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Interim Drinking Water Health Advisory For Perchlorate

Interim Drinking Water Health Advisory
for Perchlorate

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LIST OF ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose level
BW	body weight
CAS	Chemical Abstracts Registry
CSF	Cancer Slope Factor
CDC	Centers for Disease Control and Prevention
CSF	cancer slope factor
DWEL	Drinking Water Equivalent Level
GD	gestation day
HA	Health Advisory
HSDB	Hazardous Substance Data Bank
IRIS	Integrated Risk Information System
kg	kilogram
L	liter
LOAEL	lowest observed adverse effect level
MDL	method detection limit
mg	milligram
mg/kg	milligram per kilogram of body weight
mg/L	milligrams per liter (equivalent to parts per million [ppm])
µg	microgram (one-millionth of a gram)
NHANES	National Health and Nutrition Examination Survey
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NRC	National Research Council
OW	Office of Water
PBPK	Physiologically-Based Pharmacokinetic
ppb	parts per billion
ppm	parts per million
RAIU	Radioactive Iodide Uptake
RfD	reference dose
RSC	relative source contribution
SIR	standardized incidence ratio
SDWA	Safe Drinking Water Act
T3	Triiodothyronine: thyroid hormone containing three iodine atoms
T4	Thyroxine: a biologically inactive prohormone containing four iodine atoms that is activated to triiodothyronine by deiodinase. (also known as tetraiodothyronine)
TSH	Thyroid stimulating hormone (also known as thyrotropin)
UCMR	Unregulated Contaminant Monitoring Regulation
UF	uncertainty factor

EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
USDA	U.S. Department of Agriculture

1.0 INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water (OW), provides information on the environmental properties, health effects, analytical methodology, and treatment technology for regulated and unregulated drinking water contaminants. HAs establish non-regulatory concentrations of drinking water contaminants at which adverse health effects are not anticipated to occur over specific exposure durations (one day, ten days, a subchronic period, several years, and a lifetime). For perchlorate, EPA is establishing an interim health advisory level for subchronic exposure. HAs serve as informal technical guidance to assist Federal, State and local officials, and managers of public or community water systems in protecting public health when emergency spills or contamination situations occur. They are not legally enforceable Federal standards and are subject to change as new information becomes available.

The Interim Drinking Water Health Advisory level (15 µg/l) is based on the recommendations of the National Research Council (NRC) of the National Academies as reported in "Health Implications of Perchlorate Ingestion" (NRC, 2005). The NRC recommended and EPA adopted a Reference Dose (RfD) of 0.7 µg/kg/day. The NRC perchlorate committee took into consideration presentations at the committee's public meetings, submitted public comments, and the comments made by technical experts on the draft NRC perchlorate report. The NRC review followed two external draft toxicological reviews of perchlorate prepared by EPA (1998, 2002) that were also subject to public comment and independent external review. The NRC report can be accessed at http://www.nap.edu/catalog.php?record_id=11202.

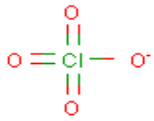
On October 10, 2008, the Agency issued a preliminary determination for perchlorate in the *Federal Register* for public review and comment (USEPA, 2008a). The notice described the Agency's preliminary decision that there is not a "meaningful opportunity for health risk reduction" through a national drinking water regulation. Based on the comments that it received, EPA believes that it would benefit once again from NRC input regarding perchlorate, this time in the context of the application of the physiologically-based pharmacokinetic (PBPK) modeling and assumptions regarding sensitive populations in development of the interim HA level. Thus in 2009, EPA will engage the NRC to provide additional advice.

The Agency is issuing this interim health advisory to assist state and local officials in advance of a final regulatory determination. EPA expects to issue a final health advisory concurrent with the final regulatory determination for perchlorate.

2.0 GENERAL INFORMATION AND PROPERTIES

2.1 Physical and Chemical Properties

Perchlorate is an inorganic contaminant containing one chlorine atom bound to four oxygen atoms in a tetrahedral configuration. As such, perchlorate (ClO_4^-) is an anion that forms salts with most cations. Commonly used perchlorate salts include ammonium perchlorate and potassium perchlorate. Perchlorate is also used as sodium perchlorate, aluminum perchlorate, hydrazine perchlorate, hydrogen perchlorate, hydroxylammonium perchlorate, lithium perchlorate, magnesium perchlorate, nitronium perchlorate, and as perchloric acid. Chemical Abstracts Service (CAS) registry numbers, as well as certain physical and chemical properties for the most common forms of perchlorate are presented in Table 2-1.



Perchlorate

Table 2-1. CAS Numbers and Physical/Chemical Properties of PerchloratePerchlorate and Its Common Salts

	Perchlorate	Ammonium perchlorate	Potassium perchlorate	Magnesium perchlorate	Sodium perchlorate
CAS number	14797-73-0	7790-98-9	7778-74-7	10034-81-8	7601-89-0
Molecular Formula	ClO_4^-	NH_4ClO_4	$KClO_4$	$Mg(ClO_4)_2$	$NaClO_4$
Physical and Chemical Properties					
Decomposition Point	-----	-----	630°C[7]	-----	-----
Melting Point	-----	439 °C [2]	525 °C [4]	250 °C [4]	480 °C [4]
Molecular Weight	99.45 g/mol [1]	117.49 g/mol [2]	138.55 g/mol [1]	223.20 g/mol [4]	122.4 g/mol [1]
Water Solubility	-----	200 g/L @ 25°C [3]	15 g/L @ 25°C [3]	99 g/1000g @ 25°C [5]	209 g/100 g @ 25 °C [6]

[1] Budavari, 1996, [2] HSDB, 2004, [3] Ashford, 1994, [4] Lide, 2000, [5] Weast, 1979, [6] Gerhartz, 1985, [7]Kubota, 2007

2.2 Uses

While perchlorate has a wide variety of uses, it is primarily used in the form of ammonium perchlorate as an oxidizer in solid fuels used in explosives, fireworks, road flares, and rocket motors. Perchlorate can also be present as an ingredient or as an impurity in road flares, lubricating oils, matches, aluminum refining, rubber manufacturing, paint and enamel manufacturing, leather tanning, paper and pulp processing (as an ingredient in bleaching powder), and as a dye mordant. Sodium hypochlorite solutions used in water and wastewater treatment plants have also been identified as a potential source of perchlorate contamination (US EPA, 2007).

3.0 OCCURRENCE AND EXPOSURE

Perchlorate occurs in the environment from its past and present use primarily in rocket fuels, explosives, and fireworks. Perchlorate can also occur naturally in the environment. For example, Chile possesses caliche ores rich in sodium nitrate ($NaNO_3$), which are also a natural source of perchlorate. These Chilean nitrate salts (saltpeter) have been mined and refined to produce commercial fertilizers (US EPA, 2001). The US EPA (2001) conducted a broad survey of fertilizers and other raw materials and found that all products surveyed were devoid of perchlorate except for those known to contain or to be derived from mined Chilean saltpeter.

3.1 Air

Perchlorate salts have very low vapor pressures and therefore are not expected to volatilize to the air as fugitive emissions during their manufacture, processing, transport, disposal, or use (ATSDR, 2005). However, persons may be exposed to perchlorate dust or particles in an occupational setting, where the risk posed by that exposure would depend on the particle size distribution (NRC, 2005).

3.2 Water

Perchlorate was sampled in drinking water supplies as part of the Unregulated Contaminant Monitoring Regulation (UCMR) 1, List 1 Assessment Monitoring program. Occurrence data for perchlorate was collected from 3,865 public water supplies between 2001 and 2005. Approximately 160 (4.1%) of these systems had at least 1 analytical detection of perchlorate (in at least 1 entry/sampling point) at levels greater than or equal to 4 µg/L. These 160 systems are located in 26 states and 2 territories. Approximately 1.9% (or 637) of the 34,331 samples collected by all 3,865 public water supplies had positive detections of perchlorate at levels greater than or equal to 4 µg/L. The maximum reported concentration of perchlorate, 420 µg/L, was found in a single surface water

sample from a public water supply in Puerto Rico. The average concentration of perchlorate for those samples with positive detections for perchlorate was 9.85 µg/L and the median concentration was 6.40 µg/L.

There is limited information on the release of perchlorate to ambient water. Perchlorate may be released to water from its manufacture, processing, or use. Perchlorate may ultimately be released to surface water from the runoff or erosion of sand or soil contaminated with the compound, while the percolation of water through contaminated sand or soil could result in perchlorate contaminating groundwater (ATSDR, 2005).

Public water systems that have not previously monitored their drinking water for perchlorate may want to review their source water assessments to determine if there are any potential sources of perchlorate contamination within the contributing area of their source.

3.3 Food

The U.S. Food and Drug Administration's (FDA) Total Diet Study (TDS) combines nationwide sampling and analysis of hundreds of food items along with national surveys of food intake to develop comprehensive dietary exposure estimates for a variety of demographic groups in the US. In addition, the Centers for Disease Control and Prevention's (CDC) National Health and Nutrition Examination Survey (NHANES) data base measured perchlorate in the urine of a representative sample of Americans. EPA and CDC used data from the NHANES data base and UCMR monitoring results to estimate perchlorate exposure from food and water together, and food alone, for different sub-populations. This section provides details on the results of these studies.

3.3.1 Food Monitoring Studies. The FDA, the United States Department of Agriculture (USDA), and other researchers have studied perchlorate in foods. The most recent and most comprehensive information available on the occurrence of perchlorate in the diet has been published by FDA. This section describes two perchlorate studies released by FDA – the TDS and FDA's *Exploratory Survey Data on Perchlorate in Food*.

3.3.1.1 FDA Total Diet Study, 2005 and 2006. Since 1961, FDA has periodically conducted a broad-based food monitoring study known as the *Total Diet Study* (TDS). The purpose of the TDS is to measure substances in foods representative of the total diet of the US population, and to make estimates of the average dietary intake of those substances for selected age-gender groups. A detailed history of the TDS can be found at the following Web site: http://www.cfsan.fda.gov/~comm/tds-toc.html.

Murray *et al.* (2008) briefly describe the design of the current TDS. Dietary intakes of perchlorate were estimated by combining the analytical results from the TDS with food consumption estimates developed specifically for estimating dietary exposure from the TDS results. While the perchlorate data for TDS foods were collected in 2005-2006, the

food consumption data in the current TDS food list is based on results (Egan *et al.*, 2007) from the USDA's 1994–96, 1998 *Continuing Survey of Food Intakes by Individuals* (94-98 CSFII), which includes data for all age groups collected in 1994-96, and for children from birth through age 9 collected in 1998. Although over 6,000 different foods and beverages were included in the food consumption surveys, these foods and beverages were collapsed into a set of 285 representative foods and beverages by aggregating the foods according to the similarity of their primary ingredients and then selecting the specific food consumed in greatest quantity from each group as the representative TDS food for that group. The consumption amounts of all the foods in a group were aggregated and assigned to the representative food for that group. It is these 285 representative foods and beverages that are on the current TDS food list. This approach to estimating dietary intake assumes that the analytical profiles (e.g., perchlorate concentrations) of the representative foods are similar to those of the larger group of foods from the original consumption survey to which they correspond. This approach provides a reasonable estimate of total dietary exposure to the analytes from all foods in the diet, and not from the representative TDS foods alone. The sampled TDS foods are purchased from grocery stores and fast-food restaurants. The foods are prepared table-ready prior to analyses, using distilled water when water is called for in the recipe. The analytical method developed and used by FDA to measure perchlorate in food samples has a nominal limit of detection (LOD) of 1.00 ppb and a limit of quantitation (LOQ) of 3.00 ppb (Krynitsky *et al.*, 2006).

Murray *et al.* (2008) reports that FDA included perchlorate as an analyte in TDS baby foods in 2005 and in all other TDS foods in 2006. Iodine also was analyzed in all TDS foods from five market baskets surveyed in late 2003 through 2004. Using these data collectively, FDA developed estimates of the average dietary perchlorate and iodine intake for 14 age-gender groups. To account for uncertainties associated with samples with no detectable concentrations of perchlorate or iodine (non-detects or NDs), FDA calculated a lower-bound and upper-bound for each estimate of the average dietary exposure, assuming that NDs equal zero and the LOD, respectively. Specifically, FDA multiplied these upper- and lower-bound average concentrations by the average daily consumption amount of the representative food for the given subpopulation group to provide a range of average intakes for each TDS food.

Table 3-1 summarizes the FDA estimated upper- and lower-bound average dietary perchlorate intakes (from food) for 14 age-gender groups on a per kilogram of body weight per day basis. Murray *et al.* (2008) reports that average body weights for each population group were based on self-reported body weights from respondents in the 94–98 CSFII.

Table 3-1. Lower- and Upper-bound (ND = 0 and LOD) Perchlorate Intakes from FDA's TDS Results for 2005–2006.

Population Group		Average Perchlorate Intake from Food (µg/kg/day)	
		Lower-bound	Upper-bound
Infants	6-11 mo	0.26	0.29
Children	2 yr	0.35	0.39
Children	6 yr	0.25	0.28
Children	10 yr	0.17	0.20
Teenage Girls	14-16 yr	0.09	0.11
Teenage Boys	14-16 yr	0.12	0.14
Women	25-30 yr	0.09	0.11
Men	25-30 yr	0.08	0.11
Women	40-45 yr	0.09	0.11
Men	40-45 yr	0.09	0.11
Women	60-65 yr	0.09	0.10
Men	60-65 yr	0.09	0.11
Women	70+ yr	0.09	0.11
Men	70+ yr	0.11	0.12

Based on their analysis of TDS data, FDA reports that detectable levels of perchlorate were found in at least one sample in 74 percent (211 of 286) of TDS foods (Murray *et al.*, 2008). The average estimated perchlorate intakes for the 14 age-gender groups range from 0.08 (for 25-30 year old men) to 0.39 (for children 2 years old) µg/kg/day, compared with the RfD of 0.7 µg/kg/day. Though not shown here, Murray *et al.* (2008) reports that the average estimated iodine intake for the 14 age-gender groups range from 138 to 353 µg/person/day, and for all groups exceed the relevant US dietary reference values used for assessing the nutritional status of populations.[1]

The results of the TDS dietary intake assessment provide an estimate of the average dietary perchlorate intake by specific age-gender groups in the US. However, Murray *et al.* note that the current TDS design "does not allow for estimates of intakes at the

[1] Murray *et al.* (2008) compared estimated average iodine intake with US Dietary Reference Intakes for iodine (NAS, 2000). The reference values cited by Murray *et al.* (2008) are as follows: 130 µg/person/day for infants, 65 µg/person/day for children 1–8 years, 73 µg/person/day for children 9–13 years, and 95 µg/person/day for the remainder of population.

extremes (i.e., upper or lower percentiles of food consumption) or for population subgroups within the 14 age/sex groups that may have specific nutritional needs (e.g., the subgroups of pregnant and lactating women within the groups of women of child bearing age)." Nevertheless, Murray *et al.* stated that: "These TDS results increase substantially the available data for characterizing dietary exposure to perchlorate and provide a useful basis for beginning to evaluate overall perchlorate and iodine estimated dietary intakes in the US population."

3.3.1.2 FDA Exploratory Survey Data on Perchlorate in Food, 2003–2005. Prior to including perchlorate in the TDS, FDA conducted exploratory surveys from October 2003 to September 2005 to determine the occurrence of perchlorate in a variety of foods. In May 2007, FDA provided an estimate of perchlorate exposure from these surveys (http://www.cfsan.fda.gov/~dms/clo4ee.html). Using the data from these exploratory studies and food and beverage consumption values from USDA's 94–98 CSFII, FDA estimated mean perchlorate exposures of 0.053 µg/kg/day for all ages (2+ years), 0.17 µg/kg/day for children (2–5 years), and 0.037 µg/kg/day for females (15–45 years). There are uncertainties associated with the preliminary exposure assessment because the 27 foods and beverages selected represent only about 32 to 42 percent of the total diet depending on the population group. Additionally, the overall goal of the sampling plan was to gather initial information on occurrence of perchlorate in foods from various locations with a high likelihood of perchlorate contamination. With the preceding caveats in mind, the results of these exploratory studies are generally consistent with the more complete results of the 2005-2006 TDS. For the purpose of developing a national estimate of dietary perchlorate exposure, while the results of FDA's exploratory studies generally support the TDS results, they are superseded by the results of the TDS, and as such they are not being used in arriving at an interim HA.

3.3.1.3 Other Published Food Studies. Pearce *et al.* (2007) published an analysis of perchlorate concentrations in 17 brands of prepared ready to eat and concentrated liquid infant formula. Perchlorate concentrations in the 17 samples ranged from 0.22 to 4.1 µg/L, with a median concentration of 1.5 µg/L. The researchers did not estimate the perchlorate dose to which infants would be exposed at the concentrations observed in the study. FDA also included sampling and analysis of infant formula in their current TDS analysis, discussed above.

Studies such as those published by Kirk *et al.* (2003, 2005) and Sanchez *et al.* (2005a, 2005b) have examined perchlorate in milk and produce.

3.4 Biomonitoring Studies

Researchers have also begun to investigate perchlorate occurrence in humans by analyzing for perchlorate in urine and breast milk. For example, CDC has included perchlorate in its National Biomonitoring Program, which develops methods to measure environmental chemicals in humans. With this information, CDC can obtain data on the levels and trends of exposure to environmental chemicals in the US population.

3.4.1 Urinary Biomonitoring. In the largest study of its kind, Blount *et al.* (2006c) measured perchlorate in urine samples collected from a nationally representative sample of 2,820 US residents as part of the 2001–2002 NHANES. Blount *et al*. (2006c) detected perchlorate at concentrations greater than 0.05 µg/L in all 2,820 urine samples tested, with a median concentration of 3.6 µg/L and a 95th percentile of 14 µg/L. Women of reproductive age (15–44 years) had a median urinary perchlorate concentration of 2.9 µg/L and a 95th percentile of 13 µg/L. The demographic with the highest concentration of urinary perchlorate was children (6–11 years), who had a median urinary perchlorate concentration of 5.2 µg/L. Blount *et al.* (2006c) estimated a total daily perchlorate dose for the NHANES participants aged 20 and older (for whom a creatinine correction method was available) and found a median dose of 0.066 µg/kg/day (about one tenth of the RfD) and a 95th percentile dose of 0.234 µg/kg/day (about one third of the RfD). Eleven adults (0.7 percent) had estimated perchlorate exposure greater than perchlorate's RfD of 0.7 µg/kg/day (the highest calculated exposure was 3.78 µg/kg/day). Because of daily variability in diet and perchlorate exposure, and the short residence time of perchlorate in the body, these single sample measurements may overestimate long-term average exposure for individuals at the upper end of the distribution and may underestimate the long-term average exposure for individuals at the lower end of the distribution. Blount *et al.* did not estimate daily perchlorate dose for children and adolescents due to the limited validation of estimation methods for these age groups at that time (Blount *et al.*, 2006c). Analyses on pregnant and lactating women were limited because no information was available regarding the trimester or stage of pregnancy for women reported as pregnant in the study, and no specific information was available on the characteristics of lactating women.

EPA and CDC investigators merged the data sets from NHANES and UCMR 1 to identify the NHANES participants from counties which had one or more perchlorate detections during the UCMR survey (USEPA, 2008b). The study assumes, based on previous analyses of perchlorate pharmacokinetics, that urine is the sole excretion pathway of perchlorate from participants other than lactating women. Since all NHANES participants' urine contained perchlorate, separating out those who had a higher potential for additional exposure via drinking water from those who had a lower potential for drinking water exposure left the remainder as those participants whose exposure was expected to be primarily from food.

The advantage of a urinary biomonitoring study is that it reflects the perchlorate actually ingested in the diets of a large number of individuals rather than using estimators

of perchlorate ingestion from a variety of foods for a diverse population. The analysis of biomonitoring data also provides a novel opportunity to use public water system occurrence and human biomonitoring data to compare perchlorate concentration in urine from people in areas with perchlorate in their drinking water with perchlorate concentration in urine from people in areas with no reported perchlorate in their drinking water. The approach is reasonable for estimating perchlorate intake at various percentiles from food and to gain an understanding of the relative contribution from drinking water. A limitation is in the use of NHANES's spot urine testing, and creatinine corrections for a population with diverse physiological characteristics, to calculate the daily perchlorate dose. The cross sectional study attempts to capture a representative exposure, but was limited by the need to match up drinking water occurrence data with biomonitoring data on a county-wide basis, even though county and public water system service area boundaries often do not coincide. There also may have been some temporal mismatch between the occurrence and biomonitoring data.

The primary goal of the study was to derive the dose of perchlorate coming from food alone by eliminating possible sources of water contribution. Individuals' data were separated based on the likelihood of perchlorate being in their tap water. Groups were further sorted by age and sex. Bin I was comprised of NHANES 2001-2002 data for individuals residing in the same counties as public water systems that had at least one positive measurement of perchlorate during the sample period, as measured in UCMR 1. This group represented those who were more likely to be exposed to perchlorate in both food and water. For the most part, the average perchlorate level in urine for all age groups was the highest in this bin, and the creatinine-corrected average dose for all individuals in this group was 0.101 µg/kg/day, with a geometric mean of 0.080 µg/kg/day.

A second group was defined in one of three ways and was comprised of data for individuals considered less likely to have exposure to perchlorate via drinking water and thus, more likely to have their perchlorate exposure caused solely by intake from food: (1) they resided in counties where there were no quantified detections of perchlorate in public drinking water systems sampled as part of UCMR (i.e., UCMR 1 results were below the minimum reporting limit of 4 µg/L); or (2) they self-reported that they had not consumed tap water in the previous 24 hours regardless of where they resided (i.e., they may have resided in a county with a positive UCMR finding, but did not drink tap water); or (3) not considering the UCMR status of the county, their response to NHANES indicated they used a reverse osmosis filter to filter their tap water, which would likely be effective for removing perchlorate. The average creatinine-corrected perchlorate dose for these individuals was 0.090 µg/kg/day, with a geometric mean of 0.062 µg/kg/day.

A summary of selected results for individuals in these two groups is shown in Table 3-2. The estimates of daily perchlorate intake presented in Table 3-2 from the NHANES-UCMR analysis are somewhat higher than those of Blount *et al.* (2006a). The Blount *et al.* (2006a) estimates were limited to adults 20 years of age and older because application of the set of creatinine excretion equations used by Blount *et al.* to estimate perchlorate dose was limited to adults. Mage *et al.* (2007) provides an expanded set of equations that

allows for estimating daily creatinine excretion rates for children, as well as for adults. Since children tend to have higher exposure on a per body weight basis than adults, it is not surprising that the estimates based on both adults and children are somewhat higher than the Blount estimates based on adults alone. The mean total exposure for persons that are more likely to be exposed to perchlorate in food and water was calculated to be 0.101 µg/kg/day. The average exposure for persons more likely to be exposed to perchlorate from food alone was 0.090 µg/kg/day.

Table 3-2. Estimated Daily Perchlorate Intakes (µg/kg/day) for Individuals With and Without Exposure Through Drinking Water

Group	Perchlorate Likely in Water (+/-)	Number of people	Average (Mean)	Geometric Mean	50th %ile	90th %tile
Total	+	320	0.101	0.080	0.075	0.193
	-	2063	0.090	0.062	0.058	0.167
Age: 6-11	+	52	0.152	0.132	0.131	0.237
	-	270	0.150	0.118	0.124	0.280
Age: 12-19	+	100	0.109	0.078	0.070	0.286
	-	608	0.080	0.061	0.060	0.158
Age: ≥20	+	168	0.091	0.074	0.071	0.186
	-	1185	0.085	0.057	0.055	0.143
Females: 15-44	+	57	0.081	0.062	0.071	0.141
	-	505	0.093	0.055	0.052	0.143
Pregnant Females	+	8	0.097	0.086	0.060	0.121
	-	98	0.123	0.064	0.056	0.263

Comparison of exposure estimates for individuals more likely to be exposed only through food to the FDA TDS, shown in Table 3-1, indicates good agreement at the mean. For example, for females 14-16, women 25-30, and women 40-45 years old, the FDA mean food dose was 0.09–0.1 µg/kg/day, while in the EPA-CDC biomonitoring study of NHANES-UCMR, the mean food dose for women of child-bearing age (15–44 years old) was 0.093 µg/kg/day. The results from calculating likely food intakes (TDS study) and from urinalysis from actual intakes (NHANES/UCMR) are in close agreement where comparisons can be made.

3.4.2 Breast Milk. A number of studies have investigated perchlorate in human breast milk. The most recent study included measurements from 49 healthy Boston-area volunteers (10–250 days postpartum, median 48 days; Pearce, *et al.*, 2007). Perchlorate

was found in all samples, ranging from 1.3–411 µg/L, with a median concentration of 9.1 µg/L and a mean concentration of 33 µg/L. No correlation was found between perchlorate and iodine concentrations in breast milk. EPA notes that the Boston-area public water systems did not detect perchlorate in drinking water samples collected for the US EPA's UCMR from 2001 to 2003, nor did Boston area systems detect perchlorate in samples collected in response to the Massachusetts Department of Environmental Protection (DEP) 2004 emergency regulations for perchlorate.

Kirk *et al.* (2005) analyzed 36 breast milk samples from 18 States (CA, CT, FL, GA, HI, MD, ME, MI, MO, NC, NE, NJ, NM, NY, TX, VA, WA, WV) and found perchlorate concentrations in all samples ranging from 1.4 to 92.2 µg/L, with a mean concentration of 10.5 µg/L. Kirk *et al.* (2007) later did a smaller study involving 10 women, which included 6 samples on each of 3 days in a temporal study. Half the women were from Texas, but the others were from CO, FL, MO, NM, and NC. They found significant variation in all samples (n=147), with a range, mean, and median perchlorate concentration of 0.5–39.5 µg/L, 5.8 µg/L, and 4.0 µg/L, respectively.

Téllez *et al.* (2005) reported maternal parameters for participants from a study conducted in Chile. Breast milk samples indicated that a significant amount of perchlorate leaves the body of the nursing mother through breast milk, in addition to urine. However, the breast milk perchlorate levels were highly variable and no significant correlations could be established between breast milk perchlorate concentrations and either urine perchlorate concentrations or breast milk iodide concentrations for the individuals evaluated in these Chilean cities (Téllez *et al.*, 2005).

Blount *et al*. (2007) also suggested breast milk as an excretion pathway and the NHANES-UCMR study authors observed a difference between the urinary perchlorate concentration of breast feeding women versus pregnant women with an overall mean concentration of 0.130 µg/kg/day for 117 pregnant women compared to a concentration of 0.073 µg/kg/day for the 24 breast-feeding women (USEPA, 2008b).

Dasgupta *et al.* (2008) analyzed breast milk samples and 24 hour urine samples from 13 lactating women from Texas for perchlorate and iodine. For breast milk, they found perchlorate concentrations ranging from 0.01 to 48 µg/L, with a median concentration of 7.3 µg/L and a mean concentration of 9.3 µg/L (457 total samples), while for iodine, concentrations ranged from 1 to 1,200 µg/L, with a median concentration of 43 µg/L and a mean concentration of 120 µg/L (447 total samples). For urine they found perchlorate concentrations ranging from 0.6 to 80 µg/L, with a median concentration of 3.2 µg/L and a mean concentration of 4.0 µg/L (110 total samples), while for iodine, concentrations ranged from 26 to 630 µg/L, with a median concentration of 110 µg/L and a mean concentration of 140 µg/L (117 total samples).

3.5 Soil

As discussed above (see section 3.0), perchlorate has been detected in fertilizers derived from Chilean caliche (US EPA, 2001), and perchlorate-containing fertilizers could result in contamination of soil as a direct result of their intended use (ATSDR, 2005). Perchlorate has also been found in other geologic materials. Orris *et al.* (2003) measured perchlorate at levels exceeding 1,000 parts per million (ppm or mg/kg) in several samples of natural minerals, including potash ore from New Mexico and Saskatchewan (Canada), playa crust from Bolivia, and hanksite from California.

4.0 HEALTH EFFECTS DATA

4.1 Human Studies and Modeling

4.1.1 Mode of Action. Perchlorate interacts with the sodium iodide symporter, reducing iodine uptake into the thyroid gland and, at sufficiently high doses, the amount of T4 produced and available for release into circulation. Sustained changes in thyroid hormone secretion can result in hypothyroidism. Thyroid hormones stimulate diverse metabolic activities in most tissues and individuals suffering from hypothyroidism experience a general slowing of metabolism of a number of organ systems. In adults, these effects are reversed once normal hormone levels are restored (NRC, 2005).

In fetuses, infants, and young children, thyroid hormones are critical for normal growth and development. Irreversible changes, particularly in the brain, are associated with hormone insufficiencies during development in humans (Chan and Kilby, 2000 and Glinoer, 2007). Disruption of iodide uptake presents particular risks for fetuses and infants (Glinoer, 2007 and Delange, 2004). Because the fetus depends on an adequate supply of maternal thyroid hormone for its central nervous system development during the first trimester of pregnancy, iodide uptake inhibition from perchlorate exposure has been identified as a concern in connection with increasing the risk of neurodevelopmental impairment in fetuses of high-risk mothers (NRC, 2005). Poor iodide uptake and subsequent impairment of the thyroid function in pregnant and lactating women have been linked to delayed development and decreased learning capability in infants and children with fetal and neonatal exposure (NRC, 2005).

The RfD used in this assessment was developed by the NRC (2005). The NRC recommended basing the RfD on a precursor to an adverse effect rather than an adverse effect *per se*. The precursor event precedes a downstream adverse effect in the dose response continuum. In this case, NRC used prevention of iodide uptake inhibition, a precursor to adverse thyroid effects, to establish a level at which no adverse effects would be anticipated in exposed populations. NRC (2005) noted that "Using a nonadverse effect that is upstream of the adverse effect is a more conservative, health-protective approach to the perchlorate risk assessment." This approach is consistent with the Agency's policy on

the use of precursor events when appropriate in establishing the critical effect upon which an RfD is based (U.S. EPA, 2002c).

Children born with congenital hypothyroidism may suffer from mild cognitive deficits despite hormone remediation (Rovet, 2002; Zoeller and Rovet, 2004), and subclinical hypothyroidism and reductions in T4 (i.e., hypothyroxinemia) in pregnant women have been associated with neurodevelopmental delays and IQ deficits in their children (Pop *et al*., 1999, 2003; Haddow *et al.*, 1999; Kooistra *et al*., 2006; Morreale de Escobar *et al.*, 2004a, 2004b). Animal studies support these observations, and recent findings indicate that neurodevelopmental deficits are evident under conditions of hypothyroxinemia and occur in the absence of growth retardation (Auso *et al.*, 2004; Gilbert and Sui, 2008; Sharlin *et al.*, 2008; Goldey *et al.*, 1995).

4.1.2 Epidemiology Data. The data from epidemiological studies of the general population provide some information on possible effects of perchlorate exposure. Based on an analysis of the data available at the time, NRC (2005) acknowledged that ecologic epidemiological data alone are not sufficient to demonstrate whether or not an association is causal, and that these studies can provide evidence bearing on possible associations. Noting the limitations of specific studies, the NRC (2005; chapter 3) committee concluded that the available epidemiological evidence is not consistent with a causal association between perchlorate and congenital hypothyroidism, changes in thyroid function in normal-birth weight, full-term newborns, or hypothyroidism or other thyroid disorders in adults. The committee considered the evidence to be inadequate to determine whether or not there is a causal association between perchlorate exposure and adverse neurodevelopmental outcomes in children. The committee noted that no studies have investigated the relationship between perchlorate exposure and adverse outcomes among especially vulnerable groups, such as the offspring of mothers who had low dietary iodide intake, or low-birth weight or preterm infants (US EPA, 2005a).

Results from studies of the effects of perchlorate exposure on hormone levels have been mixed. One recent study did not identify any effects of perchlorate on blood serum hormones (Amitai *et al*., 2007), while another study (Blount *et al*., 2006b) did identify such effects.

4.1.3 Biomonitoring Studies. After the NRC report was released, several papers were published that investigated whether biomonitoring data associated with NHANES could be used to discern if there was a relationship between perchlorate levels in the body and thyroid function. These papers also help to evaluate populations that might be considered to be more sensitive to perchlorate exposure.

Blount *et al.* (2006b) published a study examining the relationship between urinary levels of perchlorate and blood serum levels of TSH and total T4 in 2,299 men and women

(ages 12 years and older) who participated in CDC's 2001–2002 NHANES[2]. Blount *et al.* (2006b) evaluated perchlorate along with a number of covariates known or likely to be associated with T4 or TSH levels to assess the relationship between perchlorate and these hormones, and the influence of other factors on this relationship. These covariates included gender, age, race/ethnicity, body mass index, serum albumin, serum cotinine (a marker of nicotine exposure), estimated total caloric intake, pregnancy status, post-menopausal status, premenarche status, serum C-reactive protein, hours of fasting before sample collection, urinary thiocyanate, urinary nitrate, and use of selected medications. The study found that perchlorate was a statistically significant predictor of thyroid hormones in women, but not in men.

After finding evidence of gender differences, the researchers focused on further analyzing the NHANES data for the 1,111 women participants. They divided these 1,111 women into two categories, those women with higher-iodide and lower-iodide urinary content, using a cut point of 100 µg/L of urinary iodide based on the median level the World Health Organization (WHO) considers indicative of sufficient iodide intake[3] for a population. Hypothyroid women were excluded from the analysis. According to the study's authors, about 36 percent of women living in the United States have urinary iodide levels less than 100 µg/L (Caldwell *et al.*, 2005). For women with urinary iodide levels less than 100 µg/L, the study found that urinary perchlorate is associated with a decrease in (a negative predictor for) T4 levels and an increase in (a positive predictor for) TSH levels. For women with urinary iodide levels greater than or equal to 100 µg/L, the researchers found that perchlorate is a significant positive predictor of TSH, but not a predictor of T4. The researchers state that perchlorate could be a surrogate for another unrecognized determinant of the thyroid function.

Also, the study reports that while large doses of perchlorate are known to decrease thyroid function, this is the first time an association of decreased thyroid function has been observed at these low levels of perchlorate exposure. The clinical significance of the variations in T4/TSH levels, which were generally within normal limits, has not been determined. The researchers noted several limitations of the study (e.g., assumption that urinary perchlorate correlates with perchlorate levels in the stroma and tissue and measurement of total T4 rather than free T4) and recommended that these findings be affirmed in at least one more large study focusing on women with low urine iodide levels. It is also not known whether the association between perchlorate and thyroid hormone levels is causal or mediated by some other correlate of both, although the relationship between urine perchlorate and total TSH and T4 levels persisted after statistical adjustments for some additional covariates known to predict thyroid hormone levels (e.g., total kilocalorie intake, estrogen use, and serum C-reactive protein levels). A planned follow-up study will include additional measures of thyroid health and function (e.g., TPO-

[2] While CDC researchers measured urinary perchlorate concentration for 2,820 NHANES participants, TSH and total T4 serum levels were only available for 2,299 of these participants.

[3] WHO notes that the prevalence of goiter begins to increase in populations with a median urinary iodide level below 100 µg/L (WHO, 1994).

antibodies, free T4). An additional paper by Blount *et al.* (2006c) found that almost all participants in the NHANES survey, including the participants in this group, had urinary levels of perchlorate corresponding to estimated dose levels that are below the RfD of 0.7 µg/kg/day.

The Blount study suggested that perchlorate could be a surrogate for another unrecognized determinant of thyroid function. There are other chemicals, including nitrate and thiocyanate, which can affect the thyroid function. Steinmaus *et al.* (2007) further analyzed the data from NHANES 2001–2002 to assess the impact of smoking, cotinine and thiocyanate on the relationship between urinary perchlorate and blood serum T4 and TSH. Thiocyanate is a metabolite of cyanide found in tobacco smoke and is naturally occurring in some foods, including cabbage, broccoli, and cassava. Increased serum thiocyanate levels are associated with increasing levels of smoking. Thiocyanate affects the thyroid by the same mechanism as perchlorate (competitive inhibition of iodide uptake). Steinmaus *et al*. analyzed the data to determine whether smoking status (smoker or nonsmoker), serum thiocyanate, or serum cotinine were better predictors of T4 and TSH changes than perchlorate, or if the effects reflected the combined effects of perchlorate and thiocyanate

Of female subjects 12 years of age and older in NHANES 2001-2002, 1,203 subjects had data on blood serum T4, serum TSH, urinary perchlorate, iodine and creatinine. Subjects with extreme T4 or TSH (3 individuals) or with a reported history of thyroid disease (91) were excluded from further analyses. Of the remaining women, 385 (35 percent) had urinary iodine levels below 100 µg /l. Steinmaus, *et al*. evaluated serum cotinine as an indicator of nicotine exposure, with levels greater than 10 ng/ml classified as high and levels less than 0.015 ng/ml classified as low.

The authors found no association between perchlorate or T4 and smoking, cotinine or thiocyanate in men or in women with urinary iodine levels greater than 100 µg/l. In addition, they found no association between cotinine and T4 or TSH in women with iodine levels lower than 100 µg/l. However, in women with urinary iodine levels lower than 100 µg/l, an association between urinary perchlorate and decreased serum T4 was stronger in smokers than in non-smokers, and stronger in those with high urinary thiocyanate levels than in those with low urinary thiocyanate levels. Although noting that their findings need to be confirmed with further research, the authors concluded that for these low-iodine women, the results suggest that at commonly-occurring perchlorate exposure levels, thiocyanate in tobacco smoke and perchlorate interact in affecting thyroid function, and agents other than tobacco smoke might cause similar interactions (Steinmaus *et al*. 2007).

EPA also evaluated whether health information is available regarding children, pregnant women and lactating mothers. The NRC report discussed a number of epidemiological studies that looked at thyroid hormone levels in infants. A more recent study by Amitai *et al.* (2007) assessed T4 values in newborns in Israel whose mothers resided in areas where drinking water contained perchlorate at “very high” (340 µg/L), “high” (12.94 µg/L), or “low” (<3 µg/L) perchlorate concentrations. The mean (± standard deviation) T4 value of the newborns in the very high, high, and low exposure groups was 13.8 ± 3.8, 13.9 ± 3.4, and 14.0 ± 3.5 µg/dL, respectively, showing no significant

difference in T4 levels between the perchlorate exposure groups. This is consistent with the conclusions drawn by the NRC review of other epidemiological studies of newborns. The NRC (2005) also noted "no epidemiologic studies are available on the association between perchlorate exposure and thyroid dysfunction among low-birth weight or preterm newborns, offspring of mothers who had iodide deficiency during gestation, or offspring of hypothyroid mothers."

4.1.4 Physiologically-Based Pharmacokinetic (PBPK) Models. PBPK models represent an important class of dosimetry models that can be used to predict internal doses to target organs, as well as some effects of those doses (e.g., radioactive iodide uptake inhibition in the thyroid). To predict an internal dose level, PBPK models use physiological, biochemical, and physicochemical data to construct mathematical representations of processes associated with the absorption, distribution, metabolism, and elimination of compounds. With the appropriate data, these models can be used to extrapolate across and within species and for different exposure scenarios, and to address various sources of uncertainty in health assessments, including the uncertainty regarding the relative sensitivities of various subpopulations.

Clewell *et al.* (2007) developed multi-compartment PBPK models describing the absorption and distribution of perchlorate for the pregnant woman and fetus, the lactating woman and neonate, and the young child. This work built upon Merrill *et al.*'s (2005) model for the average adult. Related research that served as the basis for the more recent PBPK modeling efforts was discussed by the NRC in their January 2005 report on perchlorate.

The models estimated the levels of perchlorate absorbed through the gastrointestinal tract and its subsequent distribution within the body. Clewell *et al.* (2007) provided estimates of the internal dose and resulting iodide uptake inhibition across all life stages, and for pregnant and lactating women. The paper reported iodide uptake inhibition levels for external doses of 1, 10, 100, and 1000 µg/kg/day. Results at the lower two doses indicated that the highest perchlorate blood concentrations in response to an external dose would occur in the fetus, followed by the lactating woman and the neonate. Predicted blood levels for all three groups (i.e., fetus, lactating women and neonates) were four to five times higher than for non-pregnant adults. Smaller relative differences were predicted at external doses of 100 and 1000 µg/kg/day. The authors attributed this change to saturation of uptake mechanisms. The model predicted minimal effect of perchlorate on iodide uptake inhibition in all groups at the 1 µg/kg/day external dose (about one and one half times the RfD), estimating 1.1 percent inhibition or less across all groups. Inhibition was predicted to be 10 percent or less in all groups at an external dose of 10 µg/kg/day (about 14 times the RfD).

The results of the model extrapolations were evaluated against data developed in two epidemiologic studies performed in Chile, one studying school children (Tellez *et al.*, 2005) and another following women through pregnancy and lactation (Gibbs *et al.*, 2004).

The model predicted average blood serum concentrations of perchlorate in women from the Gibbs *et al.* (2004) study which were nearly identical to their measured perchlorate blood serum concentrations. The blood serum perchlorate concentrations predicted from the Tellez *et al.* (2005) study also were within the range of the measured concentrations, and the concentrations of perchlorate in breast milk predicted from the model were within two standard deviations of the measured concentrations. The authors concluded that the model predictions were consistent with empirical results and that the predicted extent of iodide inhibition in the most sensitive population (the fetus) is not significant at EPA's RfD of 0.7 µg/kg-day.

The NRC recommended that inhibition of iodide uptake by the thyroid, which is a precursor event and not an adverse effect, should be used as the basis for the perchlorate risk assessment (NRC, 2005). Consistent with this recommendation, iodide uptake inhibition was used by EPA as the critical effect in determining the reference dose (RfD) for perchlorate. Therefore, PBPK models of perchlorate and radioiodide, which were developed to describe thyroidal radioactive iodide uptake (RAIU) inhibition by perchlorate for the average adult (Merrill *et al.*, 2005), pregnant woman and fetus, lactating woman and neonate, and the young child (Clewell *et al.*, 2007) were evaluated by EPA based on their ability to provide additional information surrounding this critical effect for potentially sensitive subgroups and reduce some of the uncertainty regarding the relative sensitivities of these subgroups.

EPA evaluated the PBPK model code provided by the model authors and found minor errors in mathematical equations and computer code, as well as some inconsistencies between model code files. EPA made several changes to the code in order to harmonize the models and more adequately reflect the biology (see USEPA, 2008c) for more information.

Model parameters describing urinary excretion of perchlorate and iodide were determined to be particularly important in the prediction of RAIU inhibition in all subgroups; therefore, a range of biologically plausible values available in the peer-reviewed literature was evaluated in depth using the PBPK models. Exposure rates were also determined to be critical for the estimation of RAIU inhibition by the models and were also further evaluated.

Overall, detailed examination of Clewell *et al.* (2007) and Merrill *et al.* (2005) confirmed that the model structures were appropriate for predicting percent inhibition of RAIU by perchlorate in most life stages. Unfortunately, the lack of biological information during early fetal development limits the applicability of the PBPK modeling of the fetus to a late gestational timeframe (i.e., near full term pregnancy, ~GW 40), so EPA did not make use of model predictions regarding early fetal RAIU inhibition. Although quantitative outputs of EPA's revised PBPK models differ somewhat from the published values, the EPA evaluation confirmed that, with modifications (as described in USEPA, 2008c), the Clewell *et al.* (2007) and Merrill *et al.* (2005) models provide an appropriate basis for calculating the life stage differences in the degree of thyroidal RAIU inhibition at a given level of perchlorate exposure.

4.1.5 Carcinogenicity. The NRC (2005) reviewed the available human data and reached the following conclusion: "The epidemiologic evidence is insufficient to determine whether there is a causal association between perchlorate exposure and thyroid cancer. Only two studies related to this issue have been done, and both were ecologic. In one study, the number of thyroid-cancer cases was too small to have a reasonable chance of detecting an association if one existed (Li *et al*., 2001). In the second, larger study (Morgan and Cassady, 2002), mixed exposures were present (to perchlorate and TCE). In neither study was it possible to adjust for potential confounding variables. The committee notes, however, that on the basis of its understanding of the biology of human and rodent thyroid tumors, it is unlikely that perchlorate poses a risk of thyroid cancer in humans."

4.2 Animal Studies

The NRC (2005) conducted a thorough review of the animal studies and reached the following conclusions:

"The committee found that the animal studies of potential adverse effects of perchlorate provided qualitative information, but the usefulness of the studies for quantitatively estimating the risk of adverse effects in humans is small. The major conclusions from the animal data are summarized below.

- Perchlorate has an antithyroid effect on rats at high doses (30 mg/kg of ammonium perchlorate per day). That effect is characterized by decreases in serum thyroid hormone and increases in serum TSH with morphologic changes in the thyroid gland.
- The data are inadequate to determine whether or not a causal relationship exists between perchlorate exposure of pregnant rats and neurodevelopmental abnormalities in their pups, given the flaws in experimental design and methods in the studies conducted to evaluate that end point.
- The data are inadequate to determine whether or not perchlorate exposure during gestation and lactation in rats has effects on behavior, given the lack of sensitivity of the tests conducted to evaluate that end point.
- Exposure to perchlorate can increase the incidence of thyroid tumors in rats when the doses are high enough to decrease thyroid hormone production and increase TSH secretion.
- The data favor rejection of a causal relationship between perchlorate exposure and immunotoxicity.
- There are no data to suggest that perchlorate has effects that are not mediated through inhibition of iodide transport in the thyroid gland.
- It is not possible to extrapolate data quantitatively from rodents to humans for purposes of human health risk assessment. Most experimental studies in animals

designed to characterize the effects of perchlorate exposure have been done in rats. However, rats are much more sensitive to agents that disturb thyroid function than are humans, so the relevance of rat studies in quantitative terms to humans is limited."

5.0 QUANTIFICATION OF TOXICOLOGICAL EFFECTS

A subchronic HA covers a period of more than 30 days, but less than a year, and considers the following exposure assumptions: a 70 kg adult consuming 2 Liters of water per day. A relative source contribution (RSC) from water is also factored into the subchronic HA calculation to account for contaminant exposures from other sources (air, food, soil, etc.) of the contaminant.

The subchronic HA is calculated in a three-step process:

Step 1: Adopt a pre-existing Reference Dose (RfD) or calculate an RfD using the following equation:

$$RfD = \frac{NOAEL \text{ or } LOAEL \text{ or } BMDL}{UF}$$

Where:

NOAEL or LOAEL	=	No- or Lowest-Observed-Adverse-Effect Level (in mg/kg bw/day).
BMDL	=	Lower confidence bound on the Bench Mark Dose (BMD). The BMD and BMDL are obtained through modeling of the dose-response relationship.
UF	=	Uncertainty factor established in accordance with EPA guidelines.

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily human exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects. It can be derived from a NOAEL, LOAEL, or benchmark dose (BMD) with uncertainty factors generally applied to reflect limitations in the data used. It is also sometimes derived from a NOEL, as is the case for perchlorate, which provides a more health-protective value than using a NOAEL, LOAEL or BMD.

Step 2: From the RfD, calculate a Drinking Water Equivalent Level (DWEL). The DWEL assumes that 100% of the exposure comes from drinking water.

$$DWEL = \frac{RfD \times BW}{DWI}$$

Where:

RfD	=	Reference Dose (in mg/kg bw/day).
BW	=	Assumed body weight of an adult (70 kg).
DWI	=	Assumed human daily consumption for an adult (2 L/day)

Step 3: The subchronic HA is calculated by factoring in other sources of exposure (such as air, food, soil) in addition to drinking water using the relative source contribution (RSC) for the drinking water.

$$\text{Subchronic HA} = DWEL \times RSC$$

Where:

DWEL	=	Drinking Water Equivalent Level (calculated from step 2)
RSC	=	Relative source contribution

Note. The procedure for establishing the RSC for perchlorate is below.

5.1 Reference Dose Derivation

The NRC recommended data from the Greer *et al.* (2002) human clinical study as the basis for deriving a reference dose (RfD) for perchlorate (NRC, 2005). Greer *et al.* (2002) report the results of a study that measured thyroid iodide uptake, hormone levels, and urinary iodide excretion in a group of 37 healthy adults who were administered perchlorate doses orally over a period of 14 days. Dose levels ranged from 7 to 500 µg/kg/day in different experimental groups. The investigators found that the 24 hour inhibition of iodide intake ranged from 1.8 percent in the lowest dose group to 67.1 percent in the highest dose group. However, no significant differences were seen in measured blood serum thyroid hormone levels (T3, T4, total and free) in any dose group. The statistical no observed effect level (NOEL) for the perchlorate-induced inhibition of thyroid iodide uptake was determined to be 7 µg/kg/day, corresponding to iodide uptake inhibition of 1.8 percent. Although the NRC committee concluded that hypothyroidism is the first adverse effect in the continuum of effects of perchlorate exposure, NRC recommended that "the

most health-protective and scientifically valid approach" was to base the perchlorate RfD on the inhibition of iodide uptake by the thyroid (NRC, 2005). NRC concluded that iodide uptake inhibition, although not adverse, is the most appropriate precursor event in the continuum of possible effects of perchlorate exposure and would precede any adverse health effects of perchlorate exposure. The NRC also stated "if that nonadverse biochemical event is used to derive the RfD, chronic exposure will have no greater effect than that resulting from short term exposure." The lowest dose (7 µg/kg/day) administered in the Greer *et al.* (2002) study was considered a NOEL (rather than a no-observed-adverse-effect level or NOAEL) because iodide uptake inhibition is not an adverse effect, but a biochemical precursor. The NRC further determined that, "the very small decrease (1.8 percent) in thyroid radioiodide uptake in the lowest dose group was well within the variation of repeated measurements in normal subjects." A summary of the data considered and the NRC deliberations can be found in the NRC report (2005).

The NRC recommended that EPA apply an intraspecies uncertainty factor of 10 to the NOEL to account for differences in sensitivity between the healthy adults in the Greer *et al.* (2002) study and the most sensitive population, fetuses of pregnant women who might have hypothyroidism or iodide deficiency. Because the fetus depends on an adequate supply of maternal thyroid hormone for its central nervous system development during the first trimester of pregnancy, iodide uptake inhibition from low-level perchlorate exposure has been identified as a concern in connection with increasing the risk of neurodevelopmental impairment in fetuses of high-risk mothers (NRC, 2005). The NRC (2005) viewed the uncertainty factor of 10 as conservative and protective of health given that the point of departure (the NOEL) is based on a non-adverse effect (iodide uptake inhibition), which precedes the adverse effect in a continuum of possible effects of perchlorate exposure. The NRC panel concluded that no additional uncertainty factor was needed for the use of a less-than chronic study, for deficiencies in the database, or for interspecies variability. EPA's Integrated Risk Information System (IRIS) adopted the NRC's recommendations resulting in an RfD of 0.7 µg/kg/day, derived by applying a ten-fold total uncertainty factor to the NOEL of 7 µg/kg/day (USEPA, 2005b).

The NRC emphasized that its recommendation "differs from the traditional approach to deriving the RfD." The NRC recommended "using a nonadverse effect rather than an adverse effect as the point of departure for the perhlorate risk assessment. Using a nonadverse effect that is upstream of the adverse effect is a more conservative, health-protective approach to the perchlorate risk assessment." The NRC also noted that the purpose of the 10-fold uncertainty factor is to protect sensitive subpopulations in the face of uncertainty regarding their relative sensitivity to perchlorate exposure. The NRC recognized that additional information on these relative sensitivities could be used to reduce this uncertainty factor in the future (NRC, 2005).[4]

[4] "There can be variability in responses among humans. The intraspecies uncertainty factor accounts for that variability and is intended to protect populations more sensitive than the population tested. In the absence of data on the range of sensitivity among humans, a default uncertainty factor of 10 is typically applied. The factor could be set at 1 if data indicate that sensitive populations do not vary substantially from those tested." (NRC, 2005, p 173)

5.2 Relative Source Contribution Derivation

Sufficient exposure data are available for perchlorate to enable EPA to estimate a data- derived RSC for fetuses of pregnant women (the most sensitive subpopulations identified by the NRC). These exposure data include the analysis by EPA of the UCMR data and CDC's NHANES biomonitoring data, as well as FDA's TDS. The following sections describe EPA's analyses of each of these data sources to estimate RSCs and HA level for sensitive subpopulations.

5.2.1. Total Diet Study for Estimation of an RSC. The results of FDA's recent evaluation of perchlorate under the TDS were presented above. The TDS estimates are representative of average, national, dietary perchlorate exposure, for the age-gender groups that were selected. EPA used FDA's dietary exposure estimates to calculate RSC values by subtracting the dietary estimates from the RfD (0.7 µg/kg/day), dividing this difference by the RfD, and multiplying the result by 100 (to convert it to a percentage). Because EPA believes that dietary ingestion is the only significant pathway for non-drinking-water perchlorate exposure, the resulting RSCs represent the amount of perchlorate exposure (as a percentage of the RfD) that the average individual within a subgroup would have to ingest via drinking water in order to reach a level of total perchlorate exposure that equals the RfD. These RSCs, displayed as percentages, are presented in Table 5-1.

Table 5-1. Relative Source Contributions Remaining for Water Based on TDS for Various Subgroups

Population Group	Total Perchlorate Intake from Food (µg/kg/day)	RfD that Remains (µg/kg/day)	RSC Remaining for Drinking Water (as %age of the RfD)
Infants, 6–11 mo	0.26–0.29	0.41-0.44	59%–63%
Children, 2 yr	0.35–0.39	0.31-0.35	44%–50%
Children, 6 yr	0.25–0.28	0.42-0.45	60%–64%
Children, 10 yr	0.17–0.20	0.50-0.53	71%–76%
Teenage Girls, 14–16 yr	0.09–0.11	0.59-0.61	84%–87%
Teenage Boys, 14–16 yr	0.12–0.14	0.56-0.58	80%–83%
Women, 25–30 yr	0.09–0.11	0.59-0.61	84%–87%
Men, 25–30 yr	0.08–0.11	0.69-0.62	84%–89%
Women, 40–45 yr	0.09–0.11	0.59-0.61	84%–87%
Men, 40–45 yr	0.09–0.11	0.59-0.61	84%–87%

Population Group	Total Perchlorate Intake from Food (µg/kg/day)	RfD that Remains (µg/kg/day)	RSC Remaining for Drinking Water (as %age of the RfD)
Women, 60–65 yr	0.09–0.10	0.60-0.61	86%–87%
Men, 60–65 yr	0.09–0.11	0.59-0.61	84%–87%
Women, 70+ yr	0.09–0.11	0.59-0.61	84%–87%
Men, 70+ yr	0.11–0.12	0.58-0.59	83%–84%

The subpopulation that is the most sensitive to perchlorate exposure is the fetus of an iodine-deficient pregnant woman. The FDA TDS does not estimate the dietary intake of perchlorate specifically for pregnant women (nor can it specifically address iodine-deficient women), but it does present dietary estimates for three groups of women of childbearing age (Teenage girls 14–16, Women 25–30 and Women 40–45). The calculated RSCs range from 84 to 87 percent for women of childbearing age. Murray *et al.* (2008) suggested that perchlorate intake rates for pregnant and lactating women are "likely to be somewhat higher than those of women of childbearing age as a whole." If this is true, an RSC derived based upon the TDS mean dietary intake for women of childbearing age may underestimate the RSC from food for pregnant women.

5.2.2. Urinary Data for Estimation of an RSC. EPA and CDC researchers analyzed NHANES urinary data in conjunction with UCMR occurrence data at the CDC's National Center for Environmental Health (NCEH) to evaluate exposure to perchlorate. These data were partitioned to provide an estimate of what portion of the overall exposure likely came from food alone. In this analysis, EPA and CDC researchers were able to characterize the distribution of actual perchlorate exposure as seen in their urine for pregnant women. This means that the analysis could determine not only the mean exposure, but also the exposure of highly exposed individuals. Results of this analysis, presented in Table 5-2, indicate that for pregnant women, exposure to perchlorate from food is 0.263 µg/kg/day at the 90th percentile, representing nearly 38 percent of the RfD, and thus leaving an RSC for water of 62 percent.

Table 5-2. Fraction of RfD (Relative Source Contribution) Based On NHANES-UCMR Analysis Calculations of Perchlorate in Food

Group	**Mean Food Dose (µg/kg/day)**	**RfD that Remains (µg/kg/day)**	**RSC From Drinking Water as % of RfD**	**90th Percentile Food Dose (µg/kg/day)**	**RfD that Remains (µg/kg/day)**	**RSC From Drinking Water as % of RfD**
Total population	0.090	0.61	87	0.167	0.533	76
Ages 6-11	0.150	0.55	79	0.280	0.42	60
Ages 12-19	0.080	0.62	89	0.158	0.542	77

Group	**Mean** Food Dose (µg/kg/day)	RfD that Remains (µg/kg/day)	RSC From Drinking Water as % of RfD	**90th Percentile** Food Dose (µg/kg/day)	RfD that Remains (µg/kg/day)	RSC From Drinking Water as % of RfD
Ages 20 +	0.085	0.615	88	0.143	0.557	80
Female 15-44	0.093	0.607	87	0.143	0.557	80
Pregnant	0.123	0.58	82	0.263	0.437	62

EPA believes the NHANES-UCMR analysis is the best available information to characterize non-drinking water exposures to perchlorate for the most sensitive subpopulation. The FDA *Total Diet Study* provides a nationally representative estimate of the mean dietary exposure to perchlorate for 14 age and gender groups, including women of childbearing age. However, this study does not provide specific estimates for the most sensitive subpopulation, the iodine-deficient pregnant woman and her fetus. Also, this study estimates only mean exposures, so it does not account for the perchlorate exposure of highly exposed individuals. The NHANES-UCMR analysis provides a distribution of exposure (not just a mean) specific to almost 100 pregnant women who are not likely to have been exposed to perchlorate from their drinking water, although it also does not separate out iodine-deficient pregnant women because of data limitations. Table 5-3 presents the potential RSC values for the most sensitive subpopulation using the TDS data and the NHANES-UCMR data. EPA notes that the mean RSC for pregnant women estimated from the NHANES-UCMR data is very close to, but slightly lower than, the mean for women of childbearing age estimated from the TDS data. This shows close agreement between the two data sets and is consistent with the suggestion in Murray *et al.* (2008) that food exposures for pregnant women are likely to be somewhat higher than for women of childbearing age as a whole. (Note that higher food exposure equates to a lower RSC because a smaller fraction of the RfD is left to be allocated to drinking water.) While the *means* are available (and in close agreement) from both data sets, EPA believes it is more protective to determine the interim HA level for drinking water by subtracting the 90^{th} percentile exposure in food from the reference dose to assure that the highly exposed individuals from this most sensitive subpopulation are considered in the evaluation of whether perchlorate is found at levels of health concern. The NHANES-UCMR data allow for the calculation of the 90^{th} percentile food exposure, which results in an interim HA level of 15 µg/L for the pregnant woman.

Table 5-3. Potential Health Advisory Levels for Pregnant Women Using TDS Data and NHANES-UCMR Data To Derive Relative Source Contribution

Sub population	Body Weight [a]	Drinking Water Consumption [a]	Source of RSC Derivation	RSC From Drinking Water as % RfD	Potential HA level
Women of Childbearing Age	70 kg	2 liters	TDS mean (Table 5-1)	84 - 87%	21 µg/L
Pregnant Women	70 kg	2 liters	NHANES-UCMR mean (Table 5-2)	82%	20 µg/L
Pregnant Women	70 kg	2 liters	NHANES-UCMR 90th percentile (Table 5-2)	62%	15 µg/L

Footnotes:
[a]Default values used by EPA in the derivation of HA levels.

5.3 Subchronic Interim Health Advisory

Based upon the recommendations of the NRC (2005), the subchronic interim HA was calculated for a pregnant woman as presented below:

$$\text{Subchronic HA} = \frac{0.007\ \text{mg/kg/day} \times 70\ \text{kg} \times 0.6\,2}{10 \times 2\ \text{L/day}} = 0.0152\ \text{mg/L (rounded to } 0.015\ \text{mg/L or } 15\ \mu\text{g/L)}$$

Where:

0.007 mg/kg/day	=	NOEL (Greer *et al*., 2002)
70 kg	=	Assumed body weight of an adult
10	=	Uncertainty factor
2 L	=	Assumed daily water consumption of an adult
0.62	=	Relative source contribution (Using urinary data from the 2001-2002 National Health and Nutrition Examination Survey (NHANES) combined with UCMR occurrence data evaluating nationwide exposure to perchlorate (using the 90th percentile of the distribution), an RSC of 62% was calculated.)

Note: The application of a 10-fold uncertainty factor accounts for variability in responses among humans, and is intended to protect populations that are more sensitive than the population tested. Because the critical study (Greer *et al*., 2002) for perchlorate was based on healthy adult men and women, an uncertainty factor of 10 is applied to protect the most sensitive population, the fetuses of pregnant women who might have hypothyroidism or iodide deficiency.

EPA developed the interim health advisory for the subchronic drinking water exposure of the pregnant mother and her fetus. However, as noted by the NRC in their recommendations, "chronic exposure will have no greater effect than that resulting from short-term exposure. In fact, it may well have less effect because of the capacity of the pituitary –thyroid system to compensate for iodide deficiency by increasing iodide uptake."

5.4 Subchronic Health Advisories for Other Sensitive Subpopulations

Under the Safe Drinking Water Act, EPA must consider possible risk to sensitive subpopulations. EPA developed its subchronic interim HA using body weight, drinking water and food exposure data for pregnant women, in order to protect the most sensitive subpopulation identified by the NRC (i.e., the fetuses of these women), and used the 90th percentile rather than mean food exposure data to ensure that the interim HA protects highly exposed pregnant women and their fetuses. However, infants, developing children, and persons with iodine deficiency or thyroid disorders were also identified as sensitive subpopulations by the NRC. Because infants and children eat and drink more on a per body weight basis than adults, eating a normal diet and drinking water with 15 µg/L of perchlorate may result in exposure that is greater than the reference dose in these sub-groups. To address this concern, the potential effect of this intake on inhibition of iodide uptake in these subgroups (i.e., relative sensitivity) was evaluated using PBPK modeling. Because the NRC (NRC, 2005) found that the inhibition of iodide uptake by the thyroid, which is a non-adverse precursor to any adverse effect, should be used as the basis for perchlorate risk assessment, evaluating iodide uptake inhibition is important for determining whether the interim level of 15 µg/L (derived for pregnant women) is also an appropriate interim HA level for the other sensitive subpopulations. Reducing some of the uncertainty regarding the relative sensitivities of these subpopulations will help address the concerns that some groups may be exposed above the reference dose (calculated using group-specific body weight and intake information), particularly if PBPK modeling predicts that at the interim HA level, these groups do not experience precursor effects (RAIU inhibition) that exceed the no effect level from which the reference dose was derived.

5.4.1 Published PBPK Models. The Clewell *et al.* (2007) and Merrill *et al.* (2005) PBPK models predict the distribution and elimination of perchlorate after it is ingested. The models also predict the level of RAIU inhibition that would result from different levels of perchlorate exposure for different subpopulations, including children and infants.

Clewell *et al.* (2007) predicted that at a perchlorate dose of 0.001 mg/kg/day (1 µg/kg/day), approximately one and one half times the RfD, iodide uptake inhibition in the most sensitive populations, i.e., fetuses and infants, was no greater than 1.1 percent. This is below the level (1.8 percent) of inhibition at the NRC identified no-effect level (NOEL) in healthy adults and recommended as the point of departure for calculating the RfD, applying a 10-fold intraspecies uncertainty factor. The fact that for all subpopulations the predicted RAIU at a level slightly above the RfD is still below the RAIU at the NOEL is consistent with the NRC's conclusion that the RfD would protect even the most sensitive sub-populations. However, because the Clewell model does not account for reduced urinary clearance that occurs in young infants, EPA modified the model as discussed above.

5.4.2 Results of EPA's Application of the Published Models. EPA evaluated the published models (Clewell *et al.*, 2007, and Merrill *et al.*, 2005) and used them to further explore the relationship between water concentrations and iodide uptake inhibition in different subpopulations. EPA determined that it was appropriate to make several changes to the models' computer codes in order to harmonize them and more adequately reflect the biology. EPA considered in detail the data currently available for parameters determined to be particularly important to the models' predictions, and modified the model parameters describing exposure, as well as urinary excretion of perchlorate and iodide. These modifications resulted in predicted RAIU inhibition rates that were up to 1.5 times the predicted inhibition rates in the earlier versions of the model. EPA believes its revisions have improved the predictive power of the model and has used its results as the basis for the following discussion.

Consistent with both the unmodified Clewell model and the NRC's conclusions, EPA's analysis identified the near-term fetus (gestation week 40 fetus) as the most sensitive subgroup, with a percent RAIU inhibition that was 5-fold higher than the percent inhibition of the average adult at a dose equal to the point of departure (7 µg/kg/day). After correcting the model for reduced urinary clearance in infants, the same analysis shows that the predicted percent RAIU inhibition is approximately 1- to 2-fold higher for the breast-fed and bottle-fed infant (7-60 days) than for the average adult, and is slightly lower for the 1-2 year old child than for the average adult. While uncertainty remains regarding the model's predictions, EPA believes that it is a useful tool, in conjunction with appropriate exposure information, for evaluating the relative sensitivity of particular subpopulations (infants and children) that can inform our assessment of whether the interim HA is an appropriate level for all subpopulations (not just pregnant women).

EPA thus applied the adjusted model to the interim HA level of 15 µg/L to determine the predicted percent RAIU inhibition (Table 5-4). Iodide uptake inhibition levels for all other subpopulations, including infants and children, were estimated to be not greater than 2.0 percent at the 15 µg/L drinking water concentration, and not greater than 2.2 percent when also considering perchlorate in food. The highest iodide update inhibition level (2.2 percent) was seen for the 7-day bottle-fed infant; all other

subpopulations, including the 60-day bottle-fed infant, as well as the 7- and 60-day breast-fed infant had inhibition levels below 1.4 percent when also considering perchlorate in food. The 2.2 percent inhibition level for 7-day old bottle-fed infants is comparable to the 1.8 percent inhibition level that the NRC identified as a no effect level in healthy adults and recommended as the point of departure for calculating the RfD. [5]

Table 5-4 also shows the exposure to each subpopulation in µg/kg of body weight. EPA notes that for some subgroups, the modeled exposure exceeds the RfD, though not for the most sensitive subgroup (i.e., pregnant women and their fetuses) from which the interim HA level was derived. EPA has used these exposure estimates as one input into the PBPK model to reduce the uncertainty associated with the relative sensitivities of other subgroups, particularly infants and children. EPA believes use of the model enhances its assessment beyond considering exposure alone by predicting the resulting iodide uptake inhibition that may result from that exposure. As noted above, the NRC concluded that the "most health protective and scientifically valid approach" was to base the point of departure for the RfD on the inhibition of iodide uptake by the thyroid (NRC, 2005), a non-adverse precursor effect. The predicted RAIU inhibition for all subgroups is comparable to or less than the RAIU at the NOEL selected by the NRC. Therefore, EPA believes the interim HA level of 15 µg/L derived for pregnant women is also an appropriate interim HA level for other sub-populations, against which to evaluate monitored levels of perchlorate occurrence in drinking water systems.

[5] The model does not exactly match the average measured inhibition at each exposure concentration. At the point of departure (7 ug/kg/day), the model predicts a value of 2.1 percent for adults, rather than the 1.8 percent from the Greer *et al.* (2002) study. Thus, the model slightly over-predicts the level of inhibition for this group at this exposure level, though this relationship may not hold true for other sub-groups and exposure levels. In any event, the difference between the average measured value of 1.8 percent and the model-predicted value of 2.1 percent is well within the statistical uncertainty in the data.

Table 5-4. Predicted percent radioactive iodide uptake (RAIU) inhibition and corresponding perchlorate intake from water at 15 µg/L with and without food intake.

	Body Weight (kg) [a]	**90th Percentile Water Intake (L/day)** [b]	**Perchlorate Intake from only water at 15 µg/L (µg/kg-day)**	**Percent RAIU Inhibition from only water at 15 µg/L**	**TDS estimated perchlorate intake from food (µg/kg-day)**[c]	**Perchlorate Intake from food and water at 15 µg/L (µg/kg-day)**	**Percent RAIU Inhibition from food and water at 15 µg/L**
Average adult	70	2.24	0.48	0.15	0.10	0.58	0.18
Non-pregnant woman	66	2.11	0.48	0.21	0.10	0.58	0.26
Pregnant woman							
Mom -- GW 13	69	2.18	0.50	0.49	0.10	0.60	0.59
Mom -- GW 20	71	2.34	0.50	0.49	0.10	0.60	0.59
Mom -- GW 40	78	2.57	0.50	0.47	0.10	0.60	0.57
Fetus -- GW 40[g]	3.5	--	--	0.90	--	--	1.1
Breast-fed infant							
Mom -- 7 d	74	2.96	0.60	0.18	0.10	0.70	0.21
Infant -- 7 d	3.6	0.52[d]	1.36	1.1	-- [d]	1.59	1.3
Mom -- 60 d	72	2.96	0.61	0.17	0.10	0.71	0.20
Infant -- 60 d	5	0.74[d]	1.27	0.73	-- [d]	1.48	0.84

	Body Weight (kg) [a]	90th Percentile Water Intake (L/day) [b]	Perchlorate Intake from only water at 15 µg/L (µg/kg-day)	Percent RAIU Inhibition from only water at 15 µg/L	TDS estimated perchlorate intake from food (µg/kg-day)[c]	Perchlorate Intake from food and water at 15 µg/L (µg/kg-day)	Percent RAIU Inhibition from food and water at 15 µg/L
Bottle-fed infant							
Infant -- 7 d	3.6	0.84[e]	3.53	2.0	1.42 µg/L	3.87	2.2
Infant -- 60 d	5	1.14[e]	3.42	1.3	1.42 µg/L	3.74	1.4
Child							
6-12 mo[f]	9.2	1.03	1.68	0.46	0.275	1.96	0.53
1-2 yr[f]	11.4	0.64	0.84	0.23	0.370	1.21	0.33

[a] Calculations for a 70 kg "average" adult are shown, while the body weight (BW) for the non-pregnant woman is from US EPA 2004 (based on CSFII 94-96,98) and BWs for the child are mean values from Kahn and Stralka (2008). BWs for pregnant and breast feeding moms, fetuses, bottle- and breast-fed infants are predicted weights (functions of age or gestation week) using growth equations from Gentry *et al*. (2002) as implemented in the PBPK models (Clewell *et al.* 2007; non-pregnant value is BW at day 0 of gestation).

[b] Water intake levels for adults other than the lactating mother are based on normalized 90th percentile values for total water intake (direct and indirect) multiplied by the age- or gestation-week-dependent BW, as follows: 0.032 L/kg-day for average adult and non-pregnant woman; 0.033 L/kg-day for the pregnant woman. A fixed ingestion rate was used for the lactating mother because, while her BW is expected to drop during the weeks following the end of pregnancy, the demands of breast-feeding will be increasing. Values are from Kahn and Stralka (2008), except values for women are from U.S. EPA (2004).

[c] The dietary values used correspond to the midpoint of the range of lower- and upper-bound average perchlorate levels for each subgroup, as identified from the FDA TDS in Murray *et al.* (2008), except for the bottle-fed infant. EPA used 1.42 µg/L as the concentration of perchlorate in infant formula. This is based on an average of available FDA TDS data, with ½ LOD included in the average for the samples in which perchlorate was not detected.

[d] The breast-fed infants are assumed to have no direct exposure via food or water. The prediction for breast-fed infants in this table results from the dose from both food and water to the mother providing breast milk to the infant. Breast-fed infant "water intake" is the breast milk ingestion rate obtained by fitting an age-dependent function to the breast-milk ingestion data

(L/kg-day) from Arcus-Arth *et al.* (2005). Urinary clearance rates for the lactating woman equal to that of the average adult were used, consistent with data presented in Delange (2004).

[e] For the bottle-fed infant, normalized total water intake (direct and indirect, L/kg-day) was described as a smooth function of infant age fit to the results from Kahn and Stralka (2008), and multiplied by BW(age). For the 7-day-old infant, the data used to fit the function included the 90th percentile community water-consumers only intake (0.235 L/kg-day, N=40) for the < 1 month old infant. For the 60-day-old infant, the 90th percentile community water-consumers only intake (0.228 L/kg-day, N=114) for the 1- to <3 months-old infant was used.

[f] For the 6- to 12-month and 1- to 2-year-old children, EPA set the water ingestion based on published exposure tables and selected the age at which the model-predicted BW (from growth equations) matched the exposure-table mean. This approach resulted in model predictions for a 9.6-month old child (to represent 6- to 12-month-old children) and a 1.3-year old (to represent 1- to 2-year-old children).

[g] Due to data limitations, RAIU inhibition is calculated only for fetuses at GW 40.

5.4.3 Modeling Uncertainties. EPA recognizes that there are uncertainties associated with this modeling, as there are for any modeling effort. For example, this analysis does not take into account within-group variability in pharmacokinetics, uncertainty in model parameters and predictions, or population differences in pharmacodynamics (PD) of receptor binding and upregulation. Also, the NRC identified fetuses of pregnant women that are hypothyroid or iodine deficient as the most sensitive subpopulation. The model predictions of RAIU inhibition in the various subgroups are average inhibition for typical, healthy individuals, not for hypothyroid or iodine deficient individuals. However, EPA did not rely on this analysis for determining the HA. Rather, the interim HA level of 15 µg/L was calculated directly from the RfD to protect the most sensitive subpopulation, the fetuses of pregnant women, using high end exposure assumptions (e.g., estimated 90th percentile drinking water consumption and estimated 90th percentile perchlorate dietary (food) exposure). The PBPK modeling was used to provide information on the potential effects of exposure at the interim HA level for other subgroups, such as infants and children.

In addition, the predicted inhibitions are averages for the subgroup as a whole, given the exposure assumptions used in the model. Thus, some members of a group would be expected to have RAIU inhibition greater than indicated in Table 5-4 for a particular perchlorate concentration, while others would have lesser inhibition. EPA was able to partially address this variability by using 90th percentile water consumption rates and mean body weights in the analysis to consider the highly exposed portions of the various subgroups. Most members of the subgroups would be expected to have exposures less than those indicated in Table 5-4.

There is also some uncertainty regarding the water intake rates, particularly for infants. EPA described water intake by infants as a smooth function fit to the 90th percentile community water-consumers intake-rate data (intake per unit BW) of Kahn and Stralka (2008), which is then multiplied by the age-dependent BW to account for the changes occurring over the first weeks of life. This resulted in an estimated 90th percentile water intake rate of 0.84 L/day for the 7-day bottle-fed infant and used by EPA in PBPK model simulations. General information on water and formula intake for 7-day old infants is also available in guidelines for healthy growth and nutrition of the American Academy of Pediatrics (AAP, 2008). The values estimated using the guidelines from the AAP (0.126 L/kg-day assuming 80% is the percent water used in preparation of formula) for 7-day-old infants are close to the mean consumers-only intake rate for the 1-30 day-old infants from Kahn and Stralka (2008; 0.137 L/kg-day N=40).

There is also uncertainty regarding the appropriate duration of exposure (i.e., days, weeks, months) to compare to the perchlorate RfD, which EPA defines as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." Reference values, like the RfD, are derived based on an assumption of continuous exposure throughout the duration specified, while intake levels may rapidly change day to day or during certain life stages. For comparability with the RfD, continuous perchlorate exposure was assumed in EPA's modeling analysis. Using perchlorate levels predicted for a continuous exposure (constant rate of introduction to the stomach), rather than incorporating changes in exposure and other input parameters over time (i.e., simulating the timing and quantity of specific ingestion events during the day), substantially reduced the effects of parameter

uncertainty in the modeling. RAIU inhibition, on the other hand, is evaluated as the change in thyroid uptake of a pulse of iodide (radiolabeled, from an IV injection) at a time 24 hours after the pulse is administered. Thus, it represents the inhibition on a given day. This was true in the Greer study on which the RfD is based, and it is also true in the model. For all life stages except the developing infant, the day-to-day variation in RAIU inhibition at the levels under consideration will have little or no effect. However, the effects of short-term inhibition in the infant (and fetus) may be of greater consequence than in the adult, although infants may also have less short-term variability in their diet and intake levels than adults. To address this concern, we present the results for the infant at both 7 days and 60 days after birth. The model predicts a fairly smooth variation in effect between these two ages.

5.4.4 Summary of Modeling Analysis. EPA focused attention on the most sensitive subpopulation, a pregnant woman and her fetus. EPA calculated an interim HA level of 15 µg/L for pregnant women using RSC information derived from an analysis of NHANES and UCMR data. EPA also conducted PBPK modeling to evaluate predicted biological outcomes associated with drinking water concentrations at the interim HA level for different sensitive subpopulations. For pregnant women, EPA assumed a 90th percentile water ingestion rate of 0.033 L/kg-day, a food intake rate that represented the midpoint of the range of average perchlorate dietary exposures reported in Murray *et al*. (2008), and used the Clewell *et al.* (2007) PBPK model-fitted body weight. EPA believes that the model-fitted body weight provides a more realistic weight for the pregnant woman than EPA's 70 kg default assumption for adults. In addition, rather than using the default assumption of 2L/day water ingestion, EPA used a 90th percentile water ingestion rate normalized for body weight and based on data specifically for pregnant women (USEPA, 2004b). Using these assumptions, the model predicted that the pregnant woman's dose of perchlorate would not exceed the reference dose if she consumed drinking water with a concentration of 15 µg/L or less, which is consistent with the derivation of the interim HA level from the reference dose, based on average body weight, 90th percentile water consumption, and 90th percentile food exposure for pregnant women. The model further predicted that the percent inhibition in the fetus of a pregnant woman consuming drinking water with 15 µg/L perchlorate (in combination with a normal diet) is 1.1 percent which is below the 1.8 percent that the NRC determined to be a no-effect level in healthy adults. EPA evaluated other subpopulations to estimate iodide uptake inhibition and determined that 7-day old bottle-fed infants were predicted to have a 2.2 percent inhibition level, after also accounting for food exposure, and all other subpopulations, including 60-day old bottle-fed infants, 7 and 60 day old breast-fed infants, and children, were predicted to have levels of inhibition of 1.4 percent or less, after accounting for food. All of these levels are comparable to or below the 1.8 percent no effect inhibition level from the Greer study.

Based on the health protective approach for deriving the RfD (i.e., use of a NOEL rather than a NOAEL as the point of departure), the conservative assumptions used in deriving the RSC and corresponding interim HA level (use of 90th percentile food exposure data specifically from pregnant women), and the PBPK modeling analysis of RAIU inhibition in potentially sensitive subpopulations, EPA believes that drinking water with perchlorate concentrations at or below the interim HA level of 15 µg/L is protective of all subpopulations.

5.5 Evaluation of Carcinogenic Potential

The EPA currently requires that all new cancer risk assessments comply with the Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005). The EPA (2005) describes perchlorate's weight of evidence classification as "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. The epidemiological evidence is insufficient to determine whether or not there is a causal association between exposure to perchlorate and thyroid cancer."

6.0 OTHER CRITERIA, GUIDANCE, AND STANDARDS

Two states have established regulatory standards for perchlorate in drinking water. In July 2006, Massachusetts promulgated a drinking water standard of 2 µg/L for perchlorate (Mass DEP, 2006), while California established an MCL of 6 µg/L in October 2007 (CDPH, 2007). The states used the same NOEL from the Greer *et al*. (2002) study as EPA, but different methodologies for calculating RSC and addressing sensitive subpopulations. EPA believes that its analysis is based on the best currently available science, data, and analyses, including some analyses that were not available at the time these state standards were established, and that drinking water with perchlorate concentrations at or below its interim HA level of 15 µg/L is protective of all subpopulations. The SDWA allows States to establish drinking water standards that are more stringent than EPA's national standards, as well as for contaminants which EPA has determined not to regulate. EPA supports such state action, especially in cases where there are not enough public water systems above the interim HA level to warrant a national standard, but where a few individual states may have a higher concentration of such systems.

7.0 ANALYTICAL METHODS

Perchlorate can be detected in drinking water by EPA methods 314.0, 314.1, 314.2, 331.0 and 332.0. EPA method 314.0 was approved for the 2001 through 2003 monitoring of perchlorate, required in the UCMR, and employs ion chromatography with conductivity detection. The method detection limit (MDL) for method 314.0 is 0.53 µg/L and the average recovery is reported to range from 86 to 113 percent, depending on the matrix.

EPA Methods 314.1, 314.2, 331.0, and 332.0 are newer methods that were published from May 2005 through May 2008. Method 314.1 relies on ion chromatography with suppressed conductivity detection, has an MDL of approximately 0.03 µg/L and an average recovery ranging from 75.9 to 108 percent, depending on the matrix and the type of analytical column used. Method 314.2 uses two-dimensional ion chromatography followed by suppressed conductivity detection. The MDL for perchlorate using this method is 0.012 to 0.018 µg/L, depending upon the volume of sample analyzed, and the average recovery of perchlorate ranges from 92 to 110 percent, depending upon the matrix. Method 331.0 employs liquid

chromatography with electrospray ionization mass spectrometry. The MDL for perchlorate using this method is 0.008 µg/L in selected ion monitoring mode (single stage mass spectrometry) and 0.005 µg/L in multiple reactions monitoring mode (tandem mass spectrometry). The average recovery for perchlorate using Method 331.0 ranges from 95.1 to 105 percent, depending on the matrix. Method 332.0 employs ion chromatography with electrospray ionization mass spectrometry detection. The MDL for perchlorate using this method is 0.02 µg/L and the average recovery ranges for 90 to 105 percent, depending on the matrix.

8.0 TREATMENT TECHNOLOGIES

The physiochemical properties of perchlorate make its removal difficult by chemical precipitation processes, such as conventional treatment. Researchers, however, have shown that perchlorate can be effectively removed by using advanced treatment technologies, such as anion exchange, modified granular activated carbon (GAC), reverse osmosis/nanofiltration membrane filtration, chemical/electrochemical reduction (Gu and Coates, 2006) and biological reduction (Logan *et al*., 2004).

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