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January 21, 2013

Mr. Michael Baes
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Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
1515 Clay Street, 16th Floor
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Attention: PHG Project

RE: References in Intertox Report

Dear Mr. Baes:

Intertox is pleased to submit the document titled *Comments in Response to 2012 OEHHA Draft Perchlorate Public Health Goal* which will be delivered electronically on January 22, 2013. The enclosed compact disc contains a copy of our cited reference list and copies of the non-copyrighted material that we referenced in our document.

Sincerely,
INTERTOX, INC.

Lisa M. Corey

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Enclosures (1)

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COMMENTS IN RESPONSE TO 2012 OEHHA DRAFT PERCHLORATE PUBLIC HEALTH GOAL

January 22, 2013

PREPARED FOR THE PERCHLORATE STUDY GROUP

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ABBREVIATIONS AND SELECTED DEFINITIONS

ATSDR	Agency for Toxic Substances and Disease Registry.
BMD	Benchmark dose
BMDL	Benchmark dose lower limit. OEHHA defines this as the lower 95% confidence limit of the dose of perchlorate likely to cause a five percent decrease in iodide uptake.
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.
µg/kg-d	Micrograms 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 µg/d could be different in a 70 kg adult versus a 10 kg infant.
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.
NHANES	National Health and Nutrition Examination Survey
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.
OEHHA	Office of Environmental Health Hazard Assessment (California)
OIG	Environmental Protection Agency Office of the Inspector General.
PEC	Perchlorate equivalent concentration. The total goitrogenic effect of nitrate, thiocyanate, and perchlorate based on potency relative to perchlorate
PHG	Public Health Goal. Drinking water goal set by the State of California.
POD	Point of Departure
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.
RPF	Relative potency factor. The potency of a chemical to cause IUI relative to perchlorate.
RSC	Relative source contribution
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.
UF	Uncertainty Factor
US EPA	United States Environmental Protection Agency.
USFDA	United States Food and Drug Administration

EXECUTIVE SUMMARY

On December 7, 2012, the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA or the Agency) published notice of the 45-day public comment period on its *Draft Public Health Goal for Perchlorate in Drinking Water* (2012 draft; OEHHA, 2012b). The OEHHA (2012b) document is the second external draft of OEHAA's proposed Public Health Goal (PHG) and proposes to lower the PHG from 6 to 1 parts per billion (ppb; equivalent to µg/L) in drinking water. The first external draft was released in 2011 and was an update of the PHG that was published in March 2004 (OEHHA, 2004). Like the 2004 PHG, the 2011 and 2012 drafts are based on the same point of departure (POD)—the benchmark dose lower limit for a non-adverse effect (iodide uptake inhibition; IUI) in the clinical study that reported the most conservative no observable effect level (NOEL; Greer et al., 2002). This point of departure (POD) was identified by the National Research Council (NRC, 2005) as a NOEL, which is a more conservative value than the No Observable Adverse Effect Level (NOAEL) or the Lowest Observable Adverse Effect Level (LOAEL), which are commonly used PODs used by OEHHA.

We agree with using the POD identified by the NRC; however, we disagree with the Agency's use of ecologic epidemiological studies, which are based on drinking water detections in a subject's reported zip code or city, rather than individual measures of exposure, to justify changes to the most sensitive subpopulation, uncertainty factors, and drinking water intake rates. The studies cited by the Agency are scientifically unreliable and contrary to the strong weight-of-evidence provided by the best available science. Further, the 2011 and 2012 drafts fail to either provide reliable evidence that the current PHG of 6 ppb is not protective, or define the additional public health benefit provided by a PHG of 1 ppb. We provide our comments on the 2012 draft document here.

First, the most serious criticism of both the 2011 and 2012 draft documents is the lack of evidence that the infant is more susceptible than the pregnant woman and her fetus. The Agency heavily relies on cross-sectional and ecologic epidemiology studies to support both its conclusion that the infant is the most sensitive subpopulation and its assertion that adverse effects on thyroid function may occur as a result of exposure to low levels of perchlorate. These types of studies are difficult to interpret due to uncertainties in exposure classification, endpoint determination, and representativeness of the population being studied. When all of these types of uncertainties are combined, conclusions regarding adverse effects may be profoundly overestimated. Although OEHHA contends that the occurrence of non-differential misclassification and minimal confounding suggests that these studies are noteworthy, the best-available science is contrary to OEHHA's assertions and instead suggests that these studies are severely limited. OEHHA's reliance on these few studies is particularly troubling in light of the numerous well-designed studies in the peer reviewed literature.

With regard to the ecologic studies, several issues are of particular concern. OEHHA uses a number of unconventional approaches to analyze the scientific data and characterize exposure and effect; we provided the same critiques in our comments to the 2011 draft. For example, it is unprecedented to use the results of a screening-level thyroid stimulating hormone (TSH) assay, which are intended to screen newborns for congenital hypothyroidism, to instead assess the potential for adverse effects from environmental exposures (see Steinmaus et al., 2010 and the 2011 and 2012 draft documents). The assay collects TSH

measurements during the first few days of life, however TSH concentrations surge shortly following birth rendering the measures collected within the first 24 hours unreliable; using data from such a screening assay introduces substantial uncertainties and has not gained acceptance by the scientific community as a means of assessing the impact of environmental exposures. Further, the sensitivity of the screening-level TSH assay used in the studies on which OEHHA places the greatest weight (the reanalysis of Kelsh et al. (2003), Brechner et al. (2000), and Steinmaus et al. (2010)) is inadequate to scientifically support conclusions that exposure to perchlorate at environmental levels may produce adverse effects or that maternal exposure causes adverse effect in neonates.

Our second major concern is that the 2012 draft, like the 2011 draft, misrepresents the literature in presentation of the scientific rationale and supporting data for its conclusions. For example, Table 13 of the 2012 draft document summarizes five studies that are the foundation of OEHHA's assessment. Per OEHHA's assessment, these studies suggest an association between environmental perchlorate exposure and thyroid changes. However, an equal number of additional studies have been conducted that are not presented in Table 13, and, overall, these studies do not support OEHHA's conclusions (see section 3.2). An evaluation of all of the studies—the expected scientific standard— would provide much more thorough understanding of the strength of the scientific database. As is, Table 13 creates an erroneous impression of the weight-of-evidence in support of OEHHA's argument. We note also that OEHHA has reanalyzed and reinterpreted much of the data presented in the studies it cites in Table 13, and, in so doing, reaches conclusions that are different from those reached by the authors of the studies. It is scientifically inappropriate for OEHHA to present these calculations while citing (and apparently attributing the conclusions to) the original authors. This must be corrected in subsequent OEHHA reports.

Third, a robust dataset of over 60 years of scientific study makes it clear that exposure to perchlorate at environmental levels has no effect, let alone an adverse effect, on the human body; indeed, a safe dose-response threshold for perchlorate has been established based on a NOEL for a non-adverse effect determined in several peer-reviewed, clinical studies. The NOEL is based on IUI by the thyroid—a nonadverse effect that is reversible. No known or anticipated adverse effects on health will occur at or below this NOEL threshold, which is equivalent to approximately 245 ppb (assuming the standard 70-kg adult drinking 2 L/d). Standards set below this level implicitly reflect an additional margin of safety, whether acknowledged or not. OEHHA's proposed PHG of 1 ppb is many times lower than the NOEL, NOAEL, or LOAEL, yet OEHHA's 2012 draft document infers that low doses of perchlorate may diminish thyroid hormones without presenting a viable mechanism of action for this effect.

Another important consideration is that IUI is also caused by the chemicals nitrate and thiocyanate, which are found in abundance in a healthy diet. Studies have shown that, on a daily basis, exposure to perchlorate accounts for approximately 2% of the total IUI contributed by these three goitrogenic compounds. However, OEHHA disregards the negligible contribution of perchlorate relative to these other common agents, and, in so doing, vastly overestimates the impacts on IUI that can reasonably be associated with exposure to perchlorate alone.

Fourth, we note minimal changes in the text of the 2012 draft compared to the 2011 draft. We note responses to some comments from the peer reviewers, but not all. It appears that none of the comments submitted by the public on the 2011 draft were addressed at all. For

example, Intertox provided substantial comments, supported by scientific references, on numerous issues critical to the proper interpretation of the studies OEHHA relies upon to support its assessment; however, OEHHA did not address these comments in the 2012 draft document. The most significant changes to the 2012 draft document were made to the developmental and reproductive toxicity section (pp. 38-65). Here, OEHHA provides additional text intended to strengthen its argument that the infant is the most sensitive subpopulation. However, as we pointed out in our comments to the 2011 draft, the scientific support for this argument is insufficient; the material we criticized in the 2011 draft is simply repeated in the current draft without additional scientific support.

In conclusion, the 2012 draft document is essentially the same document as was presented in 2011. Substantial scientific concerns raised in comments to the 2011 draft document were not addressed in the 2012 document. While we appreciate OEHHA releasing another draft of its PHG risk assessment, the 2012 draft document provides no new scientific information to impact an assessment of perchlorate and fails to address many key issues that render the report inconsistent with 60 years of scientific investigation. As such, OEHHA cannot rely on the analysis contained in the draft document to produce a scientifically reliable PHG and we find no legitimate scientific basis for OEHHA to justify its proposed change in the PHG from 6 ppb to 1 ppb.

1.0 INTRODUCTION

In 2004, California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) published its Public Health Goal (PHG) for perchlorate of 6 parts per billion (ppb) (equivalent to 6 µg/L) in drinking water. As an environmentally-detectable chemical, perchlorate is unique in that its previous use as a pharmaceutical has resulted in a well-developed database of its toxicology and pharmacology. Perchlorate's mechanism of action—iodide uptake inhibition (IUI)[1]—has been characterized and has a well-defined threshold. IUI is recognized in the scientific community as a nonadverse effect. It has not been reported to occur in healthy adults with exposures to perchlorate levels less than or equal to 245 ppb (assuming the standard 70-kg adult drinking 2 L/d). If IUI does not occur, there can be no progression to thyroid hormone changes or other adverse effects, even in people with low iodine intake (NRC, 2005). OEHHA has not suggested that the current PHG of 6 ppb is failing to protect public health.

The 2012 draft:

- **Incorrectly interprets the weight-of-evidence from scientific studies;**
- **Inappropriately relies on screening data from newborns to suggest an effect of low level perchlorate exposure on TSH;**
- **Relies on methods of analysis that are inconsistent with accepted scientific approaches; and**
- **Ignores specific and rigorous assessments from 60 years of research on perchlorate that run contrary to the analysis presented in the OEHHA 2011 and 2012 documents.**

On December 7, 2012, OEHHA published notice of the 45-day public comment period on its *Draft Public Health Goal for Perchlorate in Drinking Water* (2012 draft; OEHHA, 2012b). The OEHHA (2012b) document is the second external draft of OEHAA's proposed PHG. The first external draft was released in 2011 and was an update of the PHG for perchlorate of 6 ppb in drinking water that was published in March 2004 (OEHHA, 2004). Like the 2004 PHG, the 2011 and 2012 drafts are based on the same point of departure (POD)—the benchmark dose lower limit for a non-adverse effect (IUI) reported in Greer et al. (2002). However, the 2011 and 2012 draft documents propose a PHG of 1 ppb based on unjustified changes in the most sensitive subpopulation, uncertainty factors, and drinking water intake rates.

Although we support the use of the No Observable Effect Level (NOEL) reported in Greer et al. (2002), the 2011 and 2012 Agency's drafts fail to provide scientific evidence that the current PHG is not protective and that a reduction is necessary.

We note that the 2012 draft PHG document contains essentially the same text as the draft PHG document released in 2011. As such, it suffers from the same critical weaknesses that we identified in the 2011 draft PHG document and critiqued in detail in our prior comments. In particular, the 2012 draft:

[1] 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. 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 14,000 ppb every day). 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.

- Incorrectly interprets the weight-of-evidence from scientific studies to suggest that thyroid hormone levels in infants were adversely affected at low-level environmental perchlorate exposure.
- Inappropriately relies on data from a screening assay from newborns to suggest an effect of low-level perchlorate exposure on TSH.
- Relies on methods of analysis that are inconsistent with accepted scientific approaches.
- Ignores specific weight-of-evidence from rigorous assessments by authoritative bodies and 60 years of research on perchlorate that run contrary to the central conclusions presented in the OEHHA 2011 and 2012 documents.

Further, we demonstrated in our previous comments that in risk assessments developed by OEHHA for other chemicals, the point of departure was either a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL), in contrast to the NOEL for a non-adverse effect relied on in developing the draft PHG for perchlorate.

In our previous comments, we concluded:

> OEHHA does not scientifically justify the change in susceptible population from pregnant women to infants. Further, the [2011] Draft document does not provide any evidence that reducing perchlorate concentrations in drinking water from 6 ppb to 1 ppb will result in additional public health benefit, particularly considering the likely substantially greater exposure to other thyroid-active chemicals that have the same mechanism of action as perchlorate, including nitrate and thiocyanate.

Given that our prior scientific comments were not addressed in the 2012 PHG draft, we have attached a link to those comments in Appendix A.

In this document, we expand on the comments provided in 2011 in four key areas:

1. The evidence provided by OEHHA to support the infant as the most sensitive subpopulation has inherent weaknesses that prohibit its use in concluding neonatal thyroid effects with environmental perchlorate exposure;
2. The 2012 draft misrepresents the weight-of-evidence for perchlorate health effects;
3. OEHHA's 2012 PHG calculation includes overly conservative parameters that serve to unnecessarily reduce the already health protective PHG of 6 ppb; and
4. We outline the differences between the 2012 and 2011 draft documents and demonstrate that most of our prior substantive scientific comments were not addressed in the 2012 document.

2.0 SCIENTIFIC CONCERNS WITH THE 2012 DOCUMENT

In our previous comments (Appendix A), we critiqued OEHHA's selection of the infant as the most sensitive population, discussed the inappropriate use of ecologic epidemiology studies, and criticized OEHHA for relying upon unstable TSH measurements taken shortly after birth to support key conclusions in its revised 2011 PHG risk assessment. We expand on our comments below, given extra time to review the 2011 draft as well as to reflect on the comments by the external peer reviewers. In addition, we comment on new information presented by OEHHA in the 2012 draft.

2.1 OEHHA's Conclusion that the Infant Is the Most Sensitive Subpopulation Is Inconsistent with the Best Available Science

> The scientific rationale that OEHHA uses to support its decision that the infant is the most sensitive subpopulation is not congruent with accepted interpretation of the literature by authoritative bodies, including US EPA, ATSDR, and US EPA OIG all reached the conclusion that the pregnant woman and her fetus are the most sensitive subpopulation.

The fundamental difference between the 2004 and draft 2011 and 2012 PHG risk assessments is the change in the central conclusion regarding the most susceptible population, which results in the adjustment of a number of parameters in the Agency's assessment. The infant is a sensitive population, but not *the* most sensitive. The weight-of-evidence and the assessments of authoritative bodies, particularly the NRC of the National Academy of Sciences, have established the pregnant woman and her fetus as the most sensitive subpopulation. However, the Agency identifies the infant as the most susceptible population in the draft 2011 and 2012 assessments, and supports this determination by using unreliable scientific studies and its own recalculations of published studies.

It is incorrect for OEHHA to infer that the infant has not been evaluated. The infant was assessed by many authoritative bodies including the Agency itself in 2004. There are no new studies that demonstrate that the infant is more susceptible to perchlorate, except for the Agency's unprecedented approach to analyzing newborn screening data based on ecologic epidemiological studies which is based on exposures in pregnant women not infants (see section 2.2.1).

In risk assessment, the goal is to determine, and then protect, the most sensitive subpopulation. As a result, all other subpopulations, including those that are more sensitive than average, will also be protected. In its 2005 review of the more than 60 year history of perchlorate health effects research, the NRC determined that the pregnant woman and her fetus are the most sensitive subpopulation. Importantly, the NRC also considered the infant and child to be a sensitive population. However, with regard to fetuses, infants and children, the NRC made the following distinction:

> The thyroid hormones are critical determinants of growth and development in fetuses, infants, and young children. Thus, fetuses and preterm newborns constitute the most sensitive populations although infants and developing children are also considered sensitive populations.

The scientific rationale that OEHHA uses to support its decision in the 2011 and 2012 draft PHG documents that the infant is the most sensitive subpopulation is not congruent with accepted interpretation of the literature by authoritative bodies. In addition to NRC, United States Environmental Protection Agency (US EPA), the Agency for Toxic Substances and Disease Registry (ATSDR), US EPA Office of the Inspector General (OIG) all reached the conclusion that the pregnant woman and her fetus are the most sensitive subpopulation. In addition, OEHHA determined that the pregnant woman and her fetus were the most sensitive in 2004, but also evaluated the infant as a sensitive subpopulation. OEHHA (2004) states:

> Four sensitive subpopulations are identified in this evaluation: (i) pregnant women and their fetuses, especially those who are getting less than a sufficient amount of

iodine; (ii) lactating women, especially those who are getting less than a sufficient amount of iodine; (iii) infants; and (iv) individuals with thyroid problems.

There are ample valid, scientific reasons why the rationale provided by OEHHA is unsupportive of its erroneous conclusion that the infant is the most sensitive subpopulation.

First, not one of the studies presented by OEHHA or in the peer-reviewed literature demonstrates that the infant is more vulnerable than the pregnant woman and her fetus. None of the studies presented directly compare effects on fetuses and infants. In fact, the studies presented in support of the infant as the most sensitive subpopulation were all based on exposures in pregnant women, not infants. Moreover, the studies cited by OEHHA to support the infant as most sensitive are ecologic—they do not report individual measures of exposure, but are based on drinking water detections. Consequently, there is no information on co-exposures to other goitrogens, exposure to perchlorate through drinking water (if any at all), exposure to perchlorate through diet, or the daily water concentration that was present during pregnancy or immediately before birth (see section 2.2).

Second, OEHHA's statement that "…new data suggests that many infants may not be receiving adequate iodine in their diets…" based on Pearce et al. (2007)—a study of breast-fed infants—as a partial justification for selection of the infant as most sensitive, is not applicable to OEHHA's most sensitive subpopulation of formula-fed infants (those exposed to drinking water in reconstituted formula). Iodine deficiency during pregnancy is a serious health concern; however, neither this study, nor any other, reports adverse effects in infants due to exposure to perchlorate through breast milk. Pearce et al. (2007) also does not report that breast milk iodine is correlated with perchlorate in water or in milk. Finally, drinking water exposures to an infant are more relevant to formula-fed infants than breast-fed infants. Formula is fortified with iodine meaning formula-fed infants are much less susceptible to any IUI (see section 4.4.3).

Third, OEHHA's statement that "…young infants have low stores of thyroid hormone (less than one day's worth, compared to several weeks' worth in adults)…" is misleading. If the point of departure is a NOEL for a non-adverse effect, the amount of thyroid hormone storage is immaterial. However, even if IUI were to occur, infant storage is also adequate to maintain homeostasis on a day-to-day basis and would require sufficient and sustained IUI to reduce stores of thyroid hormone.

Fourth, OEHHA's statement that "…human data show that perchlorate can interact with other contaminants to produce a greater effect than that caused by perchlorate alone…" is misleading. First, these studies based on NHANES 2001-2002 do not report data on infants or young children. Second, these references are superseded by a study that utilizes better and more complete thyroid measures (Bruce et al., 2013). Using the same NHANES data set with more robust thyroid measures, the results of Bruce et al. (2013) contravene the conclusions of Blount et al. (2006) and Steinmaus et al. (2007). Further, with only 2% of the total goitrogen load provided by perchlorate, controlling the other agents would provide substantially more protection and controlling for perchlorate alone would provide no appreciable health benefit.

Fifth, OEHHA's statement that "…new data available from the US EPA and OEHHA show that drinking water intakes per body weight are higher in infants than previously thought…" is scientifically unsupported. This new data is based on water intake rates with several limitations and are exceptionally high as noted by one peer reviewer. Although OEHHA

currently uses OEHHA (2012a) as the basis of its drinking water intake rates, the OEHHA risk assessment was based on the same datasets as in 2011 and may overestimate drinking water intake rates. We more thoroughly addressed this problem in our previous comments which can be found on pages 53-56 in Appendix A to these comments.

In addition, there is evidence that the infant is no different than the adult with regard to excretion of perchlorate. Clearance rates in infants and young children are the same as, or greater than, those of adults. This would lead to a shorter half-life in infants and young children (Appendix B).

Finally, IUI does not commence until the NOEL equivalent of approximately 245 ppb (assuming the standard 70-kg adult drinking 2 L/d) is exceeded. The ecologic epidemiological studies, relied upon by OEHHA, characterize parameters that are not scientifically reliable or outcomes that are not feasible at the environmental doses and, therefore, cannot to be used to demonstrate that exposure to perchlorate at the low levels typically found in the environment may lead to adverse effects (see section 2.2).

In Table 1 below, we critique the scientific rationale provided by OEHHA in support of its conclusion that the infant is the most sensitive subpopulation.

Table 1. Summary of OEHHA Statements of "Evidence that Infants are Susceptible to Perchlorate..." and Comments Outlining the Scientific Concerns

OEHHA's Statements	Intertox Comments	Result
"First, studies from California and elsewhere provide evidence that thyroid hormone levels in infants were adversely affected by perchlorate at exposure levels that were much lower than the levels shown to cause no effects in healthy adults (Kelsh et al., 2003; Brechner et al., 2000; Buffler et al., 2006; Steinmaus et al., 2010; Li et al., 2000a; Crump et al., 2000)."	Not one of these studies can demonstrate that thyroid hormone levels are adversely affected. Each of these cited studies are ecologic epidemiology studies which have inherent limitations based on their study design. The NRC reviewed many of these studies them in 2005 and found some to be useful to demonstrate that the clinical study by Greer et al. (2002) is a conservative and transparent means of establishing a safe level. *These studies reported no effect of perchlorate at environmental concentrations.* Kelsh et al., 2003; Buffler et al., 2006; Li et al., 2000; Crump et al., 2000 *This study was dismissed by NRC due to poor design.* Brechner et al., 2000 *This study lacks any reliability in documenting exposures and analytic techniques that are reliable to make any conclusions.* Steinmaus et al., 2010	Contrary to OEHHA's assertion, there is no scientific evidence provided by these studies to demonstrate that thyroid hormone levels in infants were adversely affected by exposure to perchlorate at concentrations below the NOEL. Furthermore, this is an incomplete list of available studies (section 3.2).
"Second, new data suggests that many infants may not be receiving adequate iodine in their diets. In a study of nursing mothers in Boston, 47 percent of breast milk samples did not contain enough iodine to meet the infant iodine intake recommended by the Institute of Medicine (Pearce et al., 2007)."	The study's author's state: "Perchlorate exposure was not significantly correlated with breast milk iodine concentrations. Perchlorate was detectable in infant formula, but at lower levels than in breast milk. 47% of women sampled may have been providing breast milk with insufficient iodine to meet infants' requirements." No study reports that perchlorate in breast milk has caused adverse effects.	Contrary to OEHHA's assertion, this reference does not provide support that perchlorate has any relevant relationship to maternal iodine deficiency or that perchlorate provides any added risk to the infant.

OEHHA's Statements	Intertox Comments	Result
"Third, young infants have low stores of thyroid hormone (less than one day's worth, compared to several weeks' worth in adults) (van den Hove et al., 1999)."	Understanding the mechanism of action, NRC (2005) was clear that "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." At doses below the threshold for IUI, stores of thyroid hormone are irrelevant. However, even if IUI were to occur, infant storage is also adequate to maintain homeostasis on a day-to-day basis would require sufficient and sustained IUI to reduce stores of thyroid hormone.	Contrary to OEHHA's assertion, if the point of departure is a NO OBSERVED EFFECT LEVEL for the start of a non-adverse effect, the amount of thyroid hormone storage is immaterial.
"Fourth, human data show that perchlorate can interact with other contaminants to produce a greater effect than that caused by perchlorate alone (Blount et al., 2006; Steinmaus et al., 2007)."	The studies by Blount et al. (2006) and Steinmaus et al. (2007), have been superseded by a study by Bruce et al. (2013) which reports no association between perchlorate and thyroid function. Second, perchlorate makes up approximately 2% of the total goitrogen load of other identically acting goitrogens (nitrate and thiocyanate; Tarone et al., 2010).	Contrary to OEHHA's assertion, these studies do not report data on infants or young children (See Bruce et al., 2013). Using a more robust dataset from the same NHANES produces results that are not consistent with the conclusions of the authors. Further, with only 2% of the total goitrogen provided by perchlorate, controlling the other agents would be the best way to alleviate IUI, assuming that this issue is important.
Finally, new data available from the U.S. EPA and OEHHA show that drinking water intakes per body weight are higher in infants than previously thought. (US EPA, 2004; OEHHA, 2012a).	Although OEHHA has presented new drinking water intake rates, the underlying dataset is the same as in the 2011 draft. Due to methodological issues and the introduction of recall bias, this data may overestimate actual intake rates.	Contrary to OEHHA's assertion, this new data presents water intake rates that may greatly overestimate intake rates and was criticized by a peer reviewer.

2.2 OEHHA Relies on Ecologic Studies that Are Inappropriate for Establishing Cause and Effect

The 2012 draft document places significant weight on OEHHA's interpreted results of five studies (Kelsh et al., 2003; Brechner et al., 2000; Li et al., 2000a; Crump et al., 2000; Steinmaus et al., 2010) to justify the change in susceptible population from the pregnant woman to the infant. These data are inadequate to support OEHHA's conclusions, as they rely on unstable measurements taken within the first 24 hours following birth and do not control for gestational age, time of collection, or other factors that may influence outcome (e.g., exposure misclassification). The conclusions of several of these studies, as portrayed by OEHHA, are contrary to the conclusions stated by the study authors (Kelsh et al., 2003; Brechner et al., 2000; Li et al., 2000a; Crump et al., 2000) and are based on calculations by OEHHA of data found in the study tables and figures, not by the studies' authors.

2.2.1 Ecologic Studies Have Weaknesses that Limit Their Use

> The 2012 draft heavily relies on cross-sectional and ecologic epidemiology studies which, in the face of reliable clinical scientific studies and the supporting literature, have scientific limitations (e.g., exposure classification, endpoint determination, and representativeness of the population). When all of these types of uncertainties are combined, conclusions regarding adverse effects may be profoundly overestimated.

The 2012 draft PHG document cites studies by Kelsh et al. (2003), Brechner et al. (2000), Steinmaus et al. (2010), Li et al. (2000), and Crump et al. (2000) as providing evidence that the infant is the most susceptible population. In evaluating these studies, it is important to recognize that the design of these studies (ecologic) cannot determine causality (NRC, 2005). Ecologic studies also do not include an evaluation of individual exposure measures, perchlorate exposure from other unconsidered sources, or contribution of other goitrogens. Furthermore, these types of studies are difficult to interpret due to uncertainties in exposure classification, endpoint determination, and representativeness of the population being studied. When all of these limitations and types of uncertainties are combined, conclusions regarding adverse effects may be profoundly overestimated.

Ecologic studies are important to the database because they can identify associations which, in the context of what is understood about the mechanism of action of a chemical, could provide support to other toxicological or epidemiological studies. As the NRC (2005) states:

> Ecologic studies can provide supporting evidence of a possible association but cannot themselves provide definitive evidence regarding cause… No studies have examined the relation of perchlorate exposure and adverse outcomes, either in thyroid function or in neurodevelopment, among especially vulnerable groups, such as low-birthweight or preterm infants.

More recently, the US EPA convened a Science Advisory Board (SAB) panel to assist the agency in the development of its Maximum Contaminant Level Goal (MCLG) for

perchlorate.[2] Faced with the same database of ecologic studies, the SAB in its draft report concluded that:

> For perchlorate studies where exposure is an ecologic measure based on drinking water source, there are additional concerns that may lead to further exposure misclassification. First, drinking water typically accounts for an estimated 20% of total perchlorate dose (Huber 2010). Consequently, estimating total perchlorate exposure solely by drinking water source may be grossly inaccurate. Second, perchlorate levels in drinking water may not be constant even though studies using ecologic exposure measures define them as such (e.g., person A either does or does not reside in a high exposure location). Buffler et al. notes that in southern California, the proportion of Colorado River water used for drinking water varies seasonally (2006). The Colorado River is a source of perchlorate exposure. Consequently, the level of perchlorate in water supply systems reliant on Colorado River water may change as more or less river water is diverted into the drinking water system. Categorical assignment of high/medium/low exposure water districts may not be true over time and season.
>
> Overall, the four studies [including Steinmaus et al. (2010)] examining ecologic measures of perchlorate exposure in drinking water in relation to thyroid function, regardless of whether or not they show an association, are of little value for guiding decisions regarding a MCLG for perchlorate in drinking water.

Based on this analysis, the SAB concluded that:

> …these epidemiological data are insufficient to guide causal inference of an association between perchlorate exposure and thyroid dysfunction in pregnant women, neonates or the general population. Limitations concerning study design, exposure assessment, sample size, and statistical modeling have resulted in inconsistent findings. The current body of epidemiologic evidence cannot provide validation of a safe level of perchlorate in drinking water.

Even the OEHHA document recognizes the limitations of ecologic studies, but ignores these limitations in its assessment. It states:

> Average perchlorate concentrations were then assigned to individuals without knowledge of whether or not they drank the tap water, how much they drank, or for how long they drank it. In addition, drinking water is not the only source of perchlorate, and some exposure will come from food. Lack of data on this source of perchlorate would likely cause further misclassification of the study subjects' true perchlorate exposure.

Clearly, there is no reliable scientific support for the use of ecologic epidemiology studies for the purposes employed by the Agency's 2011 and 2012 draft risk assessments.

2.2.2 Conclusions Based on Unstable TSH Measurements Collected before 24 Hours

To our knowledge, no other study conducted before or since publication of Steinmaus et al. (2010) has drawn conclusions about effects of environmental exposures based on TSH data

[2] The SAB report titled *Draft (11/9/2012) Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate* has not been released as a Final document at this time. However, we recommend that OEHHA review both the Draft document and Final when it becomes available.

collected within 24 hours following birth.[3] The Agency does not provide a reference advocating the use of this screening assay for this purpose. Thus, the use of these data introduces substantial uncertainty. As correctly stated in Steinmaus et al. (2010):

> Neonatal TSH levels normally surge within the first few hours after birth, peaking at about 2 hours after birth and steadily decreasing to normal long-term levels over the next 48 to 72 hours.

Yet the Agency dismisses these facts and reanalyzes data obtained during this dynamic period. This data was collected for screening newborns for congenital hypothyroidism (CH)—which is unrelated to perchlorate exposure. The data collected by the California Newborn Screening program was never designed to measure associations with toxicants of any kind.

In utero, a fetus receives thyroxine (T4) from its mother and, at birth, maternal T4 and cord blood T4 are similar (Abuid et al., 1973). At birth, the neonatal pituitary gland releases a surge of TSH which increases endogenous T4 and triiodothyronine (T3) (Abuid et al., 1973). The early high TSH surge ceases by approximately 30 minutes after birth, but a sustained hypersecretion of TSH persists through 24 to 48 hours after birth (Fisher and Odell, 1969). Because of this instability in TSH levels, it is recommended that screening for CH, which is mandatory in newborns, be performed at least 24 to 48 hours after birth (Rose and Brown, 2006).

To address the TSH fluctuation issue in this dynamic period shortly after birth, in Steinmaus et al. (2010) the early TSH measurements were collected in five age groups, which is explained in the study as follows:

> We addressed potential confounding or effect modification due to this surge in several ways. First, because the surge occurs mostly within the first 24 hours of birth, all analyses were stratified on the basis of whether the collection age was greater or less than 24 hours. Second, possible residual confounding was addressed by adjusting for collection age within each of these strata. This was done by dividing collection age into five categories: 0 to 5 hours (the period of early very unstable TSH values), 6 to 19 hours (the period when mean TSH levels peaked in this data set), 19 to 32 hours (the period when TSH levels decline rapidly), 33 to 70 hours (the period when TSH levels decline more slowly), and 70 hours or more (the period when TSH levels are close to long-term levels).

Despite attempting to address potential confounding issues associated with the TSH instability in the early hours after birth, serious problems remain. The authors provide no scientific rationale supporting the physiological relevance of their segregation periods, and standard practice for CH screening is to exclude much of this early collected data entirely or through the application of various collection cutoff levels.

Regarding the effect of the surge on TSH analyses in the context of screening for CH, we also note that one of OEHHA's peer reviewers authored an article (LaFranchi, 2010) which states:

> …programs need to consider the range of age of specimen collection in their newborn population. There is a rise in TSH levels after birth; serum TSH rises from cord blood

[3] Note that the author of this study is the same author of the Agency's risk assessment for perchlorate.

levels of 1–20 mU/L [µIU/mL] to peak around 60–80 mU/L 30 min after delivery. TSH levels then fall over the next few days and by a week of life are in the 1–8 mU/L range typical of early infancy.

He recommends that for programs with TSH collection before 48 hours of age, age-related cutoffs be established.

To further illustrate limitations on data collection during this period of dynamic changes in TSH levels, we note the TSH screening practices of the State of Washington. In Table 2 below, screening result classifications are presented for TSH levels in newborns based on hours post-partum, for the Washington newborn screening program. Clinical values are noted as "normal" if they are below 20 µIU/mL serum. As shown, up to 54.9 µIU/mL serum is characterized as "normal" if it is measured in a neonate within 12 hours of birth, and up to 44.9 µIU/mL serum is characterized as "normal" if it is measured within 24 hours of birth. Levels just above 25 µIU/mL serum are only considered to be potentially abnormal if they are measured at 37 to 48 hours following birth or later.

Table 2. Classification of Clinical TSH Values by Hours Postpartum

Screening Tests

The newborn screening test for CH measures the infant's *thyroid stimulating hormone (TSH)* level using a fluoroimmunoassay technique. Results are classified in the table below.

Screening Result Classifications and Corresponding Follow-up Actions for CH

TSH µIU/mL serum	1 to 12 hrs	13 to 24 hrs	25 to 36 hrs	37 to 48 hrs	49 to 504 hrs	> 504 hrs
0 - 14.9	Normal	Normal	Normal	Normal	Normal	Normal
15 - 19.9	Normal	Normal	Normal	Normal	Normal	Borderline
20 - 24.9	Normal	Normal	Normal	Normal	Borderline	Borderline
25 - 29.9	Normal	Normal	Normal	Borderline	Borderline	Borderline
30 - 44.9	Normal	Normal	Borderline	Borderline	Borderline	Borderline
45 - 54.9	Normal	Borderline	Borderline	Borderline	Borderline	Borderline
55 - 59.9	Borderline	Borderline	Borderline	Borderline	Borderline	Borderline
60 - 99.9	Borderline	Borderline	Presumptive	Presumptive	Presumptive	Presumptive
≥ 100	Presumptive	Presumptive	Presumptive	Presumptive	Presumptive	Presumptive

Typical Follow-up Actions

Normal Results	Borderline Results	Presumptive Results
Results are mailed to specimen submitter. No follow-up is required.	NBS waits for the routine second specimen or contacts health care provider to recommend newborn screening specimen as soon as possible. If previous abnormal, health care provider is contacted by phone to recommend *diagnostic testing*. Results are also mailed to submitter.	Health care provider is immediately contacted by phone to recommend a repeat newborn screening specimen and/or *diagnostic testing* as soon as possible. Results are also mailed to submitter.

Source: WADH, 2008

Age-related cutoffs also vary by program. In the Oregon Newborn Screening Program, age-related TSH cutoffs are set at the mean +3 standard deviations for each age category (LaFranchi, 2010). In that program, the cutoffs range from 103 µIU/mL (serum) for specimens collected between 0 -11 hours of age, to 40 µIU/mL for those collected between 12 - 23 hours, to 32 µIU/mL for those collected between 24 -48 hours, and to 30 µIU/mL for those collected between 49 - 96 hours.

Lott et al. (2004) found that based on data from 161,244 newborns collected at the Newborn Screening Laboratory in Columbus, Ohio, approximately 20% of newborns with specimens collected within the first 24 hours had TSH levels ≥ 20 µIU/mL, and concluded that "blood specimens collected within the first 24 h are undesirable because there are many babies with a high TSH who do not have hypothyroidism." They found no confirmed cases of hypothyroidism in babies with a TSH of <29 µIU/mL.

A complicating trend in labor and delivery on measured TSH levels is the reduced time of hospital stay: the trend is strongly toward early discharge of mothers and infants (before 48 hours of age). With early hospital discharge, the first screening specimen commonly is obtained before 48 hours of age. Although not presented in Steinmaus et al. (2010), Buffler et al. (2006) (who evaluated the same population) report that 89.8% of the population in the 5 ppb and greater perchlorate exposure group had their blood sampled prior to 24 hours after birth compared to 76.9% of the less than 5 ppb population. Thus, a greater percentage of the "exposed" population was sampled during the period of greater TSH variability.

In its Newborn Screening (NBS) Program, the State of California states the following regarding when to collect samples:

> … early collection **can** affect the results for other metabolic and hypothyroidism screening. It can result in a false positive for primary congenital hypothyroidism due to the biological phenomenon known as "neonatal surge."[emphasis in original]

And, in 2001, California Department of Public Health stated (CDPH, 2001)

> **Beginning April 2001, as a result of new California State Regulations, newborns screened at less than 12 hours of age, <u>for any reason</u>, will have to be rescreened through the NBS Program.** Included in this group are babies whose specimen collection forms have erroneous or missing information, without which the age at collection cannot be determined. Licensed perinatal facilities will be required to collect another specimen from these babies on or before the sixth day of age. The NBS Program has routinely cautioned against early specimen collection. In 1995, the Program issued interim early testing guidelines specifically warning against specimen collection prior to 12 hours of age. While multiple mailings, newsletters, and other attempts to reinforce these recommendations have substantially reduced the number of newborns tested under 12 hours of age, some newborns are still being tested inappropriately. [emphasis in original]

Importantly, the purpose of the NBS is as a screening test for CH given to a whole population of healthy and non-healthy individuals as opposed to a diagnostic test given to the subset of individuals suspected of having a health issue. Clearly, serious potential bias can be introduced in studies that interpret TSH levels measured during newborn screening programs if the study does not appropriately adjust for the times when samples are taken, gestational

age, and sensitivity of the assay. Despite this lack of scientific consensus OEHHA chose to place substantial reliance on the early TSH screening values to find a perchlorate exposure/TSH value association and ultimately to support its choice of the infant as the most sensitive population. If the early TSH screening values are excluded for the reasons outlined above, OEHHA's rationale for identification of the infant as the most sensitive subpopulation is without significant scientific support.

> OEHHA's reanalyses and conclusions based on TSH screening data collected at less than 24 hours, are not grounded in independent peer reviewed science and do not, as presented, constitute the best available science.

In comments to OEHHA on the 2011 draft, Dr. Michael Kelsh (lead author of Kelsh et al. (2003), one of the studies upon which OEHHA has relied upon for the evaluation of newborn data) observed:

> First, it is not analytically appropriate to include the first data from the first 24 hours after birth in such analyses. Numerous researchers (Li et al. 2000; Kelsh et al. 2003; Buffler et al. 2006, Amati [sic] et al. 2007), after considering the pros and cons, concluded that the best and most appropriate analysis of the newborn screening data should exclude the first 24 hours. The reasons for not including such data include: 1) clinical recommendations to collect the newborn screening data after 24 hours, 2) the high level of false positives among newborn screening data when collected in the first 24 hours after birth, 3) the natural surge levels would dwarf any subtle environmental effect of perchlorate, even if one exists, 4) selection factors among those screened earlier, which may bias results, and 5) the inability to adequately control for the increase and decrease in TSH levels within the first 24 hours that likely requires more sophisticated statistical techniques (e.g. spline regression) – which have not been applied to any of the newborn screening studies.

In addition, in a 2006 publication, Buffler et al. (2006), a study excluded from the OEHHA weight-of-evidence analysis, the authors analyzed the same datasets analyzed in Steinmaus et al. (2010) and concluded that there was no association between maternal perchlorate exposure and neonatal TSH levels. Buffler et al. (2006) deliberately excluded the data collected at less than 24 hours after birth stating, "Because of the physiologic postnatal surge of TSH, the results for newborns screened before 24 hr were uninformative for assessing an environmental impact."

2.3 Comments on Added Text in the 2012 Draft Related to the Use of Ecologic Epidemiological Studies

OEHHA relies in large part, as noted, on five ecological studies (set forth in its Table 13) to support both its finding of a perchlorate exposure/thyroid effect association and its selection of the infant as the most sensitive population. Because of the importance of these studies to OEHHA's analysis, it attempts to dismiss the limitations in these studies noted in the peer review with the addition of arguments regarding non-differential misclassification, confounding, and bias. OEHHA undertakes an analysis of these factors in an attempt to argue that these issues have minimal impact on OEHHA's conclusions, therefore supporting OEHHA's stance that the infant is the most sensitive subpopulation and low level perchlorate exposure can affect thyroid function. However, the arguments in the 2012 draft lack a thorough evaluation of the science and are misleading regarding the impact of these factors,

as discussed below. The potential for misclassification and confounding reduce the reliability of these studies and OEHHA's PHG assessment.

2.3.1 Non-Differential Misclassification

In the 2012 draft document, OEHHA relies extensively on the concept of "non-differential misclassification" as a means of dismissing the limitations of the ecologic studies. Non-differential misclassification occurs when the likelihood of error (in the measurement of exposure, effect, or other metric) is the same in both the study group and the comparison group. One potential outcome of this misclassification is that the results will be biased "towards the null"—that is, a conclusion of no association; *however*, it is also possible that results could be biased away from the null suggesting an association where none exists. Nonetheless, OEHHA only acknowledges the possibility of the former. For example, regarding non-differential misclassification, OEHHA claims:

> The 2012 draft's claim that misclassification will categorically bias towards the null is unfounded and does not increase the reliability of conclusions based on these ecologic studies. Due to random variation, misclassification is also likely to be differential.

> …any misclassification of exposure is likely to be independent of thyroid hormone status (i.e., non-differential). This type of non-differential misclassification of exposure will bias results towards the null. That is, if an association truly exists, non-differential exposure misclassification will cause the magnitude of the observed association to be less than the magnitude of the true association. It will not cause a false association and will not strengthen an association that is truly weak.

and

> … any errors in misclassifying outcome are likely to be the same as those associated with misclassifying exposure: non-differential misclassification that will bias results to the null. As with exposure misclassification, if these errors could be corrected, the effects reported in the positive studies listed above would likely be even greater than those reported.

In actuality, the 2012 draft's claim that misclassification will categorically bias towards the null is unfounded and does not increase the reliability of conclusions based on these ecologic studies. Even though misclassification may be non-differential, due to random variation, misclassification within a single study could also likely be differential. Because of this, a non-differential misclassification process does not necessarily lead to an underestimate of risk (Wacholder et al., 1991; Flegal et al., 1991; Dosemeci et al., 1990), nor does differential misclassification necessarily lead to an overestimate of risk.

While it may be true that exposure classification to perchlorate was done independently of thyroid hormone status as OEHHA states, it doesn't necessarily follow that misclassification of exposure would be non-differential. In fact, the independent measurement of these two variables (thyroid hormone and exposure to perchlorate) is a separate matter from the issue of non-differentiality. And, even if non-differential exposure misclassification is present, results are not usually biased towards the null (Jurek et al., 2005; Jurek et al., 2008).

The 2012 draft states:

> That is, if an association truly exists, non-differential exposure misclassification will cause the magnitude of the observed association to be less than the magnitude of the true association. It will not cause a false association and will not strengthen an association that is truly weak. There are some rare exceptions to this rule, but these exceptions are not likely applicable to the studies in Table 13.

However, non-differentiality by itself is not adequate to assure that the bias is towards the null and not away from the null (Jurek, et al., 2005). As has been thoroughly reported in the literature (Dosemeci et al., 1990; Wacholder et al., 1991; Flegal et al., 1991; Kristensen, 1992; Chavance et al., 1992; Maldonado et al., 2000), in order for non-differentiality to bias towards the null, there are several conditions that must be met:

1. The likelihood of error must be exactly the same between groups. Due to random variation, differential misclassification is likely and even small variations of this assumption may actually lead to substantial bias away from the null. The studies OEHHA cites as support are nearly all ecologic studies, which do not include an evaluation of individual exposure measures, perchlorate exposure from other unconsidered sources, or contribution of other goitrogens. In addition, in these studies, the study population is captured at a single point in time, without recognition of migration in and out of the study population. Therefore, to say that misclassification in these studies is uniformly non-differential is incorrect, thus, this condition is not fulfilled.
2. Exposure misclassification errors are assumed to be independent of errors in other variables in the analysis. In the ecologic studies cited by OEHHA, since other exposures to perchlorate or perchlorate-like materials may occur without being measured, it is not possible to satisfy this condition.
3. With exposures in which there are more than two discreet levels (e.g., with perchlorate, exposure is a continuous variable with a range of possible exposure concentrations) further conditions are required to guarantee bias towards the null. In ecologic studies of perchlorate, this condition cannot be satisfied since individual exposures are unknown.
4. There must be absence of interaction with other sources of error, including other bias and confounding. In the ecologic studies cited by OEHHA, because there are several instances of interaction with other sources of error, it is not possible to satisfy this condition.

Because these conditions cannot be satisfied with regard to ecological studies, for the reasons noted above, OEHHA's attempt to use non-differential analysis to overcome the weaknesses in the ecological studies is without merit.

2.3.2 Confounding and Bias

The 2012 draft document also adds substantial text to dismiss concerns about the potential influence of confounding and bias on the ecologic studies presented in Table 13 of the draft. Despite OEHHA's claim that these studies support the infant as the most sensitive subpopulation, these studies continue to be subject to confounding and bias for the reasons set forth below, and their conclusions are therefore unreliable.

Confounding occurs when a factor has a statistical relationship with both the dependent (e.g., perchlorate exposure) and independent (e.g. thyroid function) variables, failure of which to consider may lead to a spurious association between the independent and dependent variables. For example, OEHHA states:

> … in order for a factor to cause important confounding, it not only needs to be associated with the exposure and the outcome of interest, but these associations must be fairly strong (Axelson, 1978). A factor that is only weakly associated with either the exposure or the outcome may still cause some confounding, but the impact of this confounding on the study result will usually be minor and likely unimportant."

It is important to note, however, that Axelson (1978) does not categorically dismiss "weakly associated" confounders as unimportant—he simply states that it is "desirable to control such factors whenever possible…although the influence on the risk estimate would be limited."

Despite OEHHA's claim that the studies in Table 13 of the 2012 draft support the infant as the most sensitive subpopulation, these studies continue to be subject to confounding and bias and their conclusions are therefore unreliable.

OEHHA references the Axelson (1978) example to suggest that because the association of thiocyanate with thyroid hormone (T4) changes is weak, it therefore is not likely to be a significant confounder of the effect of perchlorate. However, thiocyanate exposure in this context significantly differs from the Axelson (1978) example. Axelson (1978) discusses confounders in the context of a disease that is strongly associated with an occupational exposure, while perchlorate in OEHHA's analysis is only weakly (at best) associated with T4. Given this weak association, any confounder that is associated with T4 could have a relatively significant effect on the overall relationship, even if the absolute magnitude of the effect is small.

OEHHA (2012b) presents calculations using the "methods of Axelson, 1978," as a means of demonstrating the relatively minor effect that a rather significant increase in the percentage of the population with a high thiocyanate level (considered to be a confounder) would have on T4 levels (Table 14). However, OEHHA's calculations are not transparent and there are a number of significant problems with this analysis. First, Table 14 presents mean T4 levels for an ostensibly "perchlorate-unexposed group" from the NHANES 2001-2002 dataset. However, there is no "perchlorate-unexposed group" with total T4 measurements in the NHANES 2001-2002 dataset: NHANES 2001-2002 presents total T4 measurements for 2,345 subjects (all ages/genders). Of these, 2,276 also report ion (perchlorate, thiocyanate, and/or nitrate) in urine measurements; perchlorate was reported at a concentration above the detection limit in all of these samples.

Second, the approach applied by Axelson (1978) differs from that presented in the OEHHA 2012 draft. Axelson presented a hypothetical example in which smoking is a confounder in the evaluation of occupational disease. In the evaluation, the risk of disease differed significantly between nonsmokers, moderate smokers (a 10 times higher risk of disease than nonsmokers), and heavy smokers (a 20 times higher risk of disease than nonsmokers). The criteria for differentiating between "moderate" and "heavy" smokers are not defined, but the assumed difference in risk between the groups is substantial. The potential effect of confounding on the overall relative risk estimate is evaluated by sequentially increasing or decreasing the percentage of the total population assumed to reside in each group, and

comparing the risk of disease in exposed populations (moderate and heavy smokers) to an unexposed population (nonsmokers). By comparison, there is no group "unexposed" to thiocyanate in the NHANES 2001-2002 dataset, and the differences in thiocyanate exposure between the groups are relatively minor.

Overall, we do not argue that the impact of thiocyanate on T4 levels in the NHANES 2001-2002 population is small. However, the data suggest that the impact of perchlorate is even smaller. In fact, applying the same approach presented in Table 14 to comparing mean T4 in tertials of urinary perchlorate concentration for this population yields very similar results to those presented for thiocyanate. OEHHA presents mean T4 values for the low, mid, and high tertials of urinary thiocyanate (for the women aged 12+ group) of 8.632 µg/dL, 8.496 µg/dL, and 8.272 µg/dL, respectively (we were able to roughly replicate these estimates in our own analysis of the NHANES 2001-2002 dataset). Based on these estimates, OEHHA suggests that the effect of thiocyanate on T4 is "weak" and that the "decrease is small." However, if we examine the dataset based on urinary perchlorate tertials for the same population, mean T4 values for the low, mid, and high urinary perchlorate concentration tertials are 8.70 µg/dL, 8.49 µg/dL, and 8.45 µg/dL, respectively (corresponding to maximum perchlorate concentrations within each tertial of 2.4 µg/L, 5 µg/L, and 100 µg/L, respectively). In other words, the decrease in T4 across tertials is nearly identical to (or even smaller than) that across the urinary thiocyanate tertials. If the effect of thiocyanate is considered "weak," the effect of perchlorate is clearly "weak" as well.

However, the appropriate way to evaluate the potential effect of exposure to the three goitrogenic ions evaluated in the NHANES 2001-2002 dataset (perchlorate, nitrate, thiocyanate) is to consider the effect of all three in summation, since all act through the same mechanism of action (IUI) on the thyroid—that is, to determine the perchlorate equivalent concentration (PEC) of the three ions in urine. Using relative potency factors (RPFs) for IUI at the sodium iodide symporter (NIS) of the thyroid, the PEC of each anion can be estimated by multiplying the RPF by the amount in the urine. The relative molar potency of perchlorate to inhibit radioactive iodide (^{125}I) uptake at the NIS was reported to be 240 and 15 times that of free nitrate and thiocyanate, respectively, based on internal serum concentrations (Tonacchera et al., 2004). The RPF applied to ingested thiocyanate is further adjusted to account for thiocyanate bound to albumin in human blood serum (50%). Using this approach, mean T4 values for low, mid, and high tertials of urinary perchlorate equivalent concentration are 8.58 µg/dL, 8.68 µg/dL, and 8.36 µg/dL, respectively (corresponding to maximum PEC concentrations within each tertial of 186.2 µg/L, 341.1 µg/L, and 3,446.7 µg/L, respectively— incidentally, within the three tertials, perchlorate contributes an average of 3.0%, 2.0%, and 1.5%, respectively to the total PEC). In other words, this approach clearly demonstrates that there is no association between urinary PEC concentrations and change in T4 for this population.

Applying the approach OEHHA uses in Table 14 (i.e., assessing the potential significance of confounders based on the difference in the means for each tertial from the overall population mean, using the NHANES 2001-2 data) assumes that the differences in means are real and stable (i.e., not due to chance or variability/error in measurements). However, OEHHA's presentation of these data in Table 14 has not explored whether there are in fact any other

confounders or biases that are responsible for the extremely small observed difference in mean T4 levels for the three tertials.

With regard to the potential influence of other goitrogenic agents (i.e., nitrate), OEHHA (2012b) states,

> Also, common nitrate exposures in the U.S. may not be high enough to affect thyroid function. In a clinical trial, a nitrate dose of 15 mg/kg-day for 28 days did not decrease thyroidal iodide uptake or impact thyroid hormone levels in 10 healthy volunteers (Hunault et al., 2007).

However, as we have discussed above, perchlorate, nitrate, and thiocyanate act by the same mechanism of action on the thyroid. Using the RPF for nitrate adjusted to a weight basis (150 to extrapolate from ingested doses rather than internal serum concentrations; Tonacchera et al., 2004), a nitrate dose of 15 mg/kg-day would be equal to an equivalent perchlorate dose of 0.3 mg/kg-day. As OEHHA (2012b) reports, no effect of nitrate on the thyroid was seen at this dose. Likewise, one would expect to see no effect of perchlorate at perchlorate equivalent doses up to this level, which is nearly 1000 times the acceptable daily dose that is equivalent to the proposed perchlorate acceptable daily dose of 0.00037 mg/kg-d.

OEHHA (2012b) cites other factors to discount the potential impact of confounders on its conclusions regarding the five studies cited in Table 13. For example, it states,

> …it is important to note that each of the five positive studies listed in Table 13 involved different study populations, different time periods, different study methods, and different research groups. Despite all of these differences, the effects identified across all of these studies were similar and consistent. This consistency decreases the likelihood that confounding is responsible for all of the effects identified.

However, as we highlighted in our comments on the 2011 draft document and in Section 3.2 below, there are a number of other studies that present conflicting evidence, demonstrating no association of environmental perchlorate exposure with thyroid effects. Further, some of the methods OEHHA used to reanalyze the studies (Section 3.2) are suspect. Thus, the effects identified across all relevant studies are <u>not</u> similar and consistent.

Overall, OEHHA's attempt to dismiss the impacts of confounding and bias on these studies lacks a thorough evaluation of the science and is misleading. Because it is apparent that the results of these studies may indeed have been skewed due to the impacts of these factors, these studies should not be used as support for OEHHA's PHG risk assessment.

3.0 MISREPRESENTATION OF WEIGHT-OF-EVIDENCE IN THE 2012 DRAFT DOCUMENT

In the sections above, we noted issues with the studies themselves, in this section we note concerns related the misrepresentation of the assessment by the Agency in its draft documents. A transparent process allows an evaluation of the underlying data, review of the methodology used for assessing the data, and confirmation of the results of an assessment. Transparency provides reviewers with the information required to verify each of these steps and serves to strengthen the evaluation. Transparency is crucial in scientific assessment of public health measures and in the development of regulatory action, such as the development of a PHG.

3.1 OEHHA Does Not Clearly Identify OEHHA-Generated Effect Estimates

The 2012 draft document relies on estimates of effect that are attributed to cited references yet, when examined, are actually estimates generated by OEHHA. For example, of the five studies summarized in Table 13 of the 2012 draft, effect estimates cited for four of the studies (Kelsh et al., 2003; Brechner et al., 2000; Li et al., 2000a; Crump et al., 2000) were actually calculated by OEHHA and not the authors of the study. The estimates are based on data presented in the original article, but should not be attributed to the authors of those studies.

The fifth study in Table 13 (Steinmaus et al., 2010) was authored by the cited author of the 2012 draft document.

Therefore, all of the effect estimates for the five studies that OEHHA uses as primary support for its proposed PHG were calculated by one person—the author of the OEHHA document. Dr. Steinmaus has served both a central role in developing the science and in providing the regulatory analysis supporting the PHG. In light of this dual role, which raises obvious conflict of interest issues, it is particularly troubling that the assumptions and methods OEHHA uses to arrive at the effect estimates for these studies are not presented in the 2012 draft document, nor have they been peer reviewed in the scientific literature.

One of OEHHA's three external peer reviewers noted the lack of transparency in Table 13. He stated:

> Some of the effect estimates presented in Table 13 are not the main results of the paper, but instead were calculated using data in the tables of the paper by the authors of this draft document. Therefore, these are unadjusted estimates. This should be clearly marked in this table as well.

In acknowledgement of this, OEHHA responded as follows:

> We now state in Table 13 that the Kelsh et al. (2003) results are a re-analysis, and the Li et al. (2000a) results are from a figure in their article. As mentioned above, a column with the statistical adjustments has also been added.

However, in the 2012 draft, only the study by Kelsh et al. (2003) is referred to as a "reanalysis." This suggests that the rest of the estimates provided in Table 13 were concluded by each study's authors, when this is not true.

Because this information represents new data and calculations by OEHHA, it is inappropriate that no data or calculations are shown. Table 13 presents odds ratios (ORs) for low T4 (Kelsh et al., 2003; Brechner et al., 2000), or percent differences in mean T4 or TSH levels between exposed and unexposed groups (Brechner et al., 2000; Li et al., 2000a; Crump et al., 2000). Although not included in Table 13, OEHHA also presents similar results in the text of the draft based on data from Buffler et al. (2006). It does not appear that OEHHA conducted any reanalyses using the original datasets for these calculations, rather, these calculations are based on manipulating data reported in tables and charts of the original studies.

> The 2012 draft relies on estimates of effect that are attributed to several studies, yet, when examined, are actually original calculations generated by OEHHA. OEHHA's re-analyses and conclusions based on this assessment do not have general acceptance in the scientific community and therefore do not constitute the best available science.

The analyses and conclusions OEHHA presents in Table 13 have not been subject to peer-review (i.e., not published in a peer reviewed journal). OEHHA is required to use scientific information to make informed decisions (e.g., deriving a PHG), which includes an emphasis on peer reviewed data. Authoritative bodies have highlighted the importance of peer review in regulatory risk assessments. For example, the Office of Management and Budget (OMB) has assigned responsibility for ensuring and maximizing the quality, objectivity, utility, and integration of information to federal agencies, such as US EPA (OMB, 2002). These guidelines are useful for other agencies, such as OEHHA, to consider. OMB writes that the following principles be applied to influential scientific documents:

> (A) The substance of the information is accurate, reliable and unbiased. This involves the use of:
>
> > (i) the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer reviewed science and supporting studies; and
> >
> > (ii) data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies the use of the data).
>
> (B) The presentation of information on human health, safety, or environmental risks, consistent with the purpose of the information, is comprehensive, informative, and understandable (US EPA, 2002).

Disregarding these principles, OEHHA relies on information and methods that have not gained acceptance of the scientific community as accurate, reliable, and unbiased. Furthermore, OEHHA does not present a comprehensive review of the literature with which to support its PHG risk assessment (see section 3.2). Lastly, the use of these screening TSH data collected at less than 24 hours is untested and does not have support of the scientific community as a methodology for assessment of effects from environmental agents. Also, the use of these screening TSH data collected at less than 24 hours has only been reported in one paper—Steinmaus et al. (2010). OEHHA's calculations and conclusions based on this reanalysis, as well as use of TSH data collected at less than 24 hours, do not constitute the best available science.

3.2 Studies Included and Excluded by OEHHA

OEHHA has re-analyzed and re-interpreted much of the data presented in the studies it cites in Table 13 and, in so doing, reaches conclusions that are different from those reached by the authors of the studies. It is scientifically inappropriate for OEHHA to present these calculations while citing (and apparently attributing the conclusions to) the original authors.

OEHHA bases its draft PHG on non-peer reviewed estimates calculated using data reported in tables and figures presented in four studies. A fifth study was authored by the lead author of the 2011 and 2012 drafts and is also given great weight in OEHHA's PHG analysis.

These five studies have inherent limitations with regard to establishing cause and effect, and are contrary to the more than 60 years of perchlorate research that presents conflicting results. We take serious issue with OEHHA's failure to assess the full weight of scientific evidence in the assessment of ecological studies, particularly given the unreferenced analysis of screening data collected at less than 24 hours after birth. This presentation of a limited collection of studies is speculative and not

scientific. This is in contrast to OEHHA's following statement in response to a peer reviewer:

> OEHHA does not make strong inference based on this single study alone. Instead, inference is based on the consistency of findings, detailed evaluations of other important aspects of causal inference, and a weight-of-evidence approach that incorporates the findings and evaluations of many different studies.

The five ecologic studies presented in Table 13 all suggest positive associations between environmental perchlorate exposure and thyroid effects, based on the Agency's analyses. OEHHA's presentation of these studies gives the incorrect impression that these studies reflect the weight-of-evidence. However, the authors of several of these studies present conflicting results.

- Kelsh et al. (2003) states "We also found no statistically or biologically relevant differences among Redlands' newborns for TSH levels."
- Crump et al. (2000) concludes:

  > Neonata1 thyroid-stimulating hormone levels were significantly lower in Taltal compared with Antofagasta; this is opposite to the known pharmacological effect of perchlorate, and the magnitude of difference did not seem to be clinically significant.

  The authors also caution that the reports on familial history of thyroid issues were not verified, there may have been recall bias, and it may represent historical variations in iodine supplementation.
- Li et al. (2000a) states, "We conclude that perchlorate in drinking water at a level of up to 15 ppb had no detectable effect on neonatal T4 levels in this population."

When not interpreted or reanalyzed by OEHHA, the five studies listed in Table 13 of the 2012 draft overwhelmingly report no association between environmental levels of perchlorate and thyroid function in infants. The exception—Brechner et al. (2000)—has been criticized by the NRC (2005) which stated

> The actual adjusted concentrations for each city were not reported. Neonatal T4 values did not differ significantly between Yuma and Flagstaff after adjustment for race or ethnicity. However, follow-up testing of TSH is done only in infants with the lowest 10% of T4 concentrations, so the absence of differences in T4 concentrations between the cities is not especially informative inasmuch as only the lowest part of the entire distribution was compared. …perchlorate exposures in infants' mothers were not directly measured; in fact, drinking-water concentrations of perchlorate were not derived from the same period as the newborn screening results….

Four studies that were disregarded by OEHHA are listed in Table 13B (Tellez Tellez et al., 2005; Li et al., 2000b; Amatai et al., 2007; Cao et al., 2010), and another (Buffler et al., 2006) is disregarded without explanation. Four of the five studies that are disregarded by OEHHA also present no association between environmental levels of perchlorate and thyroid function in infants. The exception—Cao et al. (2010)—was excluded by OEHHA because "Adjustments for urinary creatinine could have created false associations. No data in neonates [sic]." Several other limitations of Cao et al. (2010) further limit the validity of its conclusions. Cao and colleagues analyzed perchlorate, iodide, nitrate, and thiocyanate in

stored urine collected from diapers or in urine bags. The standard approach to reliably measuring these variables is from a urine sample not from urine extracted from diapers. Perchlorate was detected in diapers that had not been used (control diapers). Additionally, TSH and free T4 were also analyzed for in urine samples, a non-standard approach (measurements are usually made in serum).

Therefore, in this expanded group of 10 studies that measured either T4 or TSH in neonates, the weight-of-evidence supports a conclusion that there is no association between environmental levels of perchlorate and thyroid function in neonates. However, OEHHA's inconsistent application of inclusion/exclusion methodology is misleading, lacks transparency, and leads to erroneous conclusions. These inconsistencies are noted in the last column of Table 3 in our comments below.

3.3 OEHHA Does Not Explain Why the Cited Study Results Are Inconsistent with the Known Dose Response Data

The mechanism of action of perchlorate and its dose-response is well-documented and understood. IUI is a threshold effect that has not been reported to occur in healthy adults with exposures to perchlorate levels less than or equal to 245 ppb (assuming the standard 70-kg adult drinking 2 L/d). If IUI does not occur, there can be no progression to thyroid hormone changes or other adverse effects, even in people with low iodine intake (NRC, 2005).

OEHHA does not explain why its conclusions differ from this known dose response. OEHHA states,

> Data from several studies (Kelsh et al., 2003; Brechner et al., 2000; Steinmaus et al., 2010; and others) provide evidence of a possible link between perchlorate in drinking water during pregnancy and thyroid hormone levels in newborns.

However, these studies evaluated doses of perchlorate that are well-below the known threshold for IUI. It is clear that any association cannot be due to IUI; however, OEHHA does not present any alternative mechanisms that might occur for effects at doses below the NOEL.

Table 3. Review and Expansion of OEHHA Table 13 (page 53)

	OEHHA Interpretation (Quoted from Table 13)		Newly Generated Values in the 2012 Draft Document not found in the Cited Article			
Study	**T4**	**TSH**	**T4**	**TSH**	**Lack of Scientific Transparency in OEHHA Analysis**	**Lack of Scientific Consistency in OEHHA Analysis**
Kelsh et al. (2003)	"OR for low T4 = 1.18 (95% CI, 1.13-1.24; p < 0.0001)"	"OR for high TSH = 1.57 (95% CI, 1.14-2.16; p < 0.0001)"	OR for T4	OR for elevated TSH	Considering it is a new value generated by OEHHA, no data or calculation shown for low T4 OR. Considering it is a new value generated by OEHHA no data or calculation shown for elevated TSH OR. TSH only measured in infants with "low T4" which was "…lower than a prescribed threshold (typically 9.0 µg/dL) or was part of the lowest 5% of the remaining daily tray samples…" (Kelsh et al., 2003). No association was reported by authors.	OEHHA uses this study and presents its own generated values based on T4 including data collected at >24 h, while excluding Li et al. (2000b) and Amitai et al. (2007) for not having sufficient data collected prior to 24 hours.
Steinmaus et al. (2010)	No data	"OR for high TSH = 1.53 (95% CI, 1.24-1.89; p < 0.0001)"	None reported. Note that while no new values were generated, the author of the study and the cited author of the 2012 draft are the same.		Elevated TSH was defined as ≥ 25 µIU/mL. While OR is statistically significant, the mean TSH levels are within normal range for "exposed" and "unexposed." Mean TSH for ≤5 ppb group = 4.03 µIU/mL, for >5 ppb = 4.35 µIU/mL; OR for TSH ≥ 25 µIU/mL for exposed vs. unexposed = 0.72 (CI: 0.41-1.27).	This study is based on the same dataset as Buffler et al. (2006) which OEHHA excluded.

	OEHHA Interpretation (Quoted from Table 13)		Newly Generated Values in the 2012 Draft Document not found in the Cited Article		Lack of Scientific Transparency in OEHHA Analysis	Lack of Scientific Consistency in OEHHA Analysis
Brechner et al. (2000)	OR for low T4 = 1.18 (95% CI, 1.05-1.33; p = 0.006)	Mean TSH = 27% higher	OR for low T4	Mean TSH	Considering it is a new value generated by OEHHA, no data or calculation shown for low T4 OR. Considering it is a new value generated by OEHHA, no data or calculation shown for mean TSH difference. In the Brechner et al. (2000) study, only infants with "low T4" were evaluated. The definition of "low T4" was "…approximately 10% of the samples from each batch with the lowest T4 levels" (Brechner et al., 2000). The effect of age in days on TSH was highly significant (p<0.001), but OEHHA does not adjust for this. Brechner et al. (2000) state, "…the individual t tests were not significant…" for infants in the 0-1 day group, meaning there was no difference between groups.	OEHHA uses this study but study found to be unreliable by NRC (2005; see section 3.2) OEHHA uses this study and presents its own generated values based on T4 including data collected at >24 h, while Li et al. (2000b) and Amitai et al. (2007) were excluded for not having sufficient data collected prior to 24 hours.
Li et al. (2000a)	"Mean T4 ≈ 22% lower"	No data	Mean T4	None reported.	Considering it is a new value generated by OEHHA, no data or calculation shown for mean T4 difference. It appears to be based on Z. Li et al., 2000, Table 3 on the first collection day. No sample size is provided. It is noteworthy that collection on day 2, the mean is approximately 18% higher (the opposite direction)	OEHHA uses this study and presents its own generated values based on T4 data collected at <24 h, while Li et al. (2000b) is based on the same population, had the same study design and was excluded.

	OEHHA Interpretation (Quoted from Table 13)		Newly Generated Values in the 2012 Draft Document not found in the Cited Article		Lack of Scientific Transparency in OEHHA Analysis	Lack of Scientific Consistency in OEHHA Analysis
Crump et al. (2000)	No data	Mean TSH ≈ 45% higher	None reported.	Mean TSH	Considering it is a new value generated by OEHHA, no data or calculation shown for mean TSH difference. No association; decreased TSH with exposure to 100-120 ppb (mean 2.4 µIU/mL) compared with city with no perchlorate in drinking water (mean 3.4 µIU/mL) (opposite expected direction).	This study was in the same location as Tellez Tellez et al. (2005) which was excluded by OEHHA due to high iodine exposure.
Tellez Tellez et al. (2005)	Not listed in Table 13 because "…45% of women from the exposed city delivered in the unexposed city and the iodine levels were very high."		None reported.		No statistical difference for TSH for mean perchlorate of 114 ppb.	This study from the same geographical location as Crump et al. (2000) which was included in the OEHHA analysis.
Li et al. (2000b)	Not listed in Table 13 because "…TSH measurements collected on first day after birth were excluded."		None reported.		No effect up to 15 ppb. Overall TSH mean: Las Vegas = 11.5 µIU/mL; Reno = 12.5 µIU/mL; TSH mean using data for days 2-7 only: Las Vegas = 12.8 µIU/mL; Reno = 12.8 µIU/mL; Only infants with low T4 were tested.	This study was not used, but Li et al. (2000a) was. The rationale for exclusion was no TSH measurements collected on the first day after birth. Yet, Brechner et al. (2000) and Kelsh et al. (2003), were presented with data collected at >24 h.
Amitai et al. (2007)	Not listed in Table 13 because "… < 10% of newborns had thyroid hormones measured in first 36 hr after birth."		None reported.		No difference between groups with up to ≥340 ppb perchlorate	This study was not used but Brechner et al. (2000) and Kelsh et al. (2003), were presented with data collected at >24 h.

	OEHHA Interpretation (Quoted from Table 13)	Newly Generated Values in the 2012 Draft Document not found in the Cited Article		Lack of Scientific Transparency in OEHHA Analysis	Lack of Scientific Consistency in OEHHA Analysis
Cao et al. (2010)	Not listed in Table 13 because "…adjustments for urinary creatinine could have created false associations." And "No data in neonates."	None reported.		Samples were from diapers which had perchlorate present in them (unexplained by authors). Thyroid measures were from urine (not standard methodology).	This study could have been excluded for additional reasons.
Buffler et al. (2006)	Not considered. Reason not given.	None reported.	In text only: OR for elevated TSH in total population OR for elevated TSH in < 24 samples	No association; for newborns screened ≥24 hr, the adjusted POR for high TSH was 0.73 (95% CI, 0.40–1.23). "Because of the physiologic postnatal surge of TSH, the results for newborns screened before 24 hr were uninformative for assessing an environmental impact."	Steinmaus et al. (2010) was included and is based on the same dataset and similar methodologies, but uses data collected within 24 hours.

OR: Odds Ratio; CI: Confidence Interval

4.0 SPECIFIC CONCERNS WITH THE CALCULATION OF THE PROPOSED PHG

The calculation of the PHG is mathematically simple with only five variables as follows:

$$PHG\ (\mu g / L) \quad = \quad \frac{POD\ (\mu g / kg - d) \quad \times \quad BW\ (kg) \quad \times \quad RSC}{UF \quad \times \quad WC\ (L / d)}$$

i.e., the point of departure (POD), body weight (BW), relative source contribution (RSC), uncertainty factors (UF), and water consumption (WC). Each of these variables should be based on scientific data that is consistent with the most current information. However, OEHHA's draft PHG incorporates both scientific and policy-based assumptions that result in substantial additional and unwarranted conservatism in the calculation of the PHG. These assumptions are discussed in the following sections. Changes in the variables account for the numeric difference in the 2004 and draft 2011/2012 PHGs, specifically:

- Both the 2004 and 2011/2012 PHGs use a POD of 3.7 µg/kg-d based on a benchmark dose (BMD) assessment for the NOEL from Greer et al. (2002).
- The 2004 PHG applied a UF of 3 for infants and 10 for all other groups. The 2011/2012 PHGs apply a UF of 10 to all groups.
- The 2004 BW/WC for infants was 5.99 kg-d/L. The 2012 PHG uses a value of 4.2 kg-d/L.
- The RSC in 2004 was estimated to be 0.6. In the 2011/2012 drafts, a value of 0.73 is used.

We agree with OEHHA's use of Greer et al. (2002) as the most conservative clinical study that is consistent with other clinical studies. However, as described below, the changes in the UFs and drinking water intake rates are unjustified and unnecessary.

Indeed, it is noteworthy that there are three points in the PHG calculation in which OEHHA states it is accounting for uncertainty. First, OEHHA uses the lower 95th confidence interval of the Benchmark Dose for the 5% chance of observing any change in IUI (BMDL). Second, OEHHA applies a factor of 10 for intraspecies UF. Third, OEHHA applies life stage specific drinking water intake rates. This cumulative effect of these adjustments is an overly conservative PHG which is particularly notable when recalling that the starting point (POD) is based on a nonadverse effect.

> In defining the most sensitive subpopulation, all other subpopulations, including those that are more sensitive than average, will also be protected. Several authoritative bodies have determined that the pregnant woman and her fetus are the most sensitive subpopulation.

4.1 Brief Review of the Critical Study

The POD for the PHG is based on the scientific study by Greer et al. (2002), a clinical study. We agree with OEHHA's use of this study as the POD for the PHG. Of all types of scientific studies, clinical studies are best for understanding subtle effects of chemicals on many parameters of the human body, and for identifying possible human health effects associated with chemical exposures. Importantly, the results of Greer et al. (2002) should not be considered in isolation of the whole perchlorate toxicology database. Rather, the Greer et al. (2002) data are supported by the Lawrence et al. (2000, 2001) 14-day clinical study and a six

month study conducted by Braverman et al. (2006). Of these studies, Greer et al. (2002) presents the lowest, or most conservative, NOEL for perchlorate exposure.

In Greer et al. (2002), thirty-seven healthy adults were exposed to 0.007, 0.02, 0.1, or 0.5 mg/kg-d perchlorate in drinking water daily for two weeks, and changes in radioactive iodide uptake (RAIU) was measured. The study reports:

> The lowest dose producing no statistically significant inhibition of uptake was 0.007 mg/kg-day. Thus, in this study, 0.007 mg/kg-day (7 µg/kg-day) was a NOEL for inhibition of RAIU.

Therefore, based on Greer et al. (2002), the critical effect is IUI and the corresponding NOEL is 0.007 mg/kg-d (or a drinking water equivalent of 245 ppb assuming a 70 kg adult drinking 2 L/d).

4.2 Point of Departure

The POD used by OEHHA is a benchmark dose lower limit (BMDL) derived from the NOEL for IUI in adult human volunteers identified in Greer et al. (2002). This POD is 3.7 µg/kg-d, essentially half the dose of the NOEL.

As opposed to OEHHA, the other agencies opted to use the NOEL defined in Greer et al. (2002) rather than calculate a BMDL. NRC (2005) wrote:

> Although the committee recognizes that BMD modeling can be an improvement over the use of the NOAEL or LOAEL as a point of departure, there appears to be no consensus on the criteria for choosing one BMD approach over another. Because no clear justifications were provided with the individual analyses [which included the OEHHA analysis] of the Greer et al. (2002) data that allowed selection of one set of results over another, the committee concluded that using the NOEL (0.007 mg/kg per day) for iodide uptake inhibition from Greer et al. (2002) as the point of departure provides a reasonable and transparent approach to the perchlorate risk assessment. As noted above, the NOEL value from Greer et al. (2002) is consistent with other clinical studies that have investigated iodide uptake inhibition by perchlorate (Lawrence et al. 2000, 2001; Braverman et al. 2004). That the NOEL value from Greer et al. (2002) is a health-protective and conservative point of departure is supported by the results of a 4-week study of higher doses in normal subjects (Brabant et al. 1992; see Chapter 2 [of NRC, 2005]) and extensive human and animal data that demonstrate that there will be no progression to adverse effects if no inhibition of iodide uptake occurs (see Figure 5-2 [of NRC, 2005]). As discussed in Chapter 2 [of NRC, 2005], a sustained exposure at more than 0.4 mg/kg per day would most likely be required to cause a sufficient decline in iodide uptake and thyroid hormone production to result in adverse health effects in normal adults. That estimate is based on clinical studies and studies of long-term treatment of patients who had hyperthyroidism. Finally, the occupational and environmental studies described in Chapter 3 [of NRC, 2005]do not provide any evidence that would raise concerns about using the NOEL from Greer et al. (2002) as the point of departure for the perchlorate risk assessment.

OEHHA defines the BMDL as the lower 95% confidence limit of the dose of perchlorate likely to cause a five percent decrease in iodide uptake. The five percent decrease was chosen "since this is the lowest level of effect that can be identified with statistical significance in many animal and human studies" (OEHHA, 2012b). OEHHA claims that the 1.8% inhibition of iodide uptake that corresponded to the NOEL from Greer et al. (2002) constitutes a physiological event, when it is not statistically or biologically significant. However, OEHHA also recognizes IUI is not adverse and is a precursor to any adverse effect. The draft states, "…the primary toxic mechanism of perchlorate is a reduction in iodide uptake into the thyroid gland. If severe enough, this can lead to reduced thyroid hormone production."

The POD is based on a nonadverse effect, IUI. The NOEL reported in Greer et al. (2002) is the dose at which no effect—adverse or otherwise—is likely to occur. Despite these factors, the 2012 draft treats the POD which is approximately half of the NOEL based on a non-adverse effect, as equivalent to an adverse effect. The PHG calculation employed by OEHHA thereby necessarily produces a much more conservative PHG than is justified by reliable scientific studies.

Contrasted with the NOEL approach used by the other agencies, the BMD approach results in a POD that is approximately half of the NOEL. In typical BMD analyses, NOAELs were generally lower than or similar to BMDs.[4] This suggests that OEHHA's BMD is likely to be more conservative than necessary given the conservative nature of the POD.

In its guidance document, US EPA (1995) notes that

> Several considerations may influence the selection of a BMR [benchmark response]. The first consideration is that, when used for determining the RfD, the BMD is used like the NOAEL. This suggests that the BMR should be selected near the low end of the range of increased risks that can be detected in a bioassay of typical size.

Recall that the POD is based on a nonadverse effect, IUI. The NOEL reported in Greer et al. (2002) is the dose at which no effect—adverse or otherwise—is likely to occur. Despite these factors, the 2012 draft treats the POD which is approximately half of the NOEL based on an non-adverse effect, as equivalent to an adverse effect. The PHG calculation employed by OEHHA thereby necessarily produces a much more conservative PHG than is justified by the science.

[4] Regarding the comparison of BMDs and NOAEL approaches, US EPA (1995) writes, "The fact that a BMD corresponds to a specified level of change in response to an adverse effect (for quantal data, generally 1 percent to 10 percent increased risk, as discussed earlier) and a NOAEL ostensibly corresponds to an experimental dose with no adverse effect does not imply that NOAELs will necessarily be smaller than BMDs (and consequently that larger uncertainty factors may be appropriate for BMDs). First, a BMD is defined as a statistical lower limit, which introduces an element of conservatism in its definition. Second, one cannot conclude that no adverse effects are possible at a NOAEL or that effects will necessarily be observed at the BMD. The BMD corresponding to an extra risk of 1 percent was smaller than the corresponding NOAEL for each of 10 data sets studied by Gaylor (1989). Among five sets of quantal data studied by Crump (1984), the BMD corresponding to an extra risk of 1 percent was larger than the NOAEL in one case by a factor of 1.4, and smaller than the NOAEL in three cases by factors ranging from 1.1 to 2.6 (one data set did not define a NOAEL). However, it is unclear whether the data sets used in these studies are typical of those to which the BMD method would be applied if the method is used routinely. In a comparison study of a large number of developmental toxicity data sets (Allen et al., 1994a, b; Faustman et al., 1994), a BMD corresponding to an extra risk of 5 percent was on average similar to the NOAEL when expressed as probability of response per litter."

4.3 Uncertainty Factors

To develop a PHG, the selected POD is divided by UFs, which are largely based on professional judgment and policy considerations. For perchlorate, one UF is applied to the POD, to account for intraspecies uncertainty, that is, differences between the study population in Greer et al. (2002) and the general population, including sensitive subpopulations.

The intraspecies UF is meant to allow for intraspecies (i.e., human-to-human) variability and has a default value of 10. This value has been further defined to consider the differences in toxicokinetics and toxicodynamics. Toxicokinetics is the determination and quantification of the time course of absorption, distribution, biotransformation, and excretion of chemicals (sometimes referred to as pharmacokinetics) and toxicodynamics is the determination and quantification of the sequence of events at the cellular and molecular levels leading to a toxic response to an environmental agent (sometimes referred to as pharmacodynamics).

Both the 2004 and draft 2011/2012 PHGs use a UF of 10 because the Greer et al. (2002) study included only healthy adults. In calculating a potential PHG for infants, OEHHA (2004) used a UF of 3 rather than 10, and the value that was calculated for the infant was thus less conservative than that calculated for the pregnant woman. As stated in the 2004 PHG risk assessment:

> A smaller uncertainty factor of three is used for the infant. This is because traditionally, an uncertainty factor of 10 is used to account for interindividual variability, which is assumed to include a factor of approximately three (or half a log unit) for differences in toxicokinetics and another three for differences in toxicodynamics. In the case of infant exposure estimation, an infant specific BW/WC ratio was used, which accounted for up to a 6-fold difference in toxicokinetics between infants and adults. It should be noted that the differences in toxicokinetics between infants and adults might have been over-estimated. Using PBPK modeling, U.S. EPA (2002) concluded that uptake and elimination kinetics of perchlorate are such that the resultant time-integrated perchlorate concentrations in blood (area under the curve) for adults (70 kg) and children (15 kg) should be about the same. Due to these considerations, a full interindividual variability factor of 10 for infants did not appear warranted.

When using life stage specific body weights and drinking water intake rates, the uncertainty in the toxicokinetic factor is reduced. Additionally, there is evidence that there is no difference in clearance between infants and adults for pharmaceuticals that behave similarly to perchlorate in the body (Appendix B). There is no evidence that toxicodynamics differ between adults and infants or other more sensitive subpopulations; however there are no data to support or refute this. For these reasons, an interspecies UF of 3 or less is reasonable and likely to be conservative.

In practice, a UF of 10 can be applied to extrapolate from a LOAEL-to-NOAEL if the critical study was not able to determine a NOAEL. With perchlorate, there is the unique situation where a study has determined a NOEL for a nonadverse effect and a NOAEL has been suggested (NRC, 2005). Based on this situation, the actual difference between these values is approximately a factor of 57. Therefore, using the NOEL versus the NOAEL has resulted in a margin of safety for adverse effects of at least this value rendering it unnecessary for OEHHA to further reduce its POD through the application of the BMD and UFs.

Contrary to what is stated in the 2012 draft, it is not consistent with the NRC application of UFs. The draft states:

> OEHHA notes that the uncertainty factor of 10 that we use is the same as the uncertainty factor of 10 recommended and used by the NRC to calculate its most recent perchlorate reference dose for U.S. EPA (NRC, 2005).

However, NRC did not go on to apply life stage specific drinking water intake rates and calculate a drinking water equivalent value. The NRC also did not use a BMD approach to calculate it POD, despite having evaluated the OEHHA (2004) BMD approach.

OEHHA's application of the BMD approach and its application of unwarranted UFs is not scientifically justified and has produced an overly conservative PHG.

4.4 Relative Source Contribution

A breast-fed infant would not be directly exposed to municipal drinking water and rates of exposures via breast milk were not estimated in the OEHHA PHG document.

The resulting Acceptable Daily Dose (ADD) is translated into a drinking water equivalent by incorporating the factor for the RSC to account for exposures to perchlorate from different media in addition to water (e.g., food). The RSC reflects the portion of the total ADD not derived from food, and is based on mean values of estimated intake from the Food and Drug Administration Total Diet Study (TDS) (Murray et al., 2008) for adults and a study that estimated intake based on formula in infants (Schier et al., 2009). The 2004 PHG used a RSC of 60% because OEHHA believed that the daily exposure of pregnant women to perchlorate would be predominantly from contaminated drinking water, not from other sources such as food. The 2011 draft PHG uses a RSC of 73% based on the difference between the ADD and the estimated perchlorate intake from formula prepared using perchlorate free water, divided by the ADD.

4.4.1 Schier et al. *(2009) as the Basis of the RSC*

Schier et al. (2009) 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 US EPA Reference Dose (RfD). Exceeding the RfD is not 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.

As such, Schier et al. (2009) estimates exposure to formula-fed infants, but does not account for any potential health effect, particularly in light of the iodine sufficiency provided by commercial formula. OEHHA's reliance on Schier et al. as a basis for the RSC is therefore misplaced.

4.4.2 The POD Is Based on a Study Which Already Includes Background Exposure through Food

Considering the critical study for the POD, it was not necessary for OEHHA to use an RSC. Greer et al. (2002) did not control dietary intake of perchlorate or other natural agents such as nitrate, thiocyanate, or iodine. Perchlorate has been detected in many foods, including but not limited to milk, lettuce, and cantaloupe (Murray et al., 2008). Thus, the dose of perchlorate that the study subjects in Greer et al. (2002) received from drinking water can be assumed to be in addition to background intake from diet. If the background dose of perchlorate from all sources was 0.02 to 0.234 μg/kg-d (the 5th and 95th percentile estimated doses from Blount et al. (2007)), then the administered doses in Greer et al. (2002) underestimate the subjects' true exposure by this amount and the POD in the PHG equation already implicitly incorporates a RSC.

Shier et al. (2009) study was not available during assessments by OEHHA in 2004, ATSDR in 2008, or NRC in 2005. However, US EPA OIG (2010) chose not to evaluate perchlorate exposure based on the estimates provided in Schier et al. (2009). Rather, OIG uses the FDA TDS and states:

> The perchlorate exposure in non-nursing infants can be estimated using the results from the 2008 FDA Food Dietary Study. The 2008 FDA Food Dietary Study reports the total perchlorate intake from food for 6- to 11-month-old infants to be 0.26–0.29 μg/kg-day (i.e., not including potential perchlorate exposure from water) (Murray 2008, Table 5). Since the perchlorate RfD is 0.6 μg/kg-day, the perchlorate exposure from food for 6- to 11-month-old infants of 0.26–0.29 μg/kg-day represents 37% to 41% of the perchlorate RfD. This suggests a RSC of about 60% for non-nursing infants.

However, they caution,

> Unfortunately, this estimated perchlorate RSC is derived using a single chemical risk assessment process that is characterized as being outdated. In other words, limiting only perchlorate to protect public health does not insure that the total NIS inhibition load acting on the non-nursing infants is "safe" because the NIS inhibition exposure from thiocyanate and nitrate in the food and water of the non-nursing infant is not considered.

It was unnecessary for OEHHA to apply an RSC, as background exposures to perchlorate and other goitrogens was underestimated in the Greer et al. (2002) doses.

4.4.3 The RSC Proposed by OEHHA Is Only Relevant for Formula-Fed Infants

It should also be noted that OEHHA bases its draft PHG on the exclusively formula-fed infant, not the breast-fed infant or an infant that receives both. A breast-fed infant would not be directly exposed to municipal drinking water and rates of exposures via breast milk were

not estimated in the OEHHA PHG document. However, in its justification for choosing the infant as the most susceptible population, OEHHA cites studies of low iodine in breast-fed infants. OEHHA states,

> The increased susceptibility in infants is also supported by data suggesting that many infants may not be receiving adequate iodine in their diets and that young infants have low stores of thyroid hormone (less than one days [sic] worth compared to several weeks [sic] worth in adults) (van den Hove *et al*., 1999; Pearce *et al.*, 2007).

And further continues,

> …new data suggests that many infants may not be receiving adequate iodine in their diets. In a study of nursing mothers in Boston, 47 percent of breast milk samples did not contain enough iodine to meet the infant iodine intake recommended by the Institute of Medicine (Pearce et al., 2007). Since the mechanism of perchlorate toxicity is a reduced iodide uptake into the thyroid, perchlorate-related toxicity is likely to be greater in infants who are already deficient in iodine.

Formula is fortified with iodine and an exclusively formula-fed infant would receive middle to higher iodine levels through formula and would not be expected to be iodine deficient (Schier et al., 2009). The same study cited by OEHHA to determine the RSC (Schier et al., 2009) reports,

> Although the minimum levels of iodine would be insufficient based on exposure modeling, it is more likely that the true levels would approach somewhere in between (middle value). In this case, and in situations with higher iodine intakes, no infants would be expected to be iodine deficient.

OEHHA suggest that some breast-fed infants may be more susceptible due to inadequate iodine reported in breast milk samples. This, however, is misleading as the PHG is applicable to drinking water, which would not be a major source of exposure for a breast-fed infant. Furthermore, Pearce et al. (2007) report that "Breast milk iodine content was significantly correlated with urinary iodine per gram creatinine and urinary cotinine, but was not significantly correlated with breast milk or urinary perchlorate."

The PHG is relevant to formula-fed infants, particularly those that are exclusively fed formula and would have the greatest intake of tap water. The study by Schier et al. (2009) is appropriate in that it focuses on intake in formula-fed infants; however, in its application to define a RSC, OEHHA must consider that these formula-fed infants are iodine sufficient and unlikely to experience IUI that is sufficient to cause adverse effects.

4.5 Body Weight and Water Consumption

The PHG calculated in the 2011/2012 drafts is not based on new science. Instead, the PHG is derived by using different values for BW, RSC, and WC in the 2011 and 2012 draft documents based on the assumption that the infant is the most sensitive population, as opposed to the pregnant woman However, in the derivation of the proposed PHG, OEHHA fails to demonstrate that the current PHG of 6 ppb is not health protective or that the proposed PHG of 1 ppb offers additional health benefit.

The 2004 PHG used a ratio of body weight to tap water consumption rate (BW/WC) based on the 95th percentile of the pregnant woman population, or 25.2 kg-d/L (infants were 5.99

kg-d/L). The draft 2011/2012 PHG uses a ratio based on the 95th percentile for infants age 0-6 months, or 4.3 kg-d/L.

For the body weight and water consumption rate factors, OEHHA's PHG (2012) calculation uses the upper 95th percentile water consumption rate: body weight ratios for infants age 0-6 months (OEHHA, 2012a). These ratios are based on water intake for consumers, including direct water intake (used for drinking) and indirect water intake (used in the final preparation of foods at home or restaurants).

The drinking water intake rates are based on data collected in the USDA Continuing Study of Food Intakes (CSFI) by Individuals from 1994-1996 and 1998. This was a large study of dietary recall and was reported by US EPA (2004) and Kahn and Strahlka (2009); Dr. Kahn and Ms. Strahlka were the primary authors of US EPA (2004) and OEHHA (2012a) uses the same data set as reported in US EPA (2004).

Using water intake and body weight as the sole variables to make assumptions about effect makes general assumptions about numerous body functions (e.g., excretion) in lieu of actual data. In effect, this calculation does not account for absorption, distribution, or excretion, regardless of developmental state. This calculation implicitly assumes that the body's disposition of perchlorate is directly proportional to body weight. There are no scientific data to support these assumptions.

Also, the study population in OEHHA (2012a) may not be representative of the California population as the data are compiled from individuals from all 50 states and the District of Columbia. The body weights are lower than those reported in 1996-2000 NHANES, as presented by US EPA in the Child Specific Exposure Factors Handbook (US EPA, 2008d) and may not be representative of the general population. For one month olds, the mean, 90th and 95th percentile body weights are 20, 45, and 24% lower than the NHANES 1996-2000 data. A greater body weight will result in a lower total dose, if intake is the same. The use of a lower body weight, as OEHHA did, serves to decrease the PHG.

> Using the intake rates suggested by OEHHA, the 95th percentile one month old infant would consume approximately 2.6 L/d, or 280% of their blood volume. This is the equivalent of the average adult consuming nearly four gallons, every day; a conclusion that clearly demonstrates the overly conservative nature of OEHHA's water consumption analysis.

Moreover, USDA CSFI is a recall study; participants had to recall their own (or their infant's) consumption over two non-consecutive days. No direct measurements were taken. Recall studies are subject to bias from errors in memory when recalling the amounts consumed (*i.e.*, what, when, and how much did I eat or drink?). For example, it is possible and not unusual that the person reporting the infant intake estimated a high value for intake. If this occurred for one or two individuals in the study, the data would be skewed (as observed by inspection), overestimating the statistical estimation of the 90th and 95th percentile water consumption values. The mean and median values available in OEHHA (2012a) would be more rational at 127 ml/kg-d and 123 mg/kg-d, respectively.

Furthermore, a dietary recall study should represent the entire population, not just tap water consumers. OEHHA chose to use the data for consumers of tap water only, yet individuals commonly use water from other sources (e.g., bottled, in juice or soda). Since OEHHA is interested in informing a MCL, sources of water that would be regulated are municipal water

systems. One effect of choosing not to use the analysis of all individuals is that the results are higher than if all data were used. For example, OEHHA proposes to use an intake rate of 237 mL/kg-d based on consumers only. However, the value would be lower based on all individuals. Use of the values for consumers only is not a science-based decision.

One way to gauge whether the 90th and 95th percentile values suggested in OEHHA (2012a) are statistically unreliable is a simple comparison to blood volume. The average adult has a blood volume of approximately 5 L and drinks approximately 1.4 L/d, or 27% of their blood volume (US EPA, 1997). It is well understood that infants and children consume more than adults when normalized for body weight, but using the intake rates suggested by OEHHA, the 95th percentile one month old infant would consume approximately 2.6 L/d, or 280% of their blood volume. This is the equivalent of the average adult consuming nearly four gallons, every day; a conclusion that clearly demonstrates the overly conservative nature of OEHHA's water consumption analysis.

4.6 Effects of Other Goitrogens

As with perchlorate, IUI is caused by the chemicals nitrate and thiocyanate, which are found in abundance in a healthy diet. Studies have shown that, on a daily basis, exposure to perchlorate accounts for approximately 2% of the total IUI contributed by these three goitrogenic compounds.

The level of IUI that would be associated with exposure to perchlorate at the current PHG of 6 ppb is minimal compared to the IUI associated with other environmental goitrogens naturally present in many foods. Nitrate and thiocyanate are less potent (Tonacchera et al., 2004) but more plentiful inhibitors of NIS activity than perchlorate (Belzer et al., 2004). The potency of nitrate and thiocyanate relative to perchlorate has been demonstrated in vivo (Wyngaarden et al., 1952, 1953; Greer et al., 1966; Belzer et al., 2004) and in vitro (Tonacchera et al., 2004). When based on perchlorate equivalence, the effects of perchlorate are much smaller than the effects of either nitrate or thiocyanate (Belzer et al., 2004; U.S. EPA, 2008b). The potential for perchlorate to cause IUI cannot be distinguished from the effects of other NIS inhibitors (De Groef et al., 2006). Because exposure to nitrate and thiocyanate would continue even if perchlorate levels are reduced, OEHHA's attempt to isolate the effect of perchlorate will produce no public health benefit.

4.6.1 OEHHA Inappropriately Assumes that Goitrogen Exposures Are Synergistic

In developing a PHG, OEHHA is required to consider the effects of other chemicals that have the same mechanism of action. However, rather than consider the relative contribution of perchlorate compared to other goitrogens, OEHHA considers people with exposure to thiocyanate and nitrate to be sensitive subpopulations. In its list of potential susceptibility groups, OEHHA lists:

> People with high levels of thiocyanate, which typically comes from food or tobacco smoking. Data from Steinmaus *et al*. (2007) suggest that the magnitude by which perchlorate reduces T4 levels is about two times greater in people with high thiocyanate levels than in people with average or low thiocyanate levels (Table 23).
>
> Certain factors such as nitrate and thiocyanate act by the same mechanism as perchlorate, and as we discuss in the following sections some evidence exists that

> people exposed to one or more of these agents may be particularly susceptible to perchlorate.

Elsewhere the draft suggests that the effects of other goitrogens are synergistic, stating:

> Finally, many of the factors related to thyroid hormone might not cause important confounding for the reasons given above, but they may still act either cumulatively or synergistically with perchlorate to decrease thyroid function. Certain factors such as nitrate and thiocyanate act by the same mechanism as perchlorate, and as we discuss in the following sections some evidence exists that people exposed to one or more of these agents may be particularly susceptible to perchlorate.
>
> In other words, findings from these studies suggest that iodine (and thiocyanate) are more likely to produce additive or synergistic effects on thyroid hormone levels with perchlorate than cause false associations between perchlorate and thyroid hormone levels.

However, the relationship between perchlorate and other goitrogens is clearly additive, not synergistic, as they have the same mechanism of action. OEHHA presents no evidence to suggest otherwise. Casarett and Doull's Basic Science of Poisons, one of the foremost texts in toxicology, defines the two relationships as such:

> The relationship between perchlorate and other goitrogens is additive, not synergistic, and OEHHA presents no evidence to suggest otherwise. The appropriate way to evaluate potential exposures to thiocyanate and nitrate is by using a perchlorate equivalent concentration (PEC).

1. "An *additive* effect occurs when the combined effect of two chemicals is equal to the sum of the effects of each agent given alone (example: 2 + 3 = 5)."
2. "A *synergistic* effect occurs when the combined effects of two chemicals are much greater than the sum of the effects of each agent given alone (example: 2 + 2 = 20)."

Based on the well-understood mechanism of action, it is clear that co-exposure to goitrogens such as nitrate and thiocyanate, results in an additive effect only. There is no evidence that a synergistic effect occurs. The appropriate way to evaluate potential exposures to thiocyanate and nitrate is by using a PEC, as discussed in Section 2.4.2. This approach suggests that the contribution of perchlorate to total goitrogen exposure is minimal. To be scientifically correct, OEHHA must correct these misstatements.

4.6.2 Bruce et al. *(2013) Demonstrates No Effect of PEC on Free T4 or TSH Using the Reanalyzed NHANES 2001-2002 Dataset*

Since the release of earlier studies that used the NHANES 2001-2002 datasets (Blount et al., 2006; Steinmaus et al., 2007), CDC has reanalyzed stored urine samples from this cohort for perchlorate, nitrate, and thiocyanate and released a more complete suite of thyroid function measures. In the previous dataset, only total T4 and TSH were reported. The new dataset features reanalyzed total T4 and TSH and, newly analyzed free T4, total trioiodothyronine (T3), free T3, thyroglobulin (Tg), Tg antibody, and thyroperoxidase antibody. Using this newly released NHANES 2001-2002 data, Bruce et al. (2013) analyzed the association between thyroid function and urinary perchlorate, nitrate, and thiocyanate. Because perchlorate has the least impact on IUI of the three goitrogens, they also evaluated the impact of all three together in PEC. Although the study population is similar to that used in previous

assessments, this is an expanded and reanalyzed data set that was not available to previous researchers.

Clinically, the evaluation of free T4 coupled with TSH is the most meaningful for assessing thyroid function. The study reported that only total T4 was associated with PEC and that this relationship was dominated by nitrate and thiocyanate, rather than perchlorate. Neither perchlorate, nor total PEC was associated with either free T4 or TSH. The lack of association with other measures of thyroid function (TSH, free T3, and total T3) support that there is no functional thyroid effect from these three agents together or perchlorate independently with environmental exposures. Therefore, OEHHA cannot rely on the results of the Blount et al. (2006) and Steinmaus et al. (2007) in asserting an association between low level perchlorate exposure and thyroid function to justify a lower PHG of 1 ppb.

4.6.3 OEHHA Ignores the Conclusions of Other Analyses about the Negligible Effect of Perchlorate

The results of the OEHHA analysis disregard the results of other published studies with regard to the negligible effect of perchlorate on IUI.

The US EPA OIG (2010) estimates that the contribution of perchlorate to IUI is about 1% of the total contributed by agents that act through IUI, including perchlorate. At this percent contribution, addressing perchlorate alone would not significantly impact public health. As noted by ATSDR (2008),

> Nitrate and thiocyanate are widely distributed in nature and, because both anions also inhibit RAIU [radioactive iodide uptake], as demonstrated by Tonacchera et al. (2004), should also be included in the discussion of the effects of inhibition of the NIS [sodium iodide symporter] by anions.

Tarone et al. (2010) reviewed much of the published perchlorate epidemiological literature. It covered three types of epidemiological studies: cross-sectional studies (e.g., NHANES data), ecologic studies, and occupational studies. Based on its 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."

Tarone et al. (2010) 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. (2010) 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 demonstrated 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.

5.0 DIFFERENCES BETWEEN THE 2011 AND 2012 DRAFT DOCUMENTS

5.1 Comments from Intertox Are Not Addressed in the 2012 Draft

We appreciate that OEHHA provided the opportunity to review a second draft of the PHG document; however, the 2012 draft document is not scientifically improved on, and has essentially the same text as, the draft released in 2011. The comments that Intertox submitted in February 2011, which set forth a number of scientific shortcomings in OEHHA's analysis, have not been addressed in the 2012 draft. We summarize these comments and whether it is apparent that OEHHA addressed them in Table 4.

TABLE 4. Summary of Key Intertox Comments on the 2011 Draft PHG and Whether They Are Addressed in the 2012 Draft Document

Intertox 2011 Comments	Addressed in 2012 Draft Document?
The OEHHA review counters the assessments of numerous authoritative bodies, including the US EPA OIG, ATSDR, and NRC.	No, same text as in 2011 draft.
The approach OEHHA uses to develop the PHG for perchlorate differs substantively from that used to develop PHGs for other compounds.	No, same text as in 2011 draft.
IUI must be reduced by at least 75% for several months or longer to cause thyroid hormone production to decline to the point where hypothyroidism could occur. This 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 14,000 ppb every day; NRC, 2005).	No discussion noted in 2012 draft.
The potency of nitrate and thiocyanate relative to perchlorate has been demonstrated *in vivo* (Wyngaarden et al., 1952, 1953; Greer et al., 1966; Belzer et al., 2004) and *in vitro* (Tonacchera et al., 2004).	No, same text as in 2011 draft.
Authoritative bodies have carefully assessed the studies noted by OEHHA and determined that they show no association between perchlorate exposure and thyroid hormone levels.	No changes in OEHHA's assessment. See Table 3 for more details on these studies.
OEHHA considers IUI as reported in Greer et al. (2002) equivalent to an adverse effect.	No, same text as in 2011 draft.
The recognized TSH surge in neonates makes measurement of TSH levels within the first 24 to 48 hours invalid. Additionally, the studies do not control for gestational age of neonates, a key variable affecting measured TSH levels, and questions arise regarding the statistical characterization of the TSH data. There is no evidence that TSH levels in those with assumed higher exposure to perchlorate remain different after TSH levels stabilize.	Expanded text with discussion of "confounding" and "misclassification." No new evidence is provided.
Minor differences in TSH levels are not likely clinically significant.	No, same text as in 2011 draft.
The uncertainty in neonatal TSH assays is not discussed.	No discussion noted in 2012.
TSH is the only variable obtained to assess thyroid physiology in Steinmaus et al. (2010).	No discussion noted in 2012.
OEHHA deliberately excluded three studies from its analysis (Amitai et al., 2007; X. Li et al., 2000; and Tellez Tellez et al., 2005). However, each of these studies provides additional evidence that exposure to perchlorate in drinking water did not affect T4 or TSH levels in newborns.	Yes, added text is used to exclude the studies. No new studies provide evidence of exclusion.
The dose of perchlorate that the study subjects in Greer et al. (2002) received from drinking water can be assumed to be in addition to background intake from diet.	No discussion noted in 2012.

Intertox 2011 Comments	Addressed in 2012 Draft Document?
Conservative assumptions are embedded in drinking water intake rates and body weights.	No. OEHHA cites new reference for drinking water intake rates (OEHHA, 2012a); however this is based on the same dataset as the previous intake rates and suffers from the same limitations.
By changing the PHG from 6 ppb to 1 ppb, the [2011] draft document does not provide any evidence that reducing perchlorate concentrations in drinking water will result in additional public health benefit, particularly considering the continued presence of and substantially greater exposure to other thyroid-active chemicals that have the same mechanism of action as perchlorate, such as nitrate and thiocyanate.	No. Text is added but no studies provide scientific evidence.

5.2 Changes to the 2012 Draft

5.2.1 The Majority of Changes between the 2011 and 2012 Draft Documents Are Minimal

We note that minimal changes have been made to the 2012 draft, the majority being editorial or grammatical changes. These are summarized in Table 5.

Table 5. Description of Notable Changes Made in the 2012 Draft Document

Section of 2012 Draft Document	Notable Changes Made
Summary	Simple grammatical edits. No substantial scientific information provided.
Introduction	Simple grammatical edits.
Environmental Occurrence and Human Exposure	Simple edits. Added reference to Valentin-Blasini et al. (2011).
Metabolism and Pharmacokinetics	Simple grammatical edits
Toxicology	Simple grammatical edits for the following sections: ▪ Toxicology ▪ General information ▪ Toxicological effects in Animals ▪ Acute Toxicity ▪ Subchronic Toxicity ▪ Genetic Toxicity ▪ Developmental and Reproductive Toxicity ▪ Immunotoxicity ▪ Neurotoxicity ▪ Endocrine Toxicity ▪ Carcinogenicity ▪ Toxicological Effects in Humans ▪ Acute Toxicity ▪ Subchronic Toxicity ▪ Genetic Toxicity ▪ Developmental and Reproductive –*see Appendix C.* ▪ Immunotoxicity ▪ Neurotoxicity ▪ Endocrine Toxicity ▪ Carcinogenicity
Dose-Response Assessment	Simple edits.
Calculation of the PHG	Increased reliance on epidemiological studies to justify change in most sensitive subpopulation.
Risk Characterization	Simple edits. Added reference to OEHHA (2012a).
Other Regulatory Standards	Simple edits.
References	Added 14 new references. Removed 24 references.

5.2.2 More Significant Changes Were Made to Developmental and Reproductive Toxicity Section

We note that there was a greater attempt by the OEHHA 2012 draft document to overcome the limitations of several ecologic epidemiological studies which form the basis of OEHHA's shift from the pregnant woman and her fetus to the infant as the most sensitive population. Some of these limitations were noted by one peer reviewer as well. The additional text provided by OEHHA offers no new evidence to support OEHHA's assertions. The only section of the 2012 document where significant changes are made in the text is to the Human-related Developmental and Reproductive Toxicity Section. We have reproduced the current 2012 draft document text by comparing the texts from 2011 and 2012 and noted the edits in strike through and underlined fashion so that we could assess the significance and extent of any changes made by OEHHA. As is apparent from that comparison, the changes are indeed minor and for the most part non-substantive and without additional scientific import. The changes we have highlighted are presented in Appendix C.

5.3 Implications of the Changes to the 2012 Draft Document Compared to the 2011 Document

OEHHA adds more text to support its opinion of the science although no new substantive science was added to the database that provides any new scientific support for OEHHA's position. This additional text is not scientifically referenced as fact, but OEHHA presents the new material as if it is scientific fact.

OEHHA has continued to rely, for the most part, on ecologic epidemiological studies, which are far weaker than the robust existing database of toxicological and clinical studies. These ecologic epidemiological studies have weaknesses recognized by the scientific community and noted by the external peer review of the 2011 document. We discuss this further in Section 3. Also, in response to the peer review, in its 2012 draft, OEHHA has increased the discussion of inherent limitations in these studies in an attempt to strengthen its case for the conclusions OEHHA reached in the PHG document. We note with particular concern that no new evidence has been presented that supports OEHHA's position that the infant is more sensitive than the fetus of the pregnant woman.

6.0 SUMMARY AND CONCLUSIONS

OEHHA adds more text in its 2012 draft PHG document to support its opinion of the science, although no new substantive science was added to the database that provides any more scientific support for OEHHA's position. This additional text is not scientifically referenced as fact, but OEHHA presents the new material as if it is scientific fact.

In addition, OEHHA has continued to rely, for the most part, on ecologic epidemiological studies, which are far weaker than the robust existing database of toxicological and clinical studies. These ecologic epidemiological studies have weaknesses recognized by the scientific community and noted by the external peer review of the 2011 draft PHG document. We have described the problems associated with such studies in detail in Section 2.2 of these comments.

Also, in response to the peer review, in its 2012 draft, OEHHA has increased the discussion of inherent limitations in these studies in an attempt to strengthen its case for the conclusions OEHHA reached in the PHG document. OEHHA goes to great lengths to use non-

differentiality to address the inherent weaknesses in the epidemiological study record, as well as to dispel any concerns that may arise about these types of studies with regard to confounding factors and bias. In Section 3.3.1 and 3.3.2 we have set forth a detailed analysis of the problems with OEHHA's non-differential misclassification and confounding/bias analyses. Because OEHHA has improperly analyzed those factors and incorrectly dismissed them as a result, OEHHA has failed to justify the use of the cross sectional and ecologic epidemiology studies as a basis for concluding that the infant is the most sensitive population or for demonstrating that exposure to perchlorate at the low levels typically occurring in the environment can cause adverse effects.

The 2012 draft does not provide any reliable scientific evidence that reducing perchlorate concentrations in drinking water from 6 ppb to 1 ppb will result in additional public health benefit.

For these, and the numerous other reasons we have included in both our prior set of comments to the 2011 draft PHG document and in the current set of comments to the 2012 draft PHG document, we find no legitimate scientific basis for OEHHA to justify its proposed change in the PHG from 6 ppb to 1 ppb. The case for a more conservative PHG has not been established, and there is no valid scientific rationale for the proposed change provided by the Agency.

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APPENDIX A

INTERTOX COMMENTS TO 2011 DRAFT PHG

Intertox comments to the 2011 Draft PHG which were submitted on February 22, 2011, can be found online at:

http://oehha.ca.gov/water/phg/pdf/PerComs/PSGcomms042011.pdf

APPENDIX B

CLEARANCE RATES IN NEWBORNS AND CHILDREN

SUMMARY OF CLEARANCE RATES FOR RENALLY EXCRETED, NON-METABOLIZED DRUGS IN ADULTS AND CHILDREN APPROXIMATELY TWO YEARS OLD: ONE COMPARTMENT

Drug	Age	Ratio of CL_{child} to CL_{adult} (child rate/adult rate)	% of adult Css with same ADD	Reference
Gabapentin	3 – 6 y (n=8)	1.2 (4.8 ml/kg/m)/(3.9 ml/kg/m)	83%	Gatti et al., 2003
Gentamicin	2.25 y (n=17)	1.4 (0.138 L/h/kg)/(0.0966 L/h/kg)	71%	Johnson et al., 2006 citing Bass et al., 1998, Matzke et al., 1989/Wallace et al., 2002[1]
Gentamicin	0.08 – 7.2 y 1-5 y	1.3 (1.57 ml/kg/m)/(1.25 ml/kg/m) 2.2 (2.74 ml/kg/m) /(1.25 ml/kg/m)	77% 45%	Edginton et al., 2006 citing Assael et al., 1980, Ho et al., 1995, Kirkpatrick et al., 1999[1]
Isepamicin	0.4 – 5.9 y	1.9 (2.64 ml/kg/m)/(1.4 ml/kg/m)	53%	Edginton et al., 2006 citing Scaglione et al., 1995, Radwanski et al., 1997[1]
Ticarcillin	0.08 – 2 y (n=16) 2 – 12 y (n=23)	1.6 (3 ml/min-kg)/(1.9 ml/min-kg) 1.5 (2.83 ml/min-kg) /(1.93 ml/min-kg)	63% 67%	Ginsberg et al., 2002 citing Reed, 1998[1]
Vancomycin	1 – 5 y (n=12)	1.9 (0.153 L/h/kg) /(0.0786 L/h/kg)	53%	Johnson et al., 2006 citing Rodvold et al., 1997, Matzke et al., 1989/Wallace et al., 2002[1]
Geometric Mean (Range)	**1.6** (1.2 – 2.2)	**63%** (45 – 83%)		
Geometric Mean w/o gabapentin†[2]	**1.7**	**59%**		

y: year
m: minute
ml: milliliter
kg: kilogram

L: liters
h: hour
CL: clearance

Css: steady-state serum concentration
ADD: average daily dose

[1] Values not verified from primary literature.
[2] Analyzed without gabapentin as the age range does not include our range of 1-3 year old.

SUMMARY OF CLEARANCE RATES FOR RENALLY EXCRETED, NON-METABOLIZED DRUGS IN ADULTS AND NEONATES: ONE COMPARTMENT MODEL

Drug	Age	Ratio of CL_{infant} to CL_{adult} (infant rate/adult rate)	% of adult Css with same ADD	Reference
Gentamicin	0 – 1 d (n=27) 8 – 28 d (n=14)	0.87 (0.084 L/h/kg)/(0.0966 L/h/kg) 1.2 (0.118 L/h/kg)/(0.0966 L/h/kg)	115% 83%	Johnson et al., 2006 citing Bass et al., 1998, Matzke et al., 1989/Wallace et al., 2002[3]
Gentamicin	1 – 84 d	1.0 (1.04 ml/kg/m)/(1.06 ml/kg/m)	100%	Ginsberg et al., 2002 citing Rodvold, 1993
Isepamicin	2 d 2 m	0.79 (1.1 ml/kg/m)/(1.4 ml/kg/m) 1.5 (2.14 ml/kg/m)/(1.4 ml/kg/m)	127% 67%	Edginton et al., 2006 citing Scaglione et al., 1995, Radwanski et al., 1997[3]
Ticarcillin	0.08 – 2 y (n=16)	1.6 (3 ml/min-kg)/(1.9 ml/min-kg)	63%	Ginsberg et al., 2002 citing Reed, 1998[3]
Vancomycin	Premature, 4 – 17 d post-natal (n=11)	0.8 (0.74 ml/kg/m)/(0.96 ml/kg/m)	125%	Ginsberg et al., 2002 citing Jarret, 1993 and Cuttler, 1994[3]
Geometric Mean (Range)	**1.1** (0.79 – 1.6)	**91%** (63 – 127%)		

y: year
m: minute
ml: milliliter
kg: kilogram

L: liters
h: hour
CL: clearance

Css: steady-state serum concentration
ADD: average daily dose

[3] Values not verified from primary literature.

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APPENDIX C

TEXT ADDED BY OEHHA REGARDING THE SECTION OF EPIDEMIOLOGICAL STUDIES OF HUMAN-RELATED DEVELOPMENTAL AND REPRODUCTIVE TOXICITY

TEXT ADDED BY OEHHA REGARDING THE SECTION OF EPIDEMIOLOGICAL STUDIES OF HUMAN-RELATED DEVELOPMENTAL AND REPRODUCTIVE TOXICITY

Study cited by OEHHA	Words added in the 2012 draft are underlined and those deleted from the 2011 are noted in strike out.	Did OEHHA Use Study And Comments
Introduction page, 38	…most of the human studies on newborn thyroid function and maternal perchlorate exposure ~~defined~~ categorized exposure based on the concentration of perchlorate ~~concentrations~~ in the mother's residential drinking water during pregnancy, not on the actual perchlorate intake of the newborn after birth. ~~Importantly~~ This is important since the half-lives of both perchlorate and thyroid hormones in newborns are fairly short (less than 24 hours) (Greer et al., 2002; Van den Hove et al., 1999). As such, any effect that the mother's perchlorate exposure during pregnancy might have on the fetal thyroid should be seen ~~perchlorate exposure during pregnancy might have on the fetal thyroid might be seen soon after birth (e.g.,~~ within the first 24 hours after birth~~), but~~ (e.g., within the thyroid hormone and perchlorate half-lifes). But, they may not ~~necessarily~~ be seen at a later time~~. This is because the~~ if perchlorate exposure ~~of the child may change relatively soon after~~ changes at birth. For example, the newborn may be fed an infant formula with a different perchlorate concentration than that of the drinking water used by the mother during pregnancy.	OEHHA uses first 24 hours of TSH measurement without scientific support and inherent scientific concerns in parameter reliability. No significant change in text from the 2011 draft document. There is no scientific reference to support this approach rendering it novel and speculative regardless of the scientific concerns. Many scientific concerns to use these data (See Appendix A; our section on this from previous submittal)
DHS, 1997	No changes noted.	No. The study was assessed and dismissed by NRC (2005) and OEHHA (2004) as scientifically invalid

Study cited by OEHHA	Words added in the 2012 draft are underlined and those deleted from the 2011 are noted in strike out.	Did OEHHA Use Study And Comments
Kelsh et al., 2003	However, as discussed above, measurements collected in the first day after birth may actually be the most relevant, and as discussed below, the post-natal surge in TSH does not necessarily ~~limit the ability of a study to identify~~ invalidate associations identified between perchlorate and neonatal thyroid hormone levels during this time. The odds ratio for an elevated TSH for Redlands compared to San Bernardino/Riverside Counties for all subjects (regardless of the age at measurement), and for only those subjects with TSH measurements collected at ≥ 18 hours of age reported by Kelsh et al. (2003) were 1.24 (95% CI, 0.89-1.68) and 0.69 (95% CI, 0.27-1.45), respectively. The prevalence ratio for PCH standardized by ethnicity, sex, birth weight, and birth year for Redlands compared to San Bernardino/Riverside Counties was 0.45 (95% CI, 0.06-1.64). The researchers found that Hispanic ethnicity, low and high birth weight, and female sex were risk factors for PCH. Kelsh et al. (2003) did not calculate the odds ratio for having a low T4, although this can be estimated using the data in their tables. The odds ratio for having a low T4 in Redlands compared to San Bernardino/Riverside Counties was 1.18 (95% CI, 1.13-1.24; $p < 0.0001$). This odds ratio is unadjusted. However, it is unlikely that adjusting for age at collection, ethnicity, sex, birth weight, or birth year would have any major impact on this odds ratio since adjusting for these factors had little impact on the TSH odds ratios provided by the authors. Kelsh et al. (2003) also did not report specific results for neonates who had serum TSH measurements collected before 18 hours of age. However, data provided in the tables of Kelsh et al. (2003) can be used to estimate the odds ratio for having a high TSH level in subjects who had their TSH levels measured during this time. This odds ratio, comparing Redlands to all of San Bernardino/Riverside Counties, was 1.57 (95% CI, 1.14-2.16; $p <0.0001$). The data used in these calculations are shown in Table 8.	Yes, however, the opinions of the study's authors are contrary to OEHHA's interpretations. No significant change in text from the 2011 draft document. OEHHA uses first 24 hours of TSH measurement without scientific support. There are many scientific concerns in the use of these data (See Appendix A; our section on this from previous submittal).

Study cited by OEHHA	Words added in the 2012 draft are underlined and those deleted from the 2011 are noted in strike out.	Did OEHHA Use Study And Comments
Crump et al., 2000	No changed noted in text.	Yes, however the opinions of the study's authors are contrary to OEHHA's interpretations. Crump et al. (2000) conclude "Neonata1 thyroid-stimulating hormone levels were significantly lower in Taltal compared with Antofagasta; this is opposite to the known pharmacological effect of perchlorate, and the magnitude of difference did not seem to be clinically significant." Regarding the report of familial thyroid problems, the authors caution that the reports were not verified, there may have been recall bias, or it may represent historical variations in iodine supplementation.
Lamm and Doemland, 1999	Results were not adjusted for several variables related to thyroid hormone levels such as age, gender, or iodine intake, although we have no evidence these factors were related to perchlorate exposure and caused important ~~variables. In addition~~ confounding. Perhaps more importantly, although Clark County of Nevada ~~obtains~~ obtained nearly all of its drinking water from Lake Mead, which is known to be contaminated with perchlorate, the six California counties obtained their drinking water from multiple sources, many of which ~~are~~ were not contaminated with perchlorate. Because of this, there was likely significant misclassification of exposure for the California counties. Misclassification could also occur if there were errors in the county to which subjects were assigned, although there is no evidence that this would result in major bias, and bias from this source seems unlikely given the very large size of most of the exposed counties. Importantly, errors in misclassifying exposure would most likely be non-differential and cause bias towards the null. Finally, PCH is a very serious disease, usually requiring treatment with thyroid hormone, and it is generally associated with large increases in TSH.	No. The study concluded that counties with detectable perchlorate in drinking water did not have higher rates of PCH compared to counties with no detections. The detections ranged from 4-6 ppb.

Study cited by OEHHA	Words added in the 2012 draft are underlined and those deleted from the 2011 are noted in strike out.	Did OEHHA Use Study And Comments
Li et al., 2000a	Perchlorate was not detected in the Las Vegas water supply in 8 of the 15 months covered by the study, which the authors suggest may be due to the changing conditions of the water supply to this city. Separate analyses were done to evaluate births in the seven months when perchlorate was detected. Overall, Li et al. (2000a) reported no differences in mean T4 levels (approximately 17 µg/dL) between the two cities (p =0.41)~~.~~, including analyses involving those months where perchlorate was detectable in Las Vegas drinking water (Shown in their Figure 1, no p-value given). … Li et al. (2000a) used the monthly perchlorate measurements in Las Vegas drinking water to estimate the cumulative perchlorate exposure for each newborn during the first three months of pregnancy and for all nine months of pregnancy. Cumulative exposures in Las Vegas ranged from 9 ppb-months to 83 ppb-months; the Reno newborns during this period were presumed to have had no drinking water-related prenatal exposure. Cumulative exposures in Las Vegas ranged from 9 ppb-months to 83 ppb-months; the Reno newborns during this period were presumed to have had no drinking water-related prenatal exposure. In linear regression analyses involving T4 levels collected on all days after birth (not just day one), no association was found between cumulative perchlorate exposure and mean neonatal T4 levels (slope~~-~~ = 0.0003; R^2 = 0.002). Exposure assessment in this study was ecologic and information on whether or not the mothers or infants consumed water from public supplies, or how much they consumed is unknown. As discussed below, this would most likely cause bias towards finding no effect. Misclassification of true long-term thyroid hormone status could also have caused some bias, but again, this would most likely be non-differential and thus most likely cause bias toward finding no effect (also discussed below). Confounding by various factors like iodine status or other environmental chemicals may have also masked an association, although there is no evidence for this.	Yes, however, the opinions of the study's authors are contrary to OEHHA's interpretations. Li et al. (2000a) state "We conclude that perchlorate in drinking water at a level of up to 15 ppb had no detectable effect on neonatal T4 levels in this population."

Study cited by OEHHA	Words added in the 2012 draft are underlined and those deleted from the 2011 are noted in strike out.	Did OEHHA Use Study And Comments
Li et al., 2000b	(However, as discussed above, associations between maternal perchlorate exposures and neonatal thyroid hormone levels are probably best evaluated using TSH measurements ~~collected~~ taken within the first 24 hours after birth). In addition, only neonates with birth weights of 2.5 – 4.5 kg were included. The authors found that neonatal TSH levels were not significantly different between Reno and Las Vegas ~~(p-0.97). Several factors might have affected the validity of these results~~. Mean TSH values in Las Vegas and Reno were 11.5 µIU/ml (± 1.3) and 12.5 µIU/ml (± 1.3), respectively. The TSH regression coefficient adjusted for age and sex comparing Las Vegas to Reno was -0.0004 (95% CI, -0.0241– 0.0233; p=0.973). Several factors could have caused at least some bias towards finding no effect, including the lack of control of birth weight and ethnic origin, the use of broad categories to control for age at TSH collection (2-7 and 8-30 days), the small sample size, and perhaps most importantly, misclassification of exposure and effect and the exclusion of subjects who had TSH measurements at age < 24 hours.	No, citing "TSH measurements collected on first day after birth were excluded." OEHHA uses first 24 hours of TSH measurement without scientific support. There are many scientific concerns in the use of these data (See Appendix A; our section on this from previous submittal).
Brechner et al., 2000	The interpretation of this study is complicated by the fact that TSH levels were only measured in samples with low T4 measurements (discussed below). In addition, this study did not adjust for birth weight or gestational age. The difference in altitude between the two cities has also been cited as a possible bias but it is not clear that this potential confounder would be strong enough to cause the results observed. In fact, several studies suggest the opposite: that high altitudes actually decrease thyroxine levels and have little to no effect on TSH levels (Kotchen et al., 1973; Sawhney and Malhotra, 1991; Richalet et al., 2010).	Yes, however, study was assessed and dismissed by NRC (2005) as scientifically invalid.

Study cited by OEHHA	Words added in the 2012 draft are underlined and those deleted from the 2011 are noted in strike out.	Did OEHHA Use Study And Comments
Buffler et al., 2006	As discussed above, although TSH measurements collected within the first 24 hours of birth may not be the most appropriate for screening for PCH, levels collected during this time may be the most relevant for assessing associations between maternal drinking water perchlorate concentrations and changes in neonatal thyroid hormone levels that are less severe than those typically seen with PCH. The odds ratio for all subjects (those with TSH measured < 24 hours of age combined with those with TSH measurements at ≥ 24 hours of age) were not reported but can be estimated from the data given in Table 1 of ~~their paper~~ Buffler et al. (2006). The unadjusted OR for ~~a~~ high TSH comparing communities with perchlorate concentrations above and below 5 µg/L in all subjects regardless of the age of measurement was 1.59 (95 percent CI, 1.33-1.91). The data used in these calculations are presented in Table 11. Based on these numbers, the percentage of all neonates with TSH measurements collected within the first 24 hours of birth was greater in the high perchlorate communities than in the low perchlorate communities (42.1 versus 36.4 percent). Importantly though, when analyses are confined to only those subjects with TSH measurements collected at < 24 hours of age, the unadjusted odds ratio for high TSH comparing communities with and without perchlorate > 5 µg/L remained elevated (OR =1.60; 95 percent CI, 1.32-1.94).	No. OEHHA dismisses this study in favor of Steinmaus et al. (2010) which is based on the same dataset, but utilizes novel analyses OEHHA uses first 24 hours of TSH measurement without scientific support. There are many scientific concerns in the use of these data (See Appendix A; our section on this from previous submittal).

Study cited by OEHHA	Words added in the 2012 draft are underlined and those deleted from the 2011 are noted in strike out.	Did OEHHA Use Study And Comments
Steinmaus et al., 2010	In a ~~very~~ recent publication, the individual data were obtained from the Buffler et al. (2006) study, and analysis of these confirmed the elevated odds ratios discussed above. For example, the odds ratio for ~~a~~ TSH > 25 µU/mL ~~in~~ within the first 24 hours of birth was 1.53 (p < 0.0001; 95% CI, 1.24-1.89). For TSH levels ~~collected~~ measured more than 24 hours ~~of~~ after birth, the odds ratio for ~~a~~ TSH > 25 µU/mL was similar to that reported in Buffler et al. (2006). However, a TSH level of 25 µU/mL was the 99.99th percentile of all TSH levels in this age ~~strata~~ stratum and there were very few exposed cases (n = 13). Because significant neurologic effects have been seen with smaller changes in thyroid hormones (Pop et al., 1999, 2003; Haddow et al., 1999; Klein et al., 2001; Kooistra et al., 2006; Vermiglio et al., 2004), lower TSH cut-off points were also used to define ~~a~~ "high" TSH in this paper. When this was done, elevated odds ratios were seen both before and after 24 hours of age. For example, the odds ratio for having a TSH level above the 95th percentile in samples collected after 24 hours of age comparing perchlorate exposed and unexposed communities was 1.27 (p < 0.0001; 95% CI, 1.22-1.33). These analyses adjusted for age of sample collection, gender, mother's age, per capita income, race/ethnicity, birth weight, and feeding type (breast milk vs. formula), none of which had substantial effects on results. For example, the adjusted and unadjusted ORs for having a TSH level of 25 µU/mL or greater for collection ages less than 24 hours were 1.53 and 1.52, respectively. The authors of the Steinmaus et al. (2010) paper considered analyzing TSH concentrations and community perchlorate concentrations as continuous variables. But, because of the extensively overlapping and continually changing water sources in many parts of California, assigning a single perchlorate concentration to each individual would have introduced considerable misclassification. This would have introduced particularly strong bias in those subjects in the upper ranges of community perchlorate concentration. Instead, communities (and the subjects who lived in those communities) were divided into two groups based on whether or not it was likely the sources of their residential drinking water had perchlorate concentrations greater or less than 5 ppb. Some exposure misclassification was still likely with this type of categorization. However, since the misclassification was most likely non-differential, the bias would be in the direction of the null, not in the direction of causing false effects.	Yes. OEHHA uses first 24 hours of TSH measurement without scientific support. There are many scientific concerns in the use of these data (See Appendix A; our section on this from previous submittal).

Study cited by OEHHA	Words added in the 2012 draft are underlined and those deleted from the 2011 are noted in strike out.	Did OEHHA Use Study And Comments
Li et al., 2001	No changes noted.	No. Disease was classified based on Medicaid records which are not representative of the whole population.
Chang et al., 2003	In a similar study comparing Clark County (known to have elevated perchlorate levels in its drinking water) to the rest of Nevada, no differences were seen in the rates of pediatric neurobehavioral diseases including autism and attention deficit- hyperactivity disorder ~~(ADHD)~~ assessed using Medicaid records. As stated by the authors, "Perchlorate levels in drinking water were measured in Nevada waters following the 1997 detection of perchlorate in the Lower Colorado River with the newly refined perchlorate assay. The only public water system found to contain perchlorate was that of the Southern Nevada Water Authority (SNWA) that obtained its water from Las Vegas Bay and distributed it to about 96% of Clark County, including the city of Las Vegas. Perchlorate has not been detected in the public water supply of Reno, of Washoe County, or elsewhere in the state of Nevada. The perchlorate content of the raw and finished waters of SNWA have been measured at least monthly, and at times weekly, since July 1997. Perchlorate levels in 149 finished water samples taken between July 1997 and May 2002 had a mean of 10.9 ppb (SD ± 3.9; median = 10.5 ppb; range = nondetect to 23.8 ppb)." Information on the frequency of neurobehavioral diseases in Nevada youths under 18 years old came from the service records of the Nevada Medicaid program for the years 1996–2000. Patients were defined as those under age 18 who were diagnosed with or treated for either ADHD (ICD9 314) or autism (ICD9 299). The "disease incidence" in Clark County and the rest of Nevada was defined as the average annual number of new cases in Medicaid youths seen or treated in each area divided by the number of Medicaid- eligible youths in that area, in the midpoint of 1998. These unadjusted "disease incidences" were then compared, although the results of formal statistical significance testing are not provided. As discussed in many of the other studies reviewed in this section, and reviewed below, results might have been affected by exposure and outcome misclassification or confounding, although too few data are provided to quantitatively evaluate the extent of these issues for this study. ~~No difference was also seen in~~ Also, no difference was seen in comparisons of 4th grade performance results, although the methods used in this study to assess both exposure and outcome are likely too inaccurate to identify subtle or even moderate effects.	No. The methods used to assess exposure and outcome may be inaacurate.

Study cited by OEHHA	Words added in the 2012 draft are underlined and those deleted from the 2011 are noted in strike out.	Did OEHHA Use Study And Comments
Tèllez Tèllez et al., 2005	Simple grammatical changes noted.	No. OEHHA excluded study for "45% of women from the exposed city delivered in the unexposed city and the iodine levels were very high." However, OEHHA uses Crump et al., 2000, is the same geographic location and was used (see above).
Amitai et al., 2007	Simple grammatical changes noted.	No. OEHHA excluded study for "< 10% of newborns had thyroid hormones measured in first 36 hr after birth."
Cao et al., 2010	Urinary concentrations of perchlorate, nitrate, iodine, thiocyanate, T4 and TSH were measured in 92 full term infants from Pennsylvania. In analyses adjusted for age, sex, and body mass index, increasing urinary perchlorate concentrations were associated with increasing urinary TSH concentrations, but only in children with low urinary iodine. The adjusted regression coefficient between the logarithm of urinary perchlorate and logarithm of urinary TSH was 0.10 (95% CI, 0.01- 0.19) in children with urinary iodine levels < 100 µg/L and –0.04 (95% CI, –0.12-0.04) in children with higher iodine levels. Increasing urinary concentrations of perchlorate, nitrate, and thiocyanate were also associated with higher urinary T4. Both urinary levels of thyroid hormones and urinary levels of perchlorate (and other analytes) were "adjusted" for urine dilution by dividing their values by the subject's urinary creatinine concentrations. The use of urinary creatinine on both sides of the mixed model analyses (i.e., as part of the dependent variable and as part of the independent variable) may have led to the positive correlations identified in this study, making these results difficult to interpret.	No. OEHHA excluded study for "Adjustments for urinary creatinine could have created false associations. No data in neonates."