PSSEP
Partnership for Sound Science in Environmental Policy

April 25, 2011

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Bay Planning Coalition

California Association Of Sanitation Agencies

California Manufacturers & Technology Association

Chemical Industry Council

Chlorine Chemistry Council

Contra Costa Council

Tri-TAC
Sponsored by:
League of California Cities
California Association of Sanitation Agencies
California Water Environment Association

Western States Petroleum Association

Re: Revision to PSSEP Comments on OEHHA's Revised Draft Public Health Goal for Perchlorate in Drinking Water

Dear Mr. Baes,

We have recently become aware of an error in one of the Partnership for Sound Science in Environmental Policy's comments submitted on February 21, 2011 on OEHHA's Revised Draft Public Health Goal for Perchlorate in Drinking Water. On page 12 (section VI. Additional Comments, #5), we mistakenly referred to the Greer study as determining a no-observed-adverse-effect level (NOAEL) when that study determined a no-observed-effect-level (NOEL). Please accept the attached revised comments with the corrections made to this section.

Sincerely,

Craig S.J. Johns

cc: George Alexeeff, Acting Director, OEHHA
Enclosures: (1) Revised PSSEP Comments 2011 Draft Perchlorate PHG (Section VI, #5)
(2) Revised PSSEP Comments 2011 Draft Perchlorate PHG (full)

Craig S.J. Johns
Program Manager

VI. Additional Comments

5. Selection of the point of departure from the toxicity study selected: Based on their study in human volunteers, Greer et al. (2002) determined a no-observed-effect level (NOEL) of 0.007 mg/kg-day for the inhibition of thyroidal radioactive iodide uptake by orally administered perchlorate. U.S. EPA developed an oral RfD using the NOEL of 0.007 mg/kg-day from Greer et al. (2002) based on the NRC's (2005) recommendation. The NRC (2005) recognized the potential benefits of using a benchmark dose (BMD) methodology to determine the point of departure for perchlorate. However, the NRC (2005) recommended use of the NOEL of 0.007 mg/kg-day from Greer et al. (2002) because they believed there was no consensus on the criteria for choosing the most appropriate BMD analysis for the Greer et al.(2002) data, and the NOEL of 0.007 mg/kg-day was supported by other studies they reviewed. The NOEL of 0.007 mg/kg-day from Greer et al. (2002) was also used as the point of departure by the U.S. EPA during the development of their interim health advisory for perchlorate. In contrast, OEHHA used the BMD methodology and determined a 95 percent lower confidence limit on the bench mark dose (BMDL) equal to 0.0037 mg/kg-day to be an appropriate point of departure for calculation of the proposed PHG for perchlorate in drinking water. The calculated BMDL (0.0037 mg/kg-day) is below the lowest tested dose in Greer et al. (2002). Uncertainties associated with extrapolating the dose-response curve below actual tested dose concentrations should be discussed within the technical support document. Although the technical support document does mention the NRC (2005) study, it does not address the uncertainties mentioned by the NRC (2005) regarding the calculation of a BMDL using the Greer et al. (2002) data. The uncertainties associated with the calculation of a BMDL for perchlorate, as mentioned by the NRC (2005) should be explicitly considered during the development of the draft PHG for perchlorate. OEHHA should consider using the NOEL from the Greer study, since there is general scientific consensus that the NOEL is the appropriate point of departure for evaluating risks associated with oral exposures of humans to perchlorate.

Comments on:

Draft Public Health Goal for Perchlorate in Drinking Water
Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
January, 2011

Submitted by:

Partnership for Sound Science in Environmental Policy
February 23, 2011*

Background

In March 2004, the California Environmental Protection Agency (Cal-EPA) Office of Environmental Health Hazard Assessment (OEHHA) issued a Public Health Goal (PHG) of 6 parts per billion (ppb) for perchlorate to provide an estimated level of perchlorate that would not pose significant health risks to individuals through chronic consumption of drinking water. The 2004 PHG for perchlorate in drinking water was based on the potential inhibitory effect of perchlorate on the uptake of iodide by the thyroid gland in pregnant women and their fetuses from the consumption of drinking water containing perchlorate.

In January 2009, the U.S. EPA issued an interim health advisory for perchlorate to assist state and local officials in addressing perchlorate contamination in drinking water while the agency conducted its evaluation of the opportunity to reduce risks through a national primary drinking water standard. The interim health advisory is 15 ppb for perchlorate in drinking water. On January 7, 2011, OEHHA announced a proposed PHG of 1 ppb for perchlorate in drinking water based on a revised OEHHA assessment, as documented in Draft Public Health Goal for Perchlorate in Drinking Water (OEHHA, 2011).

On February 11, 2011, the U.S. EPA released its regulatory determination for perchlorate in drinking water. This action initiates the process for the U.S. EPA to propose a national primary drinking water regulation (NPDWR) for perchlorate. Under the Safe Drinking Water Act (SDWA), the U.S. EPA is required to issue a proposed draft NPDWR within 24 months of its final regulatory determination, and a final NPDWR within 18 months of the proposed draft NPDWR.

*Revised April 25, 2011 to correct Section VI, #5 at page 13.

Overall Summary

For reasons that are the subject of these comments, OEHHA has not provided a credible case that the existing PHG is not protective, or that a change is warranted. As discussed in these comments, many of the arguments presented in OEHHA, 2011, are flawed. OEHHA should not adopt a new PHG based on the 2011 draft document.

Summary of main comments

I. OEHHA argues that there are existing hazards to sensitive populations at current levels of perchlorate in drinking water. In doing so, OEHHA selectively excludes information and recommendations from expert bodies, including the National Academy of Sciences (NAS) and the American Thyroid Association (ATA), and published literature. In view of the complexity of thyroid medicine and epidemiology, OEHHA should defer to expert bodies composed of thyroid physicians and scientists, and to peer-reviewed published literature, to support its conclusions about the public health impact of perchlorate in drinking water.

II. OEHHA repeatedly interprets cross-sectional studies of populations with possible perchlorate exposure as supporting a causative relationship between low ppb levels of perchlorate in drinking water and thyroid dysfunction. OEHHA also inappropriately uses analyses of the NHANES data to support a causative relationship between iodine, perchlorate, and thyroid hormone levels. The cross-sectional epidemiological studies and NHANES studies inherently can not support such an interpretation. The ecological epidemiological studies do not provide evidence of an effect of perchlorate on currently exposed populations, do not support a change in the PHG to a focus on infants as the sensitive population, do not suggest a role of iodine nutritional status, and do not support a change in the PHG.

III. OEHHA does not adhere to its own standards of information quality. Numerous cases are noted in these comments in which OEHHA reanalyzes published studies and reaches conclusions that are contrary to the published conclusions. The full details of these analyses are not presented, and they are not subjected to adequate peer-review. Due to the complexity of thyroid physiology, thyroid medicine, and epidemiology of thyroid disease and iodine nutrition, an adequate peer review of this material should include a diverse group of thyroid physicians and scientists. OEHHA holds other sources to the standard of peer review but does not subject its own data analysis to the same rigor. OEHHA's new analysis of existing data should not be used in the development of a PHG without formal peer review.

IV. OEHHA relies heavily on analyses using the NHANES data without addressing its limitations. OEHHA inappropriately uses the urinary iodide levels as an indicator of individual iodine nutritional status. The NHANES data do not support the conclusion that existing exposures to perchlorate in drinking water cause

effects on thyroid function in any population, do not support a change to a focus on infants in the proposed PHG, and do not support a change in the existing PHG.

V. OEHHA does not provide any rationale or data to explain how a perchlorate concentration in the blood that is far below the concentration required to cause measurable inhibition of iodine uptake can be linked to thyroid dysfunction. The effects of moderate or severe iodine deficiency, high doses of goitrogenic agents, or thyroid hormone levels at the low end of the normal range are not linked in a mode of action to an effect of an immeasurable level of iodide uptake inhibition. The developmental impacts of conditions that affect thyroid hormone homeostasis are not directly linked to low doses of iodide uptake inhibitors. The OEHHA analysis is thus inadequate both in its model of thyroid physiology and in its mode of action of perchlorate.

VI. As noted above, the U.S. EPA has issued an interim health advisory for perchlorate, and they are working on the development of a national primary drinking water standard for perchlorate, as documented in *Drinking Water: Regulatory Determination on Perchlorate* (U.S. EPA, 2011). Furthermore, the U.S. EPA has initiated the development of a NPDWR, in consultation with technical experts from multiple agencies and advisory groups (e.g., the SAB and NDWAC). OEHHA should wait until the proposed NPDWR is released to revise the PHG for perchlorate in drinking water.

Detailed main comments

I. OEHHA should defer to recognized thyroid experts and published literature over its own interpretations and analysis to reach conclusions about the public heath impact of perchlorate in drinking water. The ATA is the nation's premier professional organization of thyroid doctors and scientists. The ATA Public Health Committee publishes occasional opinions on important public health topics as Public Health Statements. ATA Public Health Statements are peer reviewed within the Committee before publication. They have published three Public Health Statements on Perchlorate Exposure and Potential Effects on the Thyroid. The NAS Committee to Assess the Health Implications of Perchlorate Ingestion (NAS, 2005) was convened specifically to address the perchlorate risk assessment and included broad expertise on thyroid function and risk assessment. In addition there are several published reports that OEHHA did not adequately use. OEHHA should defer to these sources to support its PHG.

1.A. OEHHA cites six studies as their basis for focusing on infants (Kelsh et al., 2003; Brechner et al., 2000; Buffler et al., 2006; Steinmaus et al., 2010; Li et al., 2000a; Crump et al., 2000) because these studies "*provide evidence that thyroid hormone levels in infants were adversely affected by perchlorate*" (OEHHA 2011, pg 3). Of these studies, ATA, 2004, reviewed four (Kelsh et al., 2003; Brechner et al., 2000; Li et al.,

2000a; Crump et al., 2000) and concluded that "*one found a possible association of perchlorate with altered neonatal TSH levels*" and that "*the potential effect of various levels of perchlorate on a human fetus* in utero *is not fully understood*". However, the 'one study' referred to by ATA was the Brechner et al., 2000, study, and it was subsequently shown that the difference in the sampling time used by the public health agencies in the two cities studied could explain the thyroid hormone difference (Lamm, 2003), and that it was not associated with perchlorate exposure. Based on the ATA review, these studies do not support a change in the PHG. OEHHA should defer to the ATA for its understanding of these studies.

1.B. In a 2005 update, ATA added comments on the NAS review (NAS, 2005), concluding that "*The NAS report is a solid review of the existing literature and the resultant recommendations appear sound being based on thorough interpretation of the available scientific data'* (ATA, 2005). Specifically, ATA cited the NAS development of *'a reference dose of 0.0007 milligrams per kilogram body weight per day. The panel felt that basing the cut off on an added safety factor on the available data for adults would protect the health of even the most sensitive groups of people over a lifetime of exposure. This reference dose translates to a drinking water level of 24.5 ppb.*" There is no valid reason to ignore these clear recommendations from the nation's foremost authorities on thyroid health (NAS and ATA) by reducing the PHG, or to claim greater expertise than these bodies by identifying risks at lower perchlorate levels. The studies published since 2005 do not substantively change the 2005 ATA or NAS conclusions. OEHHA should defer to ATA and NAS recommendations of a reference dose for perchlorate, and to their literature review and conclusions.

1.C. ATA (2006) issued a further update addressing the Centers for Disease Control and Prevention (CDC) report of an analysis of data from the 2001-2002 National Health and Nutrition Examination Survey (NHANES) published as Blount et al., 2006. This study and others that make similar use of the NHANES data are used by OEHHA to support the focus on infants and to suggest the presence of the effect of marginal iodine deficiency in the U.S. (e.g., Steinmaus et al., 2007). The ATA's brief summary identifies at least five factors that are not controlled in the NHANES analysis that could explain hormone differences (total thyroxine measurement instead of free thyroxine, thyroid autoantibodies not measured, confounding pharmaceutical and medical factors, e.g. estrogen use or autoimmune thyroid disease, laboratory results from multiple laboratories). They also stated, "*The reason that perchlorate, but no other measured goitrogen studied, influenced thyroid function at low urinary levels of iodine is not explained*." These limitations also apply to other analyses of the NHANES data and do not allow conclusions to be made about relationships between variables when there are so many uncontrolled variables. The existing analyses of the NHANES data do not provide evidence that can support a reduction in the 2004 PHG.

1.D. NAS (2005) was prepared at the request of Federal agencies to address the risk of perchlorate. This committee included an unprecedented breadth of thyroid, brain development, and risk assessment expertise, and their conclusions and recommendations should be used to the fullest possible extent by OEHHA in order to

develop a credible PHG. Two conclusions from the NAS should be more fully considered by OEHHA. First is the reference dose of 0.0007 mg/kg/d, cited under comment **1.B**, above (NAS, 2005, Pg 178). Second, is the conclusion on the mode of action: "*The committee emphasizes that inhibition of iodide uptake by the thyroid has been the only consistently documented effect of perchlorate exposure in humans. The continuum of possible effects of iodide-uptake inhibition caused by perchlorate exposure is only proposed and has not been demonstrated in humans exposed to perchlorate (with the exception that in patients with hyperthyroidism doses of 200 mg daily or higher may reduce thyroid secretion). More important, the outcomes at the end of the continuum are not inevitable consequences of perchlorate exposure*.' (NAS, 2005, pg 165). NAS, 2005, also concludes that "*The committee notes that effects downstream of inhibition of iodide uptake by the thyroid have not been clearly demonstrated in any human population exposed to perchlorate, even at doses as high as 0.5 mg/kg per day*." (NAS, 2005, pg 177). These and other statements indicate the NAS conclusion that the available evidence does not link perchlorate exposure to any adverse thyroid or developmental effect in humans, and that the mode of action (as described by EPA, but also as used by OEHHA) inadequately describes the ability of the thyroid to adapt and maintain normal hormone levels. The studies published since 2005 have not substantially changed the conclusions of the NAS report and do not support a reduction in the 2004 PHG.

1.E. Tarone, et al., 2010, reviewed epidemiological studies related to perchlorate exposure, thyroid status, and blood or urinary levels of perchlorate, nitrate, and thiocyanate. These authors reviewed all of the epidemiological studies relied upon by OEHHA. They also reported independent analysis of the NHANES data and estimates of relative contribution of perchlorate, nitrate, and thiocyanate to total iodide uptake inhibition from published levels in various populations, including the US population. There are two important conclusions of this paper that should be considered by OEHHA. First, the authors find no evidence of effects on the thyroid in any exposed human population, including the Chilean population exposed to about 200 ppb, and the population in Israel with exposure up to 340 ppb. Secondly, based on data from several studies, the perchlorate levels contributed less than 1% of the total iodide uptake inhibition present in human populations, and >99% was due to nitrate and thiocyanate. This study was published in June, 2010, but it is not cited in OEHHA, 2011, and its conclusions address significant aspects of OEHHA's PHG development. OEHHA should justify this striking disagreement with the published literature.

1.F. Trumbo, 2010, reviews perchlorate exposure in the context of iodine nutrition and FDA recommendations. She concludes that "*Although pregnant women and their fetuses and newborns have the greatest potential for risk of adverse health effects following exposure to perchlorate, data are lacking to demonstrate a causal association between perchlorate consumption and adverse health effects in these high-risk populations*." From FDA's perspective, this conclusion leads to the Agency "*not recommending that consumers of any age alter their diet or eating habits due to perchlorate exposure*." OEHHA should accept the FDA conclusion in place of its

conclusion that exposures to current levels are causing adverse thyroid effects. This study is not cited in OEHHA, 2011.

1.G. Charnley, 2008, reviews some of the apparent inconsistencies in the perchlorate epidemiological studies and NHANES analyses and concludes that the data "*does not support a causal relationship between changes in thyroid hormone levels and current environmental levels of perchlorate exposure but does support the conclusion that the US Environmental Protection Agency's reference dose (RfD) for perchlorate is conservatively health-protective*." The main conclusions of this study contradict the OEHHA analysis, but the study conclusions are not discussed by OEHHA.

II. OEHHA misinterprets the cross-sectional epidemiological studies available for perchlorate. It is an accepted fact that a cross-sectional epidemiological study can only show an association between two variables and cannot address causation. OEHHA repeatedly interprets ecological epidemiological studies as supporting a causative interpretation between perchlorate exposures and thyroid hormone levels.

2.A. OEHHA cites five studies as their basis for focusing on infants (Kelsh et al., 2003; Brechner et al., 2000; Steinmaus et al., 2010; Li et al., 2000a; Crump et al., 2000) as "*the most relevant studies of perchlorate exposure and newborn thyroid hormone levels*" (OEHHA 2011, pg 49). In contrast to the ATA conclusion (Comment **1.A.**), OEHHA, 2011, concludes that these studies "*provide a consistent body of evidence linking perchlorate exposure during pregnancy with changes in thyroid hormone levels in the newborn*." (OEHHA, 2011, Page 53) This conclusion is incorrect because they are cross-sectional studies and cannot establish a 'link' or the causative or mechanistic relationship that 'link' implies. Likewise, cross-sectional studies can not demonstrate a 'change' since they evaluate data at a single time. These studies do not support a change in the PHG.

2.B. On Page 49, OEHHA, 2011, states that the cross-sectional epidemiological studies listed in Table 13 "*found either a perchlorate-associated decrease in T4, increase in TSH, or both*." This interpretation is incorrect because this study design can only show an association at the time of the study and can not provide information about a longitudinal change as implicit in the words 'decrease' or 'increase'. This type of misinterpretation of the ecological epidemiological studies occurs numerous times throughout the document.

2.C. On Page 49, OEHHA, 2011, implies that the consistency across several studies allows for 'causal inference'. This is incorrect because (a) all of the studies are similar in using neonatal thyroid screening data, (b) all are cross-sectional designs and therefore cannot support causal inference, which requires a longitudinal design, and (c) the 'markedly consistent results' that OEHHA refers to are the result of OEHHA's selective reanalysis and reinterpretation of the studies as described on Comments **3a, b, e, and g**. In fact, the studies are remarkably consistent in their authors' findings of no association between perchlorate and thyroid effects.

III. OEHHA presents data analyses of data from published studies without adequate information about the data, investigation methods, or other relevant factors. To promote transparency in its actions, OEHHA normally does not use unpublished data or data that are not peer-reviewed in developing PHGs. For the same reason, OEHHA should not use its own reanalysis of published or unpublished data without subjecting the analysis to an authoritative peer review. Due to the complex nature of the thyroid gland, and of thyroid health epidemiology, an adequate peer review of thyroid research and analysis must include a number of thyroid physicians, researchers, and epidemiologists.

3.A. On Page 39, OEHHA, 2011, states that their reanalysis of the Kelsh et al., 2003 data, specifically the analysis of low T4, can be done using data from the Kelsh study. The T4 data is not present in the published tables, and this analysis can not be understood from the information provided by OEHHA. OEHHA should clarify the T4 analysis and subject it to qualified peer review. In addition, the OEHHA reanalysis of the Kelsh et al., 2003, TSH data must be subjected to a qualified peer review before it is used to support the PHG.

3.B. OEHHA, 2011, notes that Figure 3 in Li et al, 2000a, shows that "*it appears that among infants who had their T4 levels collected on day one after birth, the mean T4 level in Las Vegas was about 4 µg/mL (about 22 percent) lower than the mean T4 in Reno*" (Page 42). This conclusion is based on only one of 60 data points on a single figure. It is not possible to evaluate the significance of the statement since no information is presented on the number of subjects represented by this data point, or if it is more than 1 subject. This statement, and its implication of an effect of perchlorate in the water, should be removed. The authors concluded that there is no effect.

3.C. OEHHA, 2011, states that "*any effect that the mother's 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 not necessarily at a later time*" (Page 37). No support is presented for this statement. While this statement appears to be reasonable, its accuracy depends on the endpoint used to measure thyroid function. Later, on page 39 in a discussion of Kelsh et al., 2003 and on page 43 in a discussion of Li et al., 2000b, OEHHA states that "*associations between maternal perchlorate exposures and neonatal thyroid hormone levels are probably best evaluated using TSH measurements collected within the first 24 hours after birth*." This position needs to be validated because the measurement of TSH during the TSH surge is highly dependent on the time of sampling and is extremely variable across individuals. Measurement of TSH on day 1 of life is generally not considered to be a useful measure of thyroid status. For this reason, TSH measurements on day 1 of life are not generally used in neonatal thyroid screening programs or in epidemiological studies. OEHHA's use of day 1 TSH levels is contrary to established practice and needs to be adequately supported and peer reviewed. In addition, OEHHA's interpretation of Kelsh et al., 2003, and Li et al., 2000b, as showing a difference in TSH associated with perchlorate should be subject to qualified peer review to establish its validity.

3.D. OEHHA's selective use of data from the Crump et al., 2000, study is not justified. OEHHA chooses to focus on the self-reported family history of thyroid disease going back three generations, a highly subjective endpoint with unknown relevance (unknown pathology or etiology of reported cases) to identify a LOAEL (Page 41). OEHHA then eliminates the data on infants, the focus of data collection in the study, based on the argument that some of the births took place in a city different from the city of residence, which is claimed to confound the perchlorate exposure classification. No evidence is presented to justify this decision by OEHHA, and it is in opposition to the conclusion of the authors, the NAS, and the ATA. OEHHA must present the basis for this decision in a transparent manner for qualified peer review to establish its validity.

3.E. OEHHA presents its own analysis of data presented by Buffler et al., 2006 (Page 44-46), concluding that the data showed a difference in TSH measurements associated with perchlorate. The authors reported "*no statistically or biologically relevant differences between newborns in these communities with respect to TSH concentrations*', findings which are "*consistent with the medical literature*" and similar to the NAS conclusion that "*epidemiologic studies were not consistent with a causal association between exposure to ClO4 – in the drinking water and either congenital hypothyroidism or thyroid function in normal full-term newborns*." OEHHA must subject its analysis and rationale to a qualified peer review if it is to use conclusions that are opposite of the published conclusions, especially the idea that TSH measurements on day 1 of life are useful, a measurement that Buffler et al describe as "*uninformative for assessing an environmental impact*" due to the TSH surge.

3.F. OEHHA discounts the results of Li et al., 2000b, in 'most important' part because the TSH measurements in the first day were excluded. As noted above (Comment **3.C.**), this position on timing of TSH measurement has not been supported and should be subjected to a qualified peer review.

3.G. In its discussion of the Brechner et al, 2000, study, OEHHA states that the time after birth of the TSH measurement "*was significantly earlier in Yuma than in Flagstaff, and this may have caused some of the increase in TSH levels*", but that the difference "*remained after adjusting for age in days*" (OEHHA, 2011, Pg 43). It is obvious from Figure 5 (OEHHA, 2011, Page 54), that the time of sampling after birth is a highly significant determinant of TSH level during the first 24 hours after birth and that the sampling time must be controlled for the number of hours after birth (not just the number of days) for the results to be meaningful in terms of an environmental influence. Lamm, 2003, provides analyses of several variables that could explain the difference attributed to perchlorate exposure by Brechner et al., and also compares populations in Yuma that differed in perchlorate exposure and did not differ in other variables, including TSH. OEHHA ignores the follow-up work by Lamm, and the conclusions of the NAS and ATA, and concludes that Brechner et al., 2000, shows a perchlorate related effect on newborn TSH.

3.H. It is also noted that the Steinmaus study was authored by the main author of the PHG document. A fair and impartial administrative process cannot be assured

where the author of the draft risk assessment must evaluate his own scientific work and the scientific work of others in formulation of the draft risk assessment. For example, the evidence cited by OEHHA as support for the focus on newborns (Kelsh et al., 2003; Brechner et al., 2000; Steinmaus et al., 2010; Li et al., 2000a; Crump et al., 2000) consists of one study by the authors of the PHG draft document and four studies in which the authors selectively re-analyzed or reinterpreted the papers to arrive at a conclusion that is opposite of the conclusions of the authors (See comments **3A, B, E, and G**).

IV. OEHHA relies on analyses using the NHANES data without addressing its limitations in two ways. First, OEHHA uses analyses of the NHANES data to support a causative relationship between iodine, perchlorate, and thyroid hormone levels, when in fact the NHANES data represents a cross-sectional epidemiological design and are subject to the limitations of this study type. Second, OEHHA uses the urinary iodide levels as an indicator of individual iodine nutritional status. Spot urine samples reflect recent consumption only and not nutritional status, and are useful only as population estimates. Blount et al., 2006, report an association of urinary perchlorate and TSH or T4 levels in women with spot urine iodide levels <100 ug/L. Steinmaus et al., 2007, report regression analysis of the NHANES data showing associations between several variables that represent thiocyanate exposure. There are several comments and interpretations of these studies that are incorrect and should be addressed by OEHHA, as follows:

4.A. OEHHA states that "*Blount et al. (2006) and Steinmaus et al. (2007) are key studies supporting two of the potential susceptibility groups identified by OEHHA (women with low iodine and women with high thiocyanate)*" (Pg 64). Spot urine samples are used as a basis to divide the population into those with <100 and >100 ug/L, a level "*chosen since it is used by the World Health Organization to define iodine deficiency in a population.*" This implies that the population in the NHANES data set with urinary iodine < 100 ug/L has low iodine nutritional status. Spot urine iodide levels only provide an indication of recent iodine consumption, not individual nutritional status. This is why the WHO only uses spot samples as an index of population status. By using the spot urine iodide samples as indicators of individual nutritional status (to define high and low iodine populations), these reports misinterpret the iodine data. These data can not be used to make associations between iodine nutritional status and other variables. It is not possible to know whether the two populations that differ in their spot urine iodide level are actually different in iodide nutritional status or whether the population with lower spot urine iodide levels are actually nutritionally inadequate in iodide intake. OEHHA does not provide any basis or rationale for the importance of an association between hormone measurements and spot urine iodine levels.

4.B. According to OEHHA, "*These findings provide evidence that thiocyanate interacts with perchlorate and low iodine levels*". The data inherently can not provide evidence of an interaction. Cross-sectional epidemiological data can only demonstrate associations between variables, whereas the word 'interaction' implies a causal association. Thus OEHHA is misinterpreting what the data can be used for even in the

absence of the incorrect use of the spot urine iodide levels to define different populations.

4.C. OEHHA states that the Steinmaus et al., 2007, study finding that "*similar effects are seen with all three methods used to categorize thiocyanate exposure (urine thiocyanate, serum cotinine, and smoking history) provides strong evidence that these findings are not due to chance*". This is not the case because Steinmaus et al., 2007, did not report on the correlation between the three thiocyanate related variables. Consistent associations with three different variables do not add strength to the evidence if the three variables are highly correlated.

4.D. OEHHA identifies several 'strengths' in the Blount and Steinmaus studies that should be reevaluated:

a. The studies are based on individual data – as commented above, individual data is not an appropriate use of the spot urine iodide levels;
b. Information on confounders is available – but, as described in Comment **1.C.**, ATA notes that the important confounding variables were not reported in NHANES.
c. Large sample sizes do not improve an analysis that is flawed by a misinterpretation of the independent variable.
d. Low p-values do indicate that the associations are probably not due to chance, but do not allow an interpretation beyond an association, and do not allow a causal inference.
e. Biological plausibility is cited as a strength, but no biologically plausible connection has been made between exposure to an inhibitor at levels that cause no measureable inhibition and an effect on thyroid physiology or thyroid hormone levels.

4.E. OEHHA addresses several 'potential concerns' with the Blount and Steinmaus studies:

a. OEHHA states that the short half-life of perchlorate, and the effects in animals in <1 day suggest that it is better to use short-term measures of perchlorate and thyroid hormones to show '*true associations*' (pg 63). This rationalization is counter to the well-described mode of action, which requires reduced thyroid hormone production, hormone imbalance, increased TSH production, and response to TSH stimulation of the thyroid. The effect at <1 day in rats is only an indication that something is wrong with the study or with the assumed mode of action.
b. OEHHA cites four studies with relatively small sample sizes as evidence for a strong correlation between spot urine iodide and 24-hr urine iodide. However, none of these studies are in the U.S., there are other studies that show little correlation, and there is considerable variability in the correlation between 24-hour urine iodide and long-

term average concentrations, a more reasonable measure of dietary iodine status. The use of spot urine iodide measurement in these studies as an indicator of iodine status is inappropriate and the conclusions are not supported.

4.F. OEHHA presents a series of arguments intended to rebut various limitations of the two studies that are analyses of the NHANES data (Pages 64-68). These arguments appear to be a response to the limitations of this data noted briefly by ATA, 2006 (see comment **1.C.**), among others. This OEHHA analysis presents arguments to suggest why each limitation is unimportant and/or would result in reduced likelihood of finding an association between thyroid hormones or TSH and perchlorate exposure. These two studies are critical to OEHHA's argument for the selection of the sensitive population in the draft PHG, and hence to the decision to reduce the PHG. This analysis by OEHHA should not be used without peer review by thyroid experts.

V. OEHHA does not provide any rationale, mode of action discussion, or data to explain how a perchlorate concentration in the blood that is far below the concentration required to cause measurable inhibition of iodine uptake can be linked to thyroid dysfunction.

5.A. A significant part of the reason for focusing on infants as the basis for a new PHG is the statement that "*young infants have low stores of thyroid hormone (less than one day's worth, compared to several week's worth in adults) (van den Hove et al., 1999). Because of these low stores, infants may be less able to tolerate transient periods of decreased iodide uptake and decreased thyroid hormone production compared to adults.*" It is reasonable to suggest that infants may be susceptible to conditions that can decrease iodide uptake and decrease thyroid hormone production. However, OEHHA does not provide a credible argument that a perchlorate level that was specifically derived to prevent inhibition of iodide uptake (the current PHG uses a no-effect level and an uncertainty factor of 10 to achieve this) can possibly be associated with such a condition. The van den Hove et al., 1999, study does not represent a convincing argument that the existing PHG should be reduced to account for the infant population.

5.B. Another significant part of the reason for focusing on infants as the basis for a new PHG is the statement that "*many infants may not be receiving adequate iodine in their diets*", based on Pearce et al., 2007. Again, it is reasonable to suggest that infants may be susceptible to reduced iodine intake. However, OEHHA does not provide a convincing argument that a perchlorate level that was specifically derived to prevent inhibition of iodide uptake (the current PHG uses a no-effect level and an uncertainty factor of 10 to achieve this) can affect iodide uptake. The Pearce et al., 2007, study does not represent a convincing argument that the existing PHG should be reduced to account for the infant population.

5.C. OEHHA repeatedly discusses studies that show an association between exposure to iodide uptake inhibitors and low or low-to-normal thyroid hormone levels during gestation (e.g., Pop et al., 2003; Kooistra et al., 2006), but does not provide a connection between exposure to iodide uptake inhibitors at a level far below the level associated with measurable iodide uptake inhibition and altered thyroid hormone levels.

5.D. On Page 49, OEHHA states that the cross-sectional epidemiological studies listed in Table 13 "*are consistent with the known biologic mechanism of perchlorate. That is, these results show that perchlorate may decrease T4 and increase TSH, both of which are effects that are in the direction expected based on the known mechanism of action of perchlorate*." This is a strongly misleading statement. This statement might reasonably apply to extremely high doses of perchlorate such as those used to treat Graves Disease. However, OEHHA has not provided any explanation as to how the known biologic mechanism of iodide uptake inhibition can lead to hormone changes when the inhibitor is present at a level that is much too low to cause measureable inhibition.

VI. Additional Comments

1. Page 38. OEHHA understates the value of the Crooks and Wayne, 1960, study. Despite its small sample size it is the only documented case of pregnant women receiving oral doses of perchlorate and the effects on the infant. Despite doses equivalent to 1000-fold the current PHG, only mild reversible thyroid effects were seen in the infant thyroid.

2. Page 46. In the discussion of the Steinmaus et al., 2010 study:

2A. The data in Table 2 shows the fluctuations in TSH levels during the TSH surge, within the limits of the age categories used, 0-5, 6-19, 20-32 hours. The first two periods are in the time of most rapid fluctuations in the TSH surge, and measurements during these times that can not be adjusted for exact age are not useful.

2B. The authors state that they use lower TSH cut-off points to define "high" TSH "*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)*". This suggests confusion between thyroid hormones and TSH which is produced in the pituitary gland.

2.C. The authors refer to "*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)*". The cited studies are cross-sectional epidemiological studies and do not study 'changes' which implies a longitudinal causative relationship.

3. Page 48. OEHHA excludes the Li et al. (2000) and Amitai et al. (2007) studies from consideration of the newborn ecological epidemiological studies because "*they did not include a substantial portion of subjects who had thyroid hormone levels measured within the first 24-36 hours after birth.*" As noted above, it is commonly accepted that measurement of TSH during the rapid changes of the TSH surge make such data difficult or impossible to interpret. Just as OEHHA needs to justify its focus on TSH measurements during the TSH surge and subject this decision to peer review, OEHHA also needs to do so in order to eliminate published studies from consideration. The Li et al. (2000) and Amatai et al. (2007) studies found no association between drinking water exposure to perchlorate and differences in TSH, and therefore do not support a focus on the newborn or a change in the PHG.

4. Page 48. OEHHHA excludes the Tèllez Tèllez et al. (2005) study from consideration of the newborn ecological epidemiological studies because "*45 percent of the newborns from the exposed city were born in the unexposed city and therefore were probably not exposed at the time of birth*." OEHHA does not provide any data on the time spent in the birth city, or support for the idea that perchlorate consumption on the day of birth is critical to the possible effects of perchlorate. The Chile populations remain an important source of information for a population naturally exposed to a mildly elevated dose of perchlorate.

5. Selection of the point of departure from the toxicity study selected: Based on their study in human volunteers, Greer et al. (2002) determined a no-observed-effect level (NOEL) of 0.007 mg/kg-day for the inhibition of thyroidal radioactive iodide uptake by orally administered perchlorate. U.S. EPA developed an oral RfD using the NOEL of 0.007 mg/kg-day from Greer et al. (2002) based on the NRC's (2005) recommendation. The NRC (2005) recognized the potential benefits of using a benchmark dose (BMD) methodology to determine the point of departure for perchlorate. However, the NRC (2005) recommended use of the NOEL of 0.007 mg/kg-day from Greer et al. (2002) because they believed there was no consensus on the criteria for choosing the most appropriate BMD analysis for the Greer et al.(2002) data, and the NOEL of 0.007 mg/kg-day was supported by other studies they reviewed. The NOEL of 0.007 mg/kg-day from Greer et al. (2002) was also used as the point of departure by the U.S. EPA during the development of their interim health advisory for perchlorate. In contrast, OEHHA used the BMD methodology and determined a 95 percent lower confidence limit on the bench mark dose (BMDL) equal to 0.0037 mg/kg-day to be an appropriate point of departure for calculation of the proposed PHG for perchlorate in drinking water. The calculated BMDL (0.0037 mg/kg-day) is below the lowest tested dose in Greer et al. (2002). Uncertainties associated with extrapolating the dose-response curve below actual tested dose concentrations should be discussed within the technical support document. Although the technical support document does mention the NRC (2005) study, it does not address the uncertainties mentioned by the NRC (2005) regarding the calculation of a BMDL using the Greer et al. (2002) data. The uncertainties associated with the calculation of a BMDL for perchlorate, as mentioned by the NRC (2005) should be explicitly considered during the development of the draft PHG for perchlorate. OEHHA should consider using the NOEL from the Greer study, since there is general

scientific consensus that the NOEL is the appropriate point of departure for evaluating risks associated with oral exposures of humans to perchlorate.

6. Conversion of the ADD to the PHG for perchlorate in drinking water: OEHHA converted the ADD to the PHG for perchlorate in drinking water by accounting for the relative source contribution (RSC) and the ratio of body weight and tap water consumption rate (BW/WC). The body weight and water consumption rate used in OEHHA's calculation of the BW/WC were obtained from Estimated Per Capital Water Ingestion and Body Weight in the United States – An Update (U.S. EPA, 2004). The source data for U.S. EPA (2004) were obtained from the United States Department of Agriculture's 1994-1996 and 1998 survey. Since then, the U.S. EPA has published their Final Child-Specific Exposure Factors Handbook (CSEFH) (U.S. EPA, 2008), which contains recommended body weights and water consumption rates for infants. OEHHA should use the body weights and water consumption rates from CSEFH (U.S. EPA, 2008). It appears the BW/WC used in OEHHA's calculation was based on the body weight and water consumption rate from Table 7.1 and Table 5.2.B2 of U.S. EPA (2004), respectively; and the water consumption rate of 0.234 L/kg-day from Table 5.2.B2 was converted to units of L/day using a body weight of 9 kg. The resulting BW/WC calculated by OEHHA was 4.3 kg-day/L. OEHHA should use the 95th percentile body weight and water consumption rate from Table 8-3 and Table 3-1 of the CSEFH (U.S. EPA, 2008).

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