STATE OF SCIENCE ON PERCHLORATE HEALTH EFFECTS: BRIEF SUMMARY OF RELEVANT SCIENTIFIC STUDIES SINCE THE PUBLICATION OF THE NATIONAL RESEARCH COUNCIL'S ASSESSMENT OF PERCHLORATE IN 2005

Prepared for:

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ABBREVIATIONS AND SELECTED DEFINITIONS

ATSDR	Agency for Toxic Substances and Disease Registry.
in vitro	A study conducted outside a living organism in an artificial environment.
in vivo	A study conducted in a living organism.
IUI	Iodide uptake inhibition. Reduction of iodide uptake into the thyroid through the NIS.
LOAEL	Lowest Observable Adverse Effect Level. The lowest exposure level at which there is biologically significant increase in frequency or severity of adverse effects between the exposed population and its appropriate control group.
MCL	Maximum Contaminant Level. A federally enforceable standard set by EPA; the highest level of a contaminant that is allowed in drinking water.
µg/L	Microgram per liter. A unit of mass concentration defined as the concentration of one microgram of a substance per unit volume of the mixture equal to one liter; equivalent to a part per billion.
mg/d	Milligrams of chemical per day. Daily doses of a chemical are often described in these units; they are not normalized for weight.
mg/kg-d	Milligrams of chemical per kilogram of body weight per day. Daily doses of a chemical are often described in these units, which are normalized for weight. This is important as an identical dose in mg/d could be different in a 70 kg adult versus a 10 kg infant.
NIS	Sodium iodide symporter. An ion pump that actively transports an iodide ion along with two sodium ions across the membrane into certain cells, particularly thyroid epithelial cells; perchlorate can transiently block this uptake.
NOAEL	No Observable Adverse Effect Level. The highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse or precursors of adverse effects.
NOEL	No Observable Effect Level. An exposure level at which there are no statistically or biologically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control.
NRC	National Academy of Sciences National Research Council.
OIG	Environmental Protection Agency Office of the Inspector General.
PBPK	Physiologically-based pharmacokinetic.
PHG	Public Health Goal. Drinking water goal set by the State of California.
ppb	Part per billion.
RfD	Reference Dose. 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.
T3	Triiodothyronine. A thyroid hormone, more potent than T4; can be bound to other molecules and measured as total T3, or as the fraction available for the body to use as free T3, which is more biologically relevant.
T4	Thyroxine. A thyroid hormone, that is also is a precursor of T3, a more potent thyroid hormone; can be bound to other molecules and measured as total T4, or as the fraction available for the body to use as free T4, which is more biologically relevant.
Tg	Thyroglobulin. An iodine-containing protein found in the thyroid gland that is involved in the production of the T4 and T3 hormones.
TGL	Total goitrogen load. The combined exposure to all substances that cause IUI, particularly nitrate, thiocyanate, and perchlorate.
TSH	Thyroid stimulating hormone. A pituitary hormone that stimulates the production of thyroid hormones.
US EPA	United States Environmental Protection Agency.
WHO	World Health Organization.

1.0 EXECUTIVE SUMMARY

To protect public health, scientists determine acceptable exposures by carefully examining all of the medical literature and comparing the doses and exposures necessary to cause an effect, particularly in the most sensitive group of the public. Over six decades of research, many scientists have contributed to the current understanding of perchlorate in the medical literature. This document summarizes scientific studies regarding perchlorate since the release of a key scientific analysis of perchlorate which was conducted by the National Academies of Science National Research Council (NRC) in 2005. In short, the weight of scientific research supports the following conclusions:

- There is no scientific evidence to demonstrate that perchlorate doses lower than 245 ppb will cause any effect in humans.
- The most sensitive organ in the body to perchlorate effects is the thyroid.
- The most sensitive subpopulation is the fetus of iodine deficient pregnant women.
- Perchlorate accounts for less than one percent of the total goitrogen (a chemical that inhibits iodine uptake) load on the thyroid in a typical American diet.
- The American population is not likely being exposed to perchlorate at levels above 25 ppb.
- World Health Organization (WHO) guidelines state that a population is considered iodine sufficient if at least half the population has a single urinary iodine value of 100 mg/L or greater. Based on this, the US population is considered iodine sufficient (Caldwell et al., 2005)
- Perchlorate is not an endocrine disruptor in that it does not mimic thyroid hormone.

The perchlorate database is robust, largely due to the use of perchlorate as a pharmaceutical and the fact that EPA required manufacturers and users of perchlorate to fund studies that provide data over a range of comprehensive toxicological endpoints. These data were sent directly to EPA without any review from the funding organizations.

EPA requested the NRC review its 2002 perchlorate risk assessment. The NRC developed several key scientific findings not only of the EPA risk assessment, but on the database of perchlorate literature. First, NRC affirmed what has been known since the 1950s: that perchlorate has a specific action in the body: iodide uptake inhibition (IUI). Often scientists do not have a clear

The 2005 NRC report concluded:

- IUI is not an adverse effect. It is a reversible and adaptive biochemical phenomenon.
- Thyroid hormone changes are not necessarily adverse because the thyroid gland normally adapts to various environmental stimuli (e.g., temperature, illness).
- Using the NOEL for IUI provides a reasonable and transparent approach to the perchlorate risk assessment.
- Extensive human and animal data demonstrate that there will be no progression to adverse effects if no IUI occurs.

understanding of how an environmental chemical works in the body. However, the manner in which perchlorate works in the body has been known for decades. When ingested in sufficient quantities, perchlorate causes IUI. The NRC determined that IUI is not an adverse effect. Second, the NRC defined a No Effect Observed Level (NOEL[1]), based on a study by Greer and his colleagues in 2002 (the Greer Study). The study stands today as the seminal study used by numerous government agencies to derive regulatory or health based standards. Third, the NOEL was based on the organ in the body most sensitive to the effects of perchlorate: the thyroid gland. In determining this NOEL, the NRC identified a dose threshold, at or below which, there can be no progression to adverse effects. Above the threshold dose, adverse effects are still unlikely unless the dose is sufficient and sustained to inhibit 75% of the iodide to the thyroid gland daily for weeks or months. Fourth, it is rare to have such precise knowledge of the dose-response relationship of an environmental chemical such that a NOEL can be documented. Using the NOEL is a non-standard, conservative approach seldom available to toxicologists. Finally, other chemicals, such as nitrate and thiocyanate, are naturally present in many foods, and like perchlorate, inhibit iodide uptake. These chemicals, however, are part of a healthy diet that includes leafy greens, fruits, and vegetables.

The NRC applied a ten-fold safety factor to this NOEL and proposed a level of perchlorate consumption equivalent to 24.5 ppb in drinking water. Studies published since the NRC report have helped build the scientific database on perchlorate and have affirmed that although developed in a non-standard manner, the NRC-recommended dose is both highly conservative and health protective.

The EPA subsequently adopted the NRC's recommendations and published a RfD for perchlorate which is "An estimate of a daily oral exposure for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime." In 2005, that value was equivalent to 24.5 ppb of perchlorate in drinking water using standard EPA assumptions.

Since the NRC report, at least 25 studies and three assessments by governmental organizations have been published (Table 1). Twenty-two of these 25 studies support the scientific foundation and conclusions established by the NRC in 2005. Three of the 22 studies (two of the three use the same dataset; the third study uses a similar data set previously published by Buffler et al., 2006) report associations between a limited set of thyroid measures to perchlorate doses below the threshold dose for IUI. Each of these three studies have significant limitations based on the data they used, that call their conclusions in to question. None of these new studies change the foundational science of perchlorate health effects.

Fifteen of the 25 studies characterize hypothetical or real exposures, four are epidemiological studies (two use the same data set), two are literature reviews, one is a modeling study using rat data, one is a laboratory animal study, one is an *in vitro* study, and one is a clinical study. The Agency for Toxic Substances and Disease Registry (ATSDR) reviewed the literature and affirmed the EPA's RfD. The EPA Office of the Inspector General (OIG) used a cumulative risk assessment to determine the benefit of regulating perchlorate. OIG determined that nitrate, thiocyanate, and iodine deficiency had greater impacts on the thyroid than perchlorate

[1] The US EPA defines a NOEL as "An exposure level at which there are no statistically or biologically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control."

and that "potentially lowering the perchlorate drinking water limit from 24.5 ppb to 6 ppb does not provide a meaningful opportunity to lower the public's risk."

In summary, the scientific database for perchlorate is one of the most robust of all the environmental contaminants, and provides government agencies a strong foundation from which to develop conservative and transparent regulatory standards. The studies reviewed since 2005 do not change the foundational scientific understanding (toxicology, pharmacology, and biochemistry) of perchlorate. Levels below the NOEL produce no measurable effect in the body and the first measurable effect (IUI) is not adverse.

2.0 INTRODUCTION

Studies published since the NRC report have strengthened the already robust scientific database on perchlorate and have affirmed that the NRC evaluation is scientifically valid and is conservative and health protective.

Recently, the US EPA announced its decision to regulate perchlorate under the Safe Drinking Water Act, which will require development of a Maximum Contaminant Level (MCL). Similarly, the State of California released a draft revised Public Health Goal (PHG) in January 2011. Perchlorate has received considerable attention as an environmental toxicant since the 1990s when it was detected in low concentrations in drinking water in California. The key human health concern was and has continued to be whether perchlorate at environmental concentrations can adversely affect human health. We briefly summarize the key scientific findings prior to 2005 and then summarize the key studies that have been published since then.

Perchlorate and its salts, such as ammonium perchlorate, are a solid at ambient temperatures. Perchlorate is a simple ionic molecule with one chlorine and four oxygen atoms. This chemistry makes perchlorate water soluble and the oxygen makes the chemical useful as it provides oxygen to fuel combustion processes. Because of these properties, perchlorate been used in a number of applications by the US Department of Defense, the pharmaceutical industry, pyrotechnics manufacturers, and other industries. Perchlorate has been used in fireworks, road flares, and automobile airbags and has been found in agricultural fertilizers and as a contaminant of hypochlorite used as a water disinfectant. For its use as an oxidizer in the combustion process, no other chemical has been found to replace perchlorate in terms of effectiveness, reliability, safety, and toxicity.

Importantly, environmental perchlorate has also been reported to be produced by atmospheric processes. Lightning is thought to provide sufficient energy to bond atmospheric chlorine and oxygen. Certain soils and groundwater from disparate locations have been reported to have concentrations in the low parts per million (ppm), which, solely on a concentration level, is several orders of magnitude higher than that found in finished drinking water.

The NRC judged that the fetuses of pregnant woman are the most sensitive subpopulation and that this population should be the focus for protecting public health.

Given that perchlorate is present in the environment from industry, government, and natural sources, how do toxicologists determine what levels are not expected to cause harm? The key to understanding is found in the scientific studies of a chemical.

Compared with many environmental pollutants, there exists a strong and wide breadth of scientific knowledge concerning the potential health effects of perchlorate exposure. One of the primary reasons for this is that perchlorate is a drug which was used predominantly in the 1950s and 1960s to treat hyperthyroidism, such as Graves Disease. It is still used for treating some thyroid-related diseases today, although it is no longer the drug of choice for hyperthyroidism. This medicinal use provided valuable information to scientists regarding toxicity and where data gaps remained, animal and human studies were performed in the 1990s and early 2000s.

The NRC conducted an examination of the perchlorate literature and evaluated the ingestion of perchlorate. The report, published in 2005, concluded:

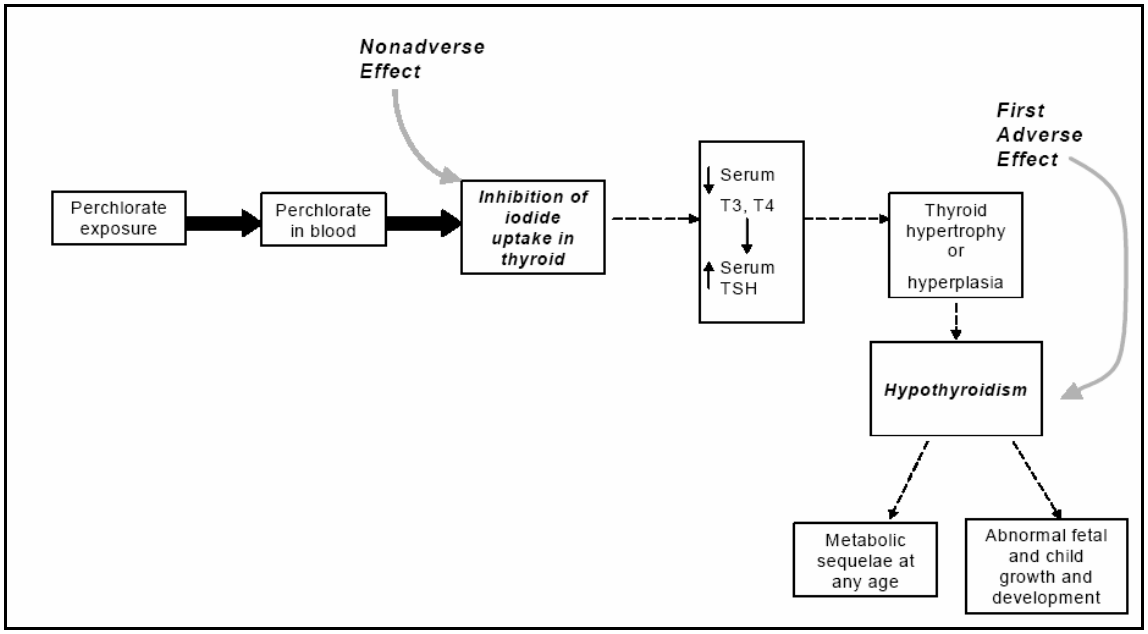
- At doses above elevated environmental levels but below therapeutic doses, IUI is the only consistently documented effect of perchlorate exposure in humans.
- IUI is only observed at doses greater than 0.007 mg/kg-d (equivalent of 245 ppb in drinking water). It is not an adverse effect. It is a reversible biochemical phenomenon.
- Extensive human and animal data demonstrate that no adverse effect will occur if no IUI occurs.
- Thyroid hormone changes are not necessarily adverse because the thyroid gland normally adapts to various environmental stimuli (e.g., temperature, illness, diet) on a daily basis.
- Using the NOEL for IUI reported in the Greer Study as the point of departure for standard setting is conservative and health protective. A more commonly used methodology uses the NOAEL or LOAEL, which is based on an adverse effect.

The reversible inhibition of the NIS by perchlorate is documented in many experiments, both *in vivo* and *in vitro*. This interaction exhibits the standard S-shaped dose-response curve in toxicology and pharmacology—as dose increases, so does the response. In the Greer Study, the response is IUI—a non adverse effect—which precedes the potential adverse effect of hypothyroidism by several biochemical steps. There is no scientific evidence to suggest that low doses of perchlorate will cause any other effect. Specifically, research has shown that perchlorate is not carcinogenic, does not cause birth defects, and neither mimics a hormone nor directly stimulates a hormonal response.

Since the NRC report, there has been no direct experimental scientific evidence to suggest that perchlorate doses lower than 245 ppb will cause any effect in humans.

The biological action of perchlorate (its "mechanism of action") on the thyroid gland including the delineation of what is and what is not considered an adverse effect is summarized in Figure 1.

Figure 1. Mechanism if action for perchlorate as summarized in the National Academy of Science Report (2005).



The NRC 's suggested mode-of-action model of perchlorate toxicity in humans. Solid arrows represent outcomes that have been observed in humans with perchlorate doses greater than 0.007 mg/kg-d. Dashed arrows represent outcomes that have not been clearly demonstrated in humans exposed to perchlorate but that are biologically possible in the absence of adequate compensation. The thyroid response to increased serum TSH and an independent increase in thyroid iodide uptake would raise T3 and T4 production to normal and therefore usually prevent the later steps from occurring (NRC, 2005).

In recommending a perchlorate RfD[2] based on a nonadverse effect, the NRC (2005) emphasized it was taking a non-standard, but unusually cautious approach:

> The committee emphasizes that its recommendation differs from the traditional approach to deriving the RfD. The committee is recommending using a nonadverse effect rather than an adverse effect as the point of departure for the perchlorate risk assessment. Using a non adverse effect that is upstream of the adverse effects is a conservative, health-protective approach to the perchlorate risk assessment.

In a typical risk assessment, safety factors are applied to the dose that causes no observable adverse effect (NOAEL) or the lowest observable adverse effect (LOAEL) to determine the RfD. The NRC concluded that individuals with normal iodide intake would require a perchlorate dose large enough to lower thyroid iodide uptake by at least 75% for a sustained period

In a typical risk assessment, safety factors are applied to the dose that causes no observable adverse effect (NOAEL) or the lowest observable adverse effect (LOAEL) to determine the RfD. By starting with a nonadverse effect, and then applying safety factors, the NRC was taking a non-standard, unusually cautious approach.

[2] 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.

of time (several months or longer) to cause thyroid hormone production to decline to the point where hypothyroidism could occur. In adults, that dose is estimated as being no lower than 30 mg/d (0.4 mg/kg-d for a 70-kg person). This is equivalent to a 70-kg adult drinking two liters of water with a perchlorate concentration of 15,000 ppb every day.

The NRC study is the capstone of the literature. Since the release of the NRC report in 2005, no scientific evidence has been developed to suggest that doses lower than the NOEL of perchlorate will cause any effect. Most of the studies that have been conducted since 2005 are different in their experimental design than the studies prior to that time. The NRC determined that the fetuses of pregnant woman are the most sensitive subpopulation and that this population should be the focus of public health standard setting. Recent studies on perchlorate were specifically designed to develop information on exposure of the chemical to men, women, and infants. For example, some studies estimate exposures to infants through breast milk or from food. These studies are useful for conducting risk assessments as these data describe possible exposures.

While media reports often classify chemical agents into two categories—toxic and nontoxic—this categorization has been understood to be scientifically invalid for more than 500 years. As Paracelsus (1493–1541) stated (translated to English):

> All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.

3.0 WHAT IS TOXICOLOGY?

Toxicology is the scientific study of adverse effects from human-made (e.g., engine oil), natural (e.g., venoms), and endogenous (e.g., hormones) compounds on living organisms. Toxicologists review the literature on the effects of exposure to the chemical(s), and compare estimated exposures with levels that have been shown to cause adverse health effects.

A toxicologist's analyses are grounded on the application of a key toxicological principle—that the mere presence of a chemical in the environment or an exposure medium does not justify an inference that exposure to that chemical will have an adverse toxicological effect. While media reports often classify chemical agents into two categories—toxic and nontoxic—this categorization has been understood to be scientifically invalid for more than 500 years. As Paracelsus (1493–1541) stated (translated to English):

> All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.

In other words, in order for harm to result from an exposure, the exposure must be of sufficient concentration and duration to exceed the chemical's threshold for effect. This is true for perchlorate. Thus, even for chemicals labeled as "toxic," exposures must be above a threshold level for there to be any possibility of adverse health effects. For example, vitamin C, which is necessary for life, is harmful at high doses.

Further, the potential for adverse health effects is highly dependent on the exposure scenario, what happens to the chemical in the body, and whether the individual is more sensitive than

average (e.g., the elderly). Therefore, to understand the potential hazard of an agent, a toxicologist must not only know

> …what type of effect it produces and the dose required to produce that effect but also information about the agent, the exposure, and its disposition by the subjects [where it goes in the body]. The major factors that influence toxicity as it relates to the exposure situation for a specific chemical are the route of administration and the duration and frequency of exposure (Klaassen, 2001).

These principles hold true for perchlorate. The scientific advantage in this case is that the biochemistry of how perchlorate acts in the body is well understood and has been known for over 50 years. The concept of threshold is important and is key to understanding the Greer Study. At a dose higher than 0.007 mg/kg-d, IUI may occur. At 0.007 mg/kg-d and below, it will not. Thus, 0.007 mg/kg-d is considered a threshold. For IUI, change in thyroid hormones, hypothyroidism, and other effects, there is a dose above which, an effect will start to occur and below which it will not. Science has demonstrated the level at which there is no biological or biochemical effect of perchlorate on the body.

4.0 HISTORY OF THE TOXICOLOGICAL SCIENCE OF PERCHLORATE

4.1 A brief review of the science prior to 1990

The earliest reference to perchlorate, written in 1868, refers to perchlorate as a malaria treatment. While its efficacy was uncertain, toxicologists clearly understood the hazards of perchlorate when provided at sufficient dose and exposures. From the 1920s to 1950s, foundational research was conducted on thyroid physiology and perchlorate and other similar anions were found to cause goiter at high doses. In 1928, Chesney et al. (as cited in Boyages, 1993) demonstrated the development of goiter in cabbage-fed rabbits. Since then other vegetables such as broccoli and Brussels sprouts have been found to cause goiters when ingested in great enough amounts. This family of vegetables contains high levels of thiocyanate, which has the same effect as perchlorate (Boyages, 1993). Supplemental iodine prevents the effects of thiocyanate-induced goiter. Because of this research, the perchlorate mechanism of action is understood to be IUI.

In the early 1950s, Stanbury and Wyngaarden (1952) explored other ionic chemicals to determine whether any of them might interfere with iodide's entry into the thyroid gland to thus slow down hyperactive thyroids in patients with Graves' disease (hyperthyroidism). Doses ranged in the hundreds of milligrams (mg) to 2,000 mg per day. At concentrations of 15 ppb in drinking water, this would be equivalent of drinking over a half million eight-ounce glasses of water per day. Side effects from taking these doses of perchlorate included nausea, rash, gastrointestinal disturbances, fever, lymph node enlargement, and kidney dysfunction in 3-4% of patients taking 400-600 mg/d and in 16-18% of patients taking 1000-2000 mg/d. At concentrations of 15 ppb in drinking water, this 400 mg dose would be equivalent of drinking over 100,000 eight-ounce glasses of water per day. In the late 1950s to early 1960s, several cases of fatal aplastic anemia and nonfatal agranulocytosis were reported in patients with Graves Disease taking 400 to 1000 mg/d for 2 to 20 weeks. Neither of these diseases has been reported with perchlorate intake since then (Wolff, 1998).

4.2 A brief review of the the science from 1990 to 2005

Perchlorate does not cause cancer, build up in the body, affect the genes, or affect the immune system. It is also not a reproductive or developmental toxicant.

US EPA and others have determined that the most sensitive organ to the effects of perchlorate is the thyroid gland and the most sensitive population to protect is the pregnant woman and her fetus. Chemicals that inhibit the ability of the maternal thyroid gland to produce thyroid hormone could affect the fetus' developing nervous system. Numerous animal studies were conducted to examine other possible adverse effects either mediated by the thyroid or as an unknown effect in the 1990s. At least twelve animal toxicological studies were conducted between 1997 and 2002 using US EPA protocols including pharmacokinetic, subchronic, developmental, immunotoxicology, and a multigenerational reproductive study. These studies were conducted using a range of doses and were evaluated independently by EPA. These studies concluded that perchlorate does not cause cancer, bioaccumulate, affect the genes, or affect the immune system. It is also not a reproductive or developmental toxicant. Perchlorate is not metabolized in the body. The half life (the time for half of a chemical to leave the body) of perchlorate is short: approximately eight hours.

Three clinical studies were conducted (Greer et al., 2002; Lawrence et al., 2000, 2001). The clinical studies (human) measure the degree of IUI by perchlorate. One study was a dose-response assessment of IUI (Greer et al., 2002). Of the clinical studies conducted, Greer et al. reported the lowest dose at which there is no measurable IUI.

4.3 Relevant science studies published from 2005 to 2010

4.3.1 Perspective

Since the release of the NRC report in 2005, scientific studies published in the literature have largely been about exposures. While these studies are significant in addressing aspects of toxicological risk assessment such as exposure and possible doses, they are not designed to assess the fundamental understanding of perchlorate toxicology such the most sensitive population or its mechanism of action. In some studies, estimated doses were compared with a Reference Dose (RfD), which is an acceptable exposure level, not a "bright line" above which adverse effects occur. The perchlorate RfD has levels of "safety" added to it even though the starting point is a dose which does not have any effect. This makes the situation with perchlorate different from nearly every other environmental pollutant. Since 2006, other researchers have published reports of the development of physiologically based pharmacokinetic (PBPK) models using fundamental and foundational human and laboratory animal data. These models, when developed using key scientific studies, can be useful to examine the effects on populations such as children where there is a lack of experimental data.

A list of all abbreviations and acronyms used can be found on page *ii*.

4.3.2 Kirk et al. (2005)

This study came out after the release of the NRC report and was not included in its evaluation. This group measured perchlorate and iodide levels in cow and human breast milk

and compared these values to corresponding levels of perchlorate in drinking water in the area. Perchlorate was measurable in 81 of the 82 samples. The average perchlorate levels in cow milk and human milk were 2 and 10.5 ppb. The maximum levels in cow and human milk were 11 and 92 ppb. There was no correlation between levels of perchlorate in breast milk and perchlorate in drinking water, meaning even if the mother was drinking water with perchlorate, it did not define the amount of perchlorate found in breast milk. The authors speculated that there was a correlation between higher levels of perchlorate and lower levels of iodine in breast milk; however, they note that this relationship only existed for the breast milk samples with the highest perchlorate levels (6 subjects out of 82). The authors recognized that this relationship may be coincidental because of the small number of samples with perchlorate levels greater than10 ppb, stating that "If we take all the available data, there is no meaningful correlation between the perchlorate and iodide levels in breast milk."

4.3.3 Braverman et al. (2006)

In an effort to study the thyroidal effects of a prolonged (six months) exposure to low perchlorate levels in humans, Braverman et al. exposed 13 healthy volunteers to 0, 0.5, or 3.0 mg/d of potassium perchlorate and measured urinary perchlorate levels, radioactive iodine uptake, and serum triiodothyronine (T3), free thyroxine (T4), thyroid stimulating hormone (TSH), and thyroglobulin (Tg) concentrations. The 0.5 and 3.0 mg/d doses are equivalent to 250 and 1500 ppb in drinking water, assuming a daily water ingestion of 2 liters by a 70 kg adult. The authors concluded that perchlorate at doses of up to 3 mg/d for six months "…had no effect on thyroid function, including inhibition of thyroid iodide uptake as well as serum levels of thyroid hormones, TSH and Tg" and, "…there was no significant change in the thyroid RAIU [radioactive iodine uptake] during perchlorate administration." Simply put, perchlorate had no effect on one of the most sensitive measurements of its effect on the thyroid. This study was similar to the Greer Study, repeating the two lower doses used in Greer with exposures that were considerably longer. The major limitation is a small sample size; however, data from the 14-day Lawrence et al. (2000, 2001) studies and Greer et al. (2002) as well as occupational studies which are consistent with the results at similar time periods as reported by Braverman et al.

4.3.4 Blount et al. (2006)

Using the NHANES 2001-2002 data set and a cross-sectional study design, Blount et al. (2006) report measurements of urinary perchlorate, urinary iodide, serum TSH, and serum total T4 levels in men and women over the age of 12. The authors report that perchlorate levels were not associated with total T4 or TSH levels in men, but were a negative predictor of total T4 (lower total T4 levels were seen in individuals with higher perchlorate levels) and a positive predictor of TSH (higher TSH levels were seen in individuals with higher perchlorate levels) in women with urinary iodine less than 100 μg/L. They report that in women with urinary iodine greater than 100 μg/L, urinary perchlorate was a positive predictor of TSH, but not associated with T4.

This study has drawn attention as some have interpreted this study to demonstrate an "effect" of perchlorate, albeit at exposures below those that cause measurable IUI. Perchlorate exposure did not lower (nor was it associated with) thyroid hormone levels outside the normal range of values. This type of study design can not be used for establishing causal relationships, but only to provide information on associations between the variables studied (Wartenberg and Buckler, 2001). Other issues are important to examine. For example, a full

set of thyroid-specific hormone and iodine measurements are needed to better understand the relationships. The significance of evaluating women with urinary iodide less than 100 μg/L is based on the World Health Organization (WHO) statement which defines iodine deficiency for an entire population not an individual based on median spot urine iodine concentration of less than 100 μg/L (WHO, 2004). Using this to divide a population is not scientifically supported. More extensive criticisms regarding study design and statistical methodology have been published by ATSDR (2008) and Tarone et al. (2010). Other studies have provided other information that contrasts the study data, including Gibbs and Van Landingham (2008) and Lamm et al. (2007).

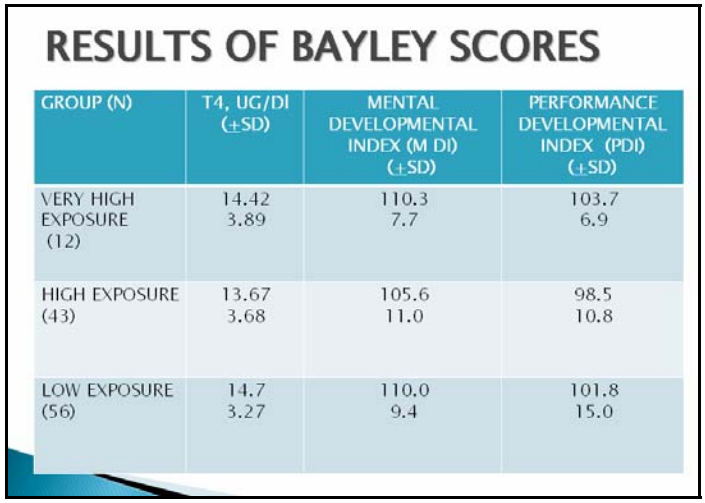
4.3.5 Amitai et al. (2007)

This study in Israel reports the highest documented drinking water levels in which mothers were exposed. Amitai and colleagues conducted an ecological epidemiological study designed to "…assess the effect of gestational perchlorate exposure through drinking water on neonatal thyroxine (T4)" by comparing T4 levels among newborns whose mothers lived in areas with drinking water perchlorate levels associated with "very high exposure" (10 to 100-fold greater compared with levels in the U.S.; ≥340 ppb), "high exposure" (42-94 ppb), or "low exposure" (<3 ppb). T4 levels were measured within 36 to 48 hours after birth but there was no comment on whether the infants were breast fed or formula fed during the postnatal period as this could affect T4 measures in infants. The authors report that there were no statistical differences between neonatal T4 levels among the groups. This means that despite what are the highest recorded and studied levels of perchlorate in drinking water, there was no effect in the thyroid hormone levels of newborns, which would have been exposed *in utero* making them the most sensitive population.

As presented in a satellite meeting of the Society of Toxicology (SOT) (Seattle 2008), Amitai et al. provided a follow-up to their previously reviewed 2007 publication (Figure 2). They located a subset of the original study population and evaluated the children using the Bayley Scales of Infant Development to assess the motor (fine and gross), language (receptive and expressive), and cognitive development of infants ages 0 to 3. They find that there is no difference between groups of children.

This study adds data regarding exposure and outcome on critical neurological endpoints. First, exposures were to pregnant women and their developing fetuses. Second, these are the highest concentrations of perchlorate ever reported in a study in which the public, including the most sensitive subpopulation was exposed. For example, 340 ppb, assuming 2 liters per day, is almost 3-fold greater than the NOEL dose from Greer et al. (2002) and would likely cause some small degree of IUI even without contribution from nitrates and thiocyanates in food. Third, the endpoints assessed are measures of neurological development—the endpoints of greatest concern when assessing thyroidal influence. The results presented thus far point to no adverse effect on neurological development from exposures to levels of perchlorate that exceed 340 ppb. Dr. Amitai is planning on publishing this and additional results during 2011 (Pleus, 2010. Personal Communication).

Figure 2. Follow up evaluation of the offspring from Amitai et al. 2008 where fetuses were exposed to perchlorate *in utero* and tested as children.



RESULTS OF BAYLEY SCORES

GROUP (N)	T4, UG/Dl (±SD)	MENTAL DEVELOPMENTAL INDEX (M DI) (±SD)	PERFORMANCE DEVELOPMENTAL INDEX (PDI) (±SD)
VERY HIGH EXPOSURE (12)	14.42 3.89	110.3 7.7	103.7 6.9
HIGH EXPOSURE (43)	13.67 3.68	105.6 11.0	98.5 10.8
LOW EXPOSURE (56)	14.7 3.27	110.0 9.4	101.8 15.0

4.3.6 Blount et al. (2007)

Blount and colleagues used the NHANES urinary perchlorate data to estimate the total daily dose for adults. The estimated 95th percentile dose (which also means that 95% of the population was estimated to have doses below this dose) in Blount et al., (2007) was 0.234 µg/kg-day with a confidence interval (a measure of error) of 0.202 – 0.268 µg/kg-d. They also reported that perchlorate was measurable in all of the samples they tested and the urinary levels were higher in children compared with adults. Importantly, the estimated doses reported here are lower than the current U.S. EPA RfD of 0.7 µg/kg-d.

4.3.7 Dohán et al. (2007)

This is an *in vitro* study, meaning it was not conducted in a whole animal, but uses cells. The main purpose of this work is to demonstrate that perchlorate crosses cell membranes via the NIS. The NIS has been known to be the molecule that transports and is blocked by iodide, perchlorate, thiocyanate, nitrate, and others. The NIS can be found in several cell types such as thyroid follicular cells and mammary gland cells. The experiment reported in this study is unique and creative and provides the first evidence that perchlorate crosses cell membranes using Mardin-Darby canine kidney (MDCK) cells that express the human NIS. This study also includes high acute doses of perchlorate in rats. The rats were given an intraperitoneal (in the abdominal cavity) injection of approximately 8 mg/kg-d in addition to a drinking water exposure of 13.6 mg/kg-d[3]. At concentrations of 15 ppb in drinking water, this injected dose would be equivalent of drinking 150,000 eight ounce glasses of water per day. The toxicological literature of perchlorate reports that doses equivalent to those administered in this study would effectively block, with complete inhibition, iodide transport by the NIS in these rats**.** The limitations of this study are 1) that given the doses, this study provides little relevant information about environmental doses of perchlorate, and 2) this work is performed in rats which have a quantitatively different thyroid physiology than humans.

[3] Assumes a 250 g rat with a daily water intake of 5.5 ml/100 g body weight.

4.3.8 Kirk et al. (2007)

To determine the variability in the excretion of perchlorate, thiocyanate, and iodide in human milk, Kirk and colleagues had lactating women collect six samples of milk on each of three days or as many samples as possible over three days. They report a significant variation over time for all the anions tested. The average iodide, perchlorate, and thiocyanate levels were 87.9 ppb, 5.8 ppb, and 35.6 ppb, respectively. The study was not designed to determine whether perchlorate or thiocyanate contributed to IUI in mammary tissue. This study was a biomonitoring study and did not measure or report any adverse effects or exposures. The limitation of the study is the study design. For example, the population was small and it is uncertain that the population was chosen randomly.

4.3.9 Pearce et al. (2007)

This study measured breast milk iodine and perchlorate concentrations as well as iodine, perchlorate, and cotinine (a surrogate for cigarette smoke which contains thiocyanate) in urine. The clinicians compared the levels of perchlorate in breast milk with 17 commercial infant formulae. Neither breast milk nor urinary perchlorate levels were significantly correlated with breast milk iodine concentrations, meaning that as levels of perchlorate in breast milk increased, iodide content in milk was not affected by perchlorate thus addressing a concern that perchlorate might affect iodine nutrition in the breast fed infant. Although perchlorate was detectable in infant formulae, the levels were lower than in breast milk. A significant number of women in this study had iodine levels that were insufficient to meet the infant's needs, but the authors did not suggest this was because of perchlorate exposure or that it represents a chronic iodine deficiency.

4.3.10 Steinmaus et al. (2007)

Steinmaus and his colleagues used the same dataset as Blount et al. (2006) to assess the correlation between smoking (which contains thiocyanate), urinary thiocyanate, urinary perchlorate, and thyroid hormone levels. As in Blount et al. (2006), they concluded that in women with urinary iodine less than 100 μg/L, perchlorate was associated with lower total T4 and greater TSH. This association was stronger when the woman was also a smoker or had high urinary thiocyanate levels. Because this study used the same dataset as Blount et al. (2006), the same limitations and methodological issues reported for Blount et al. apply to this study.

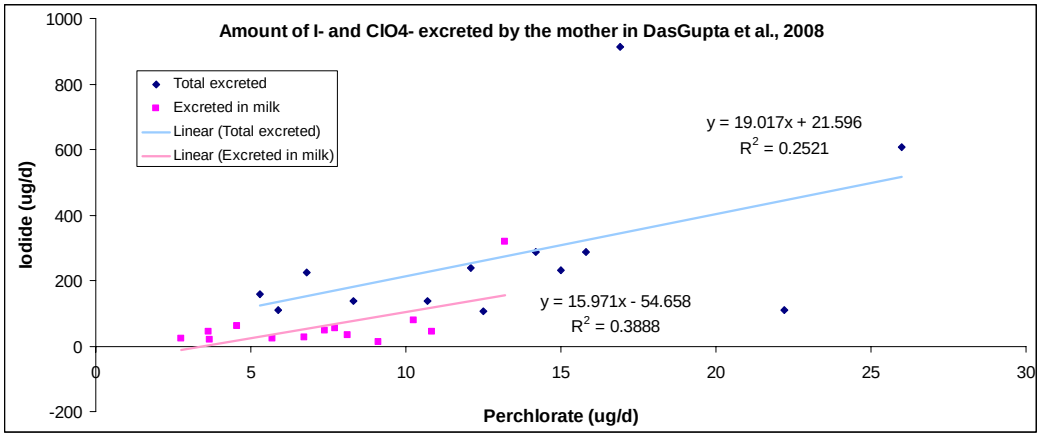
4.3.11 Dasgupta et al. (2008)

Using breast milk and urine samples from 13 lactating women and using US EPA default values for infant body weights and milk intakes, Dasgupta et al. (2008) mathematically modeled infant intakes and doses of iodide, perchlorate, and thiocyanate. They calculated the fraction of iodide, perchlorate, and thiocyanate in breast milk compared with the total excreted in both breast milk and urine. They used a ratio of these fractions in milk to determine the selectivity of either perchlorate or thiocyanate over iodide. They report "that 12 of 13 infants did not have an adequate intake of iodine…and 9 out of 13 infants were likely ingesting perchlorate at a level exceeding the reference dose…" They also concluded that the selectivity of perchlorate over iodide was 3.14 ± 1.2.

This manuscript estimates exposures to perchlorate. There are a number of unresolved issues related to the experimental design of this paper which include: a small study population, no

information on the selection process of the participants (i.e., not a random sample), and only three biological variables measured in the women as the rest of the variables, including the variables used to derive the conclusions, are calculated from these three or are default values for infant intake and weight. Despite the conclusions of Dasgupta et al., when the data are plotted, the results demonstrate that perchlorate and iodide are positively correlated (Figure 3). If perchlorate was inhibiting the transport of iodide into milk, the association would be negative.

Figure 3. Plotting of data reported by Dasgupta et al., 2008 to illustrate the association between concentrations of iodine and perchlorate in urine and milk in lactating women.



4.3.12 Leung et al. (2008)

Leung et al. evaluated associations between perchlorate and iodine in colostrum and perchlorate, iodine, cotinine, and creatinine in urine. Colostrum is a protein-rich form of breast milk that is released to a nursing infant in the first few days of life, prior to the production of breast milk. The median colostrum iodine level was 51.4 µmol/L. Perchlorate was detected in 43 or 46 colostrum samples with a median of 2.5 µmol/L. This paper provides information regarding exposure to perchlorate. They report no associations between any of the measures, meaning that perchlorate levels in colostrum did not have any influence on iodine (and other variables) in colostrum addressing the concern that perchlorate might adversely effect iodine nutrition of the breast fed infant.

4.3.13 Murray et al. (2008)

This study estimated doses of perchlorate through food based on the FDA Total Diet Study. Although the dose for the most sensitive population (pregnant women and their fetuses) was not specifically modeled, the estimated dose range for women of child bearing age was 0.09 to 0.11 µg/kg-d. The high end of the range, 0.11 µg/kg-d, is lower than the RfD of 0.7 µg/kg-d. Based on the data from Murray et al. (2008), an RSC of 70% could be allocated to water to be protective of the most sensitive population: pregnant women. If the EPA health reference level of 15 ppb had been calculated using a 70% RSC, the value would have been 17 ppb. For the type of study conducted there are no major limitations as the study is based on estimating reported information.

4.3.14 Van Wijk et al. (2008)

This study examined the effects of perinatal and chronic hypothyroidsm on neurological function in rodents using the grip test, balance beam test, open field test, and Morris water maze test. During the last two weeks of pregnancy, pregnant females and their resulting offspring were fed a diet poor in iodide with 750,000 ppb perchlorate in their drinking water. This value is almost 50,000-fold higher than a drinking water value of 15 ppb. The pups were fed until sacrifice to simulate chronic hypothyroidism or until weaning to simulate perinatal hypothyroidism. Chronic hypothyroidism had more pronounced effects on development and the authors concluded that "…early effects of hypothyroidism on functional alterations of the developing brain to be partly reversible, and to depend on developmental timing of the deficiency." The limitations of this study are 1) that given the doses used, this study provides little relevant information about environmental doses of perchlorate, and 2) this work is performed in rats which have quantitatively different thyroid physiology than humans.

4.3.15 Blount et al. (2009)

This study assesses total goitrogen exposure to the fetus, it provides more data on iodine levels in pregnant women and their fetus, and it reports no association between perchlorate on three infant body parameters. This addresses concerns that the effect of perchlorate on the developing fetal thyroid affects fetal growth of the head and the overall body.

This study evaluated the association between maternal (urine, serum) and fetal (cord blood) levels of perchlorate, thiocyanate, nitrate, and iodide compared to infant body weight, body length, and head circumference. All chemical agents were assumed to be derived from food or water. The study location was in New Jersey. The data were obtained from children born via C-section. They report no association between perchlorate, nitrate, and thiocyanate in cord blood and fetal birth weight, head circumference, and birth length. Blood levels of perchlorate, nitrate, and thiocyanate were higher in the mother than fetus, while iodine was higher in the fetus.

4.3.16 McLanahan et al. (2009)

In an attempt to evaluate the mode of action of perchlorate, McLanahan et al. coupled a biologically based dose response model of the hypothalamic-pituitary-thyroid axis with a PBPK model for perchlorate. The model was based on rats and evaluated changes in serum thyroid hormones with exposure to doses of perchlorate up to 10 mg/kg-d (equivalent to 350,000 ppb assuming a 70 kg adult drinking 2 L/d). With this high dose, the authors remark that the model outputs were inconsistent with observed data from experimental studies (Yu et al., 2002).

There are other PBPK models for perchlorate (Clewell et al., 2004, 2007; Merrill et al., 2005). The limitation of the McLanahan et al. model is that data are based exclusively on rats. As many have noted, rat and human thyroid endocrinology must be evaluated carefully as the differences between the two species are important. Rats have smaller stores of thyroid hormones and are more sensitive to IUI than humans (NRC, 2005). This model is not able to predict output that is consistent with observed experimental data. Thus, without the addition of a numerical adjustment variable (called the "proportional inhibition term") this model does not produce comparable results to experimental data. Other PBPK models integrate both

human and laboratory animal data, which assists in limiting the bias of using only rodent data.

4.3.17 Mendez et al. (2009)

This group used probabilistic modeling (a type of modeling that uses ranges of data rather than a discreet values such as the average) to estimate the total dose of perchlorate from food and drinking water using three drinking water scenarios based on Unregulated Contaminant Monitoring Rule 1 (UCMR1) data. This paper provides information regarding exposure to perchlorate. The highest estimated dose through water and food was 0.15 μg/kg-d at the 95th percentile, well below the RfD of 0.7 μg/kg-d. The 95th percentile means that 95% of the population modeled will have doses below this value; therefore, this is a conservative value to use as a comparison. When compared with the NHANES 2001-2002 estimates based on urinary output (used by Blount et al.), they report that intraday variability contributed to the overestimation of dose based on the NHANES data. Interestingly, the authors remark that the urinary excretion of perchlorate in NHANES 2003-2004 was significantly lower than in 2001-2002. Two data points do not represent a trend, but this lower urinary excretion may represent lower doses through food and water in subsequent NHANES studies.

4.3.18 Sanchez et al. (2009)

The stated objective of this study was "to evaluate potential perchlorate exposure from food crops produced in the lower Colorado River region (LCRR)." Using measurements of perchlorate concentrations in 26 food crops, including dairy milk, the authors estimated the cumulative food dose (based on USDA food intake survey) and water dose. The authors remark that in certain scenarios (where all food is from the LCRR), infants and children exceeded the RfD if they consumed drinking water with perchlorate concentrations greater than 6 ppb. This opinion assumes an 8 kg infant drinks 1 liter of water every day with perchlorate concentrations above 6 ppb.

The authors conclude: "Cumulative perchlorate exposure estimates based on this hypothetical analysis could approach or exceed the NAS reference dose (RfD) for some population groups as drinking water levels exceeded 6 ppb. However, few individuals are exposed to perchlorate in drinking water at levels above 4 ppb in the United States and few would be exposed to perchlorate levels exceeding the RfD, whether consuming food crops from within or outside the LCRR."

4.3.19 Schier et al. (2009)

This study measured the concentration of perchlorate in reconstituted powdered infant formulae and used this information to estimate a mean and upper-bound dose of perchlorate in infants solely fed formula. They also estimated the perchlorate concentration in water that would cause an infant in the 10th, 50th, or 90th percentile of body weight to receive a dose equal to the RfD. The authors concluded that some infants could be at risk for exceeding the RfD even with minimal amounts of perchlorate in water used for reconstitution, but "the clinical relevance of exceeding the perchlorate RfD in both an iodide-sufficient and iodide-deficient state are unclear."

This study provides information on potential perchlorate exposures given that all the assumptions made about exposure hold true. This study is focused on the exclusively

formula-fed infant. This is in contrast to the focus of the pregnant woman as the most sensitive subpopulation. This report does not demonstrate that this subpopulation is receiving doses of perchlorate at or above the RfD. Exceeding the RfD is not or meant to be a bright line threshold of effects. As reported by the NRC, the perchlorate RfD is based on a NOEL in addition to an UF adjustment. In other words, exposure above the RfD, if it occurs, must still be considered in the context of the NOEL at 245 ppb, which is itself a nonadverse effect, as well as other endpoints and doses

4.3.20 Brent (2010)

This paper reviews the literature on exposures to environmental contaminants and autoimmune thyroid disease. This paper notes that the "...most functional disorder of the thyroid is autoimmunity." Perchlorate is only discussed in that there were "no human studies establishing association" for perchlorate as "a trigger or accelerating autoimmune thyroid disease." This review provides an assessment that supports the results of animal studies directed by US EPA in the 1990s that perchlorate is not immunotoxic (does not affect the immune system).

4.3.21 Cao et al. (2010)

Cao and colleagues report the results from a subset of infants derived from another study (Study of Estrogen Activity and Development; SEAD). The purpose of the SEAD study was to look at endocrine disruption and infant development, but not at perchlorate. In a subset of 92 infants however, the authors analyzed perchlorate, iodide, nitrate, and thiocyanate by spot urine samples collected from diapers. Thus, this is a study of exposure. TSH and free T4 were obtained in both blood serum and spot urine samples. The standard approach to reliably measuring these variables is from a urine sample not from urine extracted from diapers, of which the authors state they are the first to do. Using a mixed linear statistical model, they analyzed associations between urinary levels of the goitrogens and urinary levels of TSH and free T4. The authors did not find any association between perchlorate, nitrate, or thiocyanate and TSH and free T4 in blood. This means that levels of perchlorate in blood were not related to any other variable measured in blood. Using TSH and free T4 values from diaper urine (not a standard medium for measurement) and evaluating perchlorate, thiocyanate, and nitrate individually, all had positive associations with TSH and free T4 (i.e., increasing concentration of perchlorate, nitrate, or thiocyanate was associated with increase in TSH and free T4). This means that as diaper urine levels of TSH increased, diaper urine levels of free T4 increased**.** This, however, is opposite of what is known about the normal function of the thyroid gland and the pituitary gland, as well as the known mechanism of action of perchlorate. When perchlorate, thiocyanate, and nitrate are evaluated together (rather than individually) in the model, perchlorate is not associated with TSH or free T4 at all. There were no associations between perchlorate and TSH or free T4 when stratified by gender. When the authors looked at children with iodine less than 100 μg/L (n = 48 children), "…those with higher perchlorate had statistically significantly higher TSH…, but not statistically significantly higher [free] T4…" The authors also remark, "In general, associations between TSH and thiocyanate were larger than those between TSH and perchlorate or nitrate."

4.3.22 Huber et al. (2010)

This paper uses UCMR1 data (which provides concentrations of perchlorate in drinking water sources; greater than or equal to 4 ppb) to divide NHANES participants into groups that estimate food and water exposure and food only exposure. The urine perchlorate is then used to estimate the background dose of perchlorate from food only and subtracts this dose from the RfD to determine an allowance for water. The age groups evaluated include males (all ages, ages 6-11, ages 12-19, ages ≥ 20) and females (all ages, ages 6-11, ages 12-19, ages ≥ 20, ages 15-44, and pregnant). The authors determined that all subgroups had estimated doses of perchlorate from food and water below the RfD. The group with the highest estimated doses was children age 6-11. The authors stated "We calculate that an average 66 kg pregnant woman consuming a 90th percentile food dose (0.198 μg/kg/day) could also drink the 90th percentile of community water for pregnant women (0.033 l/kg/day) containing 15 μg/l [ppb] perchlorate without exceeding the 0.7 μg/kg/day reference dose."

4.3.23 Pearce et al. (2010)

Pearce and her colleagues published the results from a large study of 22,000 pregnant women living in Cardiff, Wales and Turin, Italy. The authors measured iodine, thiocyanate, and perchlorate in spot urine samples and TSH, free T4, and thyroperoxidase (TPO) in blood in a subset of 2,640 participants. This study assesses exposures to a number of goitrogens that act upon the thyroid gland in the same manner. They further stratified the study population to look at women with urinary iodine less than 100 μg/L (999 women) to determine if perchlorate effects "are limited to individuals with low dietary iodine intake, as was seen in the NHANES data set" (cites Blount et al., 2006). The cause of low urinary iodine was not determined, but it was noted that only 5% of households use iodized salt in the United Kingdom and that Italian legislation requiring iodized salt (unless specifically requested) went into effect after a large number of these samples were collected. The study concluded that for pregnant women, the median urinary iodide was low in all groups compared with WHO guidelines. The authors say "There were no associations between urine perchlorate concentrations and serum TSH or FT4 in the individual euthyroid or hypothyroid/ hypothyroxinemic cohorts." This study addresses the concerns about whether environmental levels of perchlorate might affect the thyroid or pituitary gland function of iodine deficient individuals. These data demonstrate that perchlorate does not and provide results that are different than those reported by Blount et al., (2006). This could be due to the experimental design of the Pearce et al. study which was conducted in a larger population of the most sensitive subpopulation.

4.3.24 Tarone et al. (2010)

"…efforts to place a stringent allowable drinking water limit on perchlorate are not supported by the weight of the scientific evidence." Tarone et al. (2006)

This article reviewed much of the published perchlorate epidemiological literature. It covered three types of epidemiological studies: cross-sectional studies (e.g., NHANES data), ecological studies, and occupational studies. Based on their review of this literature, the paper concludes that "The absence of evidence from epidemiological studies using various study designs that environmental perchlorate exposure adversely affects thyroid function and the documented low levels of environmental perchlorate exposure in the United States lead to the conclusion that efforts to place a stringent allowable drinking water limit on perchlorate are not

supported by the weight of the scientific evidence." They concluded that perchlorate accounts for less than 1% of TGL based on five studies where there was urinary, serum, or amniotic fluid measures of nitrate, thiocyanate, and perchlorate.

Tarone et al. reported that occupational studies and other epidemiological studies were conducted acceptably to provide scientific information. They report, for example, that workers exposed to much higher concentrations of perchlorate compared with the general population, demonstrated no evidence of adverse effects of perchlorate and pregnant women and their newborns demonstrate no evidence of impaired thyroid function. Finally, the authors conducted a multiple regression analysis of the same data used by Blount et al. (2006) and Steinmaus et al. (2007). They express concerns regarding the information that can be derived from the type of data Blount et al. and Steinmaus et al. used and report that these papers are unable to determine a causal relationship.

4.3.25 Voogt and Jackson (2010)

This paper measures perchlorate, iodide, and nitrate uptake in lettuce grown in a controlled laboratory environment. They found the amount of perchlorate or iodine in the soil was directly proportional to the concentration in the plant—one is not taken up preferentially over the other. They further evaluated the amounts of perchlorate, nitrate, and iodine in lettuce, based on perchlorate equivalence (from Tonacchera et al., 2004) to evaluate total goitrogen load (TGL). They found that perchlorate has a "relatively minor impact" to TGL in lettuce, which "is almost completely dominated by NO_3^- [nitrate]." This is true even in plants (grown in water only) exposed to perchlorate water concentrations as high as 180 ppb. The contribution to TGL in plants that contain thiocyanate is less. "This is largely mirrored in the NHANES 2001-2002 urinary data for which the ClO_4^- accounts for <1% of the total TGL for the total population."

The authors state "…the impact of the consumption of lettuce containing ClO_4^- may be mitigated if the lettuce is grown using fertilizer with an appropriate amount of I [iodine] to maintain the existing ratio of serum I [iodine] to total goitrogen load (TGL)."

4.3.26 Steinmaus et al., (2010)

Similar to Blount et al. (2006), Steinmaus et al. (2007), and Cao et al. (2010), this is a study that evaluates data collected for purposes other than what is being assessed in the document. Data are from two California Department of Public Health sources, the New Born Screening (NBS) program for primary congenital hypothyroidism and Drinking Water Program (for the years 1997–1998). The stated objective is "to evaluate associations between maternal drinking water perchlorate exposure during pregnancy and newborn thyroid hormone levels." Using data from the NBS program, levels of neonatal TSH—a hormone secreted from the pituitary gland to stimulate thyroid hormone (e.g., T4 or T3) secretion from the thyroid gland—was measured in 497,458 infants born in 1998. Infants were classified as "exposed" if their mother's residence was in a community with "estimated average perchlorate" concentrations of 6 ppb or higher. Infants were classified as "unexposed" if "estimated average perchlorate" concentrations were less than 6 ppb. This level was chosen because it is the current California PHG and was also used in a previous study (Buffler et al., 2006). The paper reports odds ratios, which are the odds of an event occurring in one group of infants compared to another. In this case, "the event" is TSH at greater than a certain level

(e.g., 25 μU/mL, the level used for primary congenital hypothyroidism screening). They report that "In TSH samples collected within 24 hours of birth, the odds ratio for a TSH greater than 25 μU/mL in exposed communities was 1.53 ($P < 0.0001$). After 24 hours, the odds ratio for a TSH more than the 95th percentile [8 μU/mL] was 1.27 ($P < 0.0001$)."

While this study adds to the database of literature, there are a number of scientific questions about the interpretation of these results. Among others, the recognized TSH surge makes measurement of this variable during the first 24 to 48 hours problematic. To understand thyroid status, TSH measurement should be assessed along with other parameters including gestational age, body weight, T3, T4, free T4, etc. Although the geometric means of TSH levels (4.03 for unexposed and 4.35 μU/mL for exposed) are *statistically* significant, the TSH levels are unlikely to have clinical significance; there are no individual measures of exposure; the study does not account for other thyroid-active compounds the mother was exposed to; and finally, the reported effect is based on a low concentration of perchlorate in municipal drinking water and does not account for food, the major source of perchlorate in the average diet. In summary, follow up studies will be required to assess the scientific reliability of its results.

4.4 Reviews of the Science of Perchlorate Post NRC Report

The toxicology of perchlorate has been reviewed by a number of authoritative organizations. Since the NRC report published in 2005, the following have provided assessments of the literature. They include:

- Joint FAO/WHO Expert Committee on Food Additives (JECFA) of the World Health Organization in 2010;
- The Agency for Toxic Substances and Disease Registry in 2008;
- The US EPA Office of the Inspector General in 2010.

4.4.1 Joint FAO/WHO Expert Committee on Food Additives

In a recent meeting in 2010, JECFA summarized their assessment of perchlorate:

> The Committee established a Provisional Maximum Tolerable Daily Intake (PMTDI) of 0.01 mg/kg bw for perchlorate. The estimated dietary exposures of 0.7 μg/kg-d (highest) and 0.1 μg/kg-d (mean), including both food and drinking-water, are well below the PMTDI. The Committee considered that these estimated dietary exposures were not of health concern.

This value of 0.01 mg/kg-d is slightly higher than the NOEL identified by the NRC. This means that JECFA has determined that a daily intake that exceeds the equivalent of a water concentration of 245 ppb (assuming a 70 kg adult drinking 2 liters per day) does not pose a health concern.

4.4.2 Agency for Toxic Substances and Disease Registry, US Department of Health and Human Services

ATSDR says in relation to its Oral Minimum Risk Level:

> ATSDR adopts the National Academy of Sciences (NAS 2005, Health Implications of Perchlorate Ingestion) recommended chronic reference dose (RfD) of 0.0007 mg/kg/day for the chronic oral MRL for the perchlorate anion (rather than for individual salts).

Further, the report remarks

> ATSDR's decision was made after a careful evaluation of the NAS report and of studies that have been published after the NAS (2005) report. The results from newer studies do not change the bottom-line recommendation.

4.4.3 US EPA's Office of the Inspector General

After a number of studies pointed out that chemicals other than perchlorate cause IUI, the US EPA OIG report discusses these along with perchlorate. As noted above, thiocyanate, nitrate, and iodine are all part of the daily human diet and can all inhibit IUI. OIG reported that this situation fits the criteria for a cumulative risk assessment, in other words, accounts for several chemicals that may have an additive effect because they all cause the same effect. OIG reports that thiocyanate, nitrate, and iodine are found naturally in food and water sources. They assume that the public are not exposed to any one of these chemicals alone, but in combination. The focus on one chemical does not provide a scientific assessment of possible human health risk. The two major conclusions in OIG's report are:

> 1. "EPA's perchlorate RfD is conservative and protects human health"
>
> 2. "…limiting perchlorate exposure does not effectively address this public health issue… lowering the perchlorate drinking water limit from 24.5 ppb to 6 ppb does not provide a meaningful opportunity to lower the public's risk."

5.0 ENDOCRINE DISRUPTION AND PERCHLORATE

On November 17, 2010, the US EPA released a list of 134 chemicals, including perchlorate, which would be considered for screening under the Endocrine Disruptor Screening Program (EDSP). The EDSP was established as a part of the Federal Food, Drug, and Cosmetic Act (FFDCA), which directed EPA

> to develop a screening program…to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect as the Administrator may designate". Tier 1 Screening tests a chemical's ability to behave similarly to estrogens and androgens found naturally in the body (US EPA, 2010).

This program was subsequently expanded to evaluate effects on the androgen and thyroid systems. Although perchlorate can affect the thyroid with sufficient dose and duration of exposure, its action is fundamentally different than chemicals EPA has been considering until the

The chemical structure, function, and action of perchlorate do not mimic any of the thyroid hormones or the pituitary hormones, such as TSH. IUI is not an endocrine mediated effect.

release of this program. US EPA has historically evaluated chemicals that mimic endogenous sex hormones (produced in the body). IUI is not an endocrine mediated effect. The chemical structure, function, and action of perchlorate do not mimic any of the thyroid hormones or the pituitary hormones, such as TSH. Thus, while perchlorate is reported in the EDSP list, perchlorate does not fit the type of chemicals US EPA has historically examined.

In releasing this list of chemicals, the US EPA cautions that

> "The public should not presume the listing of a chemical or substance indicates it interferes with the endocrine systems of humans or other species simply because it has been listed for screening under the EDSP. EPA believes that these chemicals or substances should be candidates, at least for screening purposes, under EDSP testing based only on their pesticide registration status and/or because such substances may occur in sources of drinking water to which a substantial population may be exposed." (US EPA, 2010)

6.0 CONCLUSION

New studies published since 2005 remain consistent with the NRC's assessment and no change in the foundational science has occurred.

The NRC assessment remains the most comprehensive analysis of perchlorate health effects five years after its publication. This is certainly due in part to the Committee's rigorous review of the literature. New studies published since 2005 remain consistent with the NRC's assessment and no change in the foundational science has occurred. Foundational science refers to the scientific understanding of perchlorate based on its biochemistry, pharmacology, and toxicology. Other authoritative bodies have examined the literature more recently with similar findings (ATSDR, 2008; US EPA OIG, 2010).

The types of studies that have been published since 2005 fall into three general categories: 1) Exposure Characterization (includes biomonitoring, breast milk, and other food measurements); 2) literature reviews and modeling (which is based on published studies); and 3) scientific studies (e.g., clinical, animal studies, etc.).

The data presented by nearly all of these studies are in agreement with the foundational science reported by scientists and summarized in the NRC report. The clinical studies based their experimental designs on the foundational science of perchlorate. According to the NRC, the most useful study for developing an RfD was by Greer et al. (2002). Using four doses of perchlorate, Greer and his colleagues reported a dose response relationship for perchlorate and IUI. The highest dose (0.5 mg/kg-d, equivalent to 17,500 ppb assuming a 70 kg adult drinking 2 L/d), caused approximately 70% IUI (within 24 hrs), however, after 14 days of daily exposure did not cause thyroid hormone changes.[4] The IUI in the lowest dose of 0.007 mg/kg-day (245 ppb) was no different from baseline (no perchlorate) IUI. The NRC assumed that if the dose increases and is consistently ingested on daily basis for weeks or months of exposure and the body does not compensate, hypothyroidism could occur.

[4] Greer et al. stated there was "a significant relationship between TSH and blood-draw event only in the morning draws of the 0.5-mg/kg-day dose group ($p = 0.03$)."

Scientifically, the most crucial information is whether environmental doses are sufficient to cause significant IUI. None of the studies report doses sufficient to do so on a daily basis let alone the consistent basis over weeks or months that would be required to cause the thyroid gland to produce less thyroid hormones.

Further, NRC noted "Inhibition of iodide uptake by the thyroid clearly is not an adverse effect; however, if it does not occur, there is no progression to adverse health effects."

The majority of the studies since the NRC report are exposure characterization studies (See Table 1). These studies involve measuring perchlorate in body fluids such as milk or urine, estimating doses from water or food, or conducting a mathematic exploration of possible doses to a subgroup of the population. Scientifically, the most crucial information is whether environmental doses are sufficient to cause significant IUI. None of the studies report doses sufficient to do so on a daily basis let alone the consistent basis over weeks or months that would be required to cause the thyroid gland to produce less thyroid hormones. For example, studies in breast milk, formulae, or other food report consistent ability to measure environmental levels of perchlorate, however reports of adverse outcomes are not reported. This is consistent with what would be expected given the understanding of the foundational science of perchlorate.

Other studies add additional data to the database, but are consistent with what was already known or assumed. For example, Braverman and his colleagues demonstrated that doses of 0.5 and 3.0 mg/d for 6 months were insufficient to cause significant IUI or change any thyroid hormones. This study would be more useful if the dose groups had been larger. Nonetheless, the data are consistent with the short term clinical studies by Greer et al. 2002 and Lawrence et al., 2000, 2001.

Since the 2005 NRC report, many studies have been published representing effort and time by many researchers. Table 1 lists the studies that add to the already substantial literature database and adds scientific weight to the conclusions of the NRC assessment.

Table 1. List of Scientific Studies Reviewed Since 2005. Type of Study, Measurements Reported, and Whether the Data Reported Are Consistent with Foundational Science Summarized in the NRC (2005) Report.

Study	Type of Study	Measurements Reported	Consistent with Foundational Science Summarized in NRC assessment?
Kirk et al. (2005)	Exposure Characterization	ClO_4^- and I^- in cow and human breast milk and ClO_4^- in drinking water in the area	Yes, ClO_4^- was known to secrete into breast milk
Braverman et al. (2006)	Clinical	Thyroid measures after 6 months exposure at doses of 0, 0.5, or 3.0 mg/d of $KClO_4$	Yes, similar doses of ClO_4^- given for 14 days have equivalent effects
Blount et al. (2006)	Epidemiological Cross-Sectional	Statistical associations using NHANES 2001-2002	No, authors report that higher TSH and lower T4 are correlated with ClO_4^- doses below the NOEL for IUI and that thyroidal measures are different for males are females
Amitai et al. (2007)	Ecological epidemiological	Exposure to pregnant women and their fetuses up to concentrations <3, 42-94, and ≥340 ppb and outcomes of neurodevelopment	Yes, at doses that do not cause significant IUI, no adverse effects are expected
Blount et al. (2007)	Exposure Characterization	NHANES 2001-2002 data used to estimate the total daily dose for adults using urinary ClO_4^-	Yes, environmental doses are below those that cause any significant IUI
Dohán et al. (2007)	*In vitro* study	ClO_4^- crosses cell membranes in this cell type	Yes, confirms some earlier reports that ClO_4^- might briefly enter the thyroid follicular cell, although these are cells *in vitro*
Kirk et al. (2007)	Exposure Characterization	ClO_4^-, SCN^-, and I^- in human breast milk	Yes, ClO_4^- and other goitrogens were known to secrete into breast milk
Pearce et al. (2007)	Exposure Characterization	I^-, ClO_4^-, and cotinine (a surrogate for cigarette smoke which contains SCN^-; urine only) concentrations breast milk, urine, and infant formula	Yes, ClO_4^- was known to secrete into breast milk, therefore it is not unexpected in milk-based products
Steinmaus et al. (2007)	Epidemiological cross sectional	Using the same dataset as Blount et al. (2006), including activity related to smoking	No, see Blount et al. (2006), same data set used
Dasgupta et al. (2008)	Exposure Characterization	ClO_4^- in breast milk and urine samples from lactating women	Yes, ClO_4^- was known to secrete into breast milk
Leung et al. (2008)	Exposure Characterization	ClO_4^- and I^- in colostrum and ClO_4^-, I^-, cotinine, and creatinine in urine.	Yes, ClO_4^- was known to secrete into breast milk
Murray et al. (2008)	Exposure Characterization	Estimated doses of ClO_4^- through food based on the FDA Total Diet Study	Yes, doses of ClO_4^- from food are below levels that cause significant IUI

Study	Type of Study	Measurements Reported	Consistent with Foundational Science Summarized in NRC assessment?
van Wijk et al. (2008)	Rodent study	Neurological function in rodents using the grip test, balance beam test, open field test, and Morris water maze test with 750 ppm ClO_4^-	Yes, high doses (not environmental concentrations) are expected to affect neurological development
Blount et al. (2009)	Exposure Characterization	ClO_4^-, SCN^-, NO_3^-, and I^- were in maternal (urine, serum) and fetal (cord blood) compared to infant body weight, body length, and head circumference	Yes, at doses that do not cause significant IUI, no adverse effects are expected
McLanahan et al. (2009)	PBPK Model	Dose response model of the hypothalamic-pituitary-thyroid axis and PBPK model for ClO_4^- based on rodent derived experimental data	Yes, experimental data from rodents show qualitative similarities and quantitative differences to human thyroid physiology
Mendez et al. (2009)	Exposure Characterization	Estimate of ClO_4^- in food and drinking water using three drinking water scenarios based on EPA data derived from Unregulated Contaminant Monitoring Rule 1	Yes, at doses that do not cause significant IUI, no adverse effects are expected
Sanchez et al. (2009)	Exposure Characterization	ClO_4^- concentrations in 26 food crops, dairy milk and estimate of cumulative food dose (based on USDA food intake survey) and water dose	Yes, environmental doses of ClO_4^- are below levels that would cause significant IUI
Schier et al. (2009)	Exposure Characterization	ClO_4^- in reconstituted powdered infant formula	Yes, it is not unexpected to be found in milk-based products and doses of ClO_4^- are below levels that would cause significant IUI
Brent (2010)	Literature Review	Autoimmune thyroid disease	Yes, animal testing demonstrated that ClO_4^- does not effect the immune system
Cao et al. (2010)	Exposure Characterization	ClO_4^-, SCN^-, NO_3^-, and I^- in spot urine samples collected from diapers and TSH and free T4	Yes, doses of ClO_4^- are below levels that would cause significant IUI
Huber et al. (2010)	Exposure Characterization	Estimate of food and water exposure or food only exposure	Yes, doses of ClO_4^- are below levels that would cause significant IUI
Pearce et al. (2010)	Exposure Characterization	I^-, SCN^-, and ClO_4^- in spot urine samples and TSH, free T4, and TPO	Yes, doses of ClO_4^- are below levels that would cause significant IUI
Tarone et al. (2010)	Literature Review	ClO_4^- epidemiological literature	Yes, a review of studies reviewed largely by NRC, but includes Blount et al. (2006) and Steinmaus et al. (2007)

Study	Type of Study	Measurements Reported	Consistent with Foundational Science Summarized in NRC assessment?
Voogt and Jackson (2010)	Exposure Characterization	ClO_4^-, I^-, and NO_3^- uptake in lettuce grown in a controlled laboratory environment	Yes, doses of ClO_4^- are below levels that would cause significant IUI
Steinmaus et al. (2010)	Cross sectional Epidemiological	Odds ratio greater than 1 for exposed infants (≥6ppb in drinking water) for TSH values	No, authors report increased TSH odds ratio with ClO_4^- doses below the NOEL for IUI

ClO_4^-: perchlorate
I^-: iodide
NO_3^-: nitrate
SCN^-: thiocyanate
IUI: Iodide uptake inhibition, the mechanism of action for chemicals listed above

Epidemiological studies that are based on datasets (e.g., NHANES) obtained for reasons other than to reliably evaluate thyroid health status, appear the most controversial (Blount et al., 2006; Steinmaus et al., 2007; Cao et al., 2010; Steinmaus et al., 2010). However, as discussed by a number of scientists, while the results are informative and we believe more work needs to be done, they are not consistent with the foundational science. Methodological issues have been reported as well as conflicting results based on the reanalyses of these data (Tarone et al., 2010). Other studies that evaluate perchlorate in blood or urine do not support these same associations (Pearce et al., 2010; Cao et al., 2010). ATSDR (2008) has reviewed these studies as well and reported they do not change the bottom-line recommendation which is to adopt the RfD based on the NOEL reported by Greer et al. (2002).

In summary, we have examined a number of relevant studies published since 2005. By in large, these studies focus on exposure characterization and, often indirectly, reinforce that environmental levels of perchlorate are insufficient to cause significant levels of IUI and, as reported based on scientific analyses by the NRC, ATSDR, and others, no adverse effects are expected. These results mirror the basic principles of toxicology: that mere presence of a chemical does not equal effect. Rather, a chemical must reach target tissues in the body in sufficient concentrations for sufficient time to elicit an adverse effect. With perchlorate, it has been well understood for over 60 years that if environmental levels of perchlorate are equal to or below a well defined dose threshold, the NOEL--which for perchlorate is equivalent to 245 ppb—no adverse effects are expected.

In summary, we have examined a number of relevant studies published since 2005. By in large, these studies focus on exposure characterization and, often indirectly, reinforce that environmental levels of perchlorate are insufficient to cause significant levels of IUI and, as reported based on scientific analyses by the NRC, ATSDR, and others, no adverse effects are expected.

7.0 REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR), 2008. Toxicological profile for perchlorates, Centers for Disease Control, Atlanta, GA.

Amitai Y, Winston G, Sack J, Wasser J, Lewis M, Blount BC, Valentin-Blasini L, Fisher N, Israeli A, Leventhal A, 2007. Gestational exposure to high perchlorate concentrations in drinking water and neonatal thyroxine levels. *Thyroid*, v. 17: 843-850.

Blount BC, Pirkle JL, Osterloh JD, Valentin-Blasini L, Caldwell KL, 2006. Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. *Environ Health Perspect*, v. 114: 1865-1871.

Blount BC, Valentin–Blasini L, Osterloh JD, Mauldin JP, Pirkle JL, 2007. Perchlorate exposure of the US population, 2001-2002. *J Expo Sci Environ Epidemiol* 17: 400-407.

Blount BC, Rich DQ, Valentin-Blasini L, Lashley S, Ananth CV, Murphy E, Smulian JC, Spain BJ, Barr DB, Ledoux T, Hore P, Robson M, 2009. Perinatal exposure to perchlorate, thiocyanate, and nitrate in New Jersey mothers and newborns. *Environ Sci Technol*, v. 43, no. 19: 7543-7549.

Boyages SC, 1993. Clinical review 49: Iodine deficiency disorders, *J Clin Endocrinol Metab*, v. 77, no. 3: 587-591.

Braverman LE, Pearce EN, He X, Pino S, Seeley M, Beck B, Magnani B, Blount BC, Firek A, 2006. Effects of six months of daily low-dose perchlorate exposure on thyroid function in healthy volunteers. *J Clin Endocrinol Metab*, v. 91, no. 7: 2721-2724.

Brent GA, 2010. The impact of perchlorate exposure in early pregnancy: is it safe to drink the water? *J Clin Endocrinol Metab*, v. 95: 3154-3157.

Caldwell KL, Jones R, Hollowell JG, 2005. Urinary iodine concentration: United States National Health And Nutrition Examination Survey 2001-2002. *Thyroid,* v. 15, no. 7: 692-9.

Dasgupta PK, Kirk AB, Dyke JV, Ohira S, 2008. Intake of iodine and perchlorate and excretion in human milk. *Environ Sci Technol*, v. 42, no. 21: 8115-8121.

Dohán O, Portulano C, Basquin C, Reyna-Neyra A, Amzel LM, Carrasco N, 2007. The Na+/I symporter (NIS) mediates electroneutral active transport of the environmental pollutant perchlorate. *PNAS*, v. 104, no.51: 20250-20255.

Gibbs JP, Van Landingham C, 2008. Urinary perchlorate excretion does not predict thyroid function among pregnant women. *Thyroid*, v. 18: 807-808.

Greer MA, Goodman G, Pleus RC, Greer SE, 2002. Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans. *Environ Health Perspect*, v. 110, no. 9: 927-937. Erratum in: *Environ Health Perspect*, 2005, v. 113, no. 11: A732.

Huber DR, Blount BC, Mage DT, Letkiewica FJ, Kumar A, Allen RH, 2010. Estimating perchlorate exposure from food and tap water based on US biomonitoring and occurrence data, *J Expo Sci Environ Epidemiol*, [E-pub ahead of print].

Kirk AB, Martinelango PK, Tian K, Dutta A, Smith EE, Dasgupta PK, 2005. Perchlorate and iodide in dairy and breast milk. *Environ Sci Technol*, v. 39, no. 7: 2011-2017.

Kirk AB, Dyke JV, Martin CF, Dasgupta PK, 2007. Temporal patterns in perchlorate, thiocyanate, and iodide excretion in human milk. *Environ Health Perspect*, v. 115: 182-186.

Klaassen CD, 2001. Casarett & Doull's Toxicology: The basic science of poisons. 6th Edition. McGraw-Hill Publishing, New York, NY.

Lamm SH, Hollowell JG, Engel A, Chen R, 2007. Perchlorate, thiocyanate, and low iodine assoicaiton not seen with low creatinine-adjusted urine iodine among women of childbearing age. *Thyroid*, v. 17 Suppl: S51.

Lawrence JE, Lamm SH, Pino S, Richman K, Braverman LE, 2000. The effect of short-term low-dose perchlorate on various aspects of thyroid function. *Thyroid*, 10: 659–663.

Lawrence J, Lamm S, Braverman LE, 2001. Low dose perchlorate (3 mg daily) and thyroid function. *Thyroid*, v. 11: 295.

Leung AM, Pearce EN, Hamilton T, He, Xuemei, Pino, S, Merewood A, Braverman LE, 2009. Colostrum iodine and perchlorate concentrations in Boston-area women: a cross-sectional study, *Clin Endocrin*, v. 70: 326-330.

McLanahan ED, Andersen ME, Campbell. Jr. JL, Fisher JW, 2009. Competitive inhibition of thyroidal uptake of dietary iodide by perchlorate does not describe perturbations in rat serum Total T4 and TSH, *Environ Health Perspect*, v. 117: 731-738.

Mendez W, Dederick E, Cohen J, 2009. Drinking water contribution to aggregate perchlorate intake of reproductive-age women in the United States estimated by dietary intake simulation and analysis of urinary excretion data. *J Expo Sci Environ Epidemiol*, v. 20, no. 3: 288-97.

Murray CW, Egan SK, Kim H, Beru N, Bolger PM, 2008. US Food and Drug Administration's Total Diet Study: Dietary intake of perchlorate and iodine. *J Expo Sci Environ Epidemiol*, v. 18, no. 6: 571-580.

National Research Council of the National Academies of Science (NRC), 2005. Health implications of perchlorate ingestion. Committee to Assess the Health Implications of Perchlorate Ingestion, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies, The National Academies Press, Washington, DC.

Pearce EN, Leung AM, Blount BC, Bazrafshan HR, He X, Pino S, Valentin-Blasini L, Braverman LE, 2007. Breast milk iodine and perchlorate concentrations in lactating Boston-area women. *J Clin Endocr Metab*, v. 92, no. 5: 1673-1677.

Pearce EN, Lazarus JH, Smyth PP, He X, Dall'amico D, Parkes AB, Burns R, Smith DF, Maina A, Bestwick JP, Jooman M, Leung AM, Braverman LE, 2010. Perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant women, *J Clin Endocrinol Metab*, v. 95, no. 7: 3207-3215.

Sanchez CA, Barraj LM, Blount BC, Scrafford CG, Valentin-Blasi L, Smith KM, Krieger, RI, 2008. Perchlorate exposure from food crops produced in the lower Colorado River region, *J Expo Sci Environ Epidemiol*, v. 19, no. 4: 359-368.

Schier JG, Wolkin AF, Valentin-Blasini L, Belson MG, Kieszak SM, Rubin CS, Blount BC, 2009. Perchlorate exposure from infant formula and comparisons with the perchlorate reference dose. *J Expo Sci Environ Epidemiol*, v. 20, no. 3: 281-287.

Stanbury JB, Wyngaarden JB, 1952. Effect of perchlorate on the human thyroid gland, *Metabolism*, v. 1: 533-539.

Steinmaus C, Miller MD, Howd R, 2007. Impact of smoking and thiocyanate on perchlorate and thyroid hormone associations in the 2001–2002 national health and nutrition examination survey. *Environ Health Perspect*, v. 115, no. 9: 1333-1338.

Steinmaus C, Miller MD, Smith AH, 2010. Perchlorate in drinking water during pregnancy and neonatal thyroid hormone levels in California, *J Occup Environ Med*, v. 52, no. 12: 1217-1224.

Tarone RE, Lipworth L., McLaughlin JK, 2010. The epidemiology of environmental perchlorate exposure and thyroid function: a comprehensive review, *J Occup Environ Med*, v. 52, no. 6: 653-660.

United Status Environmental Protection Agency (US EPA), 2010. Endocrine Disruption Screening Program (EDSC) Second List of Chemicals for Tier 1 Screening. Accessed at http://www.epa.gov/endo/pubs/prioritysetting/draftlist2.htm.

van Wijk N, Rijntjes E, van de Heijning BJ, 2008. Perinatal and chronic hypothyroidism impair behavioural development in male and female rats. *Exp Physiol*, v. 93, no. 11: 1199-209.

Voogt W, Jackson WA, 2010. Perchlorate, nitrate, and iodine uptake and distribution in lettuce (*Lactuca sativa* L.) and potential impact on background levels in humans, *J Agric Food Chem*, [Epub ahead of print].

Wartenberg D, Buckler G, 2001. Invited commentary: Assessing latex sensitization using data from NHANES III. *Am J Epidem*, v. 153, no. 6: 523-526.

WHO, 2004. Vitamin and Mineral Requirements in Human Nutrition, 2nd ed. Geneva, World Health Organization and Food and Agriculture Organization (FAO) of the United Nations.

Wilson M, 2008. Scientific analysis of perchlorate, U.S. Environmental Protection Agency, Office of Inspector General (OIG), Washington, DC.

Wolff J, 1998. Perchorate and the thyroid gland, *Pharmacological Reviews*, v. 50, no. 1: 89-105.

Yu KO, Narayanan L, Mattie DR, Godfrey RJ, Todd PN, Sterner TR, Mahle DA, Lumpkin MH, Fisher JW, 2002. The pharmacokinetics of perchlorate and its effect on the hypothalamus-pituitary-thyroid axis in the male rat, *Toxicol Appl Pharmacol*, v. 182, no. 2: 148-159.