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WHITE PAPER

LIFE STAGE CONSIDERATIONS AND INTERPRETATION OF RECENT EPIDEMIOLOGICAL EVIDENCE TO DEVELOP A MAXIMUM CONTAMINANT LEVEL GOAL FOR PERCHLORATE

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Abbreviations

ADHD - Attention Deficit Hyperactivity Disorder
BW - Body Weight
DWI - Drinking Water Ingestion Rate
EPA - U.S. Environmental Protection Agency
FDA - Food and Drug Administration
fT4 - Free T4
GW - Gestational Week
HRL - Health Reference Level
kg - Kilogram
L - Liter
MCL - Maximum Contaminant Level
MCLG - Maximum Contaminant Goal Level
NHANES - National Health and Nutrition Examination Survey
NIS - Sodium (Na)/iodide (I) symporter
NOEL - No Observed Effect Level
NPDWR - National Primary Drinking Water Regulation
NRC - National Research Council
PBPK - Physiologically-based Pharmacokinetic
POD - Point of Departure
POR – Prevalence Odds Ratio
ppb - Parts Per Billion (equal to µg/L)
PWS - Public Water System
RAIU - Radioactive Iodide Uptake
RfD - Reference Dose
RSC - Relative Source Contribution
SAB - Science Advisory Board
SDWA - Safe Drinking Water Act
TDS - Total Dietary Study
T4 - Thyroxine
T3 - Triiodothyronine
TSH - Thyroid stimulating hormone or thyrotropin
UCMR 1 - Unregulated Contaminant Monitoring Rule 1
µg - Microgram (one-millionth of a gram)
U.S. - United States

I. PURPOSE

The U.S. Environmental Protection Agency (EPA) has prepared this white paper, "*Life Stage Considerations and Interpretation of Recent Epidemiological Evidence to Develop a Maximum Contaminant Level Goal for Perchlorate*" that presents scientific information published since the National Research Council (NRC) released their 2005 Report "*Health Implications of Perchlorate Ingestion*" and explains how EPA derived a range of Maximum Contaminant Level Goal (MCLG) values for life stages of concern. The purpose of this white paper is to seek guidance from the Science Advisory Board (SAB) on how best to consider and interpret the life stage information, the epidemiologic and biomonitoring data since the NRC Report, physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive an MCLG for perchlorate.

II. BACKGROUND

On February 11, 2011 (U.S. EPA, 2011a), EPA published a determination to regulate perchlorate under the Safe Drinking Water Act (SDWA) because:

- perchlorate may have an adverse effect on the health of persons;
- perchlorate is known to occur or there is a substantial likelihood that it will occur in public water systems with a frequency and at levels of public health concern; and,
- in the sole judgment of the Administrator, regulation of perchlorate presents a meaningful opportunity for health risk reduction for persons served by public water systems.

EPA has initiated the process to develop a MCLG and National Primary Drinking Water Regulation (NPDWR) for perchlorate. The MCLG is a non-enforceable goal defined under the SDWA (§1412.b.4.B) as *"the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety."* For perchlorate, the NPDWR will likely specify an enforceable Maximum Contaminant Level (MCL) and monitoring and reporting requirements for public water systems. The SDWA (§1412.b.4.B and D) specifies that the enforceable MCL be set as close to the MCLG as feasible using the best available technology, treatment techniques, and other means (taking cost into consideration).

The regulatory schedule established by SDWA requires EPA to publish a proposed MCLG and NPDWR within 24 months of making a determination to regulate a contaminant and promulgate a final regulation within 18 months of the proposal. As part of this proposed rulemaking, EPA also must develop a Health Risk Reduction and Cost Analysis that includes an assessment of the quantifiable and non-quantifiable health risk reduction benefits likely to occur as a result of treatment to remove the perchlorate. SDWA further requires that when proposing any NPDWR that includes an MCL, the Administrator must analyze "[*t]he effects of the contaminant on the general population and on groups within the general population such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or*

other subpopulations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population[1]."

In 2005, at the request of EPA and other federal agencies, the NRC published a comprehensive report "*Health Implications of Perchlorate Ingestion*" (NRC, 2005). The NRC concluded that perchlorate can affect thyroid function because it is an ion that competitively inhibits the transport of iodide into the thyroid by a protein known as the sodium (Na)/iodide (I) symporter (NIS). Significant inhibition of iodide uptake results in intra-thyroid iodine deficiency, decreased synthesis of key thyroid hormones (Triiodothyronine, T3 and Thyroxine, T4), and increased thyroid stimulating hormone or thyrotropin (TSH). The NRC also concluded that a prolonged decrease of thyroid hormone is potentially more likely to have adverse effects in sensitive populations (people with thyroid disorders, pregnant women, fetuses, and infants).

The NRC recommended the use of a precursor, non-adverse effect (i.e., inhibition of iodide uptake) to derive a reference dose (RfD) for perchlorate. An RfD is defined by EPA as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." The NRC identified a clinical study involving 37 healthy men and women by Greer *et al*. (2002) as the critical study and determined an RfD of 0.7 µg/kg/day for perchlorate. The RfD was based on the No Observed Effect Level (NOEL) of 7 µg/kg/day corresponding to a radioactive iodide uptake (RAIU) inhibition of 1.8 percent and application of an intraspecies uncertainty factor (UF) of 10 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. The NRC also acknowledged that the RfD may need to be adjusted upward or downward on the basis of future research. The RfD of 0.7 µg/kg/day was adopted by EPA in 2005 (U.S. EPA, 2005a). EPA believes that this RfD is the most scientifically defensible endpoint available at this time for assessing risk from perchlorate exposure.

In October 2008, EPA published a preliminary determination not to regulate perchlorate in drinking water using a health reference level (HRL) of 15 µg/L, which was derived from the RfD of 0.7 µg/kg/day, using a default body weight (70 kg), a default drinking water consumption rate (2 L/day), and a perchlorate-specific relative source contribution (RSC) of 62% for a pregnant woman (U.S. EPA, 2008). The RSC is the percentage of the RfD remaining for drinking water after the other sources of exposure to perchlorate (e.g., food) have been considered. In January 2009, EPA issued an interim health advisory (15 µg/L perchlorate in drinking water) to provide guidance to state and local officials in their efforts to address

[1] SDWA uses the term subpopulation to refer to groups within the general population such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other groups that can be identified and characterized and are likely to experience elevated health risks. In 2005 EPA started using the term life stages to refer to age-defined groups. All life stages are subpopulations but not all subpopulations are life stages. In this document, the term life stage is used predominantly because of the focus on infants and very young children.

perchlorate contamination while EPA was continuing to review scientific issues (U.S. EPA, 2009a).

In August 2009, EPA published a supplemental request for comment with a new analysis that derived potential alternative HRLs for 14 life stages, including infants and children. The analysis used the RfD of 0.7 µg/kg/day and life stage-specific body weight and exposure information (i.e., drinking water intake, RSC) (U.S. EPA, 2009b). The HRLs ranged from 1 µg/L to 47 µg/L. In February 2011, EPA published the Final Regulatory Determination to regulate perchlorate under SDWA. The Final Regulatory Determination stated that EPA was evaluating the potential alternative HRLs and considered them to be levels of public health concern for the purposes of final determination (U.S. EPA, 2011a).

III. DERIVATION OF A MAXIMUM CONTAMINANT LEVEL GOAL

As previously discussed, the SDWA (§1412.b.4.A) defines an MCLG as the level of a contaminant in drinking water "at which no known or anticipated adverse effects on the health of persons occur and which allows for an adequate margin of safety." An MCLG is a non-enforceable public health goal.

EPA generally derives an MCLG using the following formula:

$$\text{MCLG (µg/L)} = \frac{\text{RfD (µg/kg bw/day) x BW (kg)}}{\text{DWI (L/day)}} \times \text{RSC}$$

Where:

RfD is the reference dose for a contaminant (µg/kg/day).

BW is body weight in kg. A default body weight (70 kg) is typically used.

DWI is drinking water ingestion rate in L/day. A default intake (2 L/day) is typically used.

RSC is the relative source contribution. The RSC is derived as the percentage of the RfD remaining for drinking water after other sources of exposure to perchlorate (e.g., food) have been considered. EPA uses a default RSC value of 20% in deriving an MCLG when data are not available to estimate the contributions from other sources of exposure.

The SDWA also directs EPA to consider sensitive subpopulations in establishing regulations for drinking water contaminants. EPA believes that adequate information is available indicating the need to reflect specific life stage considerations for neonates, infants, and pregnant women in its assessment of perchlorate. As a result, life stage- and subpopulation-specific values are considered for BW, DWI, and RSC later in this document.

IV. LIFE STAGE CONSIDERATIONS

Although studies directly demonstrating the adverse effects of perchlorate in humans are not available, potential effects can be inferred from its mode of action, and the literature on the effects of thyroid hormone perturbations in various life stages. Based on the discussion to follow, pregnant women, fetuses, neonates, infants and children have been identified as life stages of particular concern for adverse effects due to perchlorate.

Perchlorate can affect thyroid function because of its ability to block the transport of iodide into thyroid follicular cells. Iodine, in the form of an iodide salt from diet, is needed for the synthesis of thyroid hormones. Iodide transport into the cells is mediated by NIS. Perchlorate has a higher affinity for NIS compared to iodide, so perchlorate can block iodide transport into thyroid cells. This can result in a decrease in the available iodide concentration in the cells needed for the biosynthesis of T4 and T3 (NRC, 2005).

Thyroid hormones are critical determinants of growth and development in infants and children, and of metabolic activity in infants, children and adults. Approximately 20% of T3 is produced by the thyroid gland and the rest is produced from T4 in most tissues of the body. Thyroid stimulating hormone secreted by the pituitary gland stimulates the synthesis and secretion of T3 and T4. Small increases in serum T3 and T4 result in the inhibition of the secretion of TSH, while small decreases result in the increase of TSH secretion. These homeostatic mechanisms are very effective in ensuring that thyroid hormone levels remain normal in the majority of cases. However, if the thyroid is damaged or other conditions are present that block synthesis and secretion of T4 and T3, TSH secretion may have little effect and T3 and T4 levels can continue to decrease, resulting in hypothyroidism (deficient thyroid hormone production) (NRC, 2005).

Sensitivity of Pregnant Mothers, Fetuses and Infants

Thyroid perturbations during pregnancy result in effects ranging from fetal loss to neurological deficits in children. Pregnant women who have subclinical hypothyroidism or hypothyroidism have an increased risk of fetal loss and neurological impairment in their offspring (Allan *et al*., 2000; Abalovich *et al*., 2002; Haddow *et al*., 1999). Iodide deficiency during pregnancy is associated with neurological impairments in children. Severe deficiency in iodide intake (below 20 µg per day) in pregnant women results in major neurological impairments and goiter in their offspring (Delange, 2000). Congenital hypothyroidism in the fetus and newborn, despite early identification and treatment, still results in language deficits, memory deficits, and visuospatial impairments that persist to adulthood (Rovet *et al*., 1987; Rovet *et al*., 1992; Tillotson *et al*., 1994; Oerbeck *et al*., 2003).

Thyroid hormones are essential for both fetal and postnatal neurodevelopment. Even transient changes in thyroid hormones during critical period of growth may lead to adverse neurological outcomes (Glinoer, 2001, Williams, 2008). The timing of thyroid deficiency (early

pregnancy, late pregnancy, postnatal) and it degree is critical to the type and severity of neurological deficit exhibited in infants and children (Zoeller and Rovet, 2004). Visual processing and memory and gross motor skills are predominantly affected by hormone insufficiencies in early pregnancy, visuospatial skills and fine motor deficits characterize insufficiencies in later stages of pregnancy, whereas hormone deficiencies in the late stage fetus and neonate, as in cases of congenital hypothyroidism, result in deficits in language skills and verbal memory. Therefore, thyroid hormone is essential across all stages of fetal and neonatal brain development (Morreale de Escobar *et al*., 2008; Zoeller and Rovet, 2004). As such, the impact of thyroid hormone disruption by perchlorate requires particular attention at these sensitive life stages.

As the fetus develops, the maternal supply of T4 is critical for the development of the brain. During the first trimester, maternal T4 is the only source of the hormone to the fetus and during late gestation, maternal T4 contributes approximately 30% of the fetal supply of T4 (Vulsma *et al*., 1989). A number of studies (detailed below) have reported significant deficits in cognitive function and altered development in children born to women with gestational levels of T4 or free T4 (fT4) that are within or at the low end of normal reference ranges (Smit *et al*., 2000; Haddow *et al*., 1999; Pop *et al*., 1999; 2003; Vermiglio *et al*., 2004) Kooistra *et al*., 2006). The effects of thyroid hormone insufficiencies may not be readily observable in infants. They emerge as the behavioral repertoire of the child becomes sufficiently advanced to support detailed evaluation of cognitive function, permitting the detection of subtle deficiencies.

Subclinical hypothyroidism in pregnancy has been associated with neurological deficits in children. Haddow *et al*. (1999) compared 7 to 9 year-old children born to 62 women who had subclinical hypothyroidism during the second trimester of pregnancy with 124 children born to women who had normal thyroid function. The mean full-scale IQ score was 4 points lower in the former group, and 15% had scores of 85 or lower, compared with 5% of the control children. A prospective study of seven infants born to mothers who had subclinical hypothyroidism during pregnancy and six infants born to mothers who had normal thyroid function found that the former had lower scores on the Bayley Mental Developmental Index at the ages of 6 and 12 months but not at 24 months (Smit *et al*., 2000).

The infants of mothers who have low serum fT4 concentrations early in pregnancy also have impaired neurodevelopment. Among 220 infants tested at the age of 10 months, the 22 infants whose mothers had serum fT4 concentrations in the lowest 10th percentile (but normal serum TSH concentrations) at 12 weeks of gestation scored lower on the Psychomotor Development Index (by 7 points, 93% vs. 100%), but not the Mental Developmental Index (Pop *et al*., 1999). Pop *et al*. (2003) reported an 8 to 10 point decrease in Bayley Scales of mental developmental scores in 1 to 2 year-old children of mothers who had fT4 levels in the lower 10th percentile (hypothyroxinemia) during the 12th week of gestation compared to children of women who had fT4 levels in the 50^{th} to 90^{th} percentiles (controls) during this same period.

Vermiglio *et al*. (2004) studied 16 women and their offspring from low iodine area in northern Sicily, compared to 11 control women and their offspring from a nearby, marginally iodine sufficient area. The mean maternal urinary iodine levels were reported as 48.1 µg/day and

95.2 µg/day, respectively. Maternal fT4 and T4 levels at 8, 13, and 20 weeks were 10 to 20 percent lower in women from the low iodine area than in the marginally iodine sufficient area. All the children had normal thyroid hormone levels at delivery, ages 1½ to 3 years, and ages 8 to 10 years. The mean IQ of the children from the low iodine area was 18 points lower than that of the children from the marginally iodine sufficient area (92.1 ± 7.8 vs 110 ± 10, $p < 0.00005$). Attention Deficit Hyperactivity Disorder (ADHD) was diagnosed in 11 of the children from the low iodine area and in none of the children from the marginally iodine sufficient area. The authors showed a correlation between the child's IQ and the maternal fT4 ($r = 0.56$, $p < 0.005$) and TSH ($r = -0.63$, $p < 0.001$). Although the study is small, it suggests that there is a direct relationship between indices of maternal thyroid stress due to low iodine during pregnancy and the neurodevelopment of their children.

Kooistra *et al*. (2006) used the Neonatal Behavioral Assessment Scale to assess the health status of infants at three weeks of age born to women identified as having low thyroid status at 12 weeks gestation. In a cohort of 1361 women 108 case subjects and 96 controls were selected based on fT4 levels of ≤ the 10th percentile (cases), versus the 50^{th} to 90^{th} percentile (controls) at 12 weeks' gestation. No differences in T4 levels were observed between these groups of infants at birth. Orientation to visual and auditory stimuli was decreased ($p = 0.042$) in the infants of low T4 mothers. The authors conclude that the effects on orientation are consistent with the increased ADHD disorders associated with thyroid dysfunction by other researchers, and thus may be a useful early indicator of later problems.

Henrichs *et al*. (2010) reported on cognitive performance in a large, population-based study (Generation R) of over 4000 neonates born to hypothyroxinemic women (fT4<10^{th} percentile). The strengths of this study are the large sample size, detailed information on maternal and neonatal thyroid function, and information of numerous potential confounders. Expressive language delays were evident in children assessed at 18 and 30 months of age. Nonverbal cognitive delays were reported in children born to women with more severe degrees of hypothyroxinemia (fT4<5^{th} pecentile). Neither maternal early pregnancy TSH levels nor neonatal thyroid function at birth predicted cognitive outcomes.

Distinct from maternal hypothyroidism, congenital hypothyroidism is caused by an abnormality in thyroid gland development that results in insufficient levels of thyroid hormone production during late gestational and neonatal periods. Untreated congenital hypothyroidism results in profound mental retardation. Newborn screening programs identify and provide treatment for this disorder, but because there is a brief but circumscribed period of thyroid hormone insufficiency, there is risk for neurocognitive impairment. Numerous studies reveal an average lowering of IQ of 6 points in congenital hypothyroidism identified by screening. These children are outperformed by their peers and siblings on various neuropsychological tasks including measures of learning and memory, and exhibit mild underachievement at school, and are at increased risk of learning abilities (Rovet, 2002; Oerbeck *et al*., 2005; Song *et al*., 2001). Using magnetic resonance imaging, Wheeler *et al.* (2011) recently reported reduced hippocampal volumes (an area critical for memory) that were correlated with memory deficits in 9-15 year old congenitally hypothyroid children. The data from cases of congenital hypothyroidism are instructive as they further demonstrate the negative impact of circumscribed

and mild (with early detection and appropriate treatment) thyroid hormone insufficiencies on neurodevelopment.

Factors Influencing the Sensitivity of Fetuses, Neonates, Infants and Children

A reduction in the storage of thyroid hormone and iodine, as well as rapid thyroid hormone turnover (i.e., shorter half-life) in the fetus, neonates and children makes these life stages more sensitive to thyroid disrupting agents such as perchlorate compared to adults. Furthermore, the physiological demand for thyroid hormones is far greater in the developing fetus, neonate and child compared to the adult, again increasing the vulnerability to thyroid disrupting agents.

- The half-life of T4 in neonates was estimated at 3.6 days (Vulsma *et al*., 1989). T4 half-life for older children less than 5 years old was reported as 3 days for T4 and 6 days for T3 (Lewander *et al*., 1989; van den Hove *et al*., 1999). These half-lives are shorter than the approximately 7-10 days in adults (Chopra and Sabatino, 2000).

- The storage of thyroglobulin and iodine in the fetal thyroid gland is not fully mature until near term birth, thus increasing the risk for neonatal hypothyroxinemia in preterm infants (Savin *et al*., 2003; van den Hove *et al*., 1999).

- Neonates have a higher turnover rate of intrathyroidal iodine reserves compared to adults (17% versus 1% under iodide-replete conditions). The turnover rate for iodine reserves in neonates is increased to 62% and 125% under moderate and severe iodide deficiency conditions (Delange, 1998).

- In general, infants (breast-fed and bottle-fed) and children are more susceptible to contaminant exposures than adults because their food consumption and drinking water intake per body weight are greater compared to adults (U.S. EPA, 2009b,c; U.S. EPA, 2011b).

- Slower urinary clearance in neonates relative to other other life stages leads to a longer resident time for xenobiotics. The glomerular filtration rate in one-week old neonates (11.0 ± 5.4 mL/min/1.73 m^2) is slower than in 9-12 month old infants (86.9 ± 8.4 mL/min/1.73 m^2). Data on urinary elimination of a number of compounds, including drugs and drug metabolites, also indicate that renal clearance is slower per unit body weight in neonates (U.S. EPA, 2009c).

- Breast-fed infants may be more vulnerable to perchlorate mediated effects compared to other formula–fed infants for two reasons-perchlorate accumulates in breast milk directly exposing the infant, and perchlorate inhibits transfer of iodide into breast milk resulting in low iodide levels in breast milk (Tazebay *et al*., 2000, Kirk *et al*., 2005; Kirk *et al*., 2007; Pearce *et al*., 2007; Dasgupta *et al*., 2008; Borjan *et al*., 2011). Breast fed infants also acquire a higher dose of perchlorate than formula-fed infants. The mean daily dose

estimated for breast-fed infants, cow milk-fed infants and soy milk–fed infants are 0.420, 0.208, 0.065 µg/kg/day, respectively (Valentín-Blasini *et al*., 2011).

V. DERIVATION OF LIFE STAGE-SPECIFIC MCLGS

EPA adopted the RfD of 0.7 µg/kg/day determined by NRC in 2005. EPA used this RfD to develop life stage specific MCLGs. As described in Section III above, EPA generally develops MCLGs from the RfD assuming a BW for adults (70 kg) and a corresponding adult DWI (2 L/day). However, EPA's Exposure Factors Handbook (U.S. EPA, 2011b) presents a range of values for BW and DWI which vary by life stage and subpopulation. Although absolute values for BW and DWI for infants and children may be lower than for adults, the intake per body weight for most sensitive life stages that is greater than for adults. The result is a higher exposure to a drinking water contaminant at a given water concentration than observed for adults (U.S. EPA, 2009b, Table 2).

In Table 2 of the Federal Register Notice (U.S. EPA, 2009b), EPA calculated alternative HRLs (utilizes the same calculations as MCLG) for infants and children among other life stages based upon EPA's *Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants* (U. S. EPA, 2005b) which recommends the following age groups be considered in exposure assessments for children less than 12-months old: birth to < 1 month, 1 to < 3 months, 3 to < 6 months and 6 to < 12 months. In this white paper, EPA calculated the MCLGs for infants of age 7 days, 30 days, 60 days, 6-12 months and children 1 to 2 years to align with the life stages evaluated under the PBPK modeling.

EPA believes that dietary ingestion is the only significant pathway for non-drinking water perchlorate exposure. To determine the perchlorate exposure from food for infants and children, EPA used the data from Murray *et al*. (2008) which reports the results of the Total Dietary Study (TDS) conducted by the Food and Drug Administration (FDA) for the period 2005-2006. The FDA's TDS estimates mean dietary intakes for 14 age-gender groups including infants, children and adults (Table A-1). However, the TDS design does not support estimates of intakes, of intake distributions, or intake estimates for population subgroups with specific nutritional needs (such as the subgroups of pregnant or lactating women). The TDS also does not include the perchlorate intake data for infants less than 6 months of age.

For infants less than 6 months old, the 59% RSC for 6-month olds was used (Table A-2). Since the TDS, new dietary estimates (including younger infants) were reported in the literature, and the findings from these studies are consistent with the RSC of 59% selected for infants (Schier *et al*., 2010; Valentín-Blasini *et al*., 2011). Depending upon the type of infant formula (bovine milk, soy milk, elemental formula), Schier *et al*. (2010) estimated the geometric mean at the 90^{th} percentile BW in the range of 0.04-0.35 and 0.03-0.27 µg/kg/day for one-month old and 6-month old infants, respectively. The TDS as well as Schier *et al*. (2010) did not evaluate the perchlorate exposure for infants via breast milk. In another study, Valentin-Blasini *et al*. (2011) reported the geometric mean of perchlorate intake as 0.103, and 0.027 µg/kg/day for infants of 1-377 days age fed with bovine milk and soy milk, respectively. Unlike Schier *et al*. (2010) who measured perchlorate levels in different formula types and estimated the perchlorate intake based

on body weight and formula consumption, Valentin-Blasini *et al*. (2011) estimated the perchlorate exposure based urinary volume and perchlorate concentrations excreted in the urine. The findings from these recent two studies are consistent with the estimate reported by Murray *et al*. (2008) for infants, suggesting the 59% RSC is a reasonable estimate for infants. For children of age 2 years, 44% RSC was used (Table A-2).

EPA estimated the RSC for pregnant women and females of reproductive age by a combined analysis of National Health and Nutrition Examination Survey (NHANES) 2001-2002 urinary biomonitoring data and EPA's drinking water monitoring data, Unregulated Contaminant Monitoring Rule 1 (UCMR 1) (Huber *et al*., 2011). The total daily intake of perchlorate was determined by measuring perchlorate excreted in the urine on a daily basis and correcting for urinary creatinine. The perchlorate intake for NHANES subjects whose drinking water concentrations were found negligible was assumed equivalent to the dietary intake. Using this approach, the average food intake for pregnant women (n=97) at the 90^{th} percentile was estimated at 0.198 µg/kg/day, thus leaving 72% of the RfD (0.5 µg/kg/day) for drinking water. Thus, the RSC for perchlorate for pregnant women was determined as 72%. The 72% RSC derived for pregnant women was also used for lactating women in MCLG calculations assuming higher food intake is necessary for both pregnant and lactating women compared to the average adults. The RSC for females of reproductive age was derived using the NHANES-UCMR analysis and corresponds to 80% (U.S. EPA, 2008; Huber *et al*., 2011).

Because of the greater sensitivity of fetuses, infants, and children to thyroid hormone decrements (Section IV), EPA could use life stage-specific DWIs, BWs, and RSCs in conjunction with the RfD, to develop MCLGs to protect the following life stages: females of reproductive age (13-49 years), pregnant women (for protecting fetuses), lactating women (for protecting the breast-fed infants), bottle-fed infants, and children 1 to less than 2 years of age. The MCLG for fetuses would be derived based on the perchlorate exposure for pregnant mothers. Similarly, the MCLG for breast-fed infants would be based on perchlorate exposure to lactating mothers. The MCLGs for different life stages ranged from 2 to 18 µg/L for perchlorate. The derived MCLGs are presented in Table 1.

Table 1: MCLG Derivation for Perchlorate.

Sensitive Life Stage	RfD[1] (µg/Kg BW/Day)	Mean BW (kg)[2]	DWI, 90th Percentile (L/day)[2]	RSC[3]	MCLG (µg/L)[4]
Females 13-49 years	0.7	66	2.11	0.80	18
Pregnant women for gestational week (GW) 40 fetuses	0.7	78	2.57	0.72	15
Breast-fed infants, 7 days	0.7	74	2.96	0.72	13
Breast-fed infants, 30 days	0.7	73	2.96	0.72	12
Breast-fed infants, 60 days	0.7	72	2.96	0.72	12
Bottle fed infants, 7 days	0.7	3.6	0.84	0.59	2
Bottle fed infants, 30 days	0.7	4.2	0.98	0.59	2
Bottle fed infants, 60 days	0.7	5.0	1.14	0.59	2
Infants, 6-12 months	0.7	9.2	1.03	0.59	4
Children 1 to <2 years	0.7	11.4	0.64	0.44	6

[1]RfD was derived by NRC in 2005 based on Greer *et al.* (2002) and later adopted by EPA Integrated Risk Information System (U.S. EPA, 2005a).
[2]The mean body weight and the 90th percentile drinking water intake values for different life stages were based on Exposure Factors Handbook (U.S. EPA, 2011b) and from ORD's PBPK Modeling effort (U.S. EPA, 2009c).
[3]The RSC values for various life stages were adopted from the Table 5 and 6 of the U.S. EPA report (U.S. EPA, 2008). The RSC for pregnant women and females of reproductive age 13-49 years were calculated based on the data from Huber *et al*. (2011).
[4]MCLG (in µg/L) was calculated based on the formula MCLG (µg/L) = [RfD (µg/kg bw/day) x BW (kg) /DWI] x RSC.

Issue I: Pertaining to Sensitive Life Stages

There are currently no data available to directly link perchlorate to neurobehavioral effects in infants and children. How should EPA consider the following life stage factors in deriving an MCLG?

- **Life stage specific differences in body weight and food and drinking water intake.**
- **Differences in greater severity and permanence of potential adverse effects in neonates, infants and young children compared to adults;**
- **Shorter half-life and lower reserves for thyroid hormone in infants compared to adults; and**
- **Intrauterine exposure to perchlorate and impact on thyroid status in fetuses.**

VI. PHYSIOLOGICALLY-BASED PHARMACOKINETIC ANALYSIS

Since the publication of "*Health Implications of Perchlorate Ingestion*" (NRC, 2005) and EPA's adoption of the NRC's recommended RfD for perchlorate in 2005, work on PBPK modeling of perchlorate's effect on inhibition of iodine uptake has provided substantial additional information that may assist with risk characterization for this compound. EPA's PBPK report (U.S. EPA 2009c) contains a toxicokinetic modeling analysis that predicts effects of perchlorate on iodine uptake for multiple life stages. Experimentally, the effects of perchlorate on iodine uptake have been assessed through the administration of radio-labeled iodine, with the measured uptake of radio-labeled iodine by the thyroid being termed RAIU. NRC (2005) selected the study of Greer *et al*. (2002) as the critical study for determination of a perchlorate RfD and selected the NOEL dose of 7 µg/kg/day at which no significant inhibition of RAIU was observed in the healthy volunteers as the point of departure (POD) for RfD determination. An intraspecies UF of 10 was applied to the NOEL to protect the most sensitive population, the fetuses of pregnant women who might have hypothyroidism or iodide deficiency.

Evaluation of PBPK Model Results

The PBPK model was applied in two different ways. The first application estimated the relative sensitivity for RAIU inhibition of different life stages at a fixed perchlorate dose (POD = 7 µg/kg/day, as in Greer *et al*., 2002 study). The second application compared the RAIU inhibition for various life stages exposed at fixed drinking water concentrations (e.g., 15 µg/L perchlorate) with and without perchlorate contribution via food. In addition to 15 µg/L, the models were run to predict RAIU inhibition at 20 and 24.5 µg/L drinking water concentrations. In the first application, the dose was fixed across the life stages (except for breast-fed infants for whom dosing for lactating mothers was kept at POD). In the second application, the drinking water concentration was fixed, such that the doses (adjusted for body weight) varied across the life stages, with infants and children receiving greater perchlorate doses adjusted for body weight compared to adults. The relative sensitivities of RAIU inhibition predicted for different life stages at the POD are presented in Table A-3. The predicted RAIU inhibitions for different life stages at 15, 20, and 24.5 µg/L perchlorate in drinking water are presented in Table A-4.

Tables A-3 and A-4 present predicted inhibition of RAIU for selected life stages using a PBPK model documented in EPA's externally peer reviewed report on application of PBPK modeling for perchlorate (U.S. EPA 2009c). In the first application, EPA assumed a fixed exposure at the POD (7 µg/kg/day). Model predictions were in agreement with the experimental observation from Greer *et al*. (2002) for healthy adults, a dose of 7 µg/kg of perchlorate was predicted to cause a decrease in RAIU of about 2% (i.e., Greer *et al*. = 1.8%; model prediction = 1.6%). EPA predicted the RAIU inhibition for pregnant women and GW 40 fetuses at 3.7- and 6.7-fold greater than the average adult, respectively (Table A-3). This greater sensitivity is consistent with NRC's conclusions (NRC, 2005). The RAIU inhibitions for fetuses earlier than GW40 were not modeled due to uncertainty in the parameters, although one would expect their greater sensitivity due to a higher demand for thyroid hormones necessary for fetal growth. For

bottle-fed infants from 7 to 60 days old, the PBPK model predicted approximately 2- to 3-fold greater RAIU inhibitions compared to the average adult. For breast-fed infants from 7 to 60 days old, the model predicted RAIU inhibitions approximately 5- to 8-fold greater than the average adult. The relative sensitivity for breast-fed infants was derived when lactating mothers were modeled to receive a perchlorate dose equal to POD, however, the resultant dose to breast-fed infants was greater than the POD, since the infants have greater food consumption on a body weight basis compared to the average adult. The additional sensitivity in RAIU inhibition predicted for breast-fed infants compared to bottle-fed infants can be explained by increased dosing (RAIU inhibition is predicted at the POD for bottle-fed infants versus predicted at a dose greater than POD for breast-fed infants). In addition, the model incorporates the reduction in breast milk iodide that would occur with maternal perchlorate exposure. Table A-3 also shows that at the POD lactating mothers of infants age 7 to 60 days and children age 6 months to 2 years have sensitivities for RAIU inhibition similar to (specifically, 1.1 to 1.3-fold higher than) the average adult.

In the second application of the PBPK model (Table A-4), EPA compared the RAIU inhibition for different life stages exposed to specific perchlorate concentrations in drinking water, with and without food. The NRC determined that the statistical NOEL (used as the POD) for the perchlorate-induced inhibition of thyroid iodide uptake (7 µg/kg/day) corresponded to an iodide uptake inhibition of 1.8%. The NRC (2005) stated that, "the very small decrease (1.8%) in thyroid radioiodide uptake in the lowest dose group was well within the variation of repeated measurements in normal subjects." Nonetheless, NRC recommended that a 10-fold uncertainty factor be applied to the POD to protect the fetus of the pregnant woman who might have hypothyroidism or iodine deficiency. RAIU inhibition of 1.8% was used in the second application of the PBPK model as a point of comparison.

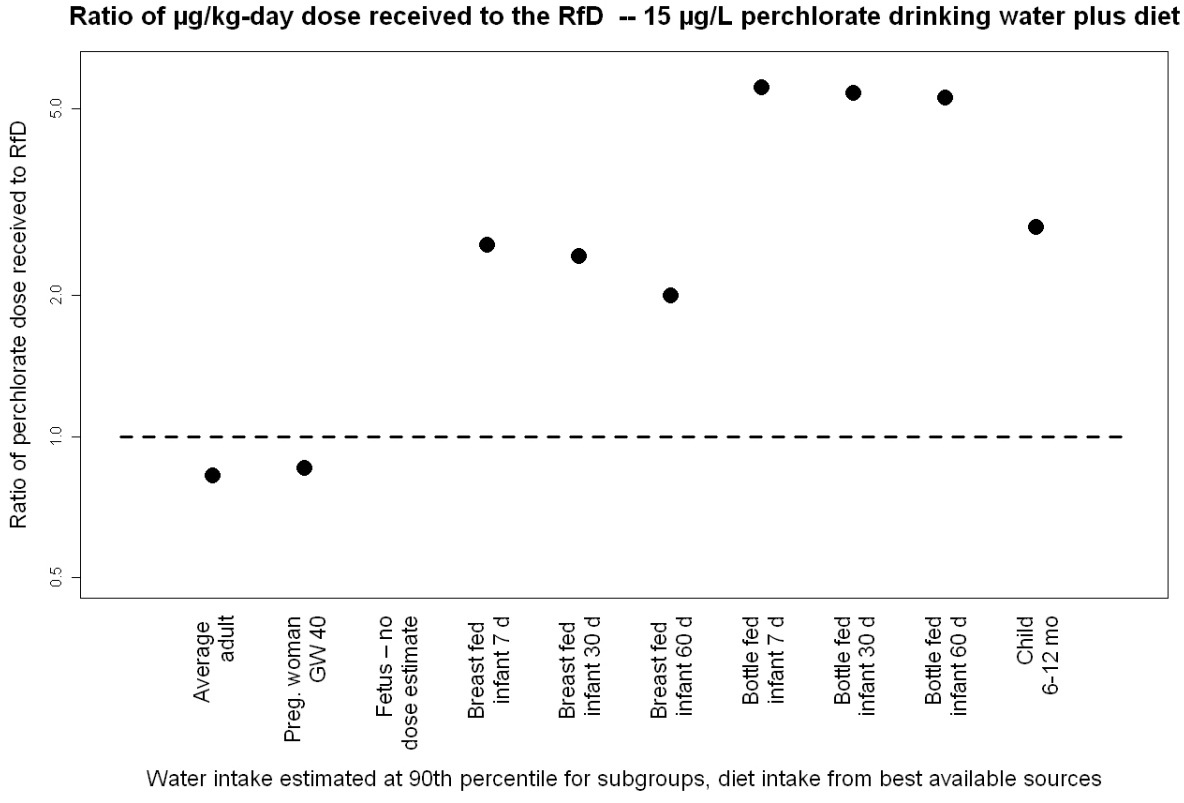
In the second application of the PBPK model (Table A-4), the perchlorate contribution from food for adults, pregnant and lactating women, and females of reproductive age were assumed to be 0.1 µg/kg/day based on FDA's TDS (Murray *et al*., 2008). Murray *et al*. (2008) did not estimate the perchlorate intake for females of reproductive age, pregnant or lactating women. However, the food intake estimates modeled are consistent with the mean food intake value reported for pregnant women (0.093 µg/kg/day) and for females of reproductive age, 15-44 years (0.071 µg/kg/day) developed by Huber *et al*. (2011) using NHANES biomonitoring data. The food intake value for lactating women is not available and assumed to be similar to that reported for pregnant women. From the fixed drinking water exposure level, EPA determined the dose for each life stage based on the average body weight and 90th percentile water consumption, such that the perchlorate dose varied across the life stages.

In EPA's 2008 Federal Register Notice that cited this application of the PBPK model (USEPA, 2008), EPA evaluated a drinking water exposure concentration of 15 µg/L perchlorate. The concentration of 15 µg/L was derived to result in an exposure for a pregnant woman that would not exceed the RfD assuming a pregnant woman's average body weight, 90th percentile drinking water consumption, and mean food exposure, as discussed above. The PBPK model predicted that the percent RAIU inhibition in the fetus of a pregnant woman consuming drinking water with 15 µg/L perchlorate (in combination with food exposure) is 1.1%. EPA also

evaluated predicted RAIU for different sensitive life stages exposed to a drinking water concentration of 15 µg/L. The model predicted a 2.2% RAIU inhibition for 7-day old bottle-fed infants, also after accounting for food exposure, and all other life stages, including 60-day old bottle-fed infants, and 7, 30, 60-day old breast-fed infants, and children (up to 2 years), were predicted to have RAIU inhibition of 1.4% or less, after accounting for food. At that time, all of these levels were determined to be comparable to or below the 1.8% no effect inhibition level from the Greer study. EPA also evaluated the RAIU inhibition for the life stages of concern at 20 and 24.5 µg/L. The model predicted the greatest RAIU inhibition of 3.4% for 7-day old bottle-fed infants and the RAIU inhibition was below 3% for the other life stages (Table A-4).

Figure 1 provides a comparison of estimated perchlorate doses under the same exposure scenario (15 µg/L perchlorate in drinking water, plus food) with the perchlorate RfD of 0.7 µg/kg/day. While the perchlorate doses to the average adult and pregnant woman are below the RfD, doses to the 6-12 months old infant and to the breast-fed and bottle-fed infants are above the RfD. Bottle-fed infants have the highest estimated exposures, at a level of approximately 4 µg/kg/day or approximately 5 times higher than the RfD.

Figure 1: Ratio of Perchlorate Dose Received to RfD at 15 µg/L Drinking Water.



PBPK Modeling Uncertainties

While PBPK modeling permits comparing the RAIU inhibition effects at different life stages, there are limitations in the application of the PBPK model predictions. Neither quantitative estimates of the uncertainty in predictions of these PBPK models nor estimates of inter-individual (within life stage) variability are available. Both of these limitations are important in characterizing perchlorate's effects. The PBPK model results are central estimates that do not quantitatively address uncertainty in parameter inputs or variability in PK parameters within life stages. The model does not predict RAIU inhibition for hypothyroid women or to reflect iodide nutritional status in populations, important considerations in thyroid function. In addition, there is uncertainty in the urinary clearance used for some sensitive life stages. The average adult urinary clearance was assumed for females of reproductive age and for lactating women. For older children (modeled as 0.97 and 2 years), the urinary clearance was assumed equal to the average adult, but adjusted with body weight scaling (The PBPK model predicts that a child 0.97 years old will weigh exactly 10 kg. Since this BW is the default value used for short term health advisories, this age was selected to provide a matching analysis). For infants, there is limited urinary clearance data, although this was addressed by using low, medium and high urinary clearance assumptions to bracket results. It is important to note the PBPK model predictions address the pharmacokinetic characteristics, but the pharmacodynamic factors are not addressed in the PBPK modeling (e.g., receptor binding, thyroid axis regulations).

Potential Adjustments to MCLGs Based on PBPK Modeling

As recommended by the NRC (2005), EPA (2005a) adopted an intraspecies UF of 10 to the NOEL from Greer *et al.* (2002) to account for variations in susceptibility within the human population (interhuman variability) and the possibility, given a lack of relevant data, that the database available is not representative of the exposure-response relationship in the subgroups of the human population that are most sensitive to the health hazards of the chemical being assessed. The UF 10 can be further subdivided into a $UF_{TK} = 10^{1/2} = 3.16$ (generally rounded to 3) to account for differences in internal dosimetry due to toxicokinetic differences, and a $UF_{TD} = 10^{1/2} = 3.16$ (generally rounded to 3) to account for differences in toxicodynamics. This convention is used by EPA in the absence of compound-specific data as is the case with perchlorate. While Greer *et al*. (2002) provided information on inhibition on RAIU in healthy, iodine sufficient adults, similar data were not available for other life stages. With the development of the PBPK model, it is now possible to provide estimates of the effect of perchlorate on the toxicokinetic aspects of RAIU in different life stages. Life stage differences in effects of perchlorate on RAIU is a major science issue for perchlorate risk assessment (NRC, 2005), thus availability of information to predict life stage differences is an important contribution to the scientific database for this compound.

The PBPK model predictions for perchlorate mediated iodide uptake as reported by RAIU inhibition differ substantially for different life stages. In the context of the RfD for perchlorate, the first application of the PBPK model results suggest that the relative sensitivities

for RAIU inhibition for different life stages included a range of 1.1 to 8-fold which is greater than that observed for normal adults reflected in Greer *et al.* (2002) upon which the NRC (2005) based the RfD. NRC recommended an intraspecies uncertainty factor of 10. As described above, EPA, in general, interprets a half of this factor (i.e., 3x) to account for uncertainties in the differences of the pharmacokinetics of perchlorate in different life stages. Based on these findings, this uncertainty factor may not account for the full differences in perchlorate pharmacokinetics between the adults tested in the Greer study and other more sensitive life stages (fetuses of pregnant mothers and breast-fed infants from 7 to 60-days old). Therefore, in deriving an MCLG, additional PBPK sensitivity may be warranted to ensure an adequate margin of safety for all life stages. To adjust for the differences in pharmacokinetics among life stages, EPA could divide PBPK model predicted life stage sensitivity for RAIU inhibition by the pharmacokinetic portion (3x) of the intraspecies uncertainty factor recommended by the NRC. No such adjustments would be needed if the predicted life stage-specific relative sensitivity for RAIU inhibition was at or below 3 (e.g., females of reproductive age, bottle-fed infants from 7 to 60 days old, children 6 months to 2 years).

Issue II: Pertaining to PBPK Evidence

- **How should EPA consider PBPK modeling to derive an MCLG for perchlorate?**
- **What are the strengths and limitations of the two PBPK model results described in this effort?**

VII. HUMAN STUDIES CONDUCTED SINCE THE 2005 NRC REPORT

Epidemiological Studies

Since the NRC review (NRC, 2005), ten epidemiologic studies on perchlorate and thyroid function in adults, pregnant women or newborns have been published. Among these studies, nine assessed the prevalence of thyroid dysfunction by the direct measures of T3, T4, fT4, or TSH (Tellez *et al*., 2005; Blount *et al*., 2006; Buffler *et al*., 2006; Amitai *et al*., 2007; Steinmaus *et al*., 2007; Pearce *et al*., 2010, 2011; Steinmaus *et al*., 2010; Cao *et al*., 2010) and one study investigated indirect measures of thyroid function such as hematocrit, hemoglobin, and serum high density lipoprotein (Schreinemachers, 2011). No studies published since 2005 were identified in the literature evaluating the neurodevelopment outcomes or chronic diseases, including cancer. All the studies published since 2005 examined potentially sensitive populations such as neonates, pregnant women, women of reproductive age, women with iodine deficiencies, or smokers. The number of subjects in the ten studies varied from 92 infants in the Study of Estrogen Activity and Development Study (Cao *et al*., 2010) to 497,458 infants in California's Newborn Screening Program (Steinmaus *et al*., 2010). These studies varied in their approaches to assessing perchlorate exposure and statistical methods. Four studies which examined thyroid function in neonates assigned perchlorate exposure using maternal residence as a surrogate (Tellez *et al*., 2005; Buffler *et al*., 2006; Amitai *et al*., 2007; Steinmaus *et al*., 2010). In other studies, perchlorate exposure was measured as a urinary biomarker, urinary perchlorate (Blount *et al*., 2006; Steinmaus *et al*., 2007; Pearce *et al*., 2010, 2011; Cao *et al*., 2010; Schreinemacher, 2011). Urinary perchlorate represents an integrated surrogate of perchlorate in

water and food. Although the study in Chile (Tellez *et al*., 2005) reported urinary and serum perchlorate levels in women during pregnancy and during post partum (a longitudinal cohort study), perchlorate assignment to subjects was based solely on geographical location. Details of the ten studies regarding subject number, exposure assessment and observed outcomes are contained in Table A-5.

Biomonitoring/Exposure Studies

Several biomonitoring studies were published after the NRC (2005) review. They are summarized in Table A-6, along with a few exposure studies which reported perchlorate levels in drinking water (Blount *et al*., 2010) or in breast milk samples and infant formula (Kirk *et al*., 2005; Kirk *et al*., 2007; Schier *et al*., 2010). In general, the biomonitoring studies measured perchlorate levels in spot urine samples for US populations and estimated total perchlorate exposure (diet and drinking water) based on urinary volume and perchlorate excretion levels. The daily perchlorate excretion was adjusted to urinary creatinine levels. The majority of the perchlorate exposure in the US population occurs via food sources compared to exposure via drinking water. However, for infants, perchlorate exposure via drinking water could comprise a significant source. The brief findings of the biomonitoring and exposure studies are summarized in Table A-6.

Issue III: Pertaining to Epidemiological and Biomonitoring Studies

How should EPA consider the post-NRC epidemiology data in deriving an MCLG?

VIII. INTEGRATION OF INFORMATION

The NRC derived an RfD of 0.0007 mg/kg/day (0.7 µg/kg/day) for perchlorate based on the clinical data in healthy adults reported by Greer *et al.* (2002). EPA believes that the perchlorate RfD is the most scientifically defensible endpoint available at this time for deriving an MCLG. EPA believes that deriving the MCLG from the RfD is health protective since the NRC selected a point of departure for the RfD based on RAIU inhibition, a precursor to adverse effects (e.g., thyroid disorders). In deriving an MCLG, EPA would generally combine the RfD with default exposure factors of 70 kg body weight, 2L of drinking water intake, and a RSC of 20% when data are not available to estimate the contributions from other sources of exposure. However, the SDWA also directs EPA to consider effects on sensitive subpopulations in establishing regulations for drinking water contaminants. EPA believes that adequate information is available indicating that the pregnant woman's fetus, infants, and children are likely to be at greater risk of adverse health effects due to exposure to perchlorate than the general population. This suggests the need to reflect life stage specific exposures in the assessment of perchlorate. EPA generally uses average body weight and 90^{th} percentile water consumption in MCLG derivations. As such, this estimate contains inherent uncertainties that may result in some possibility of over- or under-protection.

Life Stage Considerations

Thyroid is the target tissue for perchlorate mediated health effects. In 2005, NRC noted that the groups of greatest concern for exposure to perchlorate were low-birth weight or preterm newborns, offspring of mothers who had iodide deficiency during gestation, and offspring of hypothyroid mothers. In addition, as discussed in Section IV of this document, these life stages are disproportionately impacted compared to other life stages in that thyroid deficits of even short duration may have serious and irreversible impacts on neurodevelopment (Glinoer, 2001; Rovet *et al*., 1987; Rovet *et al*., 1992; Tillotson *et al*., 1994; Oerbeck *et al*., 2003; Zoeller and Rovet, 2004; Williams, 2008). Although there is no direct evidence available in the literature linking perchlorate exposure to neurodevelopmental impacts, there are several lines of evidence that show neurological impairment in children when thyroid hormone levels are affected in mothers during gestation either due to clinical or nutritional iodide deficiency conditions (Smit *et al*., 2000; Haddow *et al*., 1999; Pop *et al*., 1999, 2003; Vermiglio *et al*., 2004; Kooistra *et al*., 2006). In addition to fetuses, other life stages may be more sensitive to perchlorate exposure compared to the average adult. The reduction in storage of thyroid hormones and iodine as well as reduction in the half-life of T4 in neonates (young infants) make them more sensitive compared to adults. Also, the measurements of perchlorate in breast milk along with the evidence of iodide deficiency from the inhibition of iodide uptake by the mammary gland suggest that breast-fed infants may be more vulnerable to perchlorate mediated effects compared to formula-fed infants (Tazebay *et al*., 2000; Kirk *et al*., 2005; Kirk *et al*., 2007; Pearce *et al*., 2007; Dasgupta *et al*., 2008; Borjan *et al*., 2011). In general, food intake and drinking water consumption per body weight are greater for infants and young children than adults rendering infants and children more susceptible for environmental exposures to perchlorate. Therefore, EPA is considering using the life stage-specific exposure factors in lieu of default exposure assumptions in deriving the potential range of MCLGs for perchlorate.

Using the traditional MCLG methodology modified to reflect life stage-specific exposure factors, EPA derived a range of potential MCLG values. Table 1 reports the MCLG of 2 µg/L for young bottle-fed infants (less than 60 days) and 18 µg/L for pregnant mothers or females of reproductive age. The MCLGs derived for breast-fed infants less than 60 days was higher than the MCLG for bottle-fed infants (12 µg/L vs. 2 µg/L). This variation is reasonable because the dosing received for breast-fed infants via nursing mothers is expected to be lower compared to the direct exposure received by bottle-fed infants. It is also evident from Table 1 that the drinking water intake values adjusted per body weight for lactating mothers are much less compared to those of bottle-fed infants.

PBPK Model Considerations

The NRC applied an uncertainty factor of 10 to the NOEL (POD) to protect the most sensitive population, the fetuses of pregnant women who might have hypothyroidism or iodide deficiency. This uncertainty factor is assumed to account for two areas of uncertainty (*i.e*., a 3x factor each for uncertainties associated with pharmacokinetic and pharmacodynamic differences). The RfD as derived by the NRC (2005) was considered to be protective of all life stages. Because the dose response data used to derive the RfD was based on normal adult

subjects, EPA examined the impact of pharmacokinetic differences in the internal dose and the resulting effects on potential life stage-specific MCLGs derived for perchlorate through consideration of PBPK modeling. To pursue this question, EPA employed PBPK modeling as described in Section VI. The perchlorate life stage differential was modeled in two ways: one approach was to simulate the impacts of a fixed dose to consider inherent biological differences among life stages (Table A-3); the second approach compared the RAIU inhibition at fixed water concentrations for different life stages (Table A-4), integrating biological differences with differences in exposure patterns. The first PBPK application (effects of fixed dose of POD on RAIU inhibition) indicates that the GW 40 fetuses and the breast-fed infants are more sensitive for RAIU inhibition compared to adults and the other life-stages.

The second application of PBPK model predictions (RAIU inhibition at 15, 20 or 24.5 μg/L) differs from the first approach in that the dosing across life stages varies, and the predictions include both biological sensitivity and life stage-dependent dosing variations (Table A-4). In the preliminary regulatory determination (U.S. EPA, 2008) EPA approached the relative sensitivity issue by predicting RAIU inhibition for different subpopulations/life stages at the HRL (15 μg/L) derived for pregnant women. At this HRL, EPA determined that the RAIU inhibition for the most sensitive life stages (fetuses, breast-fed infants, bottle-fed infants) is comparable to or below 1.8%, the RAIU at the NOEL selected by NRC. Therefore, EPA concluded that the HRL of 15 μg/L was protective of all subpopulations/life stages. Another important consideration for the second application of PBPK model predictions in Table A-4 is that at a 15 μg/L drinking water concentrations, the dose received for certain life stages (e.g., breast-fed infants, bottle-fed infants and children) are ~2-fold and ~5-fold above the RfD of 0.7 μg/kg/day for breast-fed and bottle-fed infants respectively (Figure 1).

In 2009, EPA finalized the PBPK Model Report (U.S. EPA, 2009c) and the external peer reviewers were supportive of EPA's PBPK model findings. In 2009 (U.S. EPA, 2009b), EPA elaborated on the relative sensitivities of RAIU inhibition for different life stages (first application), but did not apply the PBPK model findings quantitatively. Instead, EPA derived the alternate HRLs of 1-47 μg/L for different life stages based on the RfD and life stage specific exposure assumptions.

The PBPK model predictions may provide valuable information in the risk characterization of perchlorate. EPA is seeking input from SAB on how the PBPK modeling predictions could be used in the derivation of the MCLG. The model uncertainty and limitations in data for model input are important considerations in evaluating the model's role in MCLG derivation. The PBPK model predictions provide central estimates and do not address the variations within the life stages. In addition, biological sensitivity predicted refers to pharmacokinetic characteristics; the pharmacodynamic aspects are not addressed.

Epidemiology and Biomonitoring Study Considerations

The range of MCLGs presented in this document represent plausible estimates of levels at which no adverse effect would be anticipated to occur in various life stages which allows an adequate margin of safety. However, each step in the process of developing potential MCLGs

produces valuable information, but also introduces additional sources of uncertainty. In addition, intakes and body weights are represented as point estimates.

NRC (2005) reported that epidemiological evidence relating perchlorate exposure to thyroid perturbations are mostly ecological and, acknowledged that ecologic data alone are not sufficient to demonstrate whether or not an association is causal, but can provide evidence bearing on possible association. The committee, therefore, concluded the evidence is not consistent with a causal association between exposure to perchlorate during gestation and changes in thyroid hormone and TSH production in normal birth weight, full-term newborns (in drinking water up to 120 µg/L). At that time, NRC also acknowledged that no data were available on the association of perchlorate exposure with thyroid dysfunction in the groups of greatest concern, low-birth weight or preterm newborns, offspring of mothers who had iodide deficiency during gestation, or offspring of hypothyroid mothers. With regard to neurodevelopmental outcomes, NRC found that the epidemiologic evidence is inadequate to determine whether or not there is a causal association between perchlorate exposure and adverse neurodevelopmental outcomes in children. NRC noted that only one study (Chang *et al*., 2003) examined the relationship between perchlorate exposure and adverse neurodevelopmental outcomes (i.e., ADHD and autism) in children and no adequate studies existed of maternal perchlorate exposure and neurodevelopmental outcomes in infants. NRC (2005) also acknowledged most of the epidemiological evidence suffers from lack of exposure information at the individual level.

Since the NRC perchlorate review (NRC, 2005), ten epidemiologic studies have been published on perchlorate and thyroid function in adults, pregnant women or newborns (See Section VII and Table A-5). Characteristics of four of these epidemiologic studies included ecologic and cross–sectional designs, exposure assessment based on residence location, and statistical analyses using categorical data (Tellez *et al*., 2005; Buffler *et al*., 2006; Amitai *et al*., 2007; Steinmaus *et al*., 2010). Pearce *et al*. (2010, 2011) studies were cross–sectional designs and evaluated the association between urinary perchlorate and thyroid function using correlation analyses and linear regression statistical methods with covariates. Subjects in Pearce *et al*. (2010) were a combined group of hypothyroid/hypothyroxinemic pregnant women or a group of pregnant women with normal thyroid function (euthyroid). The ranges of thyroid hormones overlapped between these two groups suggesting a possible disease misclassification. Cao *et al*. (2010), a cross-sectional study, evaluated a small number of infants less than one year old. The study assessed individual exposures using urinary perchlorate, and statistical analysis was using a linear regression with covariates. Three other studies (Blount *et al*., 2006; Steinmaus *et al*., 2007; and, Schreinemachers, 2011) analyzed data from the 2001-2002 NHANES, a program designed to provide a nationally representative sample of the US population to assess the health and nutritional status of adults and children of ≥12 years. The NHANES data are comprised of a large number of subjects. They include urinary perchlorate levels that can be used as a robust exposure surrogate for perchlorate exposure from drinking water and food. Linear regression statistical methods that controlled for potential confounders were used.

Two studies of NHANES (2001-2002) data identified a perchlorate-related increase in TSH and decrease in T4 in women >12 years of age with urinary iodide <100 µg/L, particularly

among subjects who smoked (Blount *et al*., 2006; Steinmaus *et al*., 2007). A third study of the 2001-2002 NHANES data evaluated indirect indicators of thyroid function and reported an inverse relationship between urinary perchlorate and the hematological parameters, hemoglobin and hematocrit, notably in men and pregnant and non-pregnant women of child-bearing ages, although individual thyroid hormones of T4 and TSH were not well correlated with the hematological parameters and the direction of the association varied by sex (Schreinemachers, 2011). Drinking water perchlorate exposure levels are not reported in the three NHANES analyses and some information on exposures to subjects is found in the biomonitoring study using the NHANES (2001-2002) data. Blount *et al*. (2007) reported the geometric mean perchlorate dose for US adults as 0.07 µg/kg/day. The perchlorate dose estimated by Blount *et al*. (2007) is consistent with other analyses (Mendez *et al*. 2010, Huber *et al*., 2011). It must be noted that the perchlorate dose estimated in these studies includes the exposure from food and drinking water. Cao *et al*. (2010) found an association between perchlorate exposure and increased TSH levels under iodide deficiency conditions. Based on the exposure findings using the same cohort as Cao *et al*. (2010), Valentin-Blasini *et al*. (2011) estimated the geometric mean perchlorate dose as 0.03-0.22 µg/kg/day depending upon the type of formula consumed. Both Buffler *et al*. (2006) and Steinmaus *et al*. (2010) considered the association between the concentration of perchlorate in drinking water consumed by pregnant women and TSH levels in neonates. The drinking water concentrations (≤5 µg/L or > 5 µg/L) were used to categorize the exposure groups. The associations between TSH and maternal residence in a community with perchlorate >5 µg/L was dependant on the time of the neonatal monitoring and on the critical value. Associations were reported between higher perchlorate concentration associated with TSH levels above the 95th and 99th percentile in neonates with monitoring within 24 hours of birth and TSH levels above the 95th percentile, but not TSH levels above the 99th percentile, in neonates with monitoring after 24 hours of birth (Buffler *et al*., 2006; Steinmaus *et al*., 2010). Other studies of pregnant women or neonates and thyroid function did not report associations between residence in city with perchlorate in drinking water supplies or between urinary perchlorate at similar or higher exposure levels than those estimated for Blount *et al*. (2006), Steinmaus *et al*. (2007), or Cao *et al*. (2010) (Tellez *et al*., 2005; Amitai *et al*., 2007; Pearce *et al*., 2010, 2011).

These data, while limited, provide an overview of the effects of perchlorate on thyroid hormone homeostasis, and the exposure levels at which they have been observed. The mixed pattern of observations in these ten studies is not surprising in light of their different study designs, numbers of subjects, exposure assessment approaches, and statistical methods. Together these may serve as a means to bound the drinking water exposure range of concern, and assist where within the range of potential MCLGs a scientifically appropriate regulatory value can be selected.

Issue IV: Pertaining to Integration of Information

- **How can EPA best use the total body of information to derive a health protective MCLG, while considering the results of epidemiology and biomonitoring data in establishing bounds on potential values?**
- **How can EPA use the available data to estimate reductions in adverse health effects (i.e., dose response) that are likely to result from reducing perchlorate levels in drinking water?**

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APPENDIX

Table A-1: Lower- and Upper-bound Perchlorate Intakes from FDA's TDS Results for 2005–2006.

Population Group		Total Average Intake (µg/person/day)		Total Average Intake (µg/kg/day)	
		Lower-bound	Upper-bound	Lower-bound	Upper-bound
Infants	6-11 mo	2.4	2.7	0.26	0.29
Children	2 yr	4.9	5.5	0.35	0.39
Children	6 yr	5.4	6.1	0.25	0.28
Children	10 yr	6.1	6.9	0.17	0.20
Teenage Girls	14-16 yr	5.1	6.1	0.09	0.11
Teenage Boys	14-16 yr	7.7	9.1	0.12	0.14
Women	25-30 yr	5.4	6.8	0.09	0.11
Men	25-30 yr	6.7	8.6	0.08	0.11
Women	40-45 yr	5.9	7.3	0.09	0.11
Men	40-45 yr	7.4	9.4	0.09	0.11
Women	60-65 yr	5.9	7.1	0.09	0.10
Men	60-65 yr	7.2	8.8	0.09	0.11
Women	70+ yr	5.8	6.9	0.09	0.11
Men	70+ yr	7.1	8.3	0.11	0.12

Source: Murray *et al*. (2008).

Table A-2: Relative Source Contributions Remaining for Water by Population Group, Based on TDS.

Population Group	Total Perchlorate Intake from Food (µg/kg/day)	RSC Remaining for Drinking Water (as a percentage of the RfD)
Infants, 6–11 mo	0.26–0.29	59%–63%
Children, 2 yr	0.35–0.39	44%–50%
Children, 6 yr	0.25–0.28	60%–64%
Children, 10 yr	0.17–0.20	71%–76%
Teenage Girls, 14–16 yr	0.09–0.11	84%–87%
Teenage Boys, 14–16 yr	0.12–0.14	80%–83%
Women, 25–30 yr	0.09–0.11	84%–87%
Men, 25–30 yr	0.08–0.11	84%–89%
Women, 40–45 yr	0.09–0.11	84%–87%
Men, 40–45 yr	0.09–0.11	84%–87%
Women, 60–65 yr	0.09–0.10	86%–87%
Men, 60–65 yr	0.09–0.11	84%–87%
Women, 70+ yr	0.09–0.11	84%–87%

Population Group	Total Perchlorate Intake from Food (µg/kg/day)	RSC Remaining for Drinking Water (as a percentage of the RfD)
Men, 70+ yr	0.11–0.12	83%–84%

Source: Table 5 of U.S. EPA (2008).

Table A-3: PBPK Model Predicted RAIU Inhibition for Different Life Stages and Subgroups at a Fixed Dose Equivalent to POD of 7 µg/kg/day.

Sensitive Life Stage	RAIU (Inhibition at the POD) (%)	Relative Sensitivity Compared to Average Adult
Average Adult	1.6	1
Females 13-49 years	3.0	1.8
Pregnant women at GW 40	6.1	3.7
GW 40 fetuses[a]	11	6.7
Lactating women at 7 days	2.1	1.3
Breast-fed infants[b], 7 days	12.5	7.8
Lactating women, 30 days	2.0	1.2
Breast-fed infants[b], 30 days	9.8	6.1
Lactating women, 60 days	2.0	1.2
Breast-fed infants[b], 60 days	7.9	4.9
Bottle fed infants, 7 days	4.3	2.6
Bottle fed infants, 30 days	2.9	1.8
Bottle fed infants, 60 days	2.5	1.5
Children 6-12 months	1.7	1.1
Children 1 to <2 years	1.7	1.1

Source: Table 4-3 of U.S. EPA (2009c) PBPK Report and Table 1 of U.S.EPA (2009b) Federal Register Notice.

[a]Perchlorate dosing for the fetuses was assumed via the pregnant mothers; [b]Perchlorate dosing for breast-fed infants was assumed via the lactating mothers.

Table A-4: Predicted RAIU Inhibition at Three Different Drinking Water Concentrations Without (and With) Contribution from Food.

Sensitive Life Stage	Body Weight[b] (kg)	90th Percentile DW Intake[c] (L/day)	Percent RAIU Inhibition at Different Drinking Water Levels					
			15 µg/L		20 µg/L		24.5 µg/L	
			Water Only	Water + Food	Water Only	Water + Food	Water Only	Water + Food
Average adult	70	2.24	0.11	0.13	0.15	0.17	0.18	0.20
Females 13-49 years	68	2.11	0.21	0.25	0.27	0.32	0.34	0.38
Pregnant women at GW 40	78	2.57	0.45	0.54	0.60	0.69	0.74	0.83
GW 40 fetuses[a]	-	-	0.89	1.1	1.2	1.4	1.4	1.6
Lactating women at 7 days	74	2.96	0.18	0.21	0.24	0.27	0.30	0.33
Breast-fed infants[a], 7 days	3.6	0.6[d]	1.1	1.3	1.5	1.7	1.8	2.0
Lactating women, 30 days	73	2.96	0.18	0.2	0.23	0.26	0.29	0.31
Breast-fed infants[a], 30 days	4.2	0.68[d]	0.93	1.1	1.2	1.4	1.5	1.7
Lactating women, 60 days	72	2.96	0.18	0.21	0.24	0.26	0.29	0.32
Breast-fed infants[a], 60 days	5	0.68[d]	0.75	0.87	1.0	1.1	1.2	1.3
Bottle fed infants, 7 days	3.6	0.84	2.0	2.2	2.6	2.8	3.2	3.4
Bottle fed infants, 30 days	4.2	0.98	1.5	1.6)	2.0	2.1	2.4	2.6
Bottle fed infants, 60 days	5	1.14	1.2	1.3	1.6	1.7	2.0	2.1
Children 6-12 months	9.2	1.03	0.42	0.49	0.56	0.63	0.69	0.75
Children 1 to <2 years	11.4	0.64	0.21	0.31	0.28	0.38	0.35	0.44

Source: Table 4-5 of U.S. EPA (2009c) PBPK report (except 30day old infant findings which were modeled separately).

[a]The perchlorate dosing for fetuses and breast-fed infants occur from pregnant mothers and lactating mothers, respectively.

[b]The body weight (70 kg) for the average adult is the default weight generally used by EPA. The body weight for females of reproductive age was from U.S. EPA (2004); All other body weights are generated by the model (U.S. EPA, 2009c).

[c]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 GW-dependent BW as follows: 32 mL/kg-day for average adult and nonpregnant woman; 33 mL/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 for lactating women are from Kahn and Stralka (2008) which come from U.S. EPA (2004). For the bottle-fed infants, 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 (2009) and multiplied by BW (age). For the 6- to 12-month-old 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 matched the exposure-table mean. This approach resulted in model predictions for 0.796-year-olds (to represent 6- to 12-month-old children) and 1.285-year-olds (to represent 1- to 2-year-old children). The FDA has suggested an alternate approach, using the caloric intake requirement of a 7-day-old infant as the basis for calculating consumption (USFDA, 2008). This would likely yield a lower estimate of intake than the 0.84 L/day that EPA used in the model.

[d]Breast-fed infant "water intake" is the breast milk ingestion rate obtained from the age-dependent Hill function fit to the breast milk ingestion data (L/kg-day) from Arcus-Arth *et al*. (2005), as shown in Figure 3-1. Urinary

clearance rates for the lactating woman equal to that of the average adult were used, consistent with data presented in Delange (2004).

Table A-5 Epidemiological Studies Conducted since NRC 2005 Report.

Citation	Study Population	Study Design	Exposure Variables/Biomarkers	Outcome Variables	Major Study Findings	Comments
National Health and Nutrition Examination Survey Analyses						
Blount *et al*., 2006; Steinmaus *et al*., 2007; Schreinemachers, 2011 NHANES (2001-2002), US population Survey response rate, 83.9%, exam response rate, 79.6%	2,299 (1,188 men & 1,111 women), >12 yrs age (Blount *et al*., 2006)	Cross-sectional	Urinary perchlorate, µg/L [GM (95% CI)] Women, 2.84 (2.54–3.18); Men, NR Urinary iodine, µg/L [GM (95% CI)] Women, 126 (115–138) Men, NR	Serum T4, µg/dL (AM, 95% CI) 8.27 (7.97–8.58) Serum TSH, IU/L (GM, 95% CI) 1.36 (1.31–1.42)	Perchlorate did not predict T4 or log TSH in men (model results NR) and analyses focused on women. Women with urinary iodine ≥100 µg/L, urinary perchlorate was associated with increased TSH but not T4 in serum. Log perchlorate , urinary iodine ≥100 µg/L: T4, β= 0.22 (SE, 0.37), *p*=0.55 Log TSH, β= 0.11 (SE, 0.05), *p*=0.03 Women with urinary iodine <100 µg/L, urinary perchlorate was associated with slightly increased TSH and decreased T4 levels. Log perchlorate, urinary iodine <100 µg/L: T4, β= –0.89 (SE, 0.18), *p*<0.0001 Log TSH, β= 0.12 (SE, 0.04), *p*=0.001	Women excluded if missing TSH, T4, or perchlorate specimen, with outlier values of T4 or TSH, or with thyroid disease history or current thyroid medication (Blount *et al*., 2006; Steinmaus *et al*., 2007; Schreinemacher, 2011) or diseases in which thyroid dysfunction might have played a role (e. g., congestive heart failure, coronary heart disease, angina pectoris, acute myocardial infarction, stroke, cancer, diabetes (Schreinemacher, 2011).
	1,109 women, ≥12 yrs age; 385 with urinary iodine levels < 100 µg/L and who were current or non-smokers (long-term former smoker > 1 yr since quitting or never smokers) (Steinmaus *et al*., 2007)		Urinary perchlorate, µg/L [Mean (SE)] Smokers, 2.52 (0.55) Nonsmokers, 3.15 (0.88)	Serum log TSH, µg/dL [Mean (SE)] Smokers, 0.12 (0.06) Nonsmokers, 0.14 (0.03)	Association between urinary perchlorate and T4 with adjustment in statistical analyses for smoking, cotinine or thiocyanate was found in women with urinary iodine levels < 100 µg/L, but not in women with urinary iodine levels ≥100 µg/L. Log perchlorate, urinary iodine <100 µg/L: T4, β= –0.73 (SE, 0.22), *p*=0.004 Log TSH, β= 0.13 (SE, 0.05), *p*=0.02 Stronger association observed for T4 and log perchlorate among current smokers compared to that for non-smokers; interaction between perchlorate and smoking β= 1.12, p=0.008.	

<table>
<tr><th>Citation</th><th>Study Population</th><th>Study Design</th><th>Exposure Variables/Biomarkers</th><th>Outcome Variables</th><th>Major Study Findings</th><th>Comments</th></tr>
<tr>
<td></td>
<td>2,094 (1,010 men, 1,084 women), 6-85 yrs age (Schreinemachers, 2011)</td>
<td></td>
<td>Urinary perchlorate, µg/L [Mean (SE)]
Men, 5.99 (0.20)
Women, 5.03 (0.16)</td>
<td>Indirect markers of thyroid function:
Serum hemoglobin, g/dl [Mean (SE)]
Men, 14.95 (0.04)
Women, 13.27 (0.04)

Serum hematocrit, % [Mean (SE)]
Men, 44.07 (0.13)
Women, 39.07 (0.10)

Serum high density lipoprotein, m g/dl [Mean (SE)]
Men, 48.50 (0.41)
Women, 55.55 (0.46)</td>
<td>Beta coefficients (95% CI) for association between log urinary perchlorate and indirect markers of thyroid function in men
<table>
<tr><th></th><th>Age 6-18</th><th>Age 20-85</th></tr>
<tr><td>Hbg</td><td>–0.23 (–0.41, –0.04)
p=0.02</td><td>–0.18 (–0.33, –0.02)
p=0.03</td></tr>
<tr><td>Hct</td><td>–0.57 (–1.10, –0.03)
p=0.04</td><td>–0.47 (–0.92, –0.01)
p=0.04</td></tr>
<tr><td>HDL</td><td>0.01 (–0.03, 0.06)
p=0.54</td><td>–0.01 (–0.05, 0.04)
p=0.78</td></tr>
</table>
Perchlorate effects are adjusted for age, urinary creatinine, ethnicity, cotinine, BMI, poverty index, total kcal intake, hours of fasting, urinary nitrates, urinary thiocyanates, CRP, and for age 20–85, alcohol consumption, prescriptions for betablocker, sex hormones, lipid lowering drugs, antidiabetic drugs.

Beta coefficients (95% CI) for association between log urinary perchlorate and indirect markers of thyroid function in women
<table>
<tr><th></th><th>Age 6-14</th><th>Age 15-49 (nonpregant)</th><th>Age 50-85</th><th>Any age (pregnant)</th></tr>
<tr><td>Hbg</td><td>0.14 (–0.05, 0.33)
p=0.13</td><td>–0.24 (–0.49, 0.02)
p=0.07</td><td>–0.22 (–0.67, 0.23)
p=0.31</td><td>–0.26 (–0.45, –0.08)
p=0.01</td></tr>
<tr><td>Hct</td><td>0.34 (–0.23, 0.90)
p=0.22</td><td>–0.55 (–1.28, 0.18)
p=0.13</td><td>–0.64 (–1.97, 0.69)
p=0.32</td><td>–0.86 (–1.44, –0.29)
p=0.01</td></tr>
<tr><td>HDL</td><td>0.02 (–0.04, 0.07)
p=0.57</td><td>0.00 (–0.06, 0.07)
p=0.88</td><td>0.02 (–0.07, 0.11)
p=0.64</td><td>0.01 (–0.04, 0.06)
p=0.68</td></tr>
</table>
Perchlorate effects are adjusted for age, urinary creatinine, ethnicity, cotinine, BMI, poverty index, total kcal intake, hours of fasting, urinary nitrates, urinary thiocyanates, CRP, for age 6–14, postmenarche status.</td>
<td>Different methods adopted each year for TSH and T4 analysis.

Linear regression models adjusted for urinary creatinine and different covariates. Nitrate and thiocyanate included in model of TSH on perchlorate in women with urine iodine ≥100 µg/L (Steinmaus et al., 2007).

Urinary perchlorate represents integrated proxy for all exposure routes.</td>
</tr>
</table>

<table>
<tr><th>Citation</th><th>Study Population</th><th>Study Design</th><th>Exposure Variables/Biomarkers</th><th>Outcome Variables</th><th>Major Study Findings</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Correlation coefficient between TSH and indirect indicators of thyroid hormone disruption, all subjects aged 12-85
<table>
<tr><td></td><td>Men</td><td>Women</td></tr>
<tr><td>Hgb</td><td>–0.005 (p=0.89)</td><td>0.24 (p=0.49)</td></tr>
<tr><td>Hct</td><td>–0.019 (p=0.60)</td><td>0.003 (p=0.93)</td></tr>
<tr><td>HDL</td><td>–0.07 (p=0.05)</td><td>–0.055 (p=0.11)</td></tr>
</table>
Correlation coefficient between T4 and indirect indicators of thyroid hormone disruption, all subjects aged 12-85
<table>
<tr><td></td><td>Men</td><td>Women</td></tr>
<tr><td>Hgb</td><td>0.093 (p=0.01)</td><td>–0.34 (p=0.32)</td></tr>
<tr><td>Hct</td><td>0.089 (p=0.01)</td><td>–0.039 (p=0.26)</td></tr>
<tr><td>HDL</td><td>–0.034 (p=0.34)</td><td>0.066 (p=0.05)</td></tr>
</table></td><td></td></tr>
<tr><td colspan="7">Geographic and Other Studies</td></tr>
<tr><td colspan="7">Studies in Pregnant Women</td></tr>
<tr><td>Tellez et al., 2005</td><td>184 women in three cities in Chile (65 in Antofagasta, 66 in Taltal, and 53 in Chanaral), <24 weeks gestation, residing >6 months, and without prescribed thyroid medication, and their neonates (159 total, 55 in Antofagasta, 55 in Taltal, and 49 in Chanaral), 2002-2004

Response rates not reported</td><td>Longitudinal cohort, 2002-2004</td><td>Perchlorate in tap water samples from subject homes, 1st prenatal visit, µg/L [mean (SD)]:
Antofagasta = <4 (LOD)
Chanaral = 5.82 (0.63)
Taltal = 113.9 (13.3)
p–value= NR

Serum perchlorate, 1st prenatal visit, µg/L [mean (SD)]:
Antofagasta = <4 (LOD)
Chanaral = <4 (LOD)
Taltal = 10.9 (2.1)
p=0.0001

Urinary perchlorate, 1st prenatal visit, µg/g Cr [mean (SD)]:
Antofagasta, 28.4 (22)
Chanaral, 80.2 (129.6)
Taltal, 135.5 (95)
p≤0.0001

Cord blood serum</td><td>Serum TSH, T4, fT4, T3, in mother’s prenatal and postpartum serum and urine, and in cord blood</td><td>Mean (SD)TSH, T3, fT4 in women, 1st prenatal visit, from linear regression
<table>
<tr><td></td><td>ANT</td><td>CHA</td><td>TAL</td><td>p–value</td></tr>
<tr><td>T3 (ng/dL)</td><td>183 (35.7)</td><td>207 (38.5)</td><td>187 (36.1)</td><td>0.0004</td></tr>
<tr><td>fT4 (ng/dL)</td><td>0.97 (0.15)</td><td>0.95 (0.13)</td><td>0.99 (0.13)</td><td>0.18</td></tr>
<tr><td>TSH (µUI/mL)</td><td>2.63 (1.54)</td><td>2.81 (1.78)</td><td>2.61 (1.45)</td><td>0.75</td></tr>
</table>
Models adjusted for city, parity, antibodies, mother’s age, gender, and gestation age. ANT=Antofagasta; CHA=Chanaral; TAL=Taltal

City difference in means at 2nd prenatal visit in linear regression model of T3 but not of fT4 or TSH. No city difference in means at postpartum visit in linear regression models of T3, fT4, or TSH.

Mean (SD)TSH, T3, fT4 in neonate cord blood serum from linear regression
<table>
<tr><td></td><td>ANT</td><td>CHA</td><td>TAL</td><td>p–value</td></tr>
<tr><td>T3 (ng/dL)</td><td>79 (13.4)</td><td>73 (17.9)</td><td>82 (20.6)</td><td>0.003</td></tr>
<tr><td>fT4 (ng/dL)</td><td>1.07 (0.16)</td><td>1.04 (0.13)</td><td>1.03 (0.14)</td><td>0.08</td></tr>
<tr><td>TSH (µUI/mL)</td><td>6.20 (2.96)</td><td>6.69 (4.13)</td><td>6.31 (2.91)</td><td>0.69</td></tr>
</table></td><td>Likely some exposure misclassification due to incomplete perchlorate testing or perchlorate from food.

Urinary perchlorate represents integrated proxy for all exposure routes. Overlap in urinary perchlorate levels among women and other sources of perchlorate likely contributed to subjects’ overall exposure. Dietary perchlorate exposure in Chile (22-34 µg/day) appears higher</td></tr>
</table>

<table>
<tr><th>Citation</th><th>Study Population</th><th>Study Design</th><th>Exposure Variables/Biomarkers</th><th>Outcome Variables</th><th>Major Study Findings</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>perchlorate in neonate, µg/L [mean (SD)]:
Antofagasta = <4 (LOD)
Chanaral = <4 (LOD);
Taltal = 19.9 (5.0)
p=0.005</td><td></td><td>Models adjusted for parity, antibodies, mother's age, gender and gestation age. ANT=Antofagasta; CHA=Chanaral; TAL=Taltal</td><td>than that for US.

Urinary iodine levels intermediate of those from NHANES I (1970s) and III (1990s) subjects.

One subject from Chanaral enrolled without recognition of the exclusion criteria, and eight additional subjects started on levothyroxine treatment after the first or second prenatal visit because of an elevated serum TSH level.</td></tr>
<tr><td>Pearce et al., 2010</td><td>1,641 women from Cardiff, UK and Turin, IT, 1,006 (480 from Cardiff, 526 from Turin) with normal thyroid function (euthyroid, E) and 635 (374 from Cardiff, 261 from Turin) hypo-thyroid or –thyroxinemic (H), defined as TSH >97.5th percentile or T4 <2.5nd percentile, aged</td><td>Cross-sectional</td><td>Urinary perchlorate and iodine for all subjects; cotinine and thiocyanate in urine in E subjects

Urinary perchlorate, µg/L [GM (range)]:
Cardiff: 2.1 (0.03–368), H ; 2.6 (0.4–49), E
Turin: 5.0 (0.04–108), H; 5.2 (0.2–168), E
All subjects, 3.6 (0.2–168)

Urinary thiocyanate levels, µg/L (GM), range NR:
Cardiff, 470.5, E</td><td>Serum T4,fT4, TSH at 1st prenatal visit

TSH, mIU/L [GM (range)]:
Cardiff; 3.6 (0.19–29.8), H; 1.2 (0.02–3.3), E
Turin; 2.2 (0.2 –53.5), H; 1.1 (0.005–3.3), E

fT4, pg/ml* [GM (range)]:
Cardiff: 9.1 (4.9–13.6), H;</td><td>Correlation coefficient between urine perchlorate and T4 and TSH
<table><tr><td></td><td>C, E</td><td>C, H</td><td>T, E</td><td>T, H</td></tr><tr><td>fT4</td><td>–0.07
p=0.1</td><td>0.08
p=0.11</td><td>–0.003
p=0.95</td><td>0.06
p=0.4</td></tr><tr><td>TSH</td><td>–0.04
p=0.4</td><td>0.04
p=0.5</td><td>–0.04
p=0.3</td><td>0.09
p=0.2</td></tr></table>C=Cardiff; T=Turin; E=euthyroid or subjects with normal thyroid function; H=subjects with hypothyroid or hypothyroxinemia

Correlation coefficient between urine perchlorate and T4 and TSH in women with urinary iodine <100 µg/L
<table><tr><td></td><td>C, E</td><td>C, H</td><td>T, E</td><td>T, H</td></tr><tr><td>fT4</td><td>–0.07
p=0.06</td><td>0.1
p=0. 2</td><td>0.2
p=0.6</td><td>0.001
p=0.99</td></tr><tr><td>TSH</td><td>–0.05
p=0.6</td><td>0.06
p=0.4</td><td>–0.05
p=0.3</td><td>0.06
p=0.4</td></tr></table>C=Cardiff; T=Turin; E=euthyroid or subjects with normal thyroid function; H=subjects with hypothyroid or hypothyroxinemia</td><td>Serum and urine samples collected concurrently and before initiation of any levothyroxine intervention.

Different methods adopted for each city for TSH and T4 analysis.

Urinary perchlorate represents integrated proxy for all exposure routes; urinary</td></tr>
</table>

<table>
<tr><th>Citation</th><th>Study Population</th><th>Study Design</th><th>Exposure Variables/Biomarkers</th><th>Outcome Variables</th><th>Major Study Findings</th><th>Comments</th></tr>
<tr>
<td></td>
<td>18 - 45 years, <16 weeks gestation, recruited from Controlled Antenatal Thyroid Screening Study, 2002-2006

Response rates not reported</td>
<td></td>
<td>Turin 372.5, E
Thiocyanate levels NR for H

Urinary iodine, µg/L (GM and range):
Cardiff: 98 (12–847), H ; 117 (2–497), E
Turin: 55 (12–1129), H; 50 (6–584), E</td>
<td>11.4 (8.5–28.7), E
Turin: 7.4 (6.0–11.4), H; 9.3 (7.5–16.9), E</td>
<td>Beta coefficients (SE) for association between log urinary perchlorate and thryoid function in women with normal thyroid function (combined E group)
<table>
<tr><th></th><th>Log perchlorate</th><th>Log thiocyante</th><th>Log iodine</th></tr>
<tr><td>fT4[1]</td><td>–0.0019 (0.002) p=0.3</td><td>0.0048 (0.0023) p=0.03</td><td>0.0044 (0.0019) p=0.02</td></tr>
<tr><td>TSH[1]</td><td>–0.0176 (0.0106) p=0.1</td><td>0.0139 (0.0117) p=0.2</td><td>Not included in model</td></tr>
</table>
[1] Thyroid hormonelevels transformed into multiples of median (MoM) values [MoM TSH½ or 1/MoM T4½] due to country differences in analytical methods. Regression models adjusted for thiocyanate and thyroid antibody positivity, in addition, for iodine (fT4 model only).</td>
<td>thiocyanate assayed in subjects with normal thyroid function only.

Fewer smokers than entire CATS population (12.1% in study population compared to 18.1% of CATS subjects).

TSH, 97.5th percentile: >3.65 mIU/L, Cardiff; >3.18 mIU/L, Turin; fT4, 2.5th percentile: <8.3 pg/ml, Cardiff; <7.36 pg.ml, Turin

TSH geometric mean for Turin H subjects is below 97.5th percentile. fT4 geometric mean for Cardiff H subjects is above the 2.5th percentile.

Euthyroid group includes subjects with thyroid hormone levels associated with hyperthyroid conditions. Upper range of TSH in Turin E subjects includes values >97.5th percentile.</td>
</tr>
</table>

<table>
<tr><th>Citation</th><th>Study Population</th><th>Study Design</th><th>Exposure Variables/Biomarkers</th><th>Outcome Variables</th><th>Major Study Findings</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td>* pg/ml=10 ng/dl</td></tr>
<tr><td>Pearce et al., 2011</td><td>241 women (134 from Los Angeles, CA and 107 from Cordoba, AR) ≤12 weeks gestation, 2004-2007

Response rates not reported</td><td>Cross-sectional</td><td>Urinary perchlorate , µg/L [GM (range)];
7.8 (0.4 – 284), Los Angeles; 13.5 (1 – 676), Cordoba
10.6 (0.4 – 676), All subjects

Urinary iodine, µg/L [GM (range)];
144 (16 – 733), Los Angeles; 130 (9 – 693), Cordoba
136 (91 – 733), All subjects</td><td>Serum T3, fT3 index, T4, fT4 index, TSH at 1st prenatal visit

T3, ng/dL (mean, SD)
CA, 163 (37)
AR, 174 (38)
p=0.03

fT3 index (mean, SD)
CA, 135 (30)
AR, 153 (40.2)
p=0.003

T4, µg/dL (mean, SD)
CA, 10.7 (2.0)
AR, 11.9 (2.3)
p=<0.001

fT4 index (mean, SD)
CA, 8.9 (1.7)
AR, 10.1 (2.1)
p<0.001

TSH, mIU/L (mean, SD)
CA, 1.58 (1.6)
AR, 2.27 (4.4)
p=<0.001</td><td>Correlation coefficient between urinary perchlorate and T4 and TSH for all subjects
<table><tr><th></th><th>All women</th><th>All women, urinary iodine <100 µg/L</th></tr><tr><td>T3</td><td>0.06, p=0.4</td><td>–0.03, p=0.8</td></tr><tr><td>fT4</td><td>0.12, p=0.06</td><td>0.14, p=0.2</td></tr><tr><td>TSH</td><td>0.05, p=0.5</td><td>–0.04, p=0.7</td></tr></table>Urine perchlorate not associated with serum T3, fT4, or log TSH in multiple linear regression models that controlled for creatinine, thyroid antibody titer, urinary iodine, and gestational age.
Log perchlorate (µg/L):
T3 (ng/dl), β= –0.7 (SE, 2.6), p=0.8
fT4 index, β= –0.0006 (SE, 0.1), p=1.0
log TSH (mIU/L), β= –0.03 (SE, 0.07), p=0.7

Log iodine (µg/L):
T3 (µg/L), β= –0.03 (SE, 0.03), p=0.3
fT4 (µg/L), β= –0.004 (SE, 0.002), p=0.04
log TSH (mIU/g Cr), β= 0.0008 (SE, 0.0009), p=0.4</td><td>Information on mother’s ages or assay urinary smoking biomarkers not reported.

Urinary perchlorate represents integrated proxy for all exposure routes.

Small numbers of subjects, low statistical power</td></tr>
<tr><td colspan="7">Studies in Neonates</td></tr>
<tr><td>Buffler et al., 2006; Steinmaus et al. (2010)</td><td>342,257 newborns (50,326 exposed and 291,931 non-exposed births),</td><td>Cross-sectional</td><td>CA Drinking Water Program data, excluded CA cities and towns lacking perchlorate</td><td>Serum TSH in infants with collection time ≥ 24 hours of</td><td>PCH infant of mother residing in community with >5 µg/L perchorate compared to infant of mother from ≤5 µg/L community:
All communities: POR=0.71 (95% CI, 0.40–1.19), n=15
Community water source was not Colorado River: POR=1.14</td><td>Small numbers of cases in Buffler et al. (2006) in >5 µg/L perchlorate</td></tr>
</table>

<table>
<tr><th>Citation</th><th>Study Population</th><th>Study Design</th><th>Exposure Variables/Biomarkers</th><th>Outcome Variables</th><th>Major Study Findings</th><th>Comments</th></tr>
<tr><td></td><td>California, Newborn Screening Database (NBSD), 1998 (Buffler et al., 2006)</td><td></td><td>testing of municipal water supply, 1997-1998. 311 communities, 287 with estimated average perchlorate ≤5 µg/L defined as unexposed, 24 with estimated average perchlorate >5 µg/L defined as exposed; LOD = 4-5 µg/L</td><td>age (684 with TSH > 25 µU/mL (99.9th percentile), 141 cases of physician-confirmed congenital hypothyroidism (PCH) reported to NBSD</td><td>(0.52–2.28), n=10
Colorado River water community: POR=0.43 (0.15–0.96), n=5

Newborns screened ≥24 hours of age, TSH>25 µU/mL:
All communities: POR=0.73 (95% CI, 0.40–1.23), n=14
Community water source was not Colorado River: POR=0.87 (0.37–1.83), n=8
Colorado River water community: POR=0.57 (0.22–1.20), n=6</td><td rowspan="2">group.

No individual exposure information.

POR from logistic regression model and adjusted for sex, ethnicity, multiple birth status, and birth weight (Buffler et al., 2006) or adjusted for sex, ethnicity, birth weight, food type, mother’s age, per capita income and collection age (Steinmaus et al., 2010).

Likely some exposure misclassification due to incomplete perchlorate testing or perchlorate from food.</td></tr>
<tr><td></td><td>497,458 newborns (45,750 exposed and 451,708 non-exposed births), California NBSD, 1998 (Steinmaus et al., 2010)</td><td></td><td></td><td>Serum TSH in infants, collection time ≤ 24 hours with TSH ≥15 µU/mL (95th percentile) or TSH ≥ 25 µU/mL (99.9th percentile); collection time ≥ 24 hours with TSH >8 µU/mL (95th percentile) or TSH >25 µU/mL (99.9th percentile)</td><td>Infant of mother residing in community with >5 µg/L perchorate compared to infant of mother from ≤5 µg/L community:
Collection time ≤ 24 hours:
POR=1.23 (95% CI, 1.16–1.31), TSH ≥15 µU/mL, n=1,217
POR=1.53 (95% CI, 1.24–1.89), TSH ≥25 µU/mL, n=153
Collection time >24 hours:
POR=1.27 (95% CI, 1.22–1.33), TSH ≥8 µU/mL, n=2,711
POR=0.72 (95% CI, 0.41–1.27), TSH ≥25 µU/mL, n=13</td></tr>
<tr><td>Amitai et al., 2007</td><td>1,156 newborns in Israeli Newborn Screening Program, born in 2004, mothers living in two areas in Ramat Hasharon and neighboring city of Herzlia (97 from Morasha, 216 from other</td><td>Cross-sectional</td><td>Perchlorate in well water, µg/L:
<3, Herzlia
42-94, Ramat Hasharon
As high as 1,100, Morasha

Serum perchlorate in blood donors, µg/L [means (SD)]:
0.44 (0.55), Herzlia
1.19 (1.37), Ramat</td><td>Serum T4 levels in neonates</td><td>T4 (mean (SD), µg/dL:<table><tr><th>Herzlia</th><th>Other areas in Ramat Hasharon</th><th>Morasha</th></tr><tr><td>13.98 (3.5)</td><td>13.91 (3.4)</td><td>13.93 (3.8)</td></tr></table>p=0.95

T4 (mean (SD)) in matched analysis of 50 newborns* whose mothers consumed tap water and for whom there were complete data, µg/dL:<table><tr><th>Herzlia</th><th>Morasha</th></tr><tr><td>13.5 (3.4)</td><td>14.7 (4.2)</td></tr></table>p=0.27, * Newborns matched for gestational age, gender, and</td><td>Heel prick data; > 90% samples were 36-48 hours after birth.

Serum iodide levels in the blood donor groups was 2.24 µg/L for Herzlia and 3.10 µg/L for combined Ramat</td></tr>
</table>

Citation	Study Population	Study Design	Exposure Variables/Biomarkers	Outcome Variables	Major Study Findings	Comments
	areas in Ramat Hasharon, 843 from Herzlia); 37 blood donors from same areas		Hasharon 5.99 (3.89), Morasha p=0.04 for difference between Ramat Herzlia and Herzlia, p=0.06 for difference between Morasha and Herzlia		maternal age	Hasharon/Morasha subjects, p=0.03 No individual exposure data Likely some exposure misclassification due to incomplete perchlorate testing or perchlorate from food.
Cao *et al*., 2010	92 infants (47 boys and 45 girls) between birth and 1 year, recruited from Study of Estrogen Activity and Development, Philadelphia, PA Response rates not reported	Cross-sectional and partly longitudinal (up to 4 visits)	Urinary perchlorate from diaper, µg/L [GM (95% CI)] 1.21 (0.86–1.69) Urinary iodine, µg/L [GM (95% CI)] Women, 130 (113–151)	Urinary TSH, fT4 TSH (AM, 95% CI), 4.2 µIU/ml (3.7–4.6) fT4 (GM, 95% CI), 1.4 ng/dl (1.2–1.6)	In model of all three ions, children with higher nitrate and thiocyanate had higher TSH, but no effect of perchlorate on thyroid function: Log perchlorate (µg/g Cr): Log T4 (µg/g Cr), β= 0.01 (95% CI, -0.08–0.09), $p \geq 0.05$ Log TSH (mIU/g Cr), β= 0.01 (95% CI, -0.07–0.09), $p \geq 0.05$ Log thiocyanate (µg/g Cr): Log T4 (µg/g Cr), β= 0.33 (95% CI, 0.21–0.44), $p<0.05$ Log TSH (mIU/g Cr), β= 0.26 (95% CI, 0.15–0.37), $p<0.05$ Log nitrate (µg/g Cr): Log T4 (µg/g Cr), β= 0.09 (95% CI, 0.01–0.17), $p<0.05$ Log TSH (mIU/g Cr), β= 0.13 (95% CI, 0.05–0.21), $p<0.05$ Interaction between perchlorate and iodine in children with <100 µg/L on TSH, but not T4: Log T4 (µg/g CR), β= 0.09 (95% CI, -0.01–0.19), $p<0.10$ Log TSH (mIU/g Cr), β= 0.10 (95% CI, 0.01–0.19), $p<0.05$	Linear regression models adjusted for age, sex, BMI. Urine perchlorate values corrected for control diaper perchlorate concentration. Urinary perchlorate represents integrated proxy for all exposure routes. Increased T4 with perchlorate exposure is opposite to that expected. Small numbers of subjects, low statistical power

[1] Information for authors, American Journal of Kidney Diseases, unit conversion information , http://sites.google.com/site/ajkdinfoforauthors/html/unit-conversion

ANT = Antofagasta; AM = arithmetic mean; AR = Argentina; BMI-body mass index; C=Cardiff; CA = California; CATS = Controlled Antenatal Thyroid Screening Study; CHA = Chanaral; CI = confidence interval; Cr = creatinine; CRP = C-reactive protein; E = euthyroid or normal thyroid function; fT3 = free triiodothyronine; fT4 = free thyroxine; GM = geometric mean; H = hypo-thyroid or –thyroxinemic; Hct = hematocrit; Hgb = hemoglobin; HDL = high density lipoprotein; L = liter; LOD=limit of detection; mIU = milli-International Units; ng = nanogram; NBSD=Newborn Screening

Database; NHANES = National Health and Nutrition Examination Survey; NR = Not Reported; T = Turin; T3 = triiodothyronine; T4 = thyroxine; TAL=Taltal; TSH = thyroid stimulating hormone; kg = kilogram; PA = Pennsylvania; POR = prevalence odds ratio; yrs = years; SD = standard deviation; SE = standard error; TAL = Taltal; µIU = micro International Units; µg = microgram.

Table A-6: Biomonitoring and Exposure Studies.

Citation and Study Design	Study Population	Perchlorate Levels/Dose	Comments/Other Findings
Blount *et al*., 2007	U.S. National Health and Nutrition Examination Survey (NHANES) 2001–2002 Participants ≥6 years old (n=2,820)	Geometric mean (95% CI) of urinary perchlorate for US population ≥ 6 years 3.54 (3.29-3.81) µg/L 3.56 (3.34-3.80) µg/g creatinine Geometric mean perchlorate dose for US population ≥ 20 years (95% CI) = 0.07 (0.06–0.07) µg/kg/day 95th percentile (95% CI) = 0.23 (0.20–0.27) µg/kg/day	Daily dose estimated based on spot urine perchlorate and creatinine concentrations and estimated daily excretion rate based on weight, height, age and sex. First population-based study on assessing the perchlorate exposure in US No data on drinking water
Blount *et al*., 2010	U.S. National Health and Nutrition Examination Survey (NHANES) 2005–2006 Participants ≥12 years old (n=3,084)	Median perchlorate level from tap water consumption = 0.009 µg/kg-day for U.S. adults	Median (95th percentile) level of perchlorate = 1.16 (1.89) µg/L (95th percentile = 1.89 Individual person's water consumption not measured
Borjan *et al*., 2011	Lactating mothers aged 18–38 (mean= 25 years) in New Jersey USA (n=106)	Perchlorate in breast milk 6.80±8.76 ng/L; urine 3.51±6.79 µg/g creatinine No correlation between perchlorate levels in breast milk and those in water ($r = -0.04$, $p = 0.25$) Mean ± SD of perchlorate levels in water 0.17±0.13 ng/L	78% participants (n=83) provided all three exposure samples (drinking water, urine, breast milk) Perchlorate exposure contribution from drinking water is not significant. Negative correlation between perchlorate levels in urine and those in water ($r = -0.13$, $p = 0.02$)
English *et al*., 2011	Residents of Imperial Valley (Imperial County, California) (n=31); ages 18–88 (mean=41.1 years); 64.5% female, 35.5% male	2 of 68 drinking water samples had detectable levels of perchlorate (~2.5 µg/L) Levels in the 79 produce samples ranged from nondetectable to 1816 ppb (ng of perchlorate/g of net wt of edible portion) Geometric mean (95% CI) of perchlorate in urine = 6.44 (4.83–8.58) µg/L Geometric mean perchlorate dose (95% CI) = 0.11 (0.08–0.15) µg/kg/day	Perchlorate dose is 70% higher than the NHANES reference population Perchlorate dose increased with the number of servings of dairy products consumed and with estimated perchlorate levels in produce consumed 24-hour urine samples collected
Huber *et al*., 2011	NHANES (2001-2002) subjects	Mean perchlorate dose in US = 0.101 µg/kg/day with contribution	Tap water perchlorate data from the 2001–2003 EPA Unregulated

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	(n=2708); ~53% male; ~43% between 6 and 19 years old; 57% >20 years old	from water = 0.02 µg/kg/day; Mean perchlorate dose for children aged 6–11 = 0.150 µg/kg-day with contribution from water =0.003 µg/kg-day Mean perchlorate dose for pregnant women from food = 0.09 µg/kg-day (90^{th} percentile = 0.198 µg/kg-day)	Contaminant Monitoring Regulation (UCMR) public drinking water system database Mean food to water ratio of perchlorate in US population or women of reproductive age = 80:20
Kirk *et al*., 2005	47 dairy milk samples from 11 states; 36 breast milk samples from lactating women in 18 states	Mean and maximum perchlorate in dairy/breast milk: 2.0/10.5 µg/L and 11/92 µg/L.	Mean perchlorate levels in breast milk samples are five times higher than that in dairy milk In limited breast milk samples with perchlorate content greater than 10 µg/L, the iodide content is linearly correlated with the inverse of the perchlorate concentration (r2 >0.9, n = 6).
Kirk *et al*. 2007	Lactating women (n=10) collected 6 milk samples or more on each of three days	Range/median perchlorate levels in breast milk (µg/L) 0.5-39.5/ 4.0 (n=147) Range/median iodide levels in breast milk (µg/L) 3.1-334/ 55.2 (n=108)	Individual perchlorate, iodide levels varied among individuals; also had temporal variations
Leung *et al*., 2009	Postpartum women in Boston, MA (n=97); mean age 27 ± SD 6 years; range: 18–42 years; recruited in 2006-2007	Perchlorate was detected in all 97 spot urine samples (median 0.026 µmol/L; range, 0.002 - 1.6 µmol/L). Perchlorate was detected in 43 out of 46 colostrum samples (93%); median concentration = 0.025 µmol/L (range of <0.0005 – 1.89 µmol/L)	Colostrum iodine content not significantly correlated with levels of colostrum perchlorate (r2 = 0.005, p = 0.65) or urinary perchlorate (r2 = 0.004, p = 0.64). Colostrum perchlorate concentrations not significantly associated with urinary iodine (r2 = 0.003, p = 0.71) or perchlorate (r2 = 0.001, p = 0.81), or cotinine levels (r2 = 0.006, p = 0.62)
Mendez *et al*., 2010	Women of reproductive age in the United States, ages 18-45 years, NHANES (2001-2002) subjects (n=471); and NHANES (2003-2004) subjects (n=454), ages 15-45 years	Upper bound 95th percentile estimate of perchlorate intake from food and water for reproductive age women was 0.15 µg/kg/day. Median dietary estimate of perchlorate (food +water) = 0.06-0.07 µg/kg/day with drinking water contributing from 3% to 24%;	Perchlorate concentrations in food from FDA's 2004-2005 Exploratory Survey Data Food and water consumption data from USDA's Continuing Survey of Food Intake by Individuals (CSFII) from 1994 to 1996 and 1998

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		Median perchlorate exposure estimated from urinary levels were similar for 2001-2002 as well as 2003-2004 survey NHANES survey (0.05-0.06 µg/kg/day)	
Pearce *et al*., 2007	Lactating healthy women volunteers in Boston area (n=57); age range 19-45 years; 10-250 days post-partum, median 48 days; between July 2002 and April 2006	Perchlorate was detected in 100% of samples and ranged between 1.3 – 411 µg/L in breast milk (n = 49), 0.37 – 127 µg/L in urine (n = 56); and 0.22 – 4.1 µg/L in infant formula Assuming consumption of 0.65 L of breast milk per day and an infant body weight of 3 kg, estimated perchlorate dose for infant ranged from 1.9 µg/kg/day to 88 µg/kg/day	Urinary perchlorate was significantly higher in breast milk than in formula ($p<0.0001$) but iodine was not different ($p= 1.0$) A significant positive correlation between breast milk perchlorate and urine perchlorate concentrations ($r2 = 0.11$; $p = 0.02$). Breast milk iodine was not significantly correlated with perchlorate levels in breast milk (n = 49, $r2 = 0.05$, $p = 0.1$) even at perchlorate levels > 10 µg/L (n = 23); or in urine ($r2 = 0.004$; $p = 0.7$)
Schier *et al*., 2010	Four types of powdered infant formula obtained from local stores in 2006 Different brands in each category tested	Geometric mean perchlorate levels (µg/L): Bovine milk-based with lactose = 1.72 (n=15) Soy-based = 0.21 (n=15) Bovine milk-based, lactose-free =0.27 (n=9) Elemental formula =0.18 (n=6) Estimated geometric mean for 1 month old infants at 90th percentile BW (µg/kg/day) Bovine milk-based with lactose = 0.35 Soy based formula = 0.04 Bovine milk-based, lactose-free =0.05 Elemental formula =0.04	Presence of perchlorate in all powdered infant formula Perchlorate free water was used to measure perchlorate in the formula Estimated daily dose range for 6 month old infants were lower than estimated for 1 month old infants for all formula categories.
Valentín-Blasini *et al*., 2011	Infants (n=92) from Philadelphia, PA hospital that were part of Study of Estrogen Activity and Development (SEAD)	Geometric mean perchlorate dose in breast milk-fed, cow milk formula-fed, soy formula-fed infants and all infants = 0.22, 0.10, 0.03, 0.09 µg/kg-day	Same cohort as Cao *et al*., 2010 study Breast-fed infants had significantly higher urinary perchlorate levels than infants fed cow milk-based formula ($p = 0.004$) and soy formula ($p < 0.001$) Perchlorate and iodide levels positively correlated ($r = 0.55$) in urine samples

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Woodruff *et al*., 2011	NHANES 2003–2004 data on pregnant (n=268) and non-pregnant (n=1489) women, ages 15 - 44 years old	Geometric mean (geometric standard error [GSE]) for urinary perchlorate Pregnant women = 4.17 (0.84) µg/L (n=89). Non-pregnant women = 2.68 (0.21) µg/L (n=492).	Pregnant women had significantly higher levels of perchlorate than non-pregnant women (Least-squares geometric means, LSGM=3.35 versus 2.61, respectively $p < 0.01$, after adjustment for covariates)