

August 7, 2012

Stephen M. Roberts, Ph.D.  
Chair, Science Advisory Board Perchlorate Advisory Panel  
c/o Mr. Tom Carpenter, US EPA Designated Federal Officer  
US Environmental Protection Agency  
Washington, D.C.  
Delivered via email

**RE: COMMENTS ON THE SCIENCE OF PERCHLORATE AT THE SAB MEETING**

Dear Dr. Roberts:

I appreciate the opportunity to provide more information to US EPA's Science Advisory Board (SAB) regarding the charge questions given by US EPA.

Attached please find two documents as follows:

- A summary of key scientific information in response to statements made at the [SAB meeting](#).
- An examination of several key issues considered by the SAB with regard to the dose response of perchlorate.

Each document includes hyperlinks to specific authoritative documents and references to assist the SAB in its independent assessment.

I would also ask that you and your committee consider a larger policy-related issue about which the committee might not be aware: the US EPA's charge questions could implicate the SAB in changing key components of the toxicological risk assessment process.

The SAB should be aware that the process of risk assessment within the federal agencies has at least a 30-year history (the NRC "Red Book" was published in 1983) and has undergone much review. While US EPA is one of the leading federal agencies in the evolution of toxicological risk assessments, the appropriate venue for making significant changes to the risk assessment process should include toxicologists and risk assessors with relevant expertise and experience.

Among the process alterations embedded within the charge questions are:

- Treating a non-adverse point of departure as an adverse effect
- Evaluation of only a small portion of the overall scientific database when a weight-of-evidence approach would encompass data collected since the 1960s and earlier.



Again, I appreciate the opportunity to submit information to you, your committee, and the US EPA on this matter. I would be happy to address any questions you might have.

Sincerely,  
INTERTOX, INC.

Richard C. Pleus, Ph.D.  
Managing Director and Toxicologist

cc:

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## A SUMMARY OF KEY SCIENTIFIC INFORMATION IN RESPONSE TO STATEMENTS MADE AT THE SAB MEETING

Hyperlinks are provided to authoritative references to allow independent assessment by the SAB.

<b>July 19, 2012 Quotes from <a href="#">SAB Draft Panel Comments for Discussion</a></b>	<b>Response</b>
<p>1) The infant is more susceptible to perchlorate exposure effects than adult, especially if exposure is acute. Although no data exist on the long-term adverse neurodevelopmental effects of perchlorate <i>per se</i>, the data on the adverse effects of thyroid hormone perturbations (a down stream target) on the developing brain justify the need for a life stage approach.</p>	<p><b>US EPA has not provided any study that demonstrates that the infant is more susceptible than the adult to perchlorate.</b> Alternatively, there are studies that have been conducted on neurodevelopmental effects of perchlorate which demonstrate no neurodevelopmental effects at the highest doses tested. Further, there are many studies of other goitrogenic agents that provide information on thyroidal hormone parameters and the decreases in Iodide Uptake Inhibition (IUI) needed to cause an adverse effect in offspring. These studies were not provided to the SAB. Lastly, there are data that provide evidence that clearance values for chemicals like perchlorate that are the same or slightly greater for infants and children than for adults.</p> <p><b>Epidemiological studies do not report that perchlorate causes an effect on thyroid hormones.</b> Epidemiological studies have reported no causal connection between environmental levels of perchlorate and changes in thyroid hormone. Studies using NHANES 2001-2002 have reported an association between environmental perchlorate and thyroid hormones in a subset of the total population, but these results have not been replicated in independent datasets (<a href="#">Pearce et al., 2010, 2011, 2012</a>) or in reanalyses of the same dataset (<a href="#">Tarone et al., 2010</a>; Bruce et al., in press). NHANES datasets are provided by CDC which suggests NHANES analyses be followed up with research studies by stating, “<a href="#">Research studies, separate from the Report [the dataset], are required for determining whether blood or urine levels are safe or are associated with disease or adverse effects.</a>” (See BOLD text on page 8; Interpretation of Report Data: Important Factors)</p> <p><a href="#">Leung et al. (2012)</a> reported there was no association between perchlorate levels in breast milk, maternal urine, or infant urine and infant thyroid function. There was no association between serum thyroxine (T4) and thyroid stimulating hormone (TSH) and urinary measures of perchlorate, nitrate, or thiocyanate in infants exposed through breast milk, dairy formula, and soy formula (<a href="#">Cao et al., 2010</a>). Cao et al. (2010) reported an association between TSH and free T4 measured in diaper urine (not a standard medium for measurement) and perchlorate, thiocyanate, and nitrate evaluated independently; however, all associations were positive which is the opposite direction of what would be expected based on the known mechanism of action of perchlorate.</p>

**Therapeutic doses of perchlorate are required for changes in thyroid hormones.** Based on the known mechanism of action of perchlorate and other goitrogens, perchlorate can cause a decrease in thyroid hormones with doses that exceed 0.4 mg/kg-d. For example, [Wenzel and Lente \(1984\)](#) reported that patients treated with 900 mg/d (9.2 mg/kg-d<sup>1</sup> assuming a 70 kg adult) for Graves' disease (autoimmune hyperthyroidism due to autoactivation of the TSH receptor) had reductions in thyroid hormones. In this study, as serum thyroid hormone concentrations declined (within two to four months following initiation of treatment), the dose of potassium perchlorate was reduced to between 40 and 120 mg/d (0.4 -1.2 mg/kg-d for a 70-kg person) for a total study duration of 24 months.

The NRC assessment identified the dose of 0.4 mg/kg-d as a No Observed **Adverse** Effect Level (NOAEL). The NRC found this study to be important in determining a threshold for adverse effects because

[...one could consider treatment in the latter 12 months to be equivalent to administration of perchlorate to healthy people. Therefore, the results provide evidence that moderately high doses of perchlorate given chronically to people with a history of hyperthyroidism do not cause hypothyroidism.](#)

Clinical studies have delivered doses from approximately 0.007 mg/kg-d ([Greer et al., 2002](#)) to 9.2 mg/kg-d ([Brabant et al., 1992](#)) with no reports of induced hypothyroidism. Pregnant women with Graves' disease received doses of 600 to 1,000 mg/d (6.2 to 10.3 mg/kg-d, assuming a 70 kg individual) with the only adverse effect noted being slight thyroid enlargement in one infant that resolved soon after birth ([NRC, 2005 citing Crooks and Wayne, 1960](#)).

In comparison, the Reference Dose (RfD), which incorporates an Uncertainty Factor to account for sensitive subpopulations, is 0.0007 mg/kg-d. This dose is approximately 570 times less than the [NOAEL estimated by NRC](#). It accounts for factors such as variations in clearance of the chemical from the body.

**Neurodevelopmental studies in animals report no effect of perchlorate at doses up to 10 mg/kg-d.** Two rat neurobehavioral studies were constructed to assess the potential for perchlorate to cause neurobehavioral effects in the offspring of mothers exposed to perchlorate in drinking water during pregnancy and postnatally. The results of these analyses revealed no statistically significant perchlorate-related effects. These studies were:

<sup>1</sup> The calculation for perchlorate dose equivalence in studies which used potassium perchlorate therapeutically is as follows:  $\text{Dose KClO}_4 \times \text{MW ClO}_4^- / \text{MW KClO}_4 = \text{dose ClO}_4^-$ . MW  $\text{ClO}_4^-$  = 99.45 g/mol; MW  $\text{KClO}_4$  = 138.55 g/mol.

	<ul style="list-style-type: none"> <li>• A neurodevelopmental study conducted by <a href="#">York et al. (2004)</a> that included 15 different neurobehavioral measures in four behavioral tests (passive avoidance testing, water maze testing, auditory startle habituation, and motor activity), and</li> <li>• A motor activity study conducted by <a href="#">Bekkedal et al. (2000)</a> that included nine different measures.</li> </ul> <p><b>Human studies have reported no neurodevelopmental effects of perchlorate.</b> Amitai et al. provided a follow-up to their 2007 publication in a presentation at the Society of Toxicology meeting in 2008. This population was exposed to perchlorate in drinking water at concentrations up to 340 ppb. In the 2007 report, there were no differences in neonatal T4 based on exposure group. In the 2008 report, 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.</p> <p><b>There is no evidence that the infant is more susceptible than the fetus.</b> The <a href="#">NRC</a>, <a href="#">ATSDR</a>, <a href="#">US EPA</a>, <a href="#">OIG</a>, and the states of <a href="#">California</a> and <a href="#">Massachusetts</a> have all reported the fetus of the pregnant woman to be the most sensitive subpopulation for perchlorate health effects. The most sensitive subpopulation is determined based on the effect in that population, not solely the level of exposure. All of these authoritative bodies have considered sensitive subpopulations.</p>
<p>2) We determine that no studies are useful as validation of a safe level of perchlorate in drinking water.  <u>Explanation:</u> New studies: exposure assessment (albeit with small sample sizes) studies provide information regarding:</p> <ul style="list-style-type: none"> <li>• breastfed infants as among the most highly exposed and studies suggest that intake via breast may exceed the RfD</li> <li>• 16% of infants had at least 1 dose exceeding RfD (Valentin-Blasini 2011)</li> <li>• 9/13 breast fed children ingested perchlorate at levels exceeding the RfD (Dasgupta 2008)</li> </ul>	<p><b>There are numerous studies that report the doses of perchlorate needed to cause non-adverse and adverse effects.</b> The concentrations reported in municipal water are at least an order of magnitude lower than the level that causes even a slight increase in IUI, a non-adverse effect. Thus, based on the best scientific data to date, at environmental levels, no effect is expected from perchlorate exposure. Given this, epidemiological studies would not be expected to report any perchlorate related effects.</p> <p><b>No effect is expected to occur at doses below the No Observed Effect Level (NOEL).</b> With the exception of <a href="#">Amitai et al. (2007)</a> which reported drinking water concentrations of <math>\geq 340</math> ppb, epidemiological studies reported exposure levels below the NOEL (equal to approximately 245 ppb in drinking water assuming a 70-kg adult drinking 2 L/d). It is not unexpected that most of these studies report no association between environmental perchlorate and thyroid function (<a href="#">Pearce et al., 2010, 2011, 2012</a>; <a href="#">Blount et al., 2009</a>; <a href="#">Leung et al., 2012</a>; <a href="#">Tellez et al., 2005</a>; <a href="#">Amitai et al., 2007</a>) and it is likely that the few reported statistically significant associations were due to chance.</p>

Perchlorate has been detected in infant formula ([Pearce et al., 2007](#); [Schier et al., 2008](#)) and in dairy milk ([Baier-Anderson et al., 2006](#)), but these levels have not been associated with any adverse effects. [Pearce et al. \(2007\)](#) reported that 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. [Leung et al. \(2012\)](#) reported there was no association between perchlorate levels in breast milk, maternal urine, or infant urine and infant thyroid function.

**The RfD is not a “bright line” above which adverse effects will occur.** [The RfD is 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.](#) Even if the dose were sufficient to cause IUI, the RfD is based on a non-adverse effect.

**The study by [Valentin-Blasini et al. \(2011\)](#) does not present any adverse effects with its estimated doses.** There are a number of analytical and methodological issues with extractions from diapers (e.g., this method has not been verified as a reliable approach for assessing thyroid function; perchlorate was detected in control diapers meaning there was an unknown source of perchlorate in the study).

**[Dasgupta et al. \(2008\)](#) does not report any adverse effects or actual measures of exposure in infants.** 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 were measured in the women as the rest of the variables, including the variables used to derive the conclusions regarding infant dose, are calculated using these three and default values for infant intake and weight, not actual measures of exposure.

**It is a fundamental tenet of toxicology that “the dose makes the poison.”** Knowledge of exposure level is critical; however, mere presence does not dictate toxicity. Any chemical can cause toxicity at sufficient dose. See the [Society of Toxicology](#) for background information.

<p><u>3) Recommendation for future studies:</u>  Improved understanding of perchlorate exposure assessment need repeated measures of perchlorate (need to know ½ life in urine);  improved understanding of variability over time (e.g., diurnal, etc.)  the validity of using a single sample to represent exposure (e.g., low ICC among infants: Valentin-Blasini 2011)</p>	<p><b>The narrow scope of studies provided may have created the misimpression that key studies of perchlorate science have not been completed.</b> Within the scientific process, more experiments can always be done to increase scientific knowledge. However, 13 animal studies and several clinical studies of perchlorate were conducted using US EPA guidelines (e.g., Good Laboratory Practices). These were conducted during the late 1990s and early 2000s.</p> <p>The foundational underpinnings of the pharmacology and toxicology of perchlorate span over 60 years of research. The perchlorate toxicological database is robust compared to other environmental chemicals. A number of the studies contemplated by the SAB have been conducted. The SAB may wish to review the larger database of studies and consider authoritative bodies such as <a href="#">NRC</a>, <a href="#">ATSDR</a>, <a href="#">US EPA</a>, and <a href="#">OIG</a> to determine whether information sought already exists.</p> <p><b>The half life of perchlorate is known.</b> It is <a href="#">6-8 hours</a>.</p> <p><b>Diurnal variability has been reported.</b> Perchlorate has a short half life, and like other chemicals with short half lives, when exposures stop (e.g., during overnight fasting) serum concentrations rapidly decrease. <a href="#">TSH and T3</a> have been reported to have circadian variability. Also, the dosing approach used by <a href="#">Greer et al. (2002)</a> provides insight into diurnal variability as TSH was found to follow a circadian rhythm.</p> <p><b>The use of spot urine samples compared to a 24-hour collection has been reported.</b> <a href="#">Mervish et al. (2011)</a> compared urinary concentrations of perchlorate, nitrate, and thiocyanate at six time points in children ages 6 through 10 over a five month period. They found that the absolute values were not indicative of longer-term exposures.</p>
<p>4) Modest reductions in thyroid hormone, even as early as the first trimester, can have deleterious and potentially permanent effects on the developing brain. Therefore, each of these stages are critically important for considering the public health implications of exposure to this toxicant in the human population. Additionally as the woman in pregnancy is the source of both iodide and thyroid hormone to the developing fetus and, postnatally, the lactating mother provides iodide to the nursing infant, the pregnant and lactating mother should be considered a sensitive life stage</p>	<p><b>US EPA has not provided any study that demonstrates that modest reductions in thyroid hormones can have deleterious and potentially permanent effects on the developing brain.</b> Regarding perchlorate, there are animal studies that have been conducted on neurodevelopmental effects of perchlorate which demonstrate no neurodevelopmental effects noted at the highest doses tested (up to 10 mg/kg-d). Studies of other goitrogenic agents (e.g., propylthiouracil, methimazole) provide information on thyroidal hormone parameters and the decreases necessary to cause an adverse effect in offspring. These studies provide evidence from which determinations can be made about the amount of thyroidal hormone reduction needed to cause an adverse effect.</p> <p>There are numerous studies, including evaluations by authoritative bodies, which report the doses of perchlorate that cause non adverse and adverse effects. These studies were published prior to 2005 and were not included in the materials provided to the SAB.</p>

5) Because thyroid status in the fetus cannot be readily or safely determined, one needs to monitor maternal thyroid status as a biological indicator of perchlorate exposures. If the mother's thyroidal status is impacted then one can assume the fetal status is definitely affected. However, if the mother's thyroid status is not affected, one cannot assume that the fetal thyroid has not been affected. Therefore, it is critical to find other markers of fetal effects of perchlorate exposure.

**The neonatal screening value, albeit at parturition, is an indicator of thyroidal impact at the end of pregnancy [emphasis added]**

This statement is based on a study by [Steinmaus et al. \(2010\)](#).

**Screening tests for congenital hypothyroidism (CH) are not sufficient to reliably assess effects of environmental chemical exposure.** The [screening assay for congenital hypothyroidism](#)—a condition unrelated to perchlorate exposure—consists of neonatal TSH measurement, to assess whether or not there is a functioning thyroid gland. As a screening tool, the test is considered insufficient for diagnosis. With [a positive screen](#), the infant is retested either with the same screening test or with a more specific diagnostic test.

**From a data analysis standpoint, TSH measurements for the newborn have high variability in the first 24-48 hours**, and analysis of these data to provide a measure of impact must be carefully planned before gathering data. In evaluating the results of a TSH screening program, an important question is whether the TSH assay has the sensitivity, specificity, reliability, reproducibility, and positive and negative predictive value to differentiate true TSH levels and thyroid status. In the first few days after birth, there is a surge of TSH released by the pituitary, which in turn, causes an increase in thyroid hormone. The surge is a normal developmental occurrence, and its exact timing varies individually. Comparing an infant who was sampled at the peak of this surge with another infant for whom sampling occurred after the surge would not provide a reliable comparison. Also, variability associated with this surge means measurement during this time period may be due to many other physiological phenomena unrelated chemical exposure, such as drug treatment to the mother. Further, in the State of California, six to eight contract laboratories conduct neonatal TSH assays. This introduces another source of variability.

**Individual exposures were not considered.** The only exposure data collected were reported water concentrations for a mother's zip code. There was no individual data reported for actual residence location, whether municipal water was consumed with any regularity, dietary sources of perchlorate, or dietary sources of other goitrogens, such as nitrate and thiocyanate. Recall that perchlorate typically contributes less than 1% of IUI compared to nitrate and thiocyanate.

The study defined a mother as "exposed" if she lived in a zip code with at least one measurement greater than 5 ppb. No changes in IUI, let alone changes in pituitary hormone levels, have been shown to occur at these low exposure levels.

**EXAMINATION OF SEVERAL KEY ISSUES CONSIDERED BY THE US EPA SCIENCE ADVISORY BOARD  
REGARDING THE DOSE-RESPONSE OF PERCHLORATE**

**Background**

The purpose of this document is to provide information to US EPA's SAB regarding dose-response information for perchlorate, particularly as it relates to four key issues raised by the US EPA SAB during its deliberations in Washington, D.C. These comments reflect questions raised at the meeting as well as the written documents posted at the [SAB website](#).

Hyperlinks are provided to authoritative references to allow the SAB to make its own independent assessment.

**Question 1: What level of IUI is adverse?**

The NRC concluded that individuals with normal iodide intake would require a perchlorate dose sufficient to lower thyroid iodide uptake by at least 75% for a sustained period of time (several months or longer) to cause thyroid hormone production to decline to the point where hypothyroidism could occur.

- a. Consider that the normal variability in [24-hr RAIU \(the measure of IUI\) is 7 to 26%](#).
- b. In adults, [that dose is estimated as being no lower than 30 mg/d](#) (~0.4 mg/kg-d for a 70-kg person, equivalent to drinking two liters of water with a perchlorate concentration of 15,000 ppb every day).
- c. Consider that [transient changes in thyroid hormones are not adverse](#) (also see Question 2).

**Question 2: What level of perchlorate exposure could affect thyroid hormone and adversely affect neurodevelopment?**

The dose response of perchlorate is well-documented in the scientific literature. The dose at which thyroid hormone perturbations could occur is orders of magnitude greater than doses that can arise from exposure to environmental levels of perchlorate.

- a. [IUI is the key event that precedes all thyroid-mediated effects of perchlorate exposure](#), thus doses of perchlorate below the NOEL for IUI will not affect thyroid hormones. The weight of evidence, particularly when the entire 60 years of studies are considered, strongly supports the view that no additional reductions in health benefits or any effects (adverse or not) will occur from further reducing perchlorate exposures below the current RfD. Using several scientific approaches, adverse effects have not been demonstrated at any level below the established NOEL, a level at which there were no changes in background levels of IUI, a non-adverse effect. The RfD is 10-fold below the NOEL.
- b. When doses are sufficient to cause IUI, compensation will occur. The Committee states: [Compensation for iodide deficiency or other perturbations in thyroid hormone production, as described above, is the rule. In those cases, adults have no clinical consequences; they have normal serum T4 and TSH concentrations and no clinical abnormalities. If the perturbation is greater, hypothyroidism occurs.](#)

- c. [Transient changes in thyroid hormones are not necessarily adverse](#). However, protecting against any changes in thyroid hormones, which occurs downstream of IUI, is a conservative approach according to the NRC.
- d. Thyroid hormones must be reduced sufficiently for adverse neurodevelopmental effects to occur. Neurodevelopmental effects have not been reported with exposure to perchlorate, even at therapeutic doses (Crooks and Wayne, 1960). For example, pregnant women with Graves' disease received doses of 600 to 1,000 mg/d (6.2 to 10.3 mg/kg-d, assuming a 70 kg individual) with the only adverse effect noted being slight thyroid enlargement in one infant that resolved soon after birth ([NRC, 2005 citing Crooks and Wayne, 1960](#)).

### **Question 3: Can US EPA's PBPK model predict that infants are more sensitive than fetuses?**

In general, PBPK modeling provides a science-based methodology for predicting the effects of different doses of perchlorate in different life stages. US EPA has presented a PBPK model for perchlorate based on [Merrill et al. \(2003\)](#) with modifications that affect the overall output. We have provided a scientific review of this model to US EPA and the SAB.

- a. The US EPA version of the PBPK model is not transparent, as many of the SAB stated. The model has several embedded policy-based—rather than scientifically-based—algorithms. For example, some components of US EPA's PBPK model for perchlorate use parameters selected from varying points within their distributions for different population groups. For instance, for the pregnant woman and fetus, US EPA selected a lower bound value to describe the urinary clearance of perchlorate (US EPA, 2009). In contrast, for all other population subgroups, US EPA selected values from the middle of the range of possible values (US EPA, 2009). A consistent, transparent, and science based rationale would make the model more scientifically reliable.
- b. At environmentally relevant doses, the PBPK model used in the White Paper shows biologically insignificant levels of IUI. In the first model presented in the White Paper, the highest predicted RAIU inhibition is 12.5% for 7-day old breast-fed infants. While this level is 7.8-fold greater than levels estimated for the average adult, the model is not validated to demonstrate, with accuracy, comparable levels of IUI from one group to another. The lack of transparency makes full assessment of the model and its output not possible at this time. Moreover, clinical studies demonstrate that with IUI values of 22%, 45%, or 67%, no effects of any thyroidal or clinical chemistry are noted after 2 weeks of sustained perchlorate exposure (Greer et al., 2002). This value is also within the normal variability of RAIU (see above). Thus, assuming that an IUI level of 12.5% was determined to be accurate it is below levels where actual human data demonstrate no adverse effect and also significantly below the [sustained 75% IUI required to reduce thyroid hormones to levels that could cause adverse effects](#).

In the second model presented in the White Paper, the highest predicted RAIU inhibition is 3.4% for 7-day old bottle-fed infants. This level is similar to normal fluctuations resulting from differences in diet and feeding approaches. There is no credible scientific evidence that this level of inhibition has any biological significance.

- c. The relative sensitivities predicted vary based on dose. The first model predicts that 7-day old breast-fed infants are most sensitive, whereas the second model, using different drinking water concentrations (i.e., 15, 20, and 24.5 ppb) with and without contribution from food, predicts that the highest RAIU inhibition is in 7-day old bottle-fed infants. There is no discussion regarding the inconsistency between the two models in the group predicted to have the highest IUI inhibition.

#### **Question 4: Can epidemiological studies determine if low dose effects of perchlorate cause adverse effects?**

US EPA interpreted a set of epidemiological studies to inform the SAB. However, these studies represent a limited portion of the epidemiological database on perchlorate. Although US EPA's interpretation suggests a low dose effect of perchlorate, critical evaluation of the strengths and limitations of these studies and the weight of evidence provided by other studies is not supportive.

- a. As noted above, doses of perchlorate below the NOEL have not demonstrated any effects including non-adverse and adverse effects. Thus environmental levels below the RfD would not be expected to cause adverse effects. See Question 1 and 2.
- b. None of the epidemiological studies in the SAB White Paper can determine causation. The studies US EPA summarizes are cross-sectional studies; these represent a "snap shot" in time with no temporal component. Statistical associations do not indicate whether one variable is an effect of another. These studies must be carefully evaluated in the context of [clinical significance](#).<sup>1</sup>
- c. Methodological issues in these studies limit the conclusions. Most of the epidemiological studies estimate exposure based on perchlorate measured in spot urine samples. Due to perchlorate's short half-life, spot urine samples may not be indicative of long-term exposures. [Mervish et al. \(2011\)](#) compared urinary concentrations of perchlorate, nitrate, and thiocyanate at six time points in children ages 6 through 10 over a five month period. They found that the absolute values were not indicative of longer-term exposures.
- d. US EPA provides five studies published since 2005 that make associations between perchlorate and some aspects of thyroid function ([Blount et al., 2006](#); [Steinmaus et al., 2007](#); [Schrienemachers, 2011](#); [Cao et al., 2010](#); [Steinmaus et al., 2010](#)). Of these, three used the same dataset (NHANES 2001-2002), therefore they are not independent studies per se and it would be expected that they would provide similar results ([Blount et al., 2006](#); [Steinmaus et al., 2007](#); [Schrienemachers, 2011](#)). Several other studies using independent datasets have reported no associations with environmental perchlorate ([Pearce et al., 2010, 2011, 2012](#)). Cao et al. (2010) evaluated urinary perchlorate and thyroid hormone collected from diapers, which is a nonstandard method of thyroid hormone measurement. Cao et al. (2010) reported an association between perchlorate and thyroid hormones only in a small subset (n=48) of the study population, and the association was in the direction opposite of what would be expected based on the known mechanism of action of perchlorate. Steinmaus et al. (2010) also reported an association between perchlorate and thyroid hormone, but this study had methodological limitations in that it included TSH data collected within the first 24 hours after birth, when there is a recognized surge in TSH. A previous analysis of the same dataset that evaluated TSH measured after 24 hours reported no association ([Buffler et al., 2006](#)).

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<sup>1</sup> While this paper is focused on radon, it provides an excellent summary of the strengths and weaknesses of different types epidemiological studies.