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Michael Baes
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California Environmental Protection Agency
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Dear Mr. Baes:

Exponent is pleased to provide the comments presented below on the January 11, 2011, document, "Public Health Goal for Perchlorate in Drinking Water", which was prepared by the Office of Environmental Health Hazard Assessment (OEHHA) within the California Environmental Protection Agency (CalEPA). We are presenting these comments on behalf of Whittaker Corporation.

Comments below first address flawed or inconsistent aspects of the quantitative exposure and risk assessment underlying the identified PHG. Following that discussion, we address several misinterpretations and mischaracterizations of the epidemiological data that are presented in the PHG document. Finally, we present a summary of our overall conclusions about the appropriateness of the PHG basis, strategy and identification.

In summary and based on the more detailed comments provided below, we believe the BMD modeling performed as the basis of the PHG was incorrectly performed and that the cumulative application of conservative assumptions has produced a PHG that is not technically supportable. The recommended PHG is far below levels that have been shown to cause no adverse health effects in humans in several epidemiology studies. Consequently, no health benefit would be derived by adopting the proposed PHG.

Flawed or inconsistent aspects of the quantitative exposure and risk assessment underlying the PHG

As noted in its Perchlorate Public Health Goal report (CalEPA 2011), OEHHA followed the basic approach used by the National Research Council (NRC) Committee on the Health Implications of Perchlorate Ingestion ("NRC Committee") to derive the Acceptable Daily Dose (ADD) (NRC 2005). This NRC report served as the basis of the updated CalEPA OEHHA

recommendation for a perchlorate Public Health Goal (PHG) (CalEPA 2011). Some of the noteworthy aspects of the derivation of the PHG include:

- Use of a nonadverse short-term (two-week) reduction in iodine retention as the basis of the Acceptable Daily Dose (ADD),

- Use of an infant as the sensitive receptor, rather than a pregnant woman and fetus as was assumed by the NRC Committee to be the most sensitive receptor,

- Use of a BMDL in deriving the PHG instead of a NOEL, as was used by the NRC Committee,

- Application of 10-fold factor to account for differences between sensitivities of infants relative to those of healthy adults, which is the same factor used by the NRC Committee to account for differences in sensitivity between a pregnant woman and fetus relative to healthy (non-pregnant) adults,

- Application of a Relative Source Contribution (RSC) of 0.73,

- Use of 0.234 L/kg-day as an assumed 95th percentile rate of drinking water consumption for infants (0 to 6 months)

- Application of BMD modeling methods to an improperly defined subset of data from the Greer et al. (2002) radio-iodide-uptake study

The NRC Committee noted that in selecting iodine uptake as the biological end point in the derivation of their acceptable daily dose, they were departing from traditional methods by basing the development of an acceptable daily dose on a nonadverse effect, rather than on an adverse health effect. The report noted that, "[u]sing a nonadverse effect that is upstream of the adverse effects is a conservative, health-protective approach to the perchlorate risk assessment." Using this conservative approach the NRC Committee recommended a dose of 0.007 mg/kg-day as the dose they considered to be a No Observed Effect Level (NOEL) from the Greer et al. (2002) study on human volunteers.

The NRC Committee supported this recommendation of a NOEL by noting that it was consistent with other clinical studies on iodine uptake inhibition studies on perchlorate. Specifically, they noted that 6-months of exposure at the NOEL and 4 weeks of exposures to higher doses in small test populations did not progress to adverse effects in the absence of iodide uptake inhibition. Thus, while the number of study subjects was relatively modest, the selected NOEL was consistent with other biological evidence.

Acknowledging that the Greer et al. (2002) study had been conducted using healthy adults, the NRC Committee recommended use of an uncertainty factor of 10 to protect the most sensitive subpopulations, which they identified as pregnant women and fetuses. By applying an uncertainty factor of 10 to the NOEL of 0.007 mg/kd-day, the NRC arrived at a dose of 0.0007 mg/kg-day (e.g., 35 µg/day for a pregnant 50-kg female) "that should protect even the most sensitive population".

OEHHA uses the same study (i.e., Greer et al. 2002) and the same endpoint (i.e., iodide uptake, as was used by the NRC committee as the basis of the OEHHA Acceptable Daily Dose (ADD), which is used in the derivation of the PHG). Rather than using the NOEL identified by the NRC Committee from the Greer et al. (2002) study, OEHHA uses a BMD approach to derive a conservative estimate of a dose estimated to cause a 5% reduction in iodide uptake. The estimated dose is the lower 95% confidence level estimate of the dose estimated to cause a 5% reduction in iodide uptake and is referred to as the BMDL. The BMDL estimate by OEHHA is 0.0037 mg/kg-day, a dose that is about half the level recommended by the NRC committee as a NOEL.

As explained in the PHG document, OEHHA identifies infants, rather than pregnant women and fetuses, at the population most sensitive to the effect of perchlorate. To account for uncertainties associated with extrapolating results for the Greer et al. (2002) study on health adults to infants, OEHHA applies an uncertainty factor of 10.

In converting the Acceptable Daily Dose into a corresponding drinking water concentration, OEHHA applies a Relative Source Contribution (RSC) factor to account for the fact that people will be exposed to perchlorate in their diet as well as from drinking water. Based on consideration of the amount of perchlorate likely to be present in an infant's diet, OEHHA has proposed an RSC of 0.73 to be applied to reduce the amount of perchlorate allowed in drinking water. Use of the RSC in the derivation of the RSC would be intended to keep the combined exposure to perchlorate from drinking water and diet below the ADD.

Application of an RSC to an ADD based on the Greer et al. (2002) study is not appropriate, since the people in that study would have been exposed to perchlorate in their diet in addition to the doses administered in the study. The doses administered in the Greer et al. (2002) study do not reflect total perchlorate exposure, but rather are an incremental exposure above their dietary exposure.

Finally, to account for the fact that infants may consume more water than adults on a bodyweight basis, the PHG is calculated using the 95th percentile of water consumption rate for infants of 0.234 L per kg-day. This water consumption level is approximately 10 times higher than the level traditionally assumed when setting drinking water levels (i.e.. 2 L/day ÷ 70 kg = 0.028 L/kg-day). The U.S. EPA (2006) Child-Specific Exposure Factors Handbook states (on page 4-1) that "The U.S. EPA uses the quantity 1 L per day for infants (individuals of 10 kg

body mass or less) and children as a default drinking water ingestion rate (U.S. EPA, 1980; 1991). This rate includes drinking water consumed in the form of juices reconstituted in the home and other beverages containing tapwater." An intake rate of 1 L/day corresponds to 0.2 L/kg-day for a 5 kg infant.[1] Table 4-6 of the same EPA Handbook (page 4-12) lists 95th percentile intake rates estimated based on USDA Continuing Survey of Food Intakes by Individuals (CSFII), 1994-96, 1998—using the same definition of direct and indirect water ingestion—as being 0 (i.e., zero) L/kg-day at age 0 to <1 months, 0.055 L/kg-day at 1 to <3 months, 0.053 L/kg-day at 3 to <6 months, and ≤34 L/kg-day at all older age groups, where percentiles are defined in this table as referring to "the whole population." The water-intake estimate of 0.234 L/kg-day selected by OEHHA to apply to perchlorate exposure assessment thus rather substantially exceeds the empirical 95th percentile estimates of water intake based on nationwide U.S. random-survey CSFII data. Consequently, for the purpose of perchlorate exposure assessment, a reasonable upper-bound water-intake rate for infants <6 months of age would be approximately 0.05 L/kg-day.

In the derivation of the most recently proposed PHG for perchlorate, OEHHA identified a long list of uncertainties and has adopted several conservative approaches to address these uncertainties. This particular ADD is unusual in that it begins with an effect that the NRC points out is a nonadverse effect. Although OEHHA began its process of setting their ADD with a dose estimated to cause a 5% reduction in iodide uptake, the NRC Committee noted that an adverse effect would not be expected until an iodide uptake is reduced by 75%. A lower statistical bound on the daily perchlorate dose required to reduce iodine uptake by 75% could readily be calculated from the Greer et al. (2002) study using Benchmark Dose methodology. Given that the starting point of the PHG is a non-adverse effect, OEHHA could have derived an adequately conservative, fully health protective PHG by applying modest uncertainty factors and fewer conservative assumptions to that non-adverse starting point. Instead, OEHHA applied a collection of generic uncertainty factors and specific conservative assumptions that cumulatively have an impact that is as large or larger than that of factors and assumptions

[1] The 2006 EPA Handbook lists 0.234 L/kg-day as the 95th percentile of ingested community water (defined to include both "direct and indirect" water consumption) by infants from birth to <1 month of age, with lesser intakes per unit body weight for older children and adults (EPA 2006, Table 4-7, Summary of Recommended Community Drinking Water Ingestion Rates, p. 4-13). That Handbook (at pages 41 – 4-2) defines "direct ingestion" as "direct consumption of plain water as a beverage at home and away from home from all sources including tap/fountain water from community water supply, household well or rain cistern, household or public spring, and bottled," and "indirect ingestion" as including "water added during food preparation ... not ... intrinsic to purchased foods ... for example, water used to prepare baby formulas, cake mix, and concentrated orange juice," and points out that "for the purposes of exposure assessments involving site-specific contaminated drinking water, ingestion rates based on the community supply are most appropriate. Given the assumption that bottled water, and other purchased foods and beverages are widely distributed and less likely to contain source-specific water, the use of total water ingestion rates may overestimate the potential exposure to toxic substances present only in local water supplies."

typically applied when developing exposure limits based on BMDs or NOELs in reference to adverse health effects.

A factor of 10 was formally applied by OEHHA to account for the likelihood that populations (i.e., infants) other than the healthy adults tested in the Greer et al. (2002) study will be more sensitive to effects of perchlorate. In addition to applying this factor of 10, OEHHA used the 95th percentile of water consumption for infants as the assumed water ingestion rate to further account for their assumption that infants are the population most sensitive to perchlorate. This combination of factors effectively applies a factor of 100 to the extrapolation of concentration for an adult to a concentration for an infant. Although the specific basis for the inter-individual variability factor of 10 traditionally applied when extrapolating from healthy adults to sensitive individuals is not precisely defined, it is has traditionally included the fact that some individuals have greater exposure than others. Applying both the explicit 10-fold variability factor and the 95th percentile water consumption rate is at least partially redundant, and clearly reflects some double counting for inter-individual variability. Moreover, there is no precedent for assuming greater sensitivity at younger ages to iodine deficiency when expressed on a per body weight basis; in contrast, recommended dietary allowances at different age groups are approximately equal when expressed on a per body weight basis (Delange and Ermans 1991; Delange 1994). The application of the RSC adds further to the compounding of conservative assumptions and, as noted above, this factor is not justifiable in this case.

Finally, the CalEPA (2011) PHG report describes as the basis for its PHG recommendation an application of EPA Benchmark Dose (BMD) software to data from the Greer et al. (2002) study of perchlorate effects on radio-labeled iodide uptake in humans. Particularly, pages 102–103 of the report states that "OEHHA used the BenchMark Dose Software, version 2.0.0.33 (U.S. EPA, 2008) to perform the analyses based on the human data reported by Greer et al. (2002) shown in Table 39. ... OEHHA tried several curve fitting models provided by the software and found the Hill model adequately describes the data (goodness of fit test, p=0.46), shown plotted in Figure 13. ... Footnote 1: The Hill model was run with the following settings: intercept = zero, power parameter restricted to be greater than one, a constant variance model assumed. The BMR was a 5 point decrease in [percent] iodide uptake."

The data to which the BMD model was fit, summarized in Table 39 on page 103 of the CalEPA OEHHA (2011) PHG report, are deviations in the 24-hour percent of radio-labeled iodine taken up by thyroid in the human subjects studied by Greer et al. (2002). The Hill-model parameter values listed in the report do not appear to correspond to the fit actually depicted, and incorporate an intercept term arbitrarily forced to equal zero. Alternative parameter values with a forced zero intercept give a reasonably similar plot in relation to the data fit by OEHHA. The key problem with the data fit OEHHA obtained is that the baseline data were omitted entirely from the analysis, together with their combined ~22.6% coefficient of variation, and any discussion of either the fact that baseline uptakes varied from ~10 to 35%, or the health

implications of this range of natural variation in baseline uptake in symptomatically normal human subjects. Rather, only non-baseline data were included in the fit, after normalizing as percentages of corresponding dose-group-specific sets of uptake data. The dose-specific 24-hour baseline data from the Greer et al. study are statistically homogeneous (by 1-way analysis of variance, $p = 0.62$), as are their variances (by Bartlett's test, $p = 0.24$). Therefore, ignoring the absolute values of the baseline data, and their combined variance, in the fitting procedure used by OEHHA resulted in a misleading fit to the data that mischaracterized the variance associated with its fitted parameters. The possible perchlorate exposures of subjects at or just prior to each baseline measure was not discussed by Greer et al. (2002). However, that study took place in the Portland, OR, area, which is not an area known to have elevated levels of perchlorate in drinking water (Jenkins and Sudakin, 2006). Figure 1 shows the un-normalized baseline and dose-specific 24-hour iodine-uptake percentage data from the Greer et al. (2002) study, with perchlorate exposures for all baseline measures are set to a reasonably low value of 1 microgram per kg body weight per day, with dose values plotted on a logarithmic scale. The approximate OEHHA Hill-model fit (black curve), is compared to a better fitting 2-parameter log-linear model fit (blue curve) to the four non-baseline data points. The fit, and associated 2-tail 90% confidence intervals (red curves), were obtained using the *Mathematica* 8.0 NonlinearModelFit function, with weights set to the product of sample size and inverse sample variances (Wolfram 2011). The lower 2-tail 90% (i.e., lower 1-tail 95%) confidence limit log-linear fit implies that doses below 0.004 mg/kg-day would appear unlikely to affect iodide uptake at all based on measures made among subjects studied by Greer et al. (2002). The toxicological significance of doses between this apparent threshold and 0.02 mg/kg-day is not clear in view of the substantial magnitude of variation in baseline iodine-uptake rates (down to ~10%) exhibited among the symptomatically normal subjects in this study.

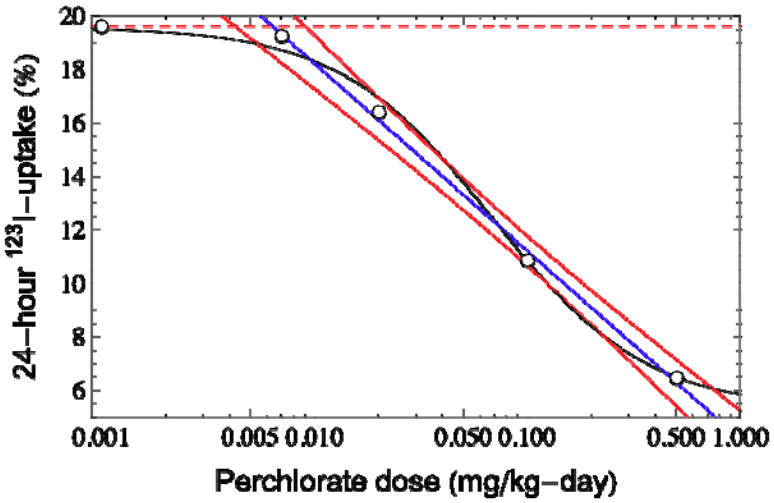

Figure 1. Model fits to un-normalized data of Greer et al. (2002). Dashed red line denotes weighted average baseline level of iodine uptake (baseline levels varied from ~10 to 35%). The three-parameter, zero-intercept OEHHA Hill model fit only to baseline-normalized values of the four non-baseline data points (approximated by the black curve), is compared to a log-linear fit (blue curve, with red 2-tail 90% confidence limits) defined for uptake values that do not exceed the subject-number weighted-average baseline value of 19.6% (dashed red curve).

Misinterpretation and mischaracterization of epidemiologic evidence

OEHHA Has Arrived at Incorrect Conclusions Regarding the Epidemiologic Studies of Newborns Thyroid Function and Perchlorate Exposure

The OEHHA Public Health Goal (PHG) report concludes that "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." This characterization of the epidemiologic literature on newborn thyroid function and perchlorate is not an accurate representation of the findings from the epidemiologic research on this topic. As noted in several recent reviews (Tarone et al. 2010; Charnley 2008), there is clearly an absence of epidemiologic evidence that current environmental exposures to perchlorate are resulting in adverse effects to infant thyroid function. Efforts to place stringent allowable drinking water levels are not supported by the epidemiologic evidence. Both of these reviews highlight the importance of other environmental goitrogens (nitrate and thiocyanate) as more influential inhibitors of iodide uptake than perchlorate, based on the widespread prevalence in the environment (Tarone et al., 2010). In fact Tarone et al. claim that even with

complete elimination of perchlorate in the environment, > 99% of environmental inhibition of iodide uptake would still be occurring (Tarone et al. 2010).

The OEHHA epidemiologic interpretation of the epidemiologic data is not considering the complete set of studies on this topic and has inappropriately excluded certain studies (e.g. Li et al. 2000, Tellez et al. 2005, Amatai et al. 2007) in their summary of key studies (Table 13 on page 50 of the PWG report). In addition, the emphasis on thyroid screening results collected within 24 hours of birth is inappropriate and not clinically justified. In short, the OEHHA review has not provided a balanced summary of the research findings. A summary of each of the studies, the OEHHA interpretation of that study and the author's interpretation of their results are presented as part of these comments to the OEHHA PWG.

The OEHHA Assumption that emphasizes research findings from epidemiologic studies of newborns for the first 24 hours when screening data are collected for evaluating the relationship with environmental perchlorate is not justified

The assumption and emphasis of the OEHHA epidemiologic review regarding newborn screening data collected within the first 24 hours from birth is not based on clinical criteria, does not adequately account for the natural surge in TSH levels at birth, and is not logical from a disease causation perspective. This assumption is also applied to studies to include or exclude in the OEHHA summary and weighting of epidemiologic studies. 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 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, the estimation of cumulative pregnancy exposure to perchlorate and the chronic impact on newborn thyroid function are the more relevant exposure and "disease" metrics. OEHHA's reliance on measures that reflect essentially cross-sectional exposure characterization the day before birth and the transient measure of TSH biomarker levels within the 24 hour period (when there is a large natural surge in TSH levels among newborns) is not particularly relevant to the health question of chronic perchlorate exposure during fetal development and TSH levels in newborns. These latter characteristics are what must be assumed in emphasizing TSH screening data from the first 24 hours after birth.

Exclusion/Inclusion Criteria Used by OEHHA to Summarize Epidemiologic Studies

Table 13 of the OEHHA Perchlorate PHG report summarizes the epidemiologic studies deemed by OEHHA staff as relevant for assessing newborn risk for adverse thyroid impacts due to perchlorate exposure. This table is incomplete, inappropriately excludes negative studies, and only emphasizes reported or re-calculated newborn screening findings for data collected within the first 24 hours instead of the complete data findings. Specifically the Buffler et al. 2006 study of California data should be included instead of the Steinmaus 2010 study, and the Amatai et al. 2007, Tellez 2005 et al. and Li eat al 2000 studies should have all been included in this table and considered in an overall weight of evidence scientific review. The Steinmaus re-analysis of California Newborn screening data originally published by Buffler et al. 2006, involved redefinition of the TSH biomarker outcome and emphasized findings from the first 24 hours of screening – both questionable and inappropriate analysis strategies.

Essentially all of the newborn studies have reported no associations between environmental perchlorate and newborn thyroid function as measured by comparisons of the prevalence of congenital hypothroidism, elevated TSH levels, or depressed T_4 levels. The only exception to this was the Brechner et al. 2000 study conducted among Arizona infants, where researchers compared TSH levels among Flagstaff newborns (unexposed) and Yuma newborns (considered exposed to perchlorate). Additional investigation into these findings (Lamm, 2003) revealed that other factors related to treatment practices could explain the differences in TSH levels among newborns from Flagstaff compared to those from Yuma.

The largely negative findings from the newborn studies are also consistent with results reported from occupational studies (Gibbs et al. 1998; Lamm et al. 1999; and Braverman et al. 2005) and other clinical studies of pregnant women with low iodine (e.g. Pearce et al. 2010). The publication of analysis of NHANES data on women's thyroid levels and perchlorate measured in urine samples from the same women reports positive associations between these two biomarkers (Blount et al. 2006). This finding was contradictory with the body of other epidemiologic literature. Possible explanations for this contradictory finding include: 1) confounding by another substance associated with perchlorate but not addressed in the analysis, 2) statistical artifact from a cross-sectional analysis or 3) that an association exists between low level perchlorate and TSH function among women (Charnley, 2008). It should be noted that the same association was not observed among men in this survey and that creatinine adjustment, and a focus on women in the child bearing age (15-44 years, instead of all women 12+ years or older) substantially reduces this reported association. It is apparent that limitations and inconsistencies of findings within study subgroups (i.e. men and reproductive age women) of the NHANES data highlight the need for further research before more firm conclusions can be drawn.

Individual Study Descriptions and Contrasting OEHHA Interpretations

Li et al. 2000 ("Nevada Study of Thyroid Function TSH Results")

This study compared neonatal TSH concentrations for 540 normal-birth-weight babies in Las Vegas and Reno from December 1998 to October 1999. Las Vegas water contained up to 15 µg/L perchlorate, while Reno had no detectable perchlorate in its drinking-water supplies, providing the opportunity for epidemiologic comparisons. Newborns that underwent TSH screening within the first 24 hours were excluded because of the known TSH surge in the first day of life. The OEHHA report criticizes this data exclusion, however, as described above, from a clinical perspective, this is a very reasonable and more defensible analytical approach than including these data in the analyses. Overall serum TSH concentrations were significantly higher during days 2–7 compared with days 8−30, and were higher for boys than for girls. The Li et al. study reported no differences in TSH levels for neonates in Las Vegas and Reno when controlling for age of blood collection and sex of infant. The OEHHA report also criticized the fact that the day of serum data collection was too broad, however, this grouping would not bias study results in a significant way – the critical time factor is data collected within the first 24 hours. In addition they mention that ethnicity was not controlled for – which may be a concern, however as noted below in the Brechner study of Arizona infants, ethnicity was not observed as a potential confounder. In summary, criticisms proposed by OEHHA staff are not that substantial to discount these results. The Li et al. study used an ecological study design with respect to exposure classification, as did many of the epidemiologic studies on this topic, and has the limitations inherent with that study design.

Li et al. 2000 ("Nevada Study of Thyroid Function – T_4 Results")

This study compared Serum T_4 concentrations for 23,190 normal-birth-weight newborns in Las Vegas and Reno from April 1998 through June 1999 and reported no difference in serum T_4 concentrations for neonates in Las Vegas and Reno. The OEHHA report again only emphasizes the approximate results from the data abstracted from a graph presented in the study manuscript giving results for when serum was collected within the first 24 hours and cannot provide any measures of statistical variability for this data point. Although the researchers observed that serum T_4 concentrations were significantly different based on age at blood collection, sex, birth weight, and season, when controlling for these factors, there was no difference between levels in Las Vegas and Reno. These findings highlight the many different factor that can effect T_4 levels.

Brechner et al. 2000 ("Arizona Study")

The Brechner et al. (2000) study data were reexamined by Lamm (2003) to assess if other factors may explain the findings of this one positive study. Lamm compared TSH levels among newborns from three cities within Yuma County (Somerton, San Luis, and Yuma), he found similar TSH levels when comparing these three communities from the same county in Arizona,

even though the city of Yuma, was the only community with detectable perchlorate in its drinking water. There was, however, a significant difference in TSH concentrations between Yuma County and Coconino County, the county containing Flagstaff. Due to the higher altitude (i.e., 7,000 feet), newborns in Flagstaff usually remain hospitalized for at least 2 days and approximately 80% receive supplemental oxygen at birth, in contrast to newborns in Yuma, who are often released within 24 hours of birth. Lamm concluded that the differences in TSH levels attributed by Brechner et al. (2000) to perchlorate concentrations are most likely due to differences in the age at sample collection in the two counties, and perhaps other factors (e.g. medical or sociodemographic factors).

Lamm 2003 ("Response to Arizona Study")

The Brechner et al. (2000) study data were reexamined by Lamm (2003) to assess if other factors may explain the findings of this one positive study. Lamm compared TSH levels among newborns from three cities within Yuma County (Somerton, San Luis, and Yuma). He found similar TSH levels when comparing these three communities from the same county in Arizona, even though the city of Yuma, was the only community with detectable perchlorate in its drinking water. There was, however, a significant difference in TSH concentrations between Yuma County and Coconino County, the county containing Flagstaff. Due to the higher altitude (i.e., 7,000 feet), newborns in Flagstaff usually remain hospitalized for at least 2 days and approximately 80% receive supplemental oxygen at birth, in contrast to newborns in Yuma, who are often released within 24 hours of birth. Lamm concluded that the differences in TSH levels attributed by Brechner et al. (2000) to perchlorate concentrations are most likely due to differences in the age at sample collection in the two counties, and perhaps other factors (e.g. medical or sociodemographic factors).

Crump et al. 2000 ("Chilean Study")

TSH concentrations from for 9,784 babies born in Chile between February 1996 and January 1999 were compared in three Chilean cities with undetectable (Antofagasta), low (Chanaral) (mean 5.5 µg/L), and high (Taltal) (mean 111.6 µg/L) perchlorate concentrations in their drinking water supplies (Crump et al. 2000). Significant differences in TSH concentrations were associated with sex and age at time of sample collection, consistent with other studies. However, newborns in the community with the highest concentration of perchlorate in drinking water had significantly lower TSH concentrations compared with newborns in the community with no detectable perchlorate (when sex and age at sample collection were controlled in the analysis). Crump and colleagues also evaluated the TSH concentrations of 162 school-age children in the three communities. After controlling for age, sex, and urinary iodine, no differences were observed between TSH concentrations for the children in the two communities with perchlorate in drinking water compared with those in the community with no detectable perchlorate. Thus, in this study comparing newborns in three communities with a marked contrast in perchlorate exposures, no association was found between perchlorate in drinking water and suppression of thyroid function. These were the primary findings of the Crump et al.

study. OEHHA reports a 45% higher mean TSH value for the exposed community compared to the low and unexposed community for data collected in the 24-36 hour period. This difference appears in error, as the mean reported TSH values were 4.2 and 3.2 µU/mL, a difference of ~ 33% (not 45%), which was not statistically significant. The OEHHA report also emphasizes the findings for self-reported family history of thyroid disease, a measure much less reliable than a measured biomarker outcome (TSH), and less relevant to the question of risk to infant populations.

Gibbs and Narayanan 2004 ("Additional Data for Chilean Study")

The OEHHA review did not mention this study where perchlorate concentrations in frozen samples of serum and urine from some participants in the Crump et al. (2000) study were analyzed to characterize exposure status of residents of the three Chilean cities. Perchlorate was found in all samples tested from participants from Taltal, whereas no perchlorate was detected in serum or urine samples from any Antofagasta or Chanaral participants. The urine perchlorate measurements were used to estimate a mean daily perchlorate intake for residents of Taltal of 0.0047 mg/kg-day. These findings supported the assumption that exposures to perchlorate in newborns and children in Taltal (high perchlorate city) had occurred and that the perchlorate/dose assessments based on drinking-water concentrations in Crump et al. are consistent with individual level internal dose assessments.

Tellez et al. 2005 ("Follow-up of Chilean Study")

The OHHEA report states that "the lack of a large contrast in exposure between the subjects from each of the cities probably decreased the likelihood that true associations, if present, could be found. The report cites that levels of perchlorate in urine across the low, medium and high exposed communities described above in the Crump et al. study summary were 22.3, 17.5 and 49.1 µg/L respectively, measured at the mothers' post-partum visit. However the OEHHA fails to mention significant differences noted during the mother's first prenatal and second prenatal visits – which show more significant contrasts in exposure levels. For example at the first prenatal visit the perchlorate levels measured in urine were 24.5, 66.7 and 132.9 µg/L respectively, for the low, medium and high exposed Chilean communities. Similar findings were recorded for the mothers' second prenatal visit. Thus a variation in exposure was confirmed by analysis of urine perchlorate levels, which showed increasing urine perchlorate levels across increasing drinking-water perchlorate concentrations (Antofagasta lowest, Chanaral medium, and Taltal highest). Tellez et al. conducted a longitudinal epidemiologic study of pregnant women in the same three cities studied by Crump et al. (2000) to evaluate whether exposures to perchlorate in these towns were related to thyroid function (assessed by TSH, thyroglobulin [Tg], and T_4) in both the mothers during various stages of gestation and in newborns at birth. No association of perchlorate and either free T_4 or TSH was observed among infants from the three different communities or among mothers across various stages of gestation and childbirth. This was the first community study to involve the use of individual perchlorate exposure measures based on urine biomarkers, based on assessment of perchlorate

concentrations in tap water samples, and involved multiple biomarkers of thyroid function. Although sample sizes were relatively small, this was one of the better designed studies at the time (and still to date) for assessing potential impacts of environmental perchlorate and thyroid function. The OEHHA report does not sufficiently acknowledge these study strengths but rather downplays the findings and presents only a non-representative subset of the exposure monitoring data among the pregnant women who participated in this study.

Kelsh et al. 2003 and Buffler et al. 2006 ("California Newborn Studies")

The OEHHA PHG report presents some re-analyses of two studies of neonatal thyroid function among California newborns in relation to perchlorate detection in drinking-water sources(Kelsh et al. 2003; Buffler et al. 2006). Both studies originally compared the prevalence of primary congenital hypothyroidism and TSH level, for newborns in communities where perchlorate was present versus where no perchlorate had been detected in drinking water. The Kelsh et al. study focused on one Southern California Community across the time period 1983-1998, where as the Buffler et al. study focused on the entire state of California for the year 1998 when both perchlorate water data were available and TSH screening among all newborns had been implemented. We selected TSH as a more appropriate biomarker for thyroid function because this was considered the clinically relevant parameter (Kelsh 2003). No effects were observed for data collected 24 hours or later from infants in the Southern California community where perchlorate was detected (Kelsh et al. 2003). The OEHHA odds ratio calculated for T_4 for this community does not appear to take into account other comparison communities in San Bernardino and Riverside counties that had perchlorate detected in water supplies, which should be excluded from the comparison group (or at least this fact was not mentioned in the OEHHA report).

After controlling for sex, ethnic status, multiple birth status, birth weight, and the time of sample collection, the risk of primary congenital hypothyroidism was not significantly increased for newborns in California whose mothers resided in communities with average perchlorate concentrations >5 μg/L (odds ratio [OR] = 0.71, 95% CI: 0.40−1.19) [Buffler et al. 2006]. Similarly, after controlling for the same factors, we did not find evidence of high TSH levels for California newborns with average perchlorate concentrations >5 μg/L in drinking-water sources compared to newborns from areas with average perchlorate concentrations ≤5 μg/L, [OR for high TSH, 0.73 (95% CI: 0.40−1.23)] among newborns screened at ≥24 hours of age. The OEHHA report and the Steinmaus (2010) re-analysis of the California data inappropriately emphasize the findings for data from the first 24 hours of screening and report positive associations. This analysis also redefined "elevated TSH" from the clinical definition applied in the Buffler et al. study to the 95th percentile of the TSH distribution.

Amitai et al. 2007 ("Israeli Study")

This study was a cross-sectional study of newborns in Israel that examined T_4 levels for neonates born to mothers residing in suburbs where the drinking water contained perchlorate

from military base activities were compared to mothers in communities with essentially no perchlorate exposure. The study used several measures to determine likely exposures including serum measurements and water concentration estimates. Mothers and their newborns were classified into three groups: very high exposure (up to 390 µg/L), high exposure (42–94 µg/L), and low exposure (<3 µg/L) based on levels of perchlorate in drinking water supplies. Serum perchlorate levels in blood from donors residing in these areas were used to confirm levels of perchlorate in drinking water in the three areas. Neonatal T_4 values (mean ± SD) were very similar across the three exposure areas (13.9 ± 3.8, 13.9 ± 3.4, and 14.0 ± 3.5 µg/dL in the very high, high, and low exposure groups, respectively), indicating no association between drinking-water perchlorate levels and T_4 in newborns. This study also controlled for nitrate and thiocyanate, both exposures known to affect the uptake of iodine by the thyroid gland, which could act as confounders of a potential perchlorate/T_4 association. This study, like that conducted in Chile represents one of the better designed epidemiologic studies and should have been included in the OEHHA weight of evidence review (i.e., Table 13).

Summary and Conclusions: Thyroid Function in Newborns and Children

As described above and shown in the appendix table, epidemiologic studies of newborn thyroid function, conducted in California, Nevada, Arizona, Chile, and Israel, have not shown an association between perchlorate in drinking water and primary congenital hypothyroidism or measures of thyroid function (elevated TSH or decreased T_4). These observations have been reported for a wide range of perchlorate concentrations in drinking water (ranging from >5.0 µg/L up to 390 µg/L [Israel] and 111.6 µg/L [Chile]), where levels are much higher than those observed in California drinking-water sources. The U.S. studies are limited by the ecologic nature of the exposure assessment (i.e., exposure is available only on a group level, rather than based on individual estimates). The Chilean and Israeli studies were able to confirm individual level exposures and examined newborns that experienced considerably higher perchlorate levels than populations studied in the U.S. These conclusions are also consistent with two recent comprehensive reviews of these studies (Tarone et al. 2010 and Charnley 2008).

This is in stark contrast to the opinions offered in the OEHHA report of "a consistent body of evidence linking perchlorate exposure during pregnancy with change in thyroid hormone levels in the newborn." This latter opinion is based on emphasis on only part of the literature and part of the data (data collected for newborns within 24 hours of birth). This selectivity of studies has apparently produced an inaccurate summary of the existing epidemiologic research.

Epidemiologic Studies of Thyroid Function and Perchlorate Exposure in Iodine-Deficient Populations

Although epidemiologic studies among newborns, children, and adults, as well as occupational cohorts, have not demonstrated adverse effects on thyroid function or other thyroid diseases associated with exposure to perchlorate in drinking water, these studies did not focus on

sensitive subpopulations, i.e., individuals with low iodine ingestion. Several recent studies have presented finding among such populations.

Blount *et al.* 2006 ("NHANES Study")

As described in OEHHA, Blount et al. (2006) used data from the NHANES 2001–2002 study to compare urinary perchlorate levels with serum TSH and total T_4 from a random subsample of NHANES participants (Blount et al. 2006). For men, urinary perchlorate was not a significant predictor of TSH or total T_4. On the other hand, among women aged 12 and over, urinary perchlorate was a significant predictor of TSH (positive association) and total T_4 (inversely associated). Urinary perchlorate was significantly positively associated with TSH ($p=0.001$) among women with urinary iodine <100 µg/L, and significantly inversely associated with total T_4 ($p<0.0001$). The NHANES study are based on a single assessment of urinary perchlorate and urinary iodine levels and serum TSH and T_4 at one point in time on a subset of women with specific urinary iodine levels, which makes it difficult to assess the causal nature of any observed association, a general limitations of cross-sectional study designs.

When examining the clinical relevance of these results, it is important to note that the estimated magnitude of change in TSH, based on increasing urinary perchlorate, is largely still within the range of normal TSH levels. Blount *et al.* (2006) describe this observation in an analysis where they estimate the magnitude in change in TSH in relation to a range of changes in urinary perchlorate. For nearly all combinations of initial TSH levels and urinary concentrations of perchlorate examined, TSH levels would not be increased to a level outside the normal range.

Lamm et al. 2007 ("Re-Analysis of NHANES Data")

Lamm et al. (2007) re-analyzed the 2001-2002 NHANES data reported by Blount et al. focusing on women age 15–44 (women of child-bearing age). (Lamm et al. 2007) When using creatinine-adjusted urinary iodine, considered a better reflection of 24-hour urinary iodine excretion to define the "low iodine" group of women, the statistically significant inverse association between urinary perchlorate and serum total T_4 was no longer observed. These analyses demonstrated the need to further evaluate the Blount et al findings and the potential limitations of this study.

Pearce et al. 2007

Urinary iodine and perchlorate levels were assessed and compared to serum free T_4 and TSH in a study by Pearce et al. (2007). These researchers reported the results of an investigation of thyroid function among pregnant women resident in three European cities in Wales (Cardiff), Italy (Turin), and Ireland (Dublin) in their first trimester of pregnancy and had low iodine status (Pearce et al. 2007). No associations were observed between urinary perchlorate levels and serum free T_4 and TSH among these European women. This was observed regardless of urinary

iodine concentration, in the group as a whole or in the large subset of women whose urinary iodine levels were <100 μg/L.

Gibbs and Van Landingham 2008

Gibbs and Van Landingham (2008) report that there was no associations between urinary perchlorate concentration with free T_4 and TSH among the pregnant women with serum iodine levels of ≥100 μg/L, nor among women who had urinary iodine concentration levels of <100 μg/L (*n* = 16 women). Although a small study – these data are not consistent with the claims made in the OEHHA report.

Table 1. Summary of Epidemiologic studies of perchlorate in drinking water and thyroid function in newborns and schoolchildren

Reference	Study Population	Biomarker Measurement or Health Outcome	Range of Perchlorate Concentration in Water (μg/L)	Overall Study Results
Lamm and Doemland (1999)	California, Nevada	Congenital hypothyroidism	4–16 (drinking water)	No difference between observed and expected congenital hypothyroidism rates in contaminated counties, based on state rates
Brechner et al. (2000)	Flagstaff and Yuma, Arizona	TSH	ND (ND limit not specified) (Flagstaff); 6 (Yuma)	Median TSH higher in Yuma than Flagstaff (p<0.000001)
Crump et al. (2000)	Chile	TSH, Congenital hypothyroidism	ND[4] (Antofagasta); ND[4]–6.7 (Chanaral); 100–120 (Taltal)	No evidence that perchlorate in drinking water at concentrations as high as 100-120 mg/L suppresses thyroid function in newborns or school-age children
Li et al. (2000a)	Las Vegas and Reno, Nevada	TSH	ND[4] (Reno); ND[4]–15 (Las Vegas)	No effect on neonatal TSH levels from living in areas with environmental perchlorate exposure of <=15 mg/L
Li et al. (2000b)	Las Vegas and Reno, Nevada	T_4	ND[4] (Reno); ND–15 (Las Vegas)	No effect on neonatal T4 levels from living in areas with environmental perchlorate exposure of <=15 mg/L
Kelsh et al. (2003)	Redlands/ Mentone, California, 1983–1997	TSH, Congenital hypothyroidism	Redlands Water System, 4–130 in sampled sources	No association between perchlorate levels and TSH levels or occurrence of congenital hypothyroidism

Reference	Study Population	Biomarker Measurement or Health Outcome	Range of Perchlorate Concentration in Water (μg/L)	Overall Study Results
Lamm (2003) [letter]	Yuma County, Arizona	TSH	Assumed ND (San Luis/Somerton); ND[4]–6 (City of Yuma)	No difference in neonatal TSH levels between those in Yuma County with perchlorate in drinking water and those without perchlorate in drinking water
Chang et al. (2003)	Clark County vs. Washoe County, vs. all other counties in Nevada	ADHD, autism	4-24 (Clark County); assumed zero for other counties	No evidence that rates of ADHD and autism in areas with perchlorate in drinking water exceeded rates in areas with no perchlorate in drinking water
Tellez et al. (2005)	Taltal, Chanaral, & Antofagasta, Chile	Neonates: T_3, free T_4, TSH, Tg, serum perchlorate, growth retardation (length, weight, head circumference	Antofagasta: mean 0.5 (all less than < 4.0); Chanaral: mean 5.8 (range 4.7-7.3) Taltal: mean 114 (range 72-139)	Authors report no increases in Tg or TSH, no decreases in T4, and no differences in growth retardation among neonates related to perchlorate in drinking water
Buffler et al. (2006)	California, 1998	TSH, Congenital hypothyroidism	Communities with average concentrations ≤ 5 and > 5	No association between estimated average perchlorate concentations in drinking water and the prevalence of congenital hypothyroidism or TSH levels
Amitai et al. (2007)	Ramat Hasharon, Israel	T4	>340 μg/L (very high); 42-94 ug/L (high) <3 ug/L (low)	No differences in T4 levels between exposure groups

Conclusions

While we understand that it is the intent of regulatory standards to err on the side of protecting public health, the accumulation of multiple conservative assumptions and calculations has produced a recommended PHG that cannot be defended as being any more health protective than the old PHG of 6 ppb. In fact, using the most current principles, practices, and methods used by public health professionals who are experienced practitioners in the fields of epidemiology, risk assessment, and toxicology, the recommended PHG provides no more health protection than would be afforded by a much higher concentration.

The low PHG is an artifact of applying redundant uncertainty factors and more conservative assumptions than are appropriate for the data on which the proposed PHG is based. More importantly, the PHG is inconsistent with the several epidemiology studies showing no health effects in populations exposed to much higher levels than even the PHG proposed in 2004 of 6 ppb. There would be no health benefit derived from reducing the PHG from 6 ppb to 1 ppb.

We appreciate the opportunity to present these comments and hope you will feel to call us with any questions you may have about them. You can reach Dr. Scofield in Oakland at (510) 268-5066.

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