binding constants (ng/hour/kg)				
Plasma binding V*maxcB*	$5.9x10^{2a}$	$5.0x10^{2c}$	$1.32x10^{3a}$	$5.0x10^{2c}$

Note: Partition coefficients for perfusion limited compartments (i.e., fat, liver, kidney, rapidly and slowly perfused tissues) were the same across species and life stages.

[a]Calculated using parallelogram approach (Clewell 2008).
[b]Set to rat value (in absence of equivalent human parameter).
[c]Set to adult human value.
[d]Adjusted to fit data set.
[e]Calculated from human perinatal iodide parameter and ClO_4^-:I^- ratio in adult.
[f]Set to human perinatal iodide value (in absence of equivalent perchlorate data).

NA = not applicable

Source: Clewell 2008; Clewell et al. 2007)

Table 3-5. Radioiodide Chemical-specific Parameters for Human Gestation and Lactation Models

Parameters	Gestation		Lactation	
	Woman	Fetus	Woman	Neonate
Gastric tissue/gastric blood *PG*	1.0[a]	1.0[a]	0.5[a]	0.6[a]
Gastric juice/gastric tissue *PGJ*	2.0[a]	2.0[a]	1.0[a]	1.0[a]
Skin tissue/skin blood *PSk*	1.0[a]	1.0[a]	1.0[a]	1.0[a]
Mammary tissue/mammary blood *PM*	0.66[b]	NA	0.8[b]	NA
Mammary/milk *PMk*	N A	NA	1.0[b]	NA
Placenta/placental blood	0.40[b]	NA	NA	NA
Maximum capacity (ng/hour/kg)				
Thyroid follicle *VmaxcTF*	$1.22x10^{5}$[a]	0–$5.0x10^{6}$[d]	$1.4x10^{5}$[a]	1.5–$6x10^{6}$[d]/$1.5x10^{5}$[c]
Thyroid colloid (lumen) *VmaxcTL*	$1.0x10^{8}$[a]	$1.0x10^{8}$[a]	$1.0x10^{8}$[a]	$1.0x10^{8}$[a]
Skin *VmaxcS*	$7.2x10^{4}$[a]	$8.4x10^{5}$[a]	$5.6x10^{5}$[a]	$3.5x10^{5}$[a]
Gastrointestinal *VmaxcG*	$4.6x10^{5}$[a]	$9.0x10^{5}$[a]	$9.0x10^{5}$[a]	$9.0x10^{5}$[a]
Mammary *VmaxcM*	$4.0x10^{4}$[a]	NA	$8.0x10^{5}$[b]	NA
Milk *VmaxcMk*	NA	NA	$5.0x10^{5}$[b]	NA
Placenta *VmaxcP*	$5.5x10^{4}$[b]	NA	NA	NA
Affinity constants (ng/L)				
Mammary *KmM*	$4.0x10^{6}$[b]	NA	$4.0x10^{6}$[b]	NA
Milk *KmMk*	NA	NA	$1.0x10^{7}$[b]	NA
Placenta *KmP*	$4.0x10^{6}$[b]	NA	NA	NA
Permeability area cross products, (L/hour/kg)				
Gastric blood to gastric tissue *PAGc*	0.16[a]	0.12[a]	0.16[a]	0.01[a]
Gastric tissue to gastric juice *PAGJc*	12.0[a]	0.3[a]	12.0[a]	1.8[a]
Thyroid stroma to thyroid follicle *PATFc*	$1.0x10^{-4}$[a]	$1.0x10^{-2}$[d]	$1x10^{-4}$[a]	$1.0x10^{-4}$[a]
Thyroid follicle to thyroid colloid (lumen) *PATLc*	$1.5x10^{-5}$[a]	$1.0x10^{-4}$[a]	$2.0x10^{-3}$[a]	$1.25x10^{-3}$[a]
Skin blood to skin tissue *PASkc*	0.06[a]	0.06[a]	0.12[a]	0.012[a]
Mammary blood to mammary tissue *PAMc*	0.01[b]	NA	0.02[b]	NA
Mammary tissue/milk *PAMkc*	NA	NA	0.02[b]	NA
Placenta blood to placenta *PAPCc*	0.005[b]	NA	NA	NA

Table 3-5. Radioiodide Chemical-specific Parameters for Human Gestation and Lactation Models

Parameters	Gestation		Lactation	
	Woman	Fetus	Woman	Neonate
Clearance values, (L/hour/kg)				
Urinary excretion *CLUc*	0.05[a]	NA	0.1[a]	0.1[c]
Placenta to fetal blood *Cltrans1c*		0.12[d]	NA	NA
Fetal blood to placenta *Cltrans2c*		0.12[b]	NA	NA

Note: Partition coefficients for perfusion limited compartments (i.e., fat, liver, kidney, rapidly and slowly perfused tissues) were the same across species and life stages.

[a]Calculated using parallelogram approach.
[b]Set to rat value (in absence of equivalent human parameter).
[c]Set to adult human value.
[d]Adjusted to fit data set.

NA = not applicable

Source: Clewell et al. 2007

Table 3-6. Perchlorate Chemical-specific Parameters for Rat Gestation and Lactation Models

	Gestation		Lactation	
Parameters	Dam	Fetus	Dam	Pup
Partition coefficients (unitless)				
Slowly perfused/plasma *PS*	0.31	0.31	0.31	0.31
Rapidly perfused/plasma *PR*	0.56	0.56	0.5	0.5
Fat/plasma *PF*	0.05	NA	0.05	0.05
Kidney/plasma *PK*	0.99	0.99	0.99	0.99
Liver/plasma *PL*	0.56	0.56	0.56	0.56
Gastric tissue/gastric blood *PGI*	0.50	1.80	1.8	3.21
Gastric juice/gastric tissue *PGIJ*	1.30	2.30	2.3	5.64
Skin tissue/skin blood *PSk*	1.15	1.15	1.15	1.15
Thyroid tissue/thyroid blood *PTF*	0.15	0.15[a]	0.13	0.13
Thyroid lumen/thyroid tissue *PTL*	7.0	7.0	7.0	7.0
Red blood cells/plasma *PRBC*	0.73	0.73	0.73	0.73
Placenta/plasma *PPl*	0.56	NA	NA	NA
Mammary/plasma *PM*	0.66	NA	NA	NA
Mammary tissue/mammary blood *PM*	NA	NA	0.66	NA
Mammary/plasma *PMk*	NA	NA	2.39	NA
Max capacity, Vmaxc (ng/hour/kg)				
Thyroid follicle *VmaxcTF*	$2.6x10^3$	0–$2.25x10^3$	$1.5x10^3$	$1.5x10^3$
Thyroid colloid *VmaxcTL*	$1.0x10^4$	$1.0x10^{4b}$	$1.0x10^4$	$1.0x10^4$
Skin *VmaxcSk*	$6.0x10^5$	$4.0x10^5$	$8.0x10^5$	$8.0x10^5$
Gut *VmaxcGI*	$8.0x10^5$	$1.0x10^5$	$1.0x10^6$	$1.0x10^6$
Placenta *VmaxcP*	$6.0x10^4$	NA	NA	NA
Mammary *VmaxcM*	$2.2x10^4$	NA	$2.0x10^4$	NA
Milk *VmaxcMk*	NA	NA	$2.0x10^4$	NA
Affinity constants, Km (ng/L)				
Thyroid follicle *KmTF*	$1.0x10^5$	$1.0x10^5$	$1.5x10^5$	$1.5x10^5$
Thyroid colloid *KmTL*	$1.0x10^8$	$1.0x10^8$	$1.0x10^8$	$1.0x10^8$
Skin *KmSk*	$1.0x10^5$	$1.0x10^5$	$1.5x10^5$	$1.5x10^5$
Gut *KmGI*	$1.0x10^5$	$1.0x10^5$	$1.5x10^5$	NA
Placenta *KmP*	$1.0x10^5$	NA	NA	NA
Mammary *KmM*	$1.0x10^5$	NA	$1.5x10^5$	NA
Milk *KmMk*	NA	NA	$1.0x10^6$	NA
Permeability area cross-products (L/hour/kg)				
Gastric blood to gastric tissue *PAGIc*	1.00	1.00	1.00	1.00
Gastric tissue to gastric juice *PAGIJc*	1.00	1.00	1.00	1.00
Thyroid stroma to follicle *PATFc*	$6.0x10^{-5}$	$6.0x10^{-5}$	$4.0x10^{-5}$	$4.0x10^{-5}$
Thyroid follicle to colloid (lumen) *PATLc*	0.01	0.01[b]	0.01	0.01
Skin blood to skin tissue *PASkc*	1.00	1.00	0.50	1.00

Table 3-6. Perchlorate Chemical-specific Parameters for Rat Gestation and Lactation Models

	Gestation		Lactation	
Parameters	Dam	Fetus	Dam	Pup
Placenta blood to placenta tissue *PAPc*	0.1	NA	NA	NA
Plasma to red blood cells *PARBCc*	1.00	1.00	1.00	1.00
Mammary blood to mammary tissue *PAMc*	0.04	NA	0.01	NA
Mammary tissue/milk *PAMkc*	NA	NA	0.10	NA
Clearance values (L/hour/kg)				
Urinary excretion *ClUc*	0.07	NA	0.07	0.0075
Fraction of pup urine ingested by dam	NA	NA	0.80	NA
Transfer from placenta to fetus *ClTrans1c*	0.065	NA	NA	NA
Transfer from fetus to placenta *ClTrans2c*	0.12	NA	NA	NA
Binding constants				
Association to binding sites *VmaxcB* (ng/hour/kg)	$4.0x10^3$	$1.5x10^3$	$9.0x10^3$	$2.0x10^3$
Affinity for binding sites *KmB* (ng/L)	$1.0x10^4$	$1.5x10^4$	$1.0x10^4$	$1.0x10^4$
Dissociation from plasma binding sites *ClUnbc* ($hour^{-1}$)	0.034	0.01	0.034	0.01

[a]Parameters with two values indicate acute and drinking water parameters, respectively.
[b]Fetus was given maternal values for Vmax (scaled by fetal body weight) in the absence of data.

NA = not applicable

Source: Clewell et al. 2003a

Table 3-7. Iodide Chemical-specific Parameters for Rat Gestation and Lactation Models

	Gestation		Lactation	
Parameters	Dam	Fetus	Dam	Pup
Partition coefficients (unitless)				
Slowly perfused/plasma *PS*	0.21	0.21	0.21	0.21
Rapidly perfused/plasma *PR*	0.40	0.40	0.40	0.40
Fat/plasma *PF*	0.05	NA	0.05	0.05
Kidney/plasma *PK*	1.09	1.09	1.09	1.09
Liver/plasma *PL*	0.44	0.44	0.44	0.44
Gastric tissue/gastric blood *PGI*	1.00	1.00	1.00	1.20
Gastric juice/gastric tissue *PGIJ*	2.00	2.00	1.00	1.00
Skin tissue/skin blood *PSk*	0.70	0.70	0.70	1.00
Thyroid tissue/thyroid blood *PTF*	0.15	0.15	0.15	0.15
Thyroid lumen/thyroid tissue *PTL*	7.0	7.0	7.0	7.0
Red blood cells/plasma *PRBC*	1.00	1.00	1.00	1.00
Placenta/plasma *PPl*	0.40	NA	NA	NA
Mammary/plasma *PM*	0.66	NA	NA	NA
Mammary tissue/mammary blood *PM*	NA	NA	0.80	NA
Mammary/plasma *PMk*	NA	NA	1.0	NA
Max capacity, *Vmaxc* (ng/hour/kg)				
Thyroid follicle *VmaxcTF*	$4.4x10^4$	$0–5.0x10^4$	$5.0x10^4$	$1.3x10^4$
Thyroid colloid *VmaxcTL*	$4.0x10^6$	$4.0x10^{6b}$	$6.0x10^7$	$6.0x10^7$
Skin *VmaxcSk*	$6.0x10^4$	$7.0x10^5$	$4.0x10^5$	$2.5x10^5$
Gut *VmaxcGI*	$1.0x10^6$	$2.0x10^6$	$2.0x10^6$	$2.0x10^6$
Placenta *VmaxcP*	$5.5x10^4$	NA	NA	NA
Mammary *VmaxcM*	$4.0x10^4$	NA	$8.0x10^5$	NA
Milk *VmaxcMk*	NA	NA	$4.0x10^5$	NA
Affinity constants, *Km* (ng/L)				
Thyroid follicle *KmTF*	$4.0x10^6$	$4.0x10^6$	$1.5x10^5$	$1.5x10^5$
Thyroid colloid *KmTL*	$1.0x10^9$	$1.0x10^9$	$1.0x10^8$	$1.0x10^8$
Skin *KmSk*	$4.0x10^6$	$4.0x10^6$	$1.5x10^5$	$1.5x10^5$
Gut *KmGI*	$4.0x10^6$	$4.0x10^6$	$1.5x10^5$	NA
Placenta *KmP*	$4.0x10^6$	NA	NA	NA
Mammary *KmM*	$4.0x10^6$	NA	$4.0x10^6$	NA
Milk *KmMk*	NA	NA	$1.0x10^7$	NA
Permeability area cross-products (L/hour/kg)				
Gastric blood to gastric tissue *PAGIc*	0.80	0.10	0.80	0.04
Gastric tissue to gastric juice *PAGIJc*	0.60	0.30	0.60	0.09
Thyroid stroma to follicle *PATFc*	$1.0x10^{-4}$	$1.0x10^{-4}$	$1.0x10^{-4}$	$1.0x10^{-4}$
Thyroid follicle to colloid (lumen) *PATLc*	$4.0x10^{-7}$	$4.0x10^{-4}$	$1.0x10^{-4}$	$1.0x10^{-4}$
Skin blood to skin tissue *PASkc*	0.10	0.02	0.20	0.02

Table 3-7. Iodide Chemical-specific Parameters for Rat Gestation and Lactation Models

	Gestation		Lactation	
Parameters	Dam	Fetus	Dam	Pup
Placenta blood to placenta tissue *PAPc*	0.005	NA	NA	NA
Plasma to red blood cells *PARBCc*	1.00	1.00	1.00	1.00
Mammary blood to mammary tissue *PAMc*	0.01	NA	0.02	NA
Mammary tissue/milk *PAMkc*	NA	NA	0.02	NA
Clearance values (L/hour/kg)				
Urinary excretion *ClUc*	0.03	NA	0.06	0.012
Fraction of pup urine ingested by dam	NA	NA	0.80	NA
Incorporation of iodide into hormones *ClProdc*	0.03	NA	0.10	0.06
Incorporated iodine secretion to serum *CSecrC*	$1.0x10^{-6}$	NA	$7.0x10^{-7}$	$1.0x10^{-6}$
Deiodination	NA	NA	0.02	0.025
Transfer from placenta to fetus *ClTrans1c*	0.06	NA	NA	NA
Transfer from fetus to placenta *ClTrans2c*	0.12	NA	NA	NA
Binding constants				
Association to binding sites *VmaxcB* (ng/hour/kg)	NA	NA	$1.5x10^{3}$	500
Affinity for binding sites *KmB* (ng/L)	NA	NA	$1.0x10^{5}$	$1.0x10^{5}$
Dissociation from plasma binding sites *ClUnbc* ($hour^{-1}$)	NA	NA	0.09	0.05

[a]Parameters with two values indicate acute and drinking water parameters, respectively.
[b]Fetus was given maternal values for Vmax (scaled by fetal body weight) in the absence of data.

NA = not applicable

Source: Clewell et al. 2003a

other changes in radioiodide metabolism in the thyroid (e.g., hormone production and secretion) that are not simulated by the model.

The adult human model (nonpregnant, non-lactating) also predicted reasonably well (i.e., within 1–2 standard deviations of observations) perchlorate concentrations in plasma and urine in subjects who received oral doses of perchlorate (Durand 1938; Eichler 1929; Greer et al. 2002; Kamm and Drescher 1973; Merrill et al. 2005). Model predictions of radioiodide in gastric juice, serum, thyroid, and urine following an intravenous dose of radioiodide also corresponded with observations made in healthy adults (Hays and Solomon 1965). Model predictions of thyroid radioiodine uptake in subjects who received oral doses of perchlorate agreed with observations when the kinetic parameters for iodide in the thyroid (i.e., maximum transport into the thyroid follicle) were adjusted to achieve good correspondence to the observations (Greer et al. 2002; Merrill et al. 2005). When the model was calibrated by adjusting the maximum transport rate for iodide into the thyroid follicle, it accurately predicted the observed time course for radioiodine uptake in a Graves' disease patient who received a single tracer dose of radioiodine (Stanbury and Wyngaarden 1952); however, the model substantially overpredicted iodide uptake after the same patient received a dose of perchlorate. The error in predictions of the effect of perchlorate on iodide uptake may reflect humoral regulation of iodide transport and organification mechanisms or a response to perchlorate in Graves' disease patients that is not simulated in the model.

The rat maternal/fetal model was evaluated by comparing predictions of perchlorate concentrations in maternal and fetal serum and maternal thyroid in rats exposed to perchlorate in drinking water (Clewell et al. 2001, 2003a). Model predictions agreed well (within 1–2 standard deviations of observations) with observations. Predictions of maternal and fetal radioiodine uptakes in thyroid were also in reasonable agreement with observations in rats that received single injections of iodine with or without single injections or oral gavage doses of perchlorate, or at the conclusion of 18 days of exposures to perchlorate in drinking water (Brown-Grant 1966; Clewell et al. 2001, 2003a; Sztanyik and Turai 1988).

Similar outcomes occurred in evaluations of the lactating dam/neonate model (Clewell et al. 2003b). The model accurately predicted serum and thyroid iodide concentrations in the dam and neonate following single intravenous injections of radioactive iodine, with or without concurrent injection of perchlorate, and in maternal thyroid following an 18-day exposure to perchlorate in drinking water (Clewell et al. 2003b). Model predictions of radioiodide levels in mammary gland and milk, in rats that did or did not receive single doses of perchlorate, corresponded with observations (Clewell et al. 2003b).

The human pregnancy and lactation models were evaluated by comparing model predictions of perchlorate concentrations in serum with observations made in pregnant women (15 and 33 weeks of gestation) and their infants at birth (from cord blood), and in a group of children (mean age 7.4 years) (Téllez et al. 2005). Exposures simulated in the model were the continuous perchlorate intake corresponding to the mean ±1 standard deviation drinking water exposure concentrations (114±13 ppm) for a cohort in the Téllez et al. (2005) study. Model predictions for maternal, fetal, and child serum perchlorate concentrations agreed well (within ±1 standard deviation of observed means) with observations. Téllez et al. (2005) also reported perchlorate concentrations in breast milk measured at 5–6 weeks postpartum. Simulation of the continuous perchlorate intake corresponding to the group means (± standard deviation) of drinking water exposure concentrations (5.8±0.6 ppm or 114±13 ppm) yielded predictions of breast milk perchlorate concentrations that were within ±1 standard deviation of the observed means.

Risk assessment. The rat (Clewell et al. 2003a, 2003b; Merrill et al. 2003) and human models (Clewell et al. 2007; Merrill et al. 2005) can be used to estimate the human equivalent exposure level for perchlorate that would give rise to a given percent inhibition of thyroidal radioiodide uptake. The models do not include downstream effects on the thyroid axis, such as decreases in serum thyroid hormones. The Clewell et al. and Merrill et al. model estimates have been used to extrapolate dose-response relationships for perchlorate observed in rats to humans, and across various human lifestages (e.g., fetus, neonate, child, adult, pregnancy, lactation). External dose–internal dose relationships for various human life-stages predicted from the human models are presented in Tables 3-8 and 3-9 (Clewell et al. 2007). The models predict a relatively high vulnerability of the fetus, pregnant woman, and lactating woman to perchlorate-induced thyroid iodine uptake, compared to other lifestages (i.e., greater inhibition of thyroid iodide uptake occurs in these lifestages in association with lower external doses), compared to neonates, child or nonpregnant or nonlactating adult). The potential impact of external exposures to perchlorate on inhibition on thyroidal radioiodide uptake is sensitive to assumptions about urinary clearance of perchlorate, especially in neonates and young infants. The estimates based on external exposures from consumption of drinking water are also dependent on assumptions regarding age-related changes in contribution of drinking water to liquid consumption across lifestages (e.g., milk in children).

Target tissues. Tissues simulated in the perchlorate models are shown in Figures 3-4 and 3-5. The models were designed to calculate perchlorate concentrations in serum and thyroid and inhibition of radioiodide uptake into the thyroid resulting from exposures to perchlorate for various lifestages (e.g., fetus, neonate, child, adult, pregnancy, lactation).

Table 3-8. Model-predicted Serum ClO_4^- Area Under the Curve (AUC) Across Lifestages

External dose (mg/kg/day)	Fetus[a] (mg/L)	Neonate[b] (mg/L)	Child (mg/L)	Adult (mg/L)	Pregnant[a] woman (mg/L)	Lactating[c] woman (mg/L)
0.001	0.010	0.008	0.001	0.002	0.005	0.008
0.01	0.06	0.05	0.01	0.01	0.04	0.05
0.1	0.2	0.2	0.1	0.1	0.3	0.3
1.0	1.2	0.5	0.8	1.0	2.5	2.5

[a]Fetus and pregnant woman shown in gestation week 38.
[b]Neonate shown at postnatal month 1.5.
[c]Lactating woman shown at postnatal day 7.

Source: Clewell et al. 2007

Table 3-9. Model-predicted Inhibition of Thyroid Iodide Uptake (Percent Inhibition) Across Lifestages

External dose (mg/kg/day)	Percent Inhibition					
	Fetus[a]	Neonate[b]	Child	Adult	Pregnant[a] woman	Lactating[c] woman
0.001	1.1	0.9	0.3	0.6	1.0	1.1
0.01	10	8	3	4	9	10
0.1	49	34	21	31	50	54
1.0	84	63	72	81	91	92

[a]Fetus and pregnant woman shown in gestation week 38 (birth).
[b]Neonate shown at postnatal month 1.5.
[c]Lactating woman shown at postnatal day 7.

Source: Clewell et al. 2007

Species extrapolation. The models are designed for applications to rat or human dosimetry and cannot be applied to other species without modification and validation.

Interroute extrapolation. The models are designed to simulate intravenous or oral exposures to perchlorate and cannot be applied to other routes of exposure without modification and validation.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Perchlorate is readily soluble in water and is quickly absorbed through the digestive tract. The mechanism by which perchlorate is transferred from the digestive system to the blood has not been investigated. Since Durand (1938) detected perchlorate in the urine of subjects 10 minutes after oral administration, it seems likely that absorption of perchlorate may begin in the stomach and continue in the small intestine. Anbar et al. (1959) determined that perchlorate eliminated in the urine 3 hours after an oral dose had not been metabolized (see Section 3.4.1). Whether microflora of the gut or intestinal enzymes modify perchlorate that is finally eliminated in the feces has not been investigated.

Whatever the mechanism of absorption, perchlorate is distributed throughout the body via the circulation (see Section 3.4.2). It apparently is not metabolized (Anbar et al. 1959) and it binds only weakly to cations. Concentrations of perchlorate rise above serum levels only for those tissues that are equipped with the anion transporter mechanism that normally takes up iodide. The effects of perchlorate on the thyroid gland are known from studies on humans and animals (see Section 3.2); perchlorate levels in the thyroid reach a maximum several hours after administration. Chow and co-workers (Chow and Woodbury 1970; Chow et al. 1969) determined that perchlorate is taken up from interstitial fluid by active transport at the base of thyroid follicular cells, which then actively transport it out into the follicular lumen. The effects of perchlorate on the transfer of maternal iodide in milk have been studied in rats and cattle (Clewell et al. 2003b; Dobian et al. 2007; Howard et al. 1996; Kirk et al. 2005). The accumulation of perchlorate in ducts of the salivary gland has been described in mice (Lazarus et al. 1974). Studies on rodents have demonstrated that perchlorate can cross the placental barrier and affect the thyroid gland of the fetus (see Section 3.2).

Perchlorate transport in the thyroid gland and in other tissues that express NIS (e.g., mammary epithelium) appears to be mediated by NIS. Perchlorate is accumulated in thyroid follicle cells and lumen

against an electrochemical gradient, indicating an active transport mechanism, and possibly different mechanisms at the basolateral and luminal membranes (Chow and Woodbury 1970; Chow et al. 1969; Clewell et al. 2004; Goldman and Stanbury 1973). Thyroid uptake of perchlorate in hypophysectomized rats is stimulated by administration of TSH (Chow et al. 1969). Perchlorate competitively inhibits iodide transport in thyroid slices, cultured thyrocytes, cultured cells transformed to express thyroid NIS, and thyrocyte membrane vesicles (Dohán et al. 2007; Eskandari et al. 1997; O'Neill et al. 1987; Tran et al. 2008; Wolff and Maurey 1962, 1963; Yoshida et al. 1997). The above observations suggest that perchlorate transport into thyroid follicle cells, and possibly into other tissues where NIS is expressed, is mediated by NIS (Wolff 1998). Perchlorate uptake into thyroid cells is stimulated by TSH (Tran et. al. 2008). Unlike the NIS-mediated transport of iodide, transport of perchlorate by NIS appears to be electroneutral (Dohán et al. 2007; Eskandari et al. 1997; Yoshida et al. 1997). Chinese hamster ovary (CHO) cells transfected with the rat thyroid NIS gene and *Xenopus* oocytes transfected with rat thyroid NIS mRNA express active NIS that exhibits a Na(2):I(1) stoichiometry, is electrogenic (inward directed current), occurs against an electrochemical gradient for iodide in the presence of an inward electrochemical gradient for sodium, and is inhibited by perchlorate (Eskandari et al. 1997; Yoshida et al. 1997). Both systems, when clamped at an interior negative potential (40–50 mV), exhibit sodium-dependent inward currents in the presence of I^- and SCN^-; the transfected oocyte exhibits sodium-dependent inward currents in the presence of a variety of anions, including I^-, ClO_3^-, SCN^-, $SeCN^-$, NO_3^-, Br^-, BF_4^-, IO_4^-, BrO_3^-, SO_4^{-2}, F^-, and HPO_4^{-2}. However, these systems do not show perchlorate-stimulated currents in the presence or absence of a favorable inward-directed Na gradient. FRTL5 cells and other cell types that have been transfected to express NIS transport the structural tetrahedral oxyanion analogs of perchlorate, perrhenate (ReO_4^-), and pertechnetate (TcO_4^-), providing further support for NIS-mediated perchlorate transport. Furthermore, in MDCK cells transfected to express NIS-mediated electrogenic transport of iodide, transport of perchlorate, perrhenate (ReO_4^-), and pertechnetate (ReO_4^-) was also electroneutral (Dohán et al. 2007).

Studies of the kinetics of excretion and elimination of perchlorate from serum in humans indicate that absorbed perchlorate is excreted in urine with an elimination half-time of 8–14 hours (Durand 1938; Greer et al. 2002; Lawrence et al. 2000). Thus, in humans, perchlorate would not be expected to accumulate in the body with prolonged exposure. Based on an elimination half-time of approximately 8–12 hours, a steady state would be achieved within 3–4 days of continuous exposure. Rapid elimination of perchlorate (half-time of 20 hours) has also been observed in rats (Eichler and Hackenthal 1962; Fisher et al. 2000; Goldman and Stanbury 1973; Yu et al. 2002). The mechanisms of renal excretion of perchlorate are not understood.

3.5.2 Mechanisms of Toxicity

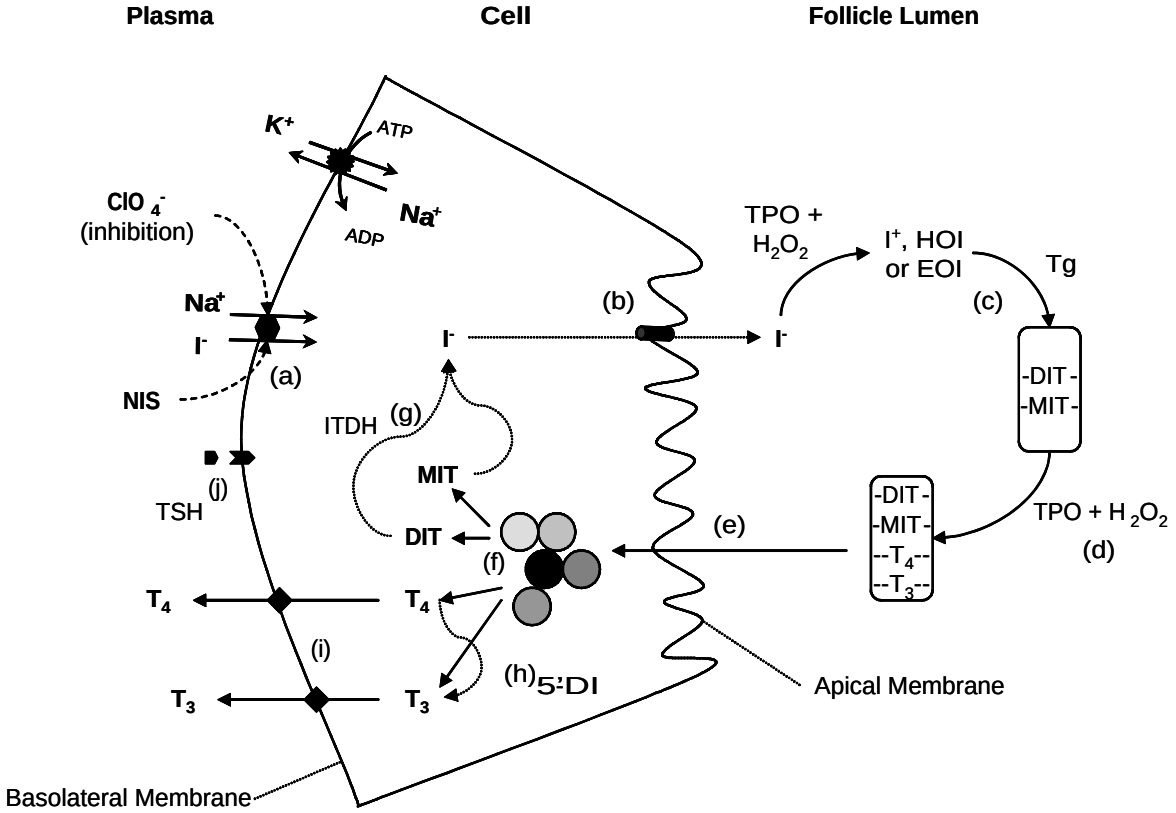
Perchlorate is an inhibitor of NIS, the primary mechanism by which iodide enters thyroid follicle cells from the blood, and the first step in the uptake of iodide into the thyroid and formation of thyroid hormones (Figure 3-6; Carrasco 1993; Taurog 2000; Wolff 1998). All toxic effects of perchlorate on the thyroid hormone system derive directly or secondarily from this mechanism. Because the primary and most sensitive target of the perchlorate anion is the thyroid gland, only toxicities related to the thyroid hormone system are addressed below.

Thyroid Hormone. The thyroid hormone, T3, is essential for normal development of the nervous system and for the regulation of metabolism of cells in nearly all tissues of the body. Adverse effects on a wide variety of organ systems can result from disruption in the availability of T3 to target tissues. Organ systems affected by disturbances in T3 levels include the skin, cardiovascular system, pulmonary system, kidneys, gastrointestinal tract, liver, blood, neuromuscular system, central nervous system, skeleton, male and female reproductive systems, and numerous endocrine organs, including the pituitary and adrenal glands.

T3 exerts its wide range of actions by binding to thyroid hormone receptors (TRs) in the cell nucleus, which, when bound with hormone, modulate the transcription of a variety of genes (Anderson et al. 2000). TRs consist of a family of structurally similar proteins within the so-called *steroid receptor superfamily* that includes receptors for steroid hormones, vitamin D, retinoic acid, and peroxisomal proliferator activators (Lazar 1993). Each receptor has DNA binding domains capable of forming two zinc fingers; the sequence of the latter determine hormone receptor specificity to response elements on DNA that modulate gene transcription of hormone-sensitive genes. A ligand binding domain is responsible for conferring specificity for hormone binding.

Modulation of gene expression occurs when the T3–TR complex binds to a region of DNA associated with a thyroid hormone response element (TRE). Studies in humans and experimental animals have identified TREs associated with a variety of genes, including growth hormone, myelin basic protein, α-myosin heavy chain, malic enzyme and protein S14 (important in lipogenesis), sarcoplasmic reticulum Ca^{2-} ATPase, Pcp-2 (in Purkinje cells), Na^{+}/K^{+}-ATPase, and TSH (Anderson et al. 2000; Klein and Levey 2000; Schwartz et al. 1994).

Figure 3-6. Pathways Uptake and Metabolism of Iodide in the Thyroid Gland*



*The diagram depicts a single thyroid follicle cell, with the plasma side of the follicle on the left and the follicle lumen on the right. Iodide uptake (a) occurs through a Na+/I- symporter (NIS) in the basolateral membrane; the perchlorate ion competitively inhibits the NIS, preventing uptake of iodide into the follicle cell. Efflux into the follicle lumen (b) is thought to occur through an I- channel in the apical membrane. Iodination occurs in the follicle lumen (c). The enzyme thyroid peroxidase (TPO), depicted in the follicle lumen, is actually located in the apical membrane. Deiodination of iodotyrosines (g) is catalyzed by a microsomal enzyme, iodotyrosine dehalogenase (ITDH); monodeiodination of T4 (h) is catalyzed by the microsomal enzyme, 5'-diodinase. All steps in the uptake of iodine and synthesis of thyroid hormones (a–h) are stimulated by binding of thyroid stimulating hormone (TSH) to a receptor in the basolateral membrane.

DIT = diiodotyrosine; EOI = enzyme-linked species; HOI = hypoidous acid; ITDH = iodotyrosine dehalogenase; MMI = methimazole; MIT = monoiodotyrosine; PTU = propylthiouracil; T3 = triiodothyronine; T4 = thyronine; Tg = thyroglobulin; TPO = thyroid peroxidase; TSH = thyroid stimulating hormone

Source: adapted from Taurog 2000

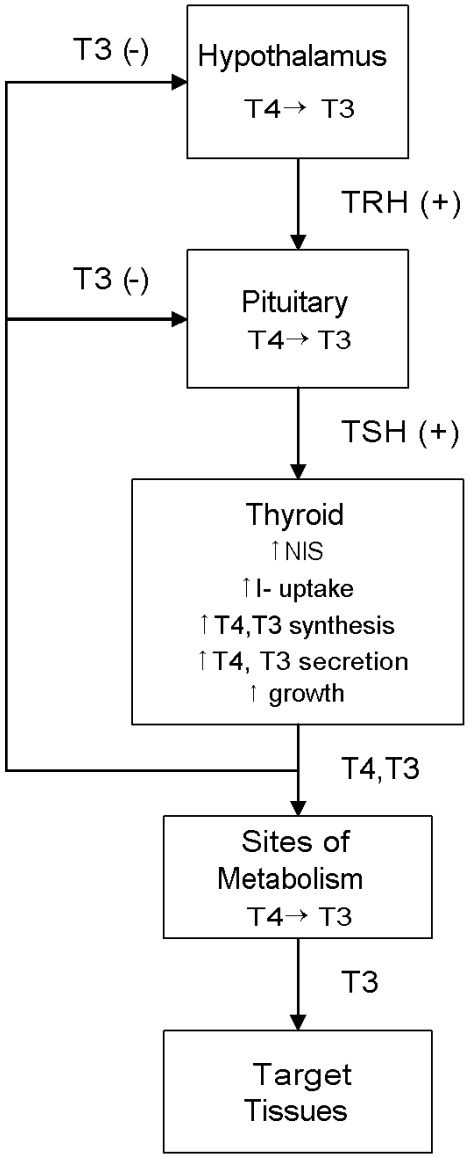
Adverse effects on cell metabolism and growth can result from either understimulation or overstimulation of target tissues by T3. The amount of T3 available to target tissues is highly controlled by feedback regulation of the production, secretion, and elimination of both T3 and its metabolic precursor, T4 (Figure 3-7). Major components of this mechanism include negative feedback control mediated by T4 and T3 of the synthesis and release of thyrotropin-releasing hormone (TRH) in the hypothalamus and of TSH in the pituitary. TRH stimulates the synthesis and secretion of TSH in the pituitary and modulates the biologic potency of TSH. The latter is thought to result from effects of TRH on posttranslational glycosylation of TSH (Cohen et al. 2000; Scanlon and Toft 2000). TSH promotes growth of the thyroid gland follicle cells and stimulates thyroid iodide uptake and synthesis and secretion of T4 and T3 (Spaulding 2000).

The metabolism of T4 and T3 is also regulated by feedback control mechanisms (Darras et al. 1999). T3 is synthesized from the deiodination of T4 in a reaction catalyzed by selenium requiring, microsomal enzymes known as iodothyronine deiodinases. Although some production of T3 occurs in the thyroid, most of the T3 that is available to extrathyroidal target tissues derives from deiodination of T4 that occurs outside of the thyroid (Figure 3-7). The liver and kidney are thought to be major sites of production of T3 in the circulation; however, local tissue production of T3 from T4 is thought to be the predominant source of T3 in the brain and pituitary. Iodothyronine deoidinases also catalyze the inactivation of T4 and T3. The activities of deiodinases are under feedback control, mediated by T3, T4, and reverseT3 (rT3) an inactive deiodination product of T4 (Darras et al. 1999).

Mechanism of Uptake of Iodide into the Thyroid. Synthesis of T4 and T3 in the thyroid is dependent on delivery of iodide into the thyroid follicle where the iodination of thyroglobulin occurs in the first steps of hormone synthesis (Figure 3-6). Uptake of iodide into the thyroid is facilitated by a membrane carrier in the basolateral membrane of the thyroid follicle cell (Carrasco 1993; Levy et al. 1998a; Shen et al. 2001). The carrier, or NIS, catalyzes the simultaneous transfer of Na^+ and I^- across the basolateral membrane (Chambard et al. 1983; Iff and Wilbrandt 1963; Nilsson et al. 1990). The NIS enables the follicle cell to achieve intracellular/extracellular concentration ratios of 10–50 for iodide (Andros and Wollman 1991; Bagchi and Fawcett 1973; Shimura et al. 1997; Vroye et al. 1998; Weiss et al. 1984b; Wolff 1964).

The NIS has been studied extensively in several *in vitro* preparations, including isolated plasma membrane vesicles of mammalian thyroid (O'Neill et al. 1987), FRTL-5 cells, a cell line derived from normal rat thyroid (Weiss et al. 1984b), *Xenopus lavis* oocytes transformed by intracellular injection of FRTL-5 RNA to express NIS (Eskandari et al. 1997), and other mammalian cells cultures transformed to

Figure 3-7. Hypothalamic-pituitary-thyroid (HPT) Feedback Pathways for Regulation of Thyroid Hormone Production and Secretion*



*T3 inhibits the synthesis and secretion of thyroid releasing hormone (TRH) in the paraventricular nuclei of the hypothalamus and the synthesis and secretion of thyroid stimulating hormone (TSH) in the thyrotrophs of the anterior pituitary. Most of the T3 in these tissues derives from local deiodination of T4; as a result, TRH and TSH synthesis and secretion are sensitive to circulating levels of both T3 and T4. Doses of perchlorate that decrease circulating levels of T3 or T4 can trigger the HPT feedback mechanism to stimulate thyroid growth, including hypertrophy and hyperplasia of follicle cells. Chronic stimulation of thyroid growth is thought to be contributor to the development of thyroid tumors in rats exposed to perchlorate.

express NIS (Levy et al. 1997; Nakamura et al. 1990; Smanik et al. 1996; Yoshida et al. 1997). Iodide transport by the NIS is inhibited by other anions, most notably, thiocyanate (SCN^-) and perchlorate (ClO_4^-) (Carrasco 1993; Wolff 1964). Thiocyanate is one of several anions other than I^- that can be transported by the NIS, including $SeCN^-$, NO_3^-, ClO_3^-, Br^-, BF_4^-, IO_4^-, BrO_3^-, ReO_4^-, and TcO_4^- (Eskandari et al. 1997; Van Sande et al. 2003). Direct evidence for perchlorate transport by NIS (i.e., measurement of radioperchlorate flux through the NIS) is lacking; however, transport activity is likely given that the NIS transports the structural analogs, perrhenate and pertechnetate. Perchlorate transport by NIS may be electroneutral, preventing its detection from measurements of ion currents or electrochemical gradients (Dohán et al. 2007; Eskandari et al. 1997; Yoshida et al. 1997).

The NIS is expressed in a variety of other tissues, including breast tissue where it is thought to function in the transport of iodide into breast milk (Levy et al. 1997; Smanik et al. 1997; Spitzweg et al. 1998). In the rat, expression of the NIS, or a structurally similar membrane protein, increases during nursing and decreases after weaning (Levy et al. 1998a). In the mouse, expression of NIS in mammary tissue appears to be stimulated by prolactin (Perron et al. 2001; Rillema and Rowady 1997; Rillema et al. 2000).

Inhibition of Thyroid NIS and Thyroid Hormone Production by Perchlorate. Perchlorate inhibition of NIS can limit the availability of iodide needed for the production of T4 and T3 in the thyroid. The degree of perchlorate-induced iodide uptake inhibition required to impair T4 or T3 synthesis has not been studied, but the duration of exposure required to produce a reduction in circulating levels of thyroid hormones appears to vary with species. In this regard, the duration of perchlorate exposure required to cause a reduction in circulating levels of thyroid hormones appears to be shorter in rats than in humans (see Section 3.5.3). This difference is thought to derive from the rat thyroid gland having a smaller store of iodinated thyroglobulin that is more quickly depleted when the availability of iodide is limited, and from the rat having a shorter T4 half-life (about 1 day) compared to humans (about 7 days). In humans, THBG functions as an important storage depot for circulating T4 and a buffer for homeostatic regulation of free T4 levels in serum (Robbins 2000). If the production of T4 and T3 is impaired sufficiently to deplete the thyroid of stored iodinated thyroglobulin, the thyroid cannot produce or secrete amounts of T4 and T3 needed to support physiological demands, circulating levels of T4 (fT4) and T3 decrease, and a state of thyroid hormone insufficiency ensues. A decrease in the levels of circulating thyroid hormones triggers HPT feedback control mechanisms that serve to adjust thyroidal iodide transport and hormone production in response to changes in circulating levels of T4, T3, and iodide. Major components of this mechanism include inhibition of the secretion of TRH from the hypothalamus, TRH-stimulated secretion of TSH from the pituitary, TSH-stimulated induction of thyroid follicle cell NIS (i.e., *upregulation*) and

other thyroid cell proteins, increased capacity for transport of iodide into thyroid follicle cells, and increased synthesis and secretion of T4 and T3 from the thyroid. This system normally maintains circulating levels of T4 and T3 within narrow individual limits (Andersen et al. 2002). Doses of perchlorate that are sufficient to decrease circulating levels of thyroid hormones outside of these individual limits will result in increased secretion of TSH. Thus, an increase in the circulating levels of TSH is a sign that perchlorate has perturbed circulating levels of thyroid hormones. In humans, intra-individual variation in T4 levels is less than inter-individual variation, suggesting that the HPT feedback mechanism can detect relatively small changes in thyroid hormone levels that are well within the range of variation expected in populations (Andersen et al. 2002). Triggering of the HPT feedback response in profound iodide deficiency can affect the response of the thyroid to perchlorate. Rats maintained on an iodine-deficient diet for sufficient periods to lower serum T_4 levels, exhibited higher 24-hour thyroid radioiodide uptake when exposed to perchlorate in drinking water (1.1–28 mg/L) for 5 weeks than iodine-replete rats (Paulus et al. 2007). The increased resistance to perchlorate-induced inhibition of thyroid iodide uptake in iodine deficiency has been attributed, at least in part, to induction of NIS in the thyroid, which partially overcomes the competitive inhibition of NIS resulting from a given dosage of perchlorate.

Perchlorate-induced Hypothyroidism. Inhibition of thyroid iodide uptake can potentially deplete stores of T4 and T3 in the thyroid and lower serum T4 and T3 levels. Thus, perchlorate has the potential for producing hypothyroidism or for aggravating an ongoing hypothyroid condition. The term hypothyroidism refers to a state of suppressed production and/or secretion of thyroid hormones. The term clinical hypothyroidism refers to a condition in which the circulating levels of T4 and/or T3 are depressed below their normal ranges (usually accompanied with elevated serum TSH levels above the normal range) and in which there are clinical symptoms of thyroid hormone insufficiency (Ladenson 2000). Typical normal ranges for hormone levels are shown in Table 3-10. Subclinical hypothyroidism refers to an increase in serum TSH (usually mild) with serum T4 and T3 remaining in their respective normal ranges for age. An important question is whether small changes in circulating levels of thyroid hormones that trigger the HPT feedback mechanism, but do not fall outside of the normal population range, are detected as thyroid hormone insufficiency in tissues other than the hypothalamus or pituitary, including the embryo or fetal brain.

In humans, relatively large doses of perchlorate (600–900 mg/day, 8–13 mg/kg/day) are required to deplete thyroidal iodine stores sufficiently to decrease serum levels of T4 (Brabant et al. 1992; Bürgi et al. 1974). A 4-week oral exposure to 900 mg/day (approximately 13 mg/kg/day) did not produce clinical hypothyroidism in healthy adults (Brabant et al. 1992); however, a dosage considerably lower,

Table 3-10. Typical Reference Ranges for Serum Thyroid Hormones and TSH in Humans

Hormone	Reference range	
	Metric	SI unit
Total T4	4–11 µg/dL	60–140 nM[a]
Free T4	0.7–2.1 ng/dL	10–25 pM[a]
Total T3	75–175 ng/dL	1.1–2.7 nM[a]
Free T3	0.2–0.5 ng/dL	3–8 pM
Reverse T3	15–45 ng/dL	0.2–0.7 nM
TSH	0.3–4.0 mU/L[b,c]	1–15 pM

[a]Children may have higher levels
[b]Assumes a biologic potency of 7–15 mU/mg
[c]Higher in neonates (de Zegher et al. 1994)

SI = Systems Integration; T3 = 3,5,3'-triiodo-L-thyronine; T4 = 3,5,3',5'-tetraiodo-L-thyronine (thyroxine); TSH = thyroid stimulating hormone

Sources: Stockigt 2000; Vanderpump and Tunbridge 1996

0.5 mg/kg/day for 14 days, produced a 70% inhibition of thyroid iodide uptake with no effects on the levels of circulating T4, T3, or TSH in serum, at least over the 14-day dosing period (Greer et al. 2002). In these short-term studies, it is possible that thyroid hormone production could have been suppressed by perchlorate inhibition of thyroid NIS without changing serum thyroid hormone levels. This could occur because the human adult thyroid contains a surplus of T4 to support normal levels of serum levels for several months (Greer et al. 2002). The ability of high dosages of perchlorate to lower T4 and T3 levels in serum is the basis for use of perchlorate in the pharmacological management of thyrotoxicosis, the clinical manifestation of abnormally elevated circulating levels of T4 and/or T3 (Soldin et al. 2001).

Perchlorate-induced Thyroid Enlargement and Cancer. Although there is no direct evidence of perchlorate causing cancer in humans, perchlorate has produced thyroid cell hyperplasia and papillary and/or follicular adenomas and/or carcinomas in rats and mice (see Section 3.2.2.7). Perchlorate itself does not appear to be genotoxic (see Section 3.3). Production of thyroid tumors in rodents appears to be related to perchlorate-induced inhibition of thyroid iodide uptake and the resulting triggering of the HPT feedback control mechanism that elevates serum TSH levels. Persistent stimulation of the thyroid by TSH results in hypertrophy and hyperplasia of thyroid follicle cells, which are reflected in an increase in the size and weight of the thyroid (goiter). Tumors appear to be a progression of this hyperplasia. The mechanism by which gland enlargement leads to thyroid tumors is not completely understood. Thyroid gland proliferation may increase the fixation of mutations in the thyroid and promote the development of autonomous nodules, regions of thyroid follicle tissue that are less responsive or unresponsive to serum TSH concentrations (Corvilain et al. 2000; Fagin 2000). Consistent with the concept that TSH-stimulation and the resulting thyroid cell hypertrophy and hyperplasia are contributing factors to thyroid tumorigenesis are the observations that thyroid tumors can be produced in rats by a variety of different treatments that chronically elevate serum TSH levels, including maintaining the animals on a diet deficient in iodide, or by exposing the animals to chemical agents (e.g., thiouracil compounds, sulfonamides) that disrupt thyroid hormone production (Capen 1997).

Developmental Effects of Perchlorate. Thyroid hormones are essential for normal development of the nervous system, lung, skeletal muscle, and possibly other organ systems (Forhead et al. 2002; Hume et al. 2001; Porterfield and Hendrich 1993). The fetus is dependent on maternal thyroid hormones at least until the fetal thyroid begins to produce T4 and T3 (Zoeller and Crofton 2000). In humans, this occurs at approximately 16–20 weeks of gestation. Brain development begins in humans prior to the onset of fetal thyroid hormone production, with a major growth spurt occurring between 12 and 18 weeks of gestation with the beginning of neuron multiplication (Pintar 2000). This is followed by glial cell multiplication,

myelination, and formation of dendritic extensions and synapses, which begin at approximately 18 weeks, reaching their peak near the end of gestation and continuing through postnatal years 1 and 2 (Boyages 2000; Fisher and Brown 2000; Oppenheimer and Schwartz 1997). Thyroid hormones are present in human amniotic fluid at 8 weeks of gestation prior to the onset of fetal thyroid hormone production (Contempre et al. 1993; Thorpe-Beeston et al. 1991). Thyroid hormone receptors are present and occupied by hormone at this time as well, suggesting that the fetus is capable of responding to maternal thyroid hormones (Bernal and Pekonen 1984; Ferreiro et al. 1988). Calvo et al. (2002) showed that first trimester fetal tissues are exposed to concentrations of free T4 (FT4) that depend ultimately on the circulating maternal levels of T4 or FT4. Thus, a decrease in the maternal supply results in lower concentrations of FT4 in fetal fluids and, consequently, of T4 available to the developing brain. The contribution of maternal thyroid hormones to the fetal thyroid hormone status is also evident from infants who have an inherited disorder that abolishes T4 production but are born, nevertheless, with normal serum thyroid hormone levels (i.e., euthyroid) and become hypothyroid after birth if not administered thyroid hormones within 2 weeks after birth (Larsen 1989; Vulsma et al. 1989). This suggests that transfer during fetal life is at least partially protective in cases where the fetus cannot produce adequate amounts of T4, providing that the maternal thyroid hormone production is not compromised. However, athyrotic babies, although born euthyroid, show retarded skeletal maturation at birth, suggesting that fetal thyroid function during earlier phases of gestation may be necessary for normal skeletal development (Rovet et al. 1987; Wolter et al. 1979). Uncorrected maternal hypothyroidism, on the other hand, may result in impaired neurodevelopment of the fetus with severe long-lasting implications. For example, Pop et al. (1999) studied a cohort of 220 healthy children and found that children of women with FT4 levels below the 5^{th} and 10^{th} percentiles at 12 weeks of gestation showed impaired psychomotor development at 10 months of age. In women with the lowest 10^{th} percentile FT4 concentrations at 12 weeks of gestation, maternal FT4 concentration was positively correlated with the children's psychomotor development. Haddow et al. (1999) measured TSH levels in serum collected from 25,216 women and found that the 7–9-year-old children of the 62 women with high TSH levels performed less well in 15 tests relating to intelligence, attention, language, reading ability, school performance, and visual-motor performance than children of women with normal TSH values. Their full-scale IQ scores on the Wechsler Intelligence Scale for Children averaged 4 points lower than those of the children of matched control women.

Studies in rats provide further support for the importance of maternal thyroid hormones in development. Both T4 and T3 are present in rat fetal tissues prior to the onset of hormone production by the fetal thyroid on approximately day 17 of gestation, and maternal hormones appear to make a significant contribution to hormone levels in the fetus in late gestation as well (Calvo et al. 1990; Escobar del Rey et

al. 1986; Morreale de Escobar et al. 1990; Zoeller and Crofton 2000). Furthermore, thyroid hormone-responsive genes that are important in early development of the brain are expressed in the rat fetus prior to fetal thyroid hormone production, and expression of these genes is sensitive to the maternal thyroid hormone status (Dowling and Zoeller 2000; Dowling et al. 2001). Disruption of the maternal thyroid hormone system of rats by removal of the maternal thyroid or maternal iodide deficiency results in decreased levels of thyroid hormones in the fetus, and maternal iodide deficiency will result in fetal iodide deficiency and congenital hypothyroidism (Escobar del Rey et al. 1986; Morreale de Escobar et al. 1985). These observations suggest an important role of maternal thyroid hormones in development of the rat fetus and that, by limiting the availability of thyroid hormones to the early fetus, suppression of maternal thyroid hormone production by perchlorate could translate into disruptions of fetal development. The availability of maternal T4 to the fetus appears to be particularly important for maintenance of T3 levels in the fetal rat brain. Treatment of pregnant rats with methimazole, an inhibitor of thyroid hormone synthesis, resulted in decreased levels of both T4 and T3 in fetal tissues, including fetal brain (Calvo et al. 1990). Maternal infusions of T4 restored brain T3 levels; however, maternal infusion of T3 had little restorative effect on brain T3 levels, although it was able to restore T3 levels in other fetal tissues. Studies in which radiolabelled T4 was administered to neonatal rats made hypothyroid by maternal or neonatal treatment with methimazole provide direct evidence for the enhanced production of brain T3 from T4 (Silva and Matthews 1984). These observations are consistent with an important role of local generation of T3 from T4 in the brain by the action of brain iodothyronine deiodinases in maintaining brain T3 levels (Darras et al. 1999; Zoeller and Crofton 2000). From a toxicological perspective, these observations also suggest that in the rat, a decrease in maternal serum T4 levels, even in the absence of changes in maternal serum T3 levels may have adverse consequences on fetal brain development. Zoeller and Rovet (2004), and others cited therein, have reviewed the issue of the role of thyroid hormones in brain development and concluded that studies of models of maternal hypothyroidism, hypothyroxinemia and congenital hypothyroidism suggest that the timing and severity of thyroid hormone insufficiency predicts the type and severity of the neurological deficits.

Perchlorate could potentially disrupt fetal thyroid hormone status by three mechanisms. Perchlorate inhibition of maternal thyroid iodide uptake, and the resulting suppression in production and levels of maternal thyroid hormones, could limit the availability of thyroid hormones needed for normal fetal development prior to the onset of fetal thyroid hormone production if thyroid function in the mother is compromised. Perchlorate can also cross the placenta and may directly inhibit fetal thyroid iodide uptake and, secondarily, fetal thyroid hormone production. By inhibiting NIS in breast tissue, perchlorate may also limit the availability of iodide to nursing infants, who depend entirely on breast milk for the iodide

needed to produce thyroid hormone (Agency for Toxic Substances and Disease Registry 2004). No information is available on the doses in humans that might decrease iodide uptake into breast milk. Radioiodine uptake into mammary milk was decreased in rats exposed to 1 or 10 mg/kg/day perchlorate in drinking water (Clewell et al. 2003b). Studies conducted in cows and goats have also shown that perchlorate can decrease radioiodine uptake into mammary milk (Howard et al. 1996).

Thyroid suppression at birth has been observed in infants born to mothers who received potassium perchlorate during pregnancy for treatment of hyperthyroidism (Crooks and Wayne 1960; Fisher et al. 1962). Direct evidence of maternal-fetal transfer of perchlorate and suppression of fetal thyroid iodide uptake and hormone production has been provided from studies of rats and guinea pigs (Clewell et al. 2003a; Postel 1957; Schröder-van der Elst et al. 2001; York et al. 2001b). Several epidemiological studies have explored the strength of possible associations between perchlorate exposures and neonatal thyroid hormone status. Although some of these studies are suggestive of a possible association between perchlorate exposures and elevated serum TSH levels in infants, the findings of the currently available epidemiological literature, taken *in toto*, is inconclusive regarding effects of perchlorate on neonatal thyroid hormone status (Brechner et al. 2000; Crump et al. 2000; Lamm and Doemland 1999; Li et al. 2000a, 2000b; Schwartz 2001). Furthermore, these studies were likely to be confounded because they did not obtain individual estimates of perchlorate exposure. Without this information, it is likely that these studies were comparing T4 levels, on average, among groups of people that were not, on average, exposed to different levels of perchlorate. Studies conducted in rats provide direct evidence that perchlorate exposures during pregnancy or lactation can disturb thyroid hormone status in the neonate (Brown-Grant 1966; Brown-Grant and Sherwood 1971; Clewell et al. 2003a, 2003b; Golstein et al. 1988; Lampe et al. 1967; Mahle et al. 2003; York et al. 2001a, 2003, 2004). The mechanisms for these effects have not been elucidated.

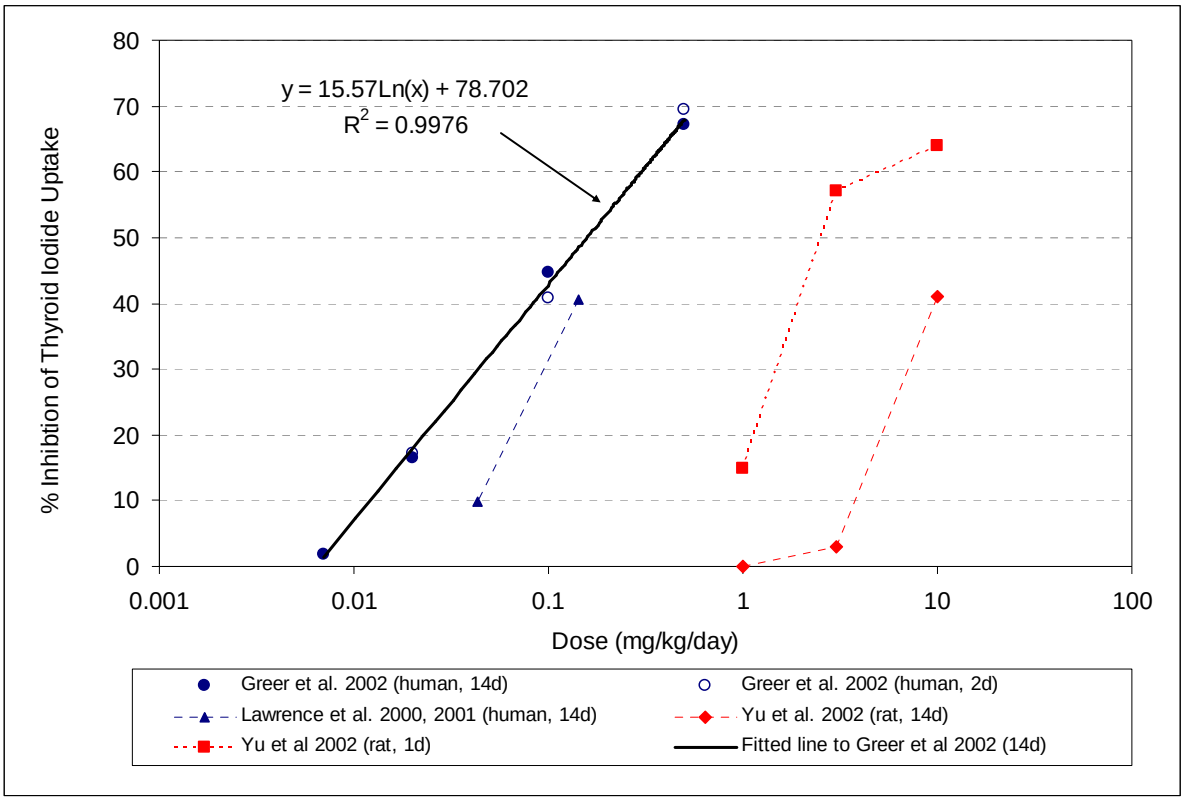
3.5.3 Animal-to-Human Extrapolations

The ability of perchlorate to inhibit thyroid uptake of iodide in both humans (Bürgi et al. 1974; DeGroot and Buhler 1971; Faure and Dussault 1975; Greer et al. 2002; Lawrence et al. 2000, 2001; Stanbury and Wyngaarden 1952) and animals (Kapitola et al. 1971; Ortiz-Caro et al. 1983; Schonbaum et al. 1965; Wyngaarden et al. 1952) is well established. Based on this ability, potassium perchlorate was widely used for a time as treatment to restore normal thyroid activity in patients with hyperactive thyroids (e.g., Crooks and Wayne 1960; Morgans and Trotter 1960). Therapeutically effective doses in humans were in the range of 5–20 mg perchlorate/kg/day.

Although abundant evidence exists to show that perchlorate can inhibit thyroid iodide uptake in humans, direct evidence that perchlorate can disrupt thyroid hormone levels and produce changes in thyroid morphology (in the absence of underlying thyroid disorder, such as Graves' disease or other causes such as thyrotoxicosis) derives largely from animal studies. Changes in serum levels of thyroid hormones, indicative of suppressed hormone production, and thyroid hypertrophy, indicative of stimulation of the thyroid gland by TSH, have been shown to occur in rats and mice exposed to perchlorate by the oral route (see Section 3.2.2.2, Endocrine Effects). Evidence that perchlorate can produce thyroid tumors also derives from the results of studies conducted in mice and rats (see Section 3.2.2.7). In humans and other mammals, a limitation in the availability of iodide for thyroid hormone production, regardless of the cause of the limitation, triggers an HPT feedback mechanism, which serves to maintain serum hormones at sufficient levels to satisfy physiological requirements. Extrapolation of dose levels that disrupt thyroid hormone status in animals to pharmacodynamically equivalent doses in humans must take into account not only potential species differences in perchlorate biokinetics, but also potential species differences in the compensatory response to a limitation in iodide availability to the thyroid.

Few studies have been reported that allow direct comparisons of the dose-response relationships for the effects of perchlorate on thyroid hormone status in humans and experimental animals. However, these studies indicate that the response of human adults to short-term oral dosages (mg/kg/day) of perchlorate is quantitatively different from the response observed in rats given comparable dosages. Inhibition of thyroid iodide uptake has been observed in healthy euthyroid adults who were exposed to dosages exceeding 0.007 mg/kg/day in drinking water (Greer et al. 2002; Lawrence et al. 2000). The dosage that produced a 50% inhibition of 24-hour thyroid iodide uptake was approximately 0.15 mg/kg/day when the exposure duration was either for 2 or 14 days (Figure 3-8; Greer et al. 2002). Oral doses that ranged from 0.007 to 0.5 mg/kg/day for 14 days had no observable effect on serum TSH or thyroid hormone levels in healthy adults (Greer et al. 2002; Lawrence et al. 2000). Oral doses of perchlorate that produced the same magnitude of inhibition of 24-hour thyroid iodide were higher in rats compared to humans. For example, in rats, 1 mg/kg/day in drinking water for 1 or 14 days produced a 0 or 15% inhibition, respectively (Figure 3-8; Yu et al. 2002). However, this same study observed inhibition of thyroid iodide uptake (10–30%) that was similar in magnitude to that observed in humans when iodide was administered to rats 2 hours following a single intravenous dose of 0.01 or 0.1 mg perchlorate/kg/day and thyroid iodide uptake was determined 2–9 hours following the radioiodide dose (Yu et al. 2002). Rats also exhibited elevated plasma levels of TSH when exposed to perchlorate for 14 days, and a pronounced attenuation of the inhibition in thyroid iodide uptake compared to the response observed following 2 days of exposure to

Figure 3-8. Comparison of Dose-Response Relationships for the Inhibitory Effect of Perchlorate on 24-hour Thyroid Iodide Uptake in Humans and Rats



Greer et al. (2002) administered perchlorate in drinking water to adult humans for 14 days and measured RAIU on exposure days 2 or 14. Lawrence et al. (2000, 2001) administered perchlorate in drinking water to adult humans for 14 days and measured RAIU on exposure day 14. Yu et al. (2002) exposed rats to perchlorate in drinking water for 1 day (24 hours) and measured RAIU on day 2 (day following cessation of exposure); rats were also exposed to perchlorate for 14 days and RAIU was measured on day 15.

perchlorate (Yu et al. 2002). Differences in the perchlorate dose-response relationships for thyroid iodide uptake between humans and rats may reflect the triggering of HPT feedback control mechanisms and induction of NIS, which serve to regulate thyroid iodide transport and hormone production in response to a decrease in serum thyroid hormones and iodide levels. The involvement of the HPT control mechanism in the response to perchlorate in the rat is consistent with the observed dose-response relationship for changes in serum T3, T4, and TSH levels (Figure 3-9). Perchlorate dosages of 1–5 mg/kg/day for 14 days in drinking water depressed serum levels of T3 and T4 and increased levels of TSH (Caldwell et al. 1995; Siglin et al. 2000; Yu et al. 2002). By contrast, serum hormone levels were unchanged in human adults who received dosages of up to 0.5 mg/kg/day for the same duration and who exhibited as much as a 70% inhibition of thyroid iodide uptake (Greer et al. 2002; Lawrence et al. 2000). These observations suggest that dosages of perchlorate that inhibit thyroid iodide uptake must occur over a longer duration to produce effects on circulating levels of thyroid hormones in healthy, euthyroid adult humans than in healthy, euthyroid adult rats (see Lewandowski et al. 2004 for review on interspecies differences). This is thought to be related to a smaller and more rapid turnover of the hormone pool in the rat thyroid, and to a more rapid clearance of secreted hormone in the rat (serum half-life for T4 is shorter in rats than in humans).

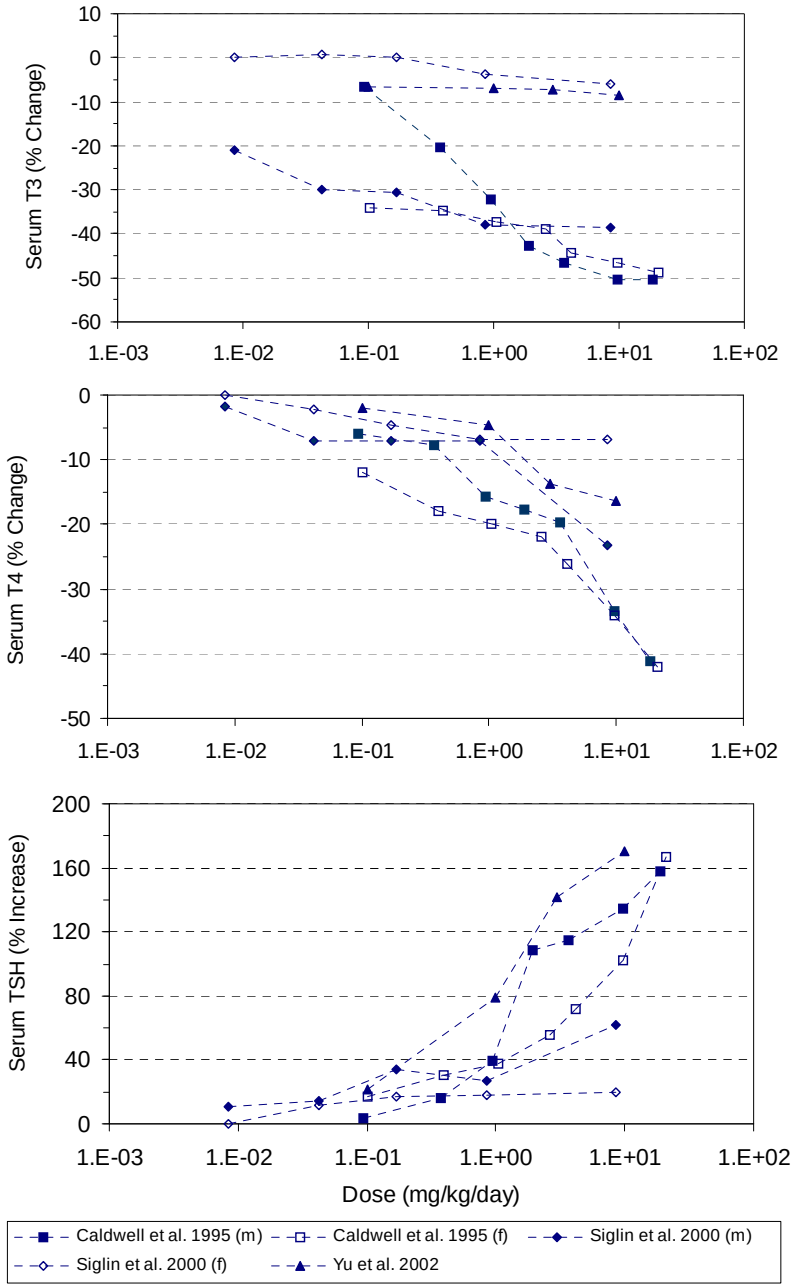
Less is known about the relative sensitivities of humans and experimental animals to developmental effects of perchlorate. Outstanding uncertainties include potential differences in kinetics of maternal-fetal and maternal-infant transfer of perchlorate, as well as potential differences in the degree to which the fetus of the human, in comparison to experimental animals, is dependent on maternal thyroid hormone for development, particularly during the period of gestation prior to the onset of fetal hormone production.

NAS (2005) reviewed the human and animal data and concluded that the human data provided a more reliable point of departure for the risk assessment than the animal data. In agreement with the above discussion, NAS (2005) further noted that: “the rat is a good quantitative model for assessing inhibition of iodide uptake by the thyroid caused by perchlorate exposure, but it is only a good *qualitative* model for the effects of that inhibition.”

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate

Figure 3-9. Changes in Serum Thyroid Hormone Levels in Rats Exposed to Perchlorate in Drinking Water for 14 Days



terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents.* The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997a). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Perchlorate can impair thyroid hormone production and, therefore, can be classified as an *endocrine disruptor*. As discussed in Sections 3.2.2.2 (Systemic-Endocrine Effects) and 3.5.2 (Mechanisms of Toxicity), at sufficiently high dosages, perchlorate can limit the availability of iodide needed for the production of the hormones in the thyroid and can depress serum levels of the thyroid hormones, T4 and T3. The latter effect triggers HPT feedback control mechanisms to produce TSH, which stimulates growth of the thyroid and induces NIS, the primary mechanism by which iodide enters thyroid follicle cells from the blood and the first step in the uptake of iodide into the thyroid and formation of thyroid hormones. Thus, perchlorate exposure at sufficiently high doses has the potential for producing all of the adverse consequences of hypothyroidism including impairments in the development of the nervous systems and other organ systems, thyroid gland enlargement, and follicular cell hyperplasia and neoplasia.

However, studies discussed earlier indicate that at perchlorate levels routinely found in the environment, no evidence of such adverse effects have been observed or documented.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when most biological systems have fully developed. However, the brain continues to develop until about 25 years of age. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and

Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Fetuses, infants and children may be especially susceptible to the thyroid effects of perchlorate. Thyroid hormones regulate cell proliferation, migration, and differentiation during development, therefore, maintenance of normal levels is essential to normal growth and development. Disruption of circulating hormone levels can have markedly different effects, depending on the stage of development. Effects can include mental retardation, impaired motor skills, and hearing and speech impediments (Boyages 2000; Fisher and Brown 2000; Haddow et al. 1999; Pop et al. 1999). Several factors may contribute to a high vulnerability of the fetus and neonate to perchlorate (see Section 3.10, Susceptible Populations, for further details). In addition, as discussed by NAS (2005), preterm infants are more sensitive to thyroid hormone perturbations than term infants.

Thus far, there is no conclusive evidence that exposure to perchlorate produces developmental effects in humans. Two studies of newborns in Arizona and California reported that neonates from women whose drinking water contained perchlorate had higher TSH values than those from women with no exposure to perchlorate (Brechner et al. 2000; Schwartz 2001). However, the methods used in the two latter studies have been questioned. Other similar studies in the United States have found no significant associations between maternal exposure to perchlorate via the drinking water and T4 levels (Li et al. 2000a), TSH levels (Li et al. 2000b), and incidence of congenital hypothyroidism (Kelsh et al. 2003; Lamm and Doemland 1999). Two studies of Chilean neonates whose mothers may have been chronically exposed to up to 100–120 μg/L (ppb) of perchlorate in the drinking water found no evidence of adverse thyroid

effects among the neonates (Crump et al. 2000; Téllez et al. 2005). Studies in experimental animals have shown that exposure of the mother to perchlorate during gestation, or even during lactation, can lead to reduced thyroid hormone levels and associated thyroid effects in the offspring (Brown-Grant and Sherwood 1971; Golstein et al. 1988; Lampe et al. 1967; Postel 1957; York et al. 2001a, 2003, 2004). Evaluation of a series of neurobehavioral parameters in rat pups exposed to perchlorate *in utero* (maternal exposure up to 8.5 mg perchlorate/kg/day) and through maternal milk revealed no significant treatment-related effects (Bekkedal et al. 2000; York et al. 2004). Microscopic examination of the brain from 12-day-old pups showed a significant increase in the thickness of the corpus callosum from females in the highest dose group, 8.5 mg/kg/day (York et al. 2004), but a subsequent study by the same group of investigators reported a similar effect at 0.09 and 0.9 mg/kg/day, but not at highest dose tested, 25.5 mg/kg/day (York et al. 2005b). The toxicological significance of this finding is controversial and its biological significance has been questioned (NAS 2005). High-dose male offspring sacrificed at about 80 days of age had a significant increase in brain weight and in the weight of the prefrontal cortex and corpus callosum (York et al. 2004). Exposure to perchlorate has not caused teratogenic effects in animals.

Perchlorate has been shown to cross the placenta of rats (Clewell et al. 2003a; Schröeder-van der Elst et al. 2001). Thus, in addition to the potential for perchlorate to exert effects on fetal development by depressing levels of maternal thyroid hormones, perchlorate may exert direct effects on the fetal thyroid. Thyroid suppression at birth has been observed in infants born to mothers who received potassium perchlorate during pregnancy for treatment of hyperthyroidism (Crooks and Wayne 1960; Fisher et al. 1962). Direct evidence of maternal-fetal transfer of perchlorate and suppression of fetal thyroid hormone production has been provided from studies of rats and guinea pigs (Postel 1957; York et al. 2001b; Yu et al. 2002).

Studies conducted in experimental animals have shown that perchlorate enters mammary milk (Clewell et al. 2003b). Perchlorate has also been detected in human breast milk at a mean concentration of 10 ppb (Kirk et al. 2005). Whereas this indicates that nursing infants may be exposed to perchlorate in breast milk, whether the amount of perchlorate in the breast milk is great enough to affect thyroid function of the infant has not been demonstrated. However, a recent study in rats showed that the NIS actively concentrates perchlorate in the milk and suggested that exposure of newborns to high levels of perchlorate may pose a greater health risk than previously thought because it could directly inhibit the newborn thyroidal iodide uptake (Dohán et al. 2007). Nevertheless, the beneficial aspects (biological and

psychological) of breast-feeding outweigh any risks from exposure to perchlorate from mother's milk, especially if they consume adequate iodine from food and supplements.

Models of the biokinetics of perchlorate in adult humans and rats have been developed (Fisher et al. 2000; Merrill et al. 2003, 2005). An adult rat model has been extended to include pregnancy and maternal-fetal transfer of perchlorate, and lactation and maternal-pup perchlorate transfer through milk (Clewell et al. 2003a, 2003b). These models have been used to develop predictive models for the human gestation and postnatal period (Clewell et al. 2007). In the latter study, pregnant and lactating women, the fetus, and nursing infants were predicted to have higher concentrations of perchlorate in blood and greater thyroid iodide uptake inhibition at a given concentration of perchlorate in drinking water than either nonpregnant adults or older children. Although the fetus was predicted to receive the greatest dose, the predicted extent of iodide inhibition was not significant (approximately 1%) at the NAS-recommended reference dose of 0.7 µg/kg/day for perchlorate.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to perchlorates are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by perchlorates are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Perchlorates

Studies in workers exposed to perchlorate (Lamm et al. 1999) and in volunteers who ingested daily doses of perchlorate for 14 days (Lawrence et al. 2000) indicate that perchlorate is rapidly eliminated unchanged in the urine (see Section 3.4.4). Urine, therefore, is a convenient testing medium for perchlorate. However, the excretion of perchlorate is so rapid that an acute exposure might be detectable for only a few days after exposure. Both occupational studies and studies with volunteers have estimated an elimination half-life for perchlorate of approximately 8–12 hours (Greer et al. 2002; Lamm et al. 1999; Lawrence et al. 2000). The methods used for measuring perchlorate in urine have not been standardized (see also Section 7.1).

Using a highly selective analytical method of coupled ion chromatography and electrospray tandem mass spectrometry, Valentín-Blasini et al. (2005) found an association between urinary levels of perchlorate with the concentrations of perchlorate in drinking water in a population of women from Chile. In a population with no known perchlorate drinking water contamination, concentrations of perchlorate adjusted for urinary creatinine showed a median level of 7.8 µg perchlorate/g creatinine, with a range of 1–35 µg perchlorate/g creatinine. Although the intake of perchlorate through food had not been measured in this population, this population probably has a high background dietary intake of perchlorate because

Chilean soil is a natural source of of perchlorate. When the urine samples of the pregnant women in three cities in the study in Chile (Crump et al. 2000) were analyzed by this method, the women in the city with a drinking water concentration of perchlorate of about 0.4 ng/mL had a median urinary concentration of 21 μg perchlorate/g creatinine, those with a drinking water concentration of about 5.8 ng/mL had a median urinary concentration of 37 μg perchlorate/g creatinine, and those with a drinking water concentration of about 114 ng/mL had a median urinary concentration of 120 μg perchlorate/g creatinine (Valentín-Blasini et al. 2005). Recently, Gibbs (2006) demonstrated a highly significant linear correlation between the concentration of perchlorate in serum and dose over a dose range covering almost four orders of magnitude. The studies that contributed data for Gibbs' analysis included Brabant et al. (1992), Crump et al. (2000), Lawrence et al. (2000), and Merrill et al. (2005).

Perchlorate has also been detected in human breast milk, but the concentrations were not correlated with the water consumed by the lactating women. As perchlorate is fairly rapidly cleared when exposure ceases, the presence of perchlorate in breast milk may be highly variable with time and recent dietary history (Kirk et al. 2005; Pearce et al. 2007).

Other potential biomarkers of exposure to perchlorate relate to their effect on the thyroid gland. As described in Section 3.5.2, Mechanisms of Toxicity, perchlorate blocks uptake of iodide into the thyroid, leading to an increase in the serum level of free iodine (i.e., not bound to T4), which is then excreted in urine. No study has developed a correlation between exposure to particular dose levels of perchlorate and specific relative increases of free iodine in serum or urine. In serum, the normal level of free iodine ranges from 1.0 to 5.2 μg/L and the level of protein-bound iodine ranges from 32 to 72 μg/L. Iodine is excreted in urine at a rate that is nearly equal to the rate of intake, or approximately 100–200 μg/24 hours (Agency for Toxic Substances and Disease Registry 2004). Saliva also has potential as a source of noninvasive biomarker because anions such as perchlorate are actively sequestered into the salivary gland by the NIS. Perchlorate produces a decrease in the levels of T3 and T4 in serum, while increasing the serum level of TSH in rats, but this has not been shown in humans at doses below those used in clinical medicine to treat thyrotoxicosis. Specific correlations between levels and duration of exposure to perchlorate and alterations in serum levels of T3, T4, or TSH in humans have not been developed. Furthermore, these potential biomarkers are not specific to perchlorate; other antithyroid agents, such as carbimazole, can have similar effects.

3.8.2 Biomarkers Used to Characterize Effects Caused by Perchlorates

The thyroid is the critical target for perchlorate. Perchlorate blocks uptake of iodide into the thyroid, leading to an increase in the serum level of free iodine (i.e., not bound to T4), which is then excreted in urine. If the dosage is sufficient to limit the availability of iodide for the production of thyroid hormones, then perchlorate can also produce a decrease in the levels of T3 and T4 in serum, while increasing the serum level of TSH. Therefore, levels of iodide in serum or urine, and levels of T3, T4, and TSH in serum, can all be considered to be biomarkers of effect for perchlorate. A recent study showed that in women with urinary iodine <100 µg/L, urinary perchlorate (which is a measure of perchlorate intake) was a significant negative predictor of TT4 and a positive predictor of TSH (Blount et al. 2006). It should be noted that none of these biomarkers is specific to perchlorate; other antithyroid agents such as carbimazole can have similar effects. It should also be noted that TT4 is not routinely measured for clinical significance as it is too impacted by other biological variables. Although the specific amount of change in these biomarkers associated with a demonstrably adverse effect has not been established, changes in these parameters can be considered to indicate potential impairment of health. Typical normal ranges for hormone levels are shown in Table 3-4.

3.9 INTERACTIONS WITH OTHER CHEMICALS

No studies were located regarding health effects in humans exposed to perchlorate in combination with other chemicals that are likely to be found with perchlorate in the environment, in the workplace, or at hazardous waste sites.

Limited information was found in studies in animals. Administration of a single dose of 7.5 or 75 µg/kg of 3,3',4,4'5-pentachlorobiphenyl (PCB 126) to rats followed 9 days later by doses of up to 1 mg perchlorate/kg/day in the drinking water for additional 14 days showed less than additive effects on serum TSH, TT4, FT4, and hepatic T4-glucuronide (McLanahan et al. 2007). Exposure to lower doses of each chemical (NOEL doses), resulted in no interaction between the chemicals for the thyroid indices measured. In another study, simultaneous exposure of rats to various concentrations of ammonium perchlorate and sodium chlorate for 7 days reduced serum total T4 to a greater extent than either chemical alone (Khan et al. 2005).

Tonacchera et al. (2004) investigated the simultaneous joint effects of perchlorate and other competitive inhibitors of iodide uptake (thiocyanate, nitrate, and non-radioactive iodide) in inhibiting RAIU in an *in vitro* test system in which human NIS was stably transfected into a Chinese hamster ovary (CHO) cell

line. The relative potency of perchlorate to inhibit $^{125}I^-$ uptake at the NIS was 15, 30, and 240 times that of thiocyanate, non-radioactive iodide, and nitrate, respectively, on a molar concentration basis. The results showed that the anions interact in a simple additive fashion and that the concentration response for each inhibitor was indistinguishable from that of each of the others after adjusting for differences in inhibition potencies.

Nitrate and thiocyanate are widely distributed in nature and, because both anions also inhibit RAIU, as demonstrated by Tonacchera et al. (2004), should also be included in the discussion of the effects of inhibition of the NIS by anions. Nitrate is a natural constituent of green leafy vegetables and is also used as a preservative. Administration of a diet containing 3% potassium nitrate to rats for 4 weeks resulted in a significant increase in thyroid weight and serum TSH levels and in reductions in serum T3 and T4 (Mukhopadhyay et al. 2005). Thiocyanate can be derived from thioglucosides present in foods such as cabbage, cauliflower, and broccoli, and is also found in tobacco. The effects of thiocyanate on thyroidal function of humans have been known for a long time. Gibbs (2006) reviewed the literature and reported that no adverse or non-adverse thyroidal effects of thiocyanate occur at serum concentrations of thiocyanate <50 µmol/L. This concentration of thiocyanate is equivalent to approximately 3.3 µmol perchlorate/L in terms of iodine uptake inhibition (Tonacchera et al. 2004). To achieve such concentration of perchlorate in serum, the daily dose of perchlorate would have to be 0.27 mg/kg/day, or a 70-kg adult would have to drink 2 L of water daily containing 9 mg perchlorate (Gibbs 2006). However, extrapolating data from the *in vitro* studies such as the Tonacchera et al. (2004) study to situations *in vivo* may not be appropriate because the *in vitro* studies cannot account for the relative human half-lives of perchlorate, thiocyanate, and nitrate or other factors such as protein binding and chronicity. In a related study, De Groef et al. (2006) examined the possible contribution of nitrate and thiocyanate to NIS inhibition. Using EPA's current Maximum Contaminant Level (MCL) for nitrate in drinking water, De Groef et al. (2006) showed that the concentration of nitrate allowed in water would cause an inhibition of iodine uptake by the NIS equivalent to 300 ppb perchlorate, 12 times greater than the concentration of about 25 ppb that corresponds to the RfD for perchlorate proposed by the NAS (assuming a 70-kg adult consuming 2 L of water per day). The same exercise with thiocyanate showed that the MCL for thiocyanate is equivalent to approximately 23 ppb perchlorate. The conclusion reached by the investigators was that "when considering the potential thyroid-related health risks posed by monovalent anions, perchlorate only accounts for a small fraction (<10%) of the exposure from drinking water."

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to perchlorates than will most persons exposed to the same level of perchlorates in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of perchlorates or compromised function of organs affected by perchlorates. Populations who are at greater risk due to their unusually high exposure to perchlorates are discussed in Section 6.7, Populations with Potentially High Exposures.

Any condition affecting processes by which circulating iodide ultimately becomes part of a functional thyroid hormone will increase the susceptibility to substances that affect thyroid function such as perchlorate. Among these conditions are genetic factors. This topic has been reviewed by Scinicariello et al. (2005) and original citations can be obtained therein. For example, people with congenital iodide transport deficit (ITD), an infrequent autosomic recessive condition that has been linked to mutations of the perchlorate-sensitive NIS gene, may exhibit a defective transport of iodide from circulation into the thyroid cell. People who suffer from Pendred Syndrome (PDS), an autosomal recessive disorder characterized by deafness and goiter, may have a diminished iodide transport over the apical membrane, which causes iodide to remain in the thyrocyte. The PDS gene product pendrin is a protein that transports chloride and iodide and mediates the exchange of chloride and formate. Increased susceptibility to perchlorate can also result from defects in iodide organification, a process by which iodide is oxidized and bound to thyrosine residue in thyroglobulin. Mutations identified in proteins involved in the iodination of the thyrosine residue may result in accumulation of iodide in the thyrocyte.

As discussed in NAS (2005), fetuses and preterm newborns constitute the most sensitive populations, although infants and developing children are also considered sensitive populations. The expected high sensitivity of developing organisms is due to the important role played by thyroid hormones during development (Zoeller 2006; see also Section 3.5.2). Perchlorate may reduce the level of circulating thyroid hormones in the blood, and low thyroid hormone levels during embryonic or fetal development can lead to effects such as mental retardation, impaired motor skills, and hearing and speech impediments (Haddow et al. 1999; Pop et al. 1999; Soldin et al. 2001). This is because the fetus is dependent on maternal thyroid hormones at least until the fetal thyroid begins to produce T4 and T3 (Zoeller and Crofton 2000). In humans, this occurs at approximately 16–20 weeks of gestation. Perchlorate also can inhibit the NIS in breast tissue (Levy et al. 1997; Smanik et al. 1997; Spitzweg et al. 1998), and therefore may limit the availability of iodide to nursing infants, who depend entirely on breast milk for the iodide

needed to produce thyroid hormone (Agency for Toxic Substances and Disease Registry 2004). However, in a study of 57 lactating women in Boston, Massachusetts, no correlation was found between perchlorate concentrations in breast milk and concentrations of iodide in breast milk (Pearce et al. 2007). As discussed by Ginsberg et al. (2007), additional factors that make neonates a sensitive group include their shorter serum half-life for T4 of approximately 3 days compared to approximately 7–10 days in adults, a lower storage capacity of the thyroid for T4, and possibly slower urinary clearance of perchlorate due to immature renal function. Hypothyroid pregnant women also constitute a susceptible group who may also put the fetus at higher risk if maternal hypothyroidism is present before the onset of fetal thyroid function at 10–12 weeks of gestation (Zoeller and Crofton 2000). Human models of pregnancy, maternal-fetal transfer, and maternal-infant transfer of perchlorate have also been developed (Clewell et al. 2007, see Section 3.4.5). These models have yielded predictions of external dose–internal dose relationships for various human lifestages (Clewell et al. 2007; see Tables 3-6 and 3-7). The models predict a relatively high vulnerability of the fetus, pregnant women, and lactating women to perchlorate-induced thyroid iodine uptake, compared to other lifestages (e.g., greater inhibition of thyroid iodide uptake occurs in the fetus in association with lower external doses). Women with low iodine intake may also constitute a susceptible group, as suggested by a recent study in which urinary perchlorate was reported to be a significant negative predictor of serum TT4 and a significant positive predictor of serum TSH in women with urinary iodine <100 µg/L (Blount et al. 2006).

People with reduced thyroid activity from other causes may also be an unusually susceptible population. This includes people living in endemic goiter areas with low iodine intake, people with exposure to other anti-thyroid drugs (e.g., lithium) (Green 1996; Spaulding et al. 1972), and people with Hashimoto's disease (autoimmune hypothyroidism [Weetman 2000]) or other diseases that reduce thyroid hormone levels. Exposure to perchlorate may produce additional deficiencies in these people beyond those due to their pre-existing conditions, potentially increasing the severity of their conditions.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to perchlorates. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to perchlorates. When specific exposures have occurred, physicians who specialize in thyroid disorders should be consulted for medical advice.

No texts were located that provided specific information about treatment following exposures to perchlorate.

3.11.1 Reducing Peak Absorption Following Exposure

There are no established methods for managing initial exposure to perchlorate or for reducing peak absorption

Since perchlorate is readily excreted in the urine, it is reasonable to assume that increasing the water uptake would help the body eliminate perchlorate. No studies have investigated this issue.

3.11.2 Reducing Body Burden

Perchlorate is readily eliminated from the body and does not bioaccumulate or result in a body burden. The elimination half-life for perchlorate has been estimated to be 8–12 hours (Durand 1938; Greer et al. 2002; Lamm et al. 1999).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

There are no published studies on the treatment of perchlorate exposure by interfering with its mechanism of toxicity. Since the inhibition of the NIS by perchlorate can limit the availability of iodide needed for the production of T4 and T3 in the thyroid, it is important to maintain an adequate intake of iodine.

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of perchlorates is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of perchlorates.

The following categories of possible data needs have been identified. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In

the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Perchlorates

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to perchlorates are summarized in Figure 3-10. The purpose of this figure is to illustrate the existing information concerning the health effects of perchlorates. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

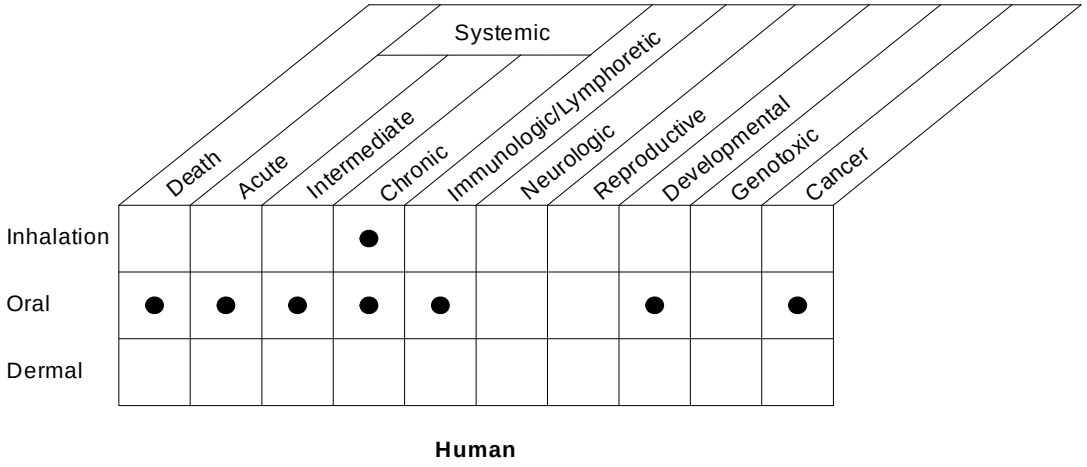
Human studies on perchlorate include cross-sectional epidemiology studies of perchlorate workers with inhalation exposure, short-term oral experimental studies on healthy and hyperthyroid subjects, general population studies of adults, school-age children, and neonates, and case reports of hyperthyroid patients with intermediate- or chronic-duration oral treatment with perchlorate.

Animal studies for perchlorate are available only by the oral route. The available studies have included investigation of systemic effects by acute, intermediate, and chronic exposure, as well as immunological, reproductive, and developmental effects, lethality, and cancer. Limited information is available regarding effects of perchlorate on the nervous system in adult animals. No experimental studies have been conducted that examine the interactions of perchlorate exposure and dietary iodine levels.

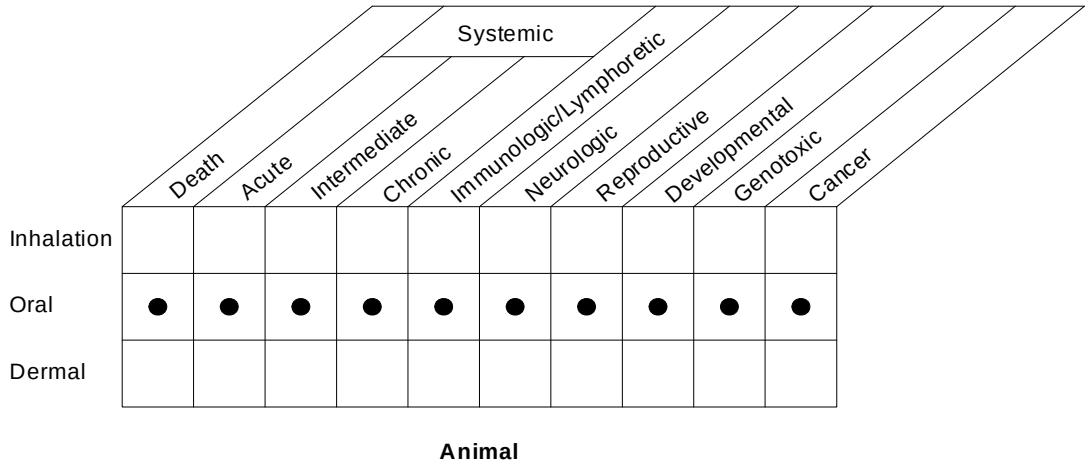
3.12.2 Identification of Data Needs

Acute-Duration Exposure. Acute-duration studies are available for healthy humans (Bürgi et al. 1974; DeGroot and Buhler 1971; Faure and Dussault 1975; Greer et al. 2002; Lawrence et al. 2000, 2001) and animals (Arieli and Chinet 1985; BRT 2000; Caldwell et al. 1995; DOD 1999; Kapitola et al. 1971; Mannisto et al. 1979; Matsuzaki and Suzuki 1981; Schonbaum et al. 1965; Siglin et al. 2000; Spreca and Musy 1974) orally exposed to perchlorate. These studies suggest that the thyroid is the main target for acute exposure to perchlorate. The study by Greer et al. (2002) identified a NOEL for radioactive iodine

Figure 3-10. Existing Information on Health Effects of Perchlorate



Human



Animal

● Existing Studies

uptake by the thyroid of 0.007 mg/kg/day. NAS (2005) recently completed an evaluation of the literature on perchlorate and derived an RfD of 0.0007 mg/kg/day based on the findings of Greer et al. (2002). ATSDR has adopted the EPA's chronic RfD recommended by NAS (2005) for the chronic oral MRL. Acute and intermediate MRL values will need to be assessed as relevant data from new studies are published. Conducting acute studies by the inhalation route does not seem warranted since this route of exposure does not play a significant role in environmental exposures to perchlorate. Although dermal absorption of perchlorate should be negligible, information on dermal absorption and dermal toxicity studies could be useful because skin contact with perchlorate in water supplies is likely when water contains perchlorate. In its review of perchlorate toxicity, NAS (2005) notes that further studies of perchlorate in rats would be of limited utility for clarifying the health effects of perchlorate in humans. Instead, NAS recommends conducting a series of *in vitro* studies using human tissues and animal studies to determine the role of NIS in placental iodide transport, the susceptibility of breast NIS to perchlorate inhibition, the role of iodide status in these effects, and the effects of perchlorate on development independently of effects on iodide transport. NAS (2005) further notes studies on the effects of perchlorate on other tissues that contain NIS could be conducted.

Intermediate-Duration. Intermediate-duration studies are available for humans (Brabant et al. 1992; Braverman et al. 2006) and animals (Bekkedal et al. 2000; BRT 2000; DOD 1999; Eskin et al. 1975; Gauss 1972; Hiasa et al. 1987; Logonder-Mlinsek et al. 1985; MacDermott 1992; Ortiz-Caro et al. 1983; Pajer and Kalisnik 1991; Postel 1957; Sangan and Motlag 1986, 1987; Selivanova and Vorobieva 1969; Shevtsova et al. 1994; Siglin et al. 2000; Tarin-Remohi and Jolin 1972; Vijayalakshmi and Motlag 1989a, 1989b, 1990, 1992; York et al. 2001a, 2001b, 2003, 2004, 2005a, 2005b) orally exposed to perchlorates. Brabant et al. (1992) studied the effect of administration of perchlorate for 4 weeks on thyroid hormone levels in healthy volunteers and their findings suggested that a period of iodide deficiency may increase the sensitivity of the thyroid to TSH. Braverman et al. (2006) reported that administration of up to approximately 0.04 mg perchlorate/kg/day to volunteers for 6 months caused no significant alterations in thyroid function tests, including radioiodine uptake. The studies in animals provided information on systemic, immunologic, reproductive, and developmental effects of perchlorate. The thyroid gland was shown to be the most sensitive target. Almost all of the earlier studies used only one dose level, usually quite high. Studies conducted in the past few years have used much lower doses, which allow the construction of dose-response relationships and the identification of NOAELs and LOAELs. In three of these studies (Siglin et al. 2000; York et al. 2003, 2005a), ATSDR identified LOAELs of 0.009 mg/kg/day. Additional studies in animals would be useful to clarify some controversial findings of the studies recently available. These findings concern effects of perchlorate on neurobehavioral effects

and brain morphometry in young animals exposed *in utero.* As indicated above, additional studies in rats for the purpose of clarifying the health effects of perchlorate in humans seem unnecessary given the difference in the manner rats and humans handle the inhibition of iodide uptake by the thyroid. As mentioned above, studies by inhalation and dermal exposure do not seem necessary at this time since the most relevant route of exposure for perchlorate is the oral route, specifically drinking water.

Chronic-Duration Exposure and Cancer. Humans with chronic inhalation exposure to perchlorate at work were the subject of cross-sectional epidemiology studies (Braverman et al. 2005; Gibbs et al. 1998; Lamm et al. 1999). These studies found no significant effects associated with perchlorate exposure. Cancer has not been reported in humans with exposure to perchlorate. A study by Li et al. (2001) found no significant association between perchlorate in drinking water and the prevalence of thyroid diseases or thyroid cancer residents in Nevada counties. However, no information was available on age, gender, ethnicity, iodine intake, and other risk factors. An additional study of cancer among residents of San Bernardino County, California, was limited by mixed exposures and lack of adjustment for potential confounding variables (Morgan and Cassady 2002). A few chronic-duration studies of toxicity and carcinogenicity are available in animals exposed to perchlorate orally (Kessler and Kruskemper 1966; Toro Guillen 1991). A few intermediate-duration carcinogenicity studies by the oral route are also available (Florencio Vicente 1990; Gauss 1972; Pajer and Kalisnik 1991). The data from these studies are limited for assessment of toxicity or carcinogenicity, however, because only a high dose level was used. Still, it was evident that the main target of toxicity was the thyroid gland, as thyroid adenomas and/or carcinomas were observed in the animals. It is unclear whether additional studies would provide new key information. As noted above, ATSDR has adopted the NAS (2005) recommended RfD for the chronic oral MRL. EPA adopted this chronic RfD based on the NAS (2005) recommendation. NAS (2005) recommended a clinical study designed to provide information on the potential chronic effects of low-dose perchlorate exposure on thyroid function, with a special focus on the ability and mechanisms of thyroid compensation. If for ethical or other reasons it is not possible to conduct studies in humans, NAS (2005) suggested that chronic studies in nonhuman primates could provide useful information. However, baseline thyroid studies would have to be conducted first to compare strains of monkeys to humans.

Genotoxicity. No genotoxicity studies were located for perchlorate in humans, but two studies were located in animals *in vivo.* Siglin et al. (2000) found no evidence of bone marrow micronucleus formation in male and female rats exposed to perchlorate in the drinking water for 90 days. Similar negative results were reported by Zeiger et al. (1998b) in mice treated with perchlorate intraperitoneally

for 3 days. *In vitro* studies were limited to a test for SOS-inducing activity in *S. typhimurium* (Nakamura and Kosaka 1989), a test for production of DNA-protein cross links in cultured human lymphocytes (Costa et al. 1996), tests for mutagenicity in various *Salmonella* strains (Zeiger et al. 1998a), and a mouse lymphoma assay (San and Clarke 1999). Perchlorate gave negative results in all tests. Additional testing does not seem necessary at this time.

Reproductive Toxicity. No data on reproductive effects of perchlorate in humans were located. Earlier reproductive toxicity studies available for perchlorate in animals (Brown-Grant 1966; Brown-Grant and Sherwood 1971) were of limited utility for assessing reproductive toxicity because they included only brief exposure of females during gestation, limited investigation of reproductive end points, and single dose levels. In a two-generation reproduction study, exposure of rats to up to 25.5 mg perchlorate/kg/day did not affect any reproductive index (York et al. 2001b). In another study, exposure of rats to up to 25.5 mg perchlorate/kg/day beginning 2 weeks before cohabitation with untreated males and continuing during gestation did not result in any significant alterations in numbers of corpora lutea and implantations, percent implantation loss, litter size, early or late resorptions, or sex ratio (York et al. 2005a). In addition, a 90-day drinking water in rats did not find gross or microscopic alterations in the testes, prostate, epididymis, uterus, ovaries, or mammary glands (Siglin et al. 2000). That study also reported no significant effects on sperm motility, concentration, count, or morphology. Further studies do not appear to be necessary at this time.

Developmental Toxicity. There are several oral studies available that evaluated the effects of perchlorate on thyroid parameters in human newborns (Amitai et al. 2007; Brechner et al. 2000; Crump et al. 2000; Kelsh et al. 2003; Lamm and Doemland 1999; Li et al. 2000a, 2000b; Schwartz 2001; Téllez et al. 2005). Crump et al. (2000) also examined the effects of perchlorate on thyroid function in school-age children. For the most part, no significant alterations were reported, although Brechner et al. (2000) and Schwartz (2001) reported an association between high levels of perchlorate in the drinking water and elevated serum levels of TSH, but the methods used in the two latter studies have been criticized. The neurodevelopmental progress of children presumed to have been exposed to perchlorate *in utero* could be followed in longitudinal studies in search of possible long-term effects. Developmental toxicity studies are available for perchlorate in animals (Bekkedal et al. 2000; Brown-Grant and Sherwood 1971; Golstein et al. 1988; Lampe et al. 1967; Mahle et al. 2003; Postel 1957; York et al. 2001a, 2001b, 2003, 2004, 2005a, 2005b). Although the earlier studies were of limited utility because standard developmental toxicity end points were not monitored and only single high dose levels were administered, the studies conducted in the past few years have been able to establish dose-response relationships using relatively

low exposure levels of perchlorate. Exposure of pregnant rats to perchlorate has resulted in thyroid alterations in the pups at maternal doses as low as 0.009 mg/kg/day (York et al. 2003, 2005a). In addition to evaluating thyroid effects in the offspring, some recent studies have conducted neurobehavioral testing in the offspring at various ages and have also conducted histological and morphometric evaluations of pups' brains (Bekkedal et al. 2000; York et al. 2003, 2004, 2005b). However, these studies have not evaluated known thyroid hormone-responsive end points in brain; for example, expression of genes that are known to respond to thyroid hormone or maturation specific brain structures (i.e., Purkinje cells) that respond to thyroid hormone (Porterfield and Hendrich 1993; Zoeller and Crofton 2000). Furthermore, there is no evidence that the linear measures of specific brain areas that have been evaluated in animal studies are responsive to changes in circulating levels of thyroid hormone. Studies directed at characterizing the reaction of thyroid hormone responsive end points in brain to small changes in thyroid hormone have not been conducted. NAS (2005) noted that studies of pregnant monkeys could provide useful information on the effects of perchlorate on fetal and neonatal development. Continued research is necessary to help improve our understanding of the potential mechanistic steps resulting in thyroid hormone level changes from exposure to low levels of perchlorate and other environmental contaminants such as thyocyanate and nitrate that can inhibit iodide uptake and potentially result in prenatal and infant/early childhood effects. In addition, metabolic differences between perchlorate and other goitrogens, such as nitrate and thiocyanate (availability in the body) need to be further explored.

Immunotoxicity. Immune system and lymphoreticular effects due to perchlorate have not been systematically studied in healthy humans. Lymphoreticular effects were reported in one case series of human thyrotoxicosis patients treated with potassium perchlorate (Morgans and Trotter 1960). Immune effects in animals treated with very high doses of perchlorate (300–2,600 mg/kg/day) were reported as increases in the number and degranulation of mast cells in the thyroid and other tissues (Logonder-Mlinsek et al. 1985; Spreca and Musy 1974). More recent acute- and intermediate-duration studies assessed indices of humoral- and cell-mediated immunocompetence in mice (0.1–50 mg/kg/day), but there were deficiencies in the studies (BRT 2000; DOD 1999). It would be helpful if some other end points were studied, such as the determination of whether perchlorate increases the sensitizing response to other chemicals or whether perchlorate is a sensitizer itself.

Neurotoxicity. No data were located regarding neurological effects in humans or animals exposed to perchlorate. Neither 14-day nor 90-day studies in animals observed any signs indicative of neurotoxicant in adult animals. However, since thyroid hormone insufficiency is known to affect brain function in adult humans, and perchlorate can produce decreased circulating levels of thyroid hormone, it is likely that

perchlorate can, at some dose, impair brain function in adults. The dose-response relationship for these effects has not been characterized. As mentioned above under Developmental Effects, some studies in rats have suggested that exposure to perchlorate during pregnancy can cause neurodevelopmental alterations in the offspring (York et al. 2004, 2005b). The biological significance of some of the neurodevelopmental alterations, particularly the changes in thickness of the corpus callosum (York et al. 2004, 2005b), has been questioned (NAS 2005).

Epidemiological and Human Dosimetry Studies. Information on effects of exposure to perchlorate in healthy humans is derived from occupational studies (Braverman et al. 2005; Gibbs et al. 1998; Lamm et al. 1999), studies of the general population, including adults, children, and neonates (Brechner et al. 2000; Chang et al. 2003; Crump et al. 2000; Kelsh et al. 2003; Li et al. 2000a, 2000b, 2001; Schwartz 2001; Téllez et al. 2005) and controlled exposures in volunteers (Braverman et al. 2006; Greer et al. 2002; Lawrence et al. 2000, 2001). All of these studies provide information on the effects of perchlorate on thyroid parameters, but a few of them provide additional information on hematological, hepatic, and renal effects. Although it is well known that the thyroid is the target organ for perchlorate, the existing studies of the general population have had design limitations that preclude establishing with confidence the levels of environmental exposure that may induce clinically significant alterations in thyroid function and, therefore, represent a health risk. Well-designed epidemiological studies of environmentally exposed populations could provide valuable information and decrease the uncertainty of using data collected in acute studies in volunteers to establish long-term safe exposure levels. NAS (2005) identified pregnant women, their fetuses, and newborns as populations at greatest risk of the adverse effects of iodide deficiency and recommended that epidemiologic research should focus on assessing possible health effects of perchlorate exposure in these populations. These studies should use direct methods of exposure to perchlorate in individuals and methods more suitable for examining potentially causal associations. NAS (2005) further suggested that future research could be organized into additional analysis of existing data, new studies of health effects in selected populations, and monitoring of the frequencies of specific conditions in communities affected by the continuing efforts to reduce perchlorate in drinking water. Regarding a study in Chile (Téllez et al. 2005), NAS (2005) recommended incorporating more extensive neurodevelopmental assessments of the children beginning in infancy and continuing through school age. Specific end points that should be assessed in follow-up studies include auditory function, including measures of otoacoustic emissions; visual attention; cognitive function, including tests for executive function and memory; and tests of motor function, particularly balance, coordination, and rapid finger movements (NAS 2005). Increasing the sample sizes of the birth cohorts from the cities studied in Chile would be desirable to achieve appropriate statistical power for

detecting possible differences among exposure groups on the developmental assessments. NAS (2005) also suggested that the question of whether or not exposures to perchlorate at concentrations present in municipal drinking water are related to an increased incidence of maternal hypothyroidism during gestation could be addressed in the study of pregnant women in Chile (Téllez et al. 2005) and that using larger samples would improve the precision of the estimates.

Biomarkers of Exposure and Effect.

Exposure. Potential biomarkers of exposure include perchlorate in urine, breast milk, iodide in blood and urine, thyroid (T4, T3) and pituitary (TSH) hormones in blood, and radioactive iodine uptake. Perchlorate in urine is a biomarker that is specific for exposure to perchlorate; however, the biomarkers for iodine and thyroid hormones are not exclusive to perchlorate (changes may be produced by other anti-thyroid compounds and may be influenced by diet). One study of women from Chile found an association between urinary levels of perchlorate and drinking water concentrations of perchlorate (Valentín-Blasini et al. 2005). Further studies designed to correlate levels of one or more of these potential biomarkers with exposure levels would be useful to facilitate medical surveillance that can lead to early detection of exposure to perchlorate.

Effect. Biomarkers of effect for perchlorate also include levels of iodine in blood and urine, and thyroid (T4, T3) and pituitary (TSH) hormones in blood. Dosimetry has not been established to relate specific degrees of change in these markers to demonstrably adverse effects. Studies designed to perform this dosimetry would be useful to determine whether exposed populations may be experiencing adverse health effects due to perchlorate exposure.

Absorption, Distribution, Metabolism, and Excretion. Existing studies of absorption, distribution, metabolism, and excretion of perchlorate in humans provide information about the extent of absorption of ingested perchlorate and the extent and kinetics of urinary excretion of absorbed perchlorate (Anbar et al. 1959; Durand 1938; Greer et al. 2002; Lawrence et al. 2000). These studies lend support to estimates of elimination half-time of absorbed perchlorate of approximately 8–12 hours. Studies in animals provide support for the above estimates as well as information about the tissue distribution and kinetics of elimination of perchlorate from various tissues after intravenous or oral exposures (Chow and Woodbury 1970; Chow et al. 1969; Clewell et al. 2003a, 2003b; Durand 1938; Fisher et al. 2000; Goldman and Stanbury 1973; Lazarus et al. 1974; Selivanova et al. 1986; Yu et al. 2002). The above information has been used to support the development of PBPK models of perchlorate in adult humans,

adult rats, pregnant rats and rat fetus, and lactating rats and rat pups (Clewell et al. 2003a, 2003b, 2007; Fisher et al. 2000; Merrill et al. 2003, 2005).

All of the above studies were by the oral or parenteral routes; no information is available regarding absorption following inhalation or dermal exposure. Inhalation is a potential route of exposure for perchlorate workers, but may not be relevant for the general population; however, dermal absorption is expected to be negligible, but experimental information could confirm this expectation as dermal contact with water is likely when water contains perchlorate.

Comparative Toxicokinetics. Existing studies in humans and rats provide comparative information on the extent of absorption of ingested perchlorate, the routes of excretion of absorbed perchlorate, and the kinetics of excretion of absorbed perchlorate. PBPK models have been developed for the adult human and rat for the purpose of species extrapolation of oral or intravenous dosages of perchlorate (Clewell et al. 2003a, 2003b, 2007; Merrill et al. 2003, 2005). However, further research is necessary to determine how differences in thyroid physiology between humans and rats may affect the use of these models for human risk characterization and risk assessment. NAS (2005) identified a number of issues as potential data gaps with existing rat PBPK models including the need to: "(1) develop a more biologically-based description of placental transfer of perchlorate and iodide in rats, (2) determine whether perchlorate is transported by thyroid NIS if analytic methods of sufficient sensitivity can be developed or radiolabeled perchlorate with high radiochemical purity can be synthesized, (3) modify the adult human model to include the physiology of pregnancy and lactation to incorporate data from the recommended human clinical studies (if they are conducted), and (4) modify models to incorporate dietary iodide measurements from biomonitoring studies in pregnant or lactating women." Issue (2) has been partially addressed by a study that showed that the NIS actively transports perchlorate (Dohán et al. 2007). Issue (3) also has been partially addressed by a recent study that described a model that is able to predict iodide and perchlorate kinetics in the human from fetal life through adulthood, thus allowing the quantitative estimation of dose in the target tissue, the developing thyroid (Clewell et al. 2007).

Methods of Reducing Toxic Effects. There are no established methods for reducing the toxic effects of perchlorate. Removal of the individual from exposure would also be effective since perchlorate is rapidly eliminated from the body (elimination half-time 8–12 hours) (Greer et al. 2002). Research into methods for reducing the toxic effects of perchlorate would enable treatment for individuals experiencing adverse health effects due to perchlorate exposure.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

Children, infants, and the developing embryo and fetus may be especially susceptible to the thyroid effects of perchlorate because thyroid hormones are essential to normal growth and development. The embryo and fetus is dependent on maternal thyroid hormones prior to the onset of fetal thyroid hormone production at mid-gestation. Perchlorate studies in animals have shown that exposure of the mother to perchlorate during gestation, or even during lactation, can lead to reduced thyroid hormone levels and associated thyroid effects in the offspring (Brown-Grant and Sherwood 1971; Golstein et al. 1988; Lampe et al. 1967; Postel 1957; York et al. 2001b, 2003, 2004). Human models of pregnancy, maternal-fetal transfer, and maternal-infant transfer of perchlorate have also been developed (Clewell et al. 2007, see Section 3.4.5). These models have yielded predictions of external dose–internal dose relationships for various human lifestages (Clewell et al. 2007; see Tables 3-6 and 3-7). The models predict a relatively high vulnerability of the fetus, pregnant women, and lactating women to perchlorate-induced thyroid iodine uptake, compared to other lifestages (e.g., greater inhibition of thyroid iodide uptake occurs in the fetus in association with lower external doses). Further characterization of the toxicokinetics of perchlorate during pregnancy and lactation as well as comparisons of neurobehavioral tests between young animals exposed only *in utero* with animals exposed solely through lactation would provide valuable information.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

The following ongoing research has been identified in the Federal Research in Progress database (FEDRIP 2008).

Dr. J. Hershman from the Department of Veterans Affairs, Medical Center West Los Angeles, California, has proposed research to test the hypothesis that increasing iodide intake will prevent the deleterious effects of perchlorate on thyroid function; perchlorate does not alter thyroid cell growth; and perchlorate does not impair neural development through a direct effect on the brain. The research is sponsored by the Department of Veterans Affairs, Research and Development.

Drs. J. Fisher, F. Duncan, and J. Wagner from the University of Georgia are conducting research to develop biologically based pharmacokinetic (BBPK) maternal and fetal/neonatal models of the HPT axis in the rat by conducting experimental and computational research. The BBPK models of the HPT will describe the highly nonlinear relationships between the administered dose of thyroid active chemicals, mode-of-action, specific perturbations in the HPT axis, and developmental neurotoxicity. The research is sponsored by EPA's National Center for Environmental Research.

Dr. T. Zoeller from the University of Massachusetts is conducting research to test the hypothesis that thyroid hormone produces nonlinear, dose-dependent effects on end points within the developing brain, heart, and liver and to determine if some end points are more sensitive than others to thyroid hormones. Dr. Zoeller proposes that thyroid toxicants disrupting the HPT axis by different mechanisms will produce different dose-response curves on these end points. Dr. Zoeller suggests that a principle mechanism shaping the dose-response curve to thyroid hormone or by extension, thyroid disrupters, is a change in tissue metabolism of thyroid hormone in response to perturbations in the HPT axis. The research is sponsored by EPA's National Center for Environmental Research.