Responses to Public Comments on Technical Support Document

Public Health Goal for Perchlorate in Drinking Water

Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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Contents

Introduction

The draft technical support document *Public Health Goal for Perchlorate in Drinking Water* by the Office of Environmental Health Hazard Assessment (OEHHA) was released for public comment on January 7, 2011. The draft proposed an update to the public health goal (PHG) for perchlorate established in 2004, and provided the scientific basis for the update. This draft also received formal external scientific peer review pursuant to Health and Safety Code Section 116365(c)(3)(D). The document was revised in response to public comments and the external scientific peer review. The second draft was released for public comment on December 7, 2012.

OEHHA's responses to the public comments received on the two drafts are summarized herein. Public comments are in bold, followed by OEHHA's responses (unbolded). Similar comments from different submissions were combined, and some comments were shortened and paraphrased. The comments and responses cite journal publications and reports. The full citations for these are given in the PHG document.

The full text of the public comments is available on OEHHA's website.[1] OEHHA's responses to the scientific peer reviewers' comments were released earlier and are also available on OEHHA's website.[2]

Public comments on the December 2012 draft were received from**:**

American Chemistry Council
Association of California Water Agencies
California Building Industry Association and other California building trade associations
California Manufacturers and Technology Association
The Chlorine Institute Clean Water Action
Environmental Working Group
Health Risk Strategies
Herwig Opdebeeck
International Formula Council
Intertox, Inc., on behalf of the Perchlorate Study Group
Partnership for Sound Science in Environmental Policy
Southern California Water Committee
Western Growers Association and other California agricultural organizations

Public comments on the January 2011 draft were received from:

Association of California Water Agencies

[1] Public comments on the January 2011 draft available at:
http://www.oehha.ca.gov/water/phg/perch_coms042011.html
Public comments on the December 2012 document are available at:
http://www.oehha.ca.gov/water/phg/120712Perchlorate.html#coms
[2] Responses to scientific peer review comments on the January 2011 draft available at:
http://www.oehha.ca.gov/water/phg/pdf/120712resptocom.pdf

Citizens for Safe Water Around Badger
City of Riverside Public Utilities Department
Clean Water Action - California
Department of Defense Regional Environmental Coordinator, Region 9
East Bay Municipal Utility District
Environmental Working Group
Exponent, on behalf of Whittaker Corporation
Golden State Water Company
Health Risk Strategies
National Resources Defense Council and Center for Public Environmental Oversight
Partnership for Sound Science in Environmental Policy
Perchlorate Study Group and Intertox, Inc.
San Bernardino County Department of Land Use
Western Growers Association and other California agricultural organizations

The public comment and response process is an important part of the overall PHG development process under Health and Safety Code Section 57003. They provide for deliberation and in depth consideration of the underlying scientific issues during PHG development. Many modifications of the *Public Health Goal for Perchlorate in Drinking Water* were made in response to the comments received. The document has now been finalized and is available on OEHHA's website at www.oehha.ca.gov.

For further information about the PHG process or to obtain copies of PHG documents, visit the OEHHA website. OEHHA may also be contacted at:

Office of Environmental Health Hazard Assessment
P.O. Box 4010
Sacramento, California 95812-4010
(916) 324-7572

2013 Comments Received on the Second Draft PHG Document

HEALTH IMPACTS FROM PERCHLORATE

Comment 1: Eleven of 14 studies in humans on perchlorate and thyroid hormone associations show no evidence of an association. (California Manufacturers and Technology Association)
Response: OEHHA performed a thorough evaluation of the strengths and weaknesses of each study in summarizing the evidence. This is a better way to derive overall conclusions than a simple counting of "positive" and "negative" studies. The overall evidence is supportive of an association between perchlorate and thyroid hormone levels.

Comment 2: OEHHA has "cherry-picked" studies that support its conclusions and no peer reviewed studies contradicting those conclusions are discussed. This includes the study by Bruce *et al.* (2013). (Association of California Water Agencies)
Response: This is incorrect. OEHHA has thoroughly reviewed the perchlorate literature and the PHG document discusses many studies identifying evidence of an association between perchlorate and thyroid function, as well as many studies that do not. The Bruce *et al.* (2013) study was published at about the same time the December 2012 draft PHG was released and is now discussed in the final PHG document.

Comment 3: There is no new scientific or public health justification for California to lower its health protective standard of 6 ppb. The IUI is recognized by the National Research Council and every other authoritative scientific body as a routine, reversible and non-adverse biological event, several steps removed from harmful health effects. (California Building Industry Association and other California building trade associations)
Response: The PHG is based on IUI. The NAS (NRC, 2005) recommended using IUI as the key biochemical event in the risk assessment. The NAS made the recommendation subsequent to the publication of the 2004 PHG, which also used IUI.

There are several sources of new scientific evidence that contributed to the lowering of the PHG: 1) Several new epidemiologic studies and several new analyses of existing studies linking perchlorate to altered thyroid hormone levels in infants and adults (Kelsh *et al.,* 2003; Buffler *et al.,* 2006; Steinmaus *et al.,* 2010; Li *et al.,* 2000; Crump *et al.,* 2000; Blount *et al.,* 2006; Steinmaus *et al.,* 2007; Mendez and Eftim, 2012; Steinmaus *et al.,* 2013 [pages 60-110]); 2) Several new studies linking small changes in thyroid hormone levels or deficiencies in iodine levels during pregnancy to significant decrements in cognitive function or changes in brain development in the offspring (van Wijk *et al.,* 2008; Gilbert and Sui 2008; Kooistra *et al.,* 2006; Bath *et al.,* 2013) [pages 39-56]); and 3) The higher drinking water intake per unit body weight in infants and young children (pages 155-156).

Comment 4: We are writing to express our strong support for the proposal by the Office of Environmental Health Hazard Assessment to lower the Public Health Goal (PHG) for perchlorate. Setting the PHG for perchlorate at 1 ppb is a necessary step toward protecting the health of the state's residents. (Environmental Working Group, Clean Water Action)
Response: OEHHA acknowledges the comment.

Comment 5: Iodide uptake inhibition is a threshold effect and has not been reported to occur in healthy adults with exposures to perchlorate levels less than or equal to 245 ppb. (Southern California Water Committee)
Response: The threshold referred to in this comment is for healthy adults, and this may not apply to everyone, including potentially susceptible groups like infants, young children, fetuses, pregnant women, or those with thyroid conditions or other serious medical conditions. As discussed below (Comment 15), while OEHHA considers healthy adults, OEHHA is also mandated to consider infants and children.

Comment 6: A robust dataset of over 60 years of scientific study makes it clear that exposure to perchlorate at environmental levels has no effect, let alone an adverse effect, on the human body. (Intertox)
Response: OEHHA is not aware of any data that establishes that environmental exposure to perchlorate has no health effects in infants or other susceptible populations. While there are some negative studies in adults and a few negative studies in infants and other susceptible groups, these all have significant weaknesses. In addition, as detailed in the PHG document, several studies have found evidence of an association between perchlorate and thyroid hormone levels. Both the positive and negative studies and their strengths and weaknesses are described throughout the PHG document (pages 60-112).

Comment 7: OEHHA disregards the contribution of thiocyanate and nitrate, which act by the same mechanism as perchlorate (iodide uptake inhibition). Based on their relative potencies and typical exposure levels, the effect of these agents on thyroid iodide uptake inhibition should far outweigh that of perchlorate. The U.S. Environmental Protection Agency's Office of the Inspector General (OIG) states that perchlorate's total contribution to thyroid iodide uptake inhibition is less than 1%. In California, perchlorate's relative contribution to the total goitrogen load in drinking water is only about 3.5%. (American Chemistry Council, Herwig Opdebeeck, Intertox, Southern California Water Committee)
Response: The argument that iodide uptake inhibition (IUI) from thiocyanate and nitrate should overwhelm that from perchlorate, and the estimates of perchlorate's contribution to IUI provided in these comments, are primarily based on the results of the Tonacchera *et al.* (2004) study. In this study, human sodium-iodide symporter (NIS) was transfected into Chinese hamster ovary cells, which were then seeded in 24-well plates and cultured in Dulbecco modified Eagle's medium containing 10% fetal calf serum. When the cells reached 100% confluence, the medium was removed, and the cells were washed with physiologic solution and combined with 500 mL buffer A (Hanks' balanced salt solution containing 0.5% bovine serum albumin and 10 mmol N-2-hydroxy-

ethylpiperazine-N-2-ethanesulfonic acid) containing 100,000 counts per minute of carrier-free $Na^{125}I$. After the cells were incubated for 45 minutes at 37°C, they were washed twice with 2 mL of ice-cold buffer A, and then solubilized with 1 mL of 0.1 mol/L sodium hydroxide. ^{125}I uptake was then determined by measuring the radioactivity counts per minute from each well.

The reason OEHHA chose not to use this study as a key component of the PHG is that it is not known how well these particular laboratory conditions actually simulate what occurs in people. In other words, it is not known how well transfected NIS simulates endogenously expressed NIS, how well NIS in Chinese hamster cells simulates NIS in human cells, how well hamster ovarian cells simulate human thyroid cells, or how well conditions in these laboratory wells simulate the complex environment of the human body. It is also not known how the effects seen for the very high concentrations of perchlorate and the other agents used in this study correlate to those that may be associated with lower, more common serum concentrations of these agents; how the auto-regulatory mechanisms in humans (Dohan *et al.,* 2003) may affect relative potencies; how the fairly short-term exposures in this study correlate with the longer-term, more chronic exposures commonly seen with drinking water chemical exposures; whether or not there may be age-related or other susceptibility effects; how well urinary concentrations of each of these agents correlate with their actual concentrations at the NIS; what role the endogenous production of nitrate might play in affecting relative potencies, the use of urine nitrate concentrations as an exposure metric; or how the presence of other agents or conditions may inhibit the NIS, affect auto-regulatory mechanisms, or affect the thyroid in other ways that might change the relative potencies reported in Tonacchera *et al.* (2004).

Because of these unknowns, OEHHA judged that the Tonacchera *et al.* (2004) study and related findings should not have a pivotal role in establishing the perchlorate PHG. These reasons and the Tonacchera *et al.* (2004) study are now described in the PHG document (page 111).

Comment 8: There is no new scientific justification to lower the health protective standard of 6 ppb and OEHHA should not continue with a process that imposes additional cost on water users. The IUI is recognized by the National Research Council as a routine, reversible and non-adverse biological event. (California Building Trade Industry Association and other California Building Trade Associations)

Response: The process that imposes additional cost on water users is beyond the scope of this PHG. The reasons why both OEHHA and the NRC have used IUI as the basis for perchlorate risk assessment are discussed below (Comment 52). The current PHG document summarizes a large number of new studies and new analyses that provide the scientific justification for lowering the perchlorate PHG.

Comment 9: OEHHA assumes that goitrogen exposures are synergistic. (Intertox, Partnership for Sound Science in Environmental Policy)
Response: OEHHA stated that, "…many of the factors related to thyroid hormone might not cause important confounding for the reasons given above, but they may still act either cumulatively or synergistically with perchlorate to decrease thyroid function (page 82)." Thus, although OEHHA notes that synergism is possible, the PHG does not assume that this is the case. The perchlorate-thyroxine findings reported from the NHANES studies are consistent with either a cumulative or a synergistic (biologic) association (Blount *et al.,* 2006; Steinmaus *et al.,* 2007; Steinmaus *et al.,* 2013), and this is now noted on page 82 of the PHG document. The important point is that people with high intakes of thiocyanate or low intakes of iodine may be particularly susceptible to perchlorate, and this point is independent of whether these relationships are cumulative or synergistic.

HEALTH VALUE FROM THE GREER ET AL. STUDY

Comment 10: Greer *et al.* (2002) is only one of five key clinical studies, and the others were ignored. The fact that five human clinical studies have been conducted and that the studies produced remarkably consistent results, serves to account for variability in the dose-response estimate. (California Manufacturers and Technology Association)
Response: All of the published clinical dosing studies were evaluated and are discussed in the PHG document (pages 91-97). Consistent with OEHHA, the NAS (2005) also selected the Greer *et al.* (2002) study as the key study for its perchlorate risk assessment (NRC, 2005). Like OEHHA, the NAS found no major weaknesses in the Greer *et al.* (2002) study that precluded it from being used in a quantitative assessment.

Comment 11: Several studies published since 2005 indicate that the human thyroid system compensates for inhibited iodide uptake from environmental and occupational perchlorate exposure. The commenter cited several studies to support this position. The available human data for perchlorate indicate higher exposure levels than the Greer *et al*. (2002) NOEL that resulted in initial inhibition of iodide uptake, but produced no adverse effect on thyroid hormone levels or thyroid tissue health. (The Chlorine Institute)
Response: Several of these studies (e.g., Braverman *et al.,* 2006; Lamm *et al.,* 1999) were limited to healthy adults and did not examine the potentially susceptible populations identified by OEHHA. Because they have lower stores of thyroid hormone, infants may not be able to compensate as well as adults to reductions in thyroidal iodide uptake (van den Hove *et al.,* 1999) (page 135 of the PHG document). A re-analysis of the Buffler *et al.* (2006) study using data on all available subjects and using cut-off points for defining a high thyroid stimulating hormone (TSH) level from a risk assessment instead of a clinical perspective found evidence of an association between perchlorate and neonatal TSH (Steinmaus *et al.,* 2010). In Tèllez Tèllez *et al.* (2005), almost half of the children from the exposed city were born in the lesser-exposed comparison city, a fact that could significantly bias the neonatal results of this study. The strengths and weaknesses of the other epidemiologic studies are discussed throughout the PHG document.

Comment 12: OEHHA claims that the 1.8% inhibition of iodide uptake that corresponded to the NOEL from Greer *et al.* (2002) constitutes a physiological event, when it is not statistically or biologically significant. The 2012 draft treats the point of departure (POD) which is approximately half of the NOEL based on a non-adverse effect, as equivalent to an adverse effect. (Intertox)

Response: As mentioned above, a key advantage of the BMD approach is that it uses all of the data points in the study and the entire dose-response curve to calculate the point of departure. Because of this, no single data point is over emphasized. Another advantage of this approach is that by using the lower 95% confidence interval of the BMD as the POD, it takes into account the precision and possible variability in the shape of the dose-response curve due to small sample sizes and variability in responses between subjects. Accounting for this variability is the reason why the POD was below the lower dose of the Greer *et al.* (2002) study. OEHHA treats iodide uptake inhibition as it would an adverse event because it is in the direct causal pathway between perchlorate exposure and several important adverse events. OEHHA states on page 2 that, "The perchlorate PHG of 1 ppb is intended to help prevent any perchlorate-related decrease in iodide uptake by the thyroid that could lead to decreased thyroid hormone production and that could disrupt the important functions of this hormone."

Comment 13: Background exposures to perchlorate in the Greer *et al.* (2002) study subjects were not incorporated into OEHHA's BMD calculations. OEHHA's PHG for perchlorate in drinking water is based only on the response of the applied doses from the Greer *et al. (*2002) critical study. The background goitrogen exposure (perchlorate, nitrate and thiocyanate) has been omitted. (Herwig Opdebeeck)

Response: At each dose level in the Greer *et al.* (2002) study, subjects were compared to themselves before, during, and after dosing. There is no indication in this study that subjects made substantial changes in their diets throughout the study. As such, it appears most likely that each subject was exposed to roughly the same background levels of goitrogens in each phase of the study. Because of this, any *change* in iodide uptake inhibition (IUI) that may have occurred from before dosing to during dosing was likely due to the perchlorate dose given by the investigators. Since it was this change, and not the absolute value of IUI, that was used as the outcome metric in OEHHA's BMD calculations, it is unnecessary to add in the baseline exposures. While it is true that the Greer *et al.* (2002) authors did not control for iodine, nitrate, or thiocyanate, OEHHA sees no obvious reason why these agents would have varied across the perchlorate dosing groups.

Comment 14: The short duration of the Greer *et al.* (2002) study fails to account for the cumulative effect of longer-term exposure. (Environmental Working Group)

Response: The data used from the Greer *et al.* (2002) study were for a relatively short-term effect: inhibition of iodide uptake by the thyroid. OEHHA is not aware of any conclusive data in humans that cumulative exposures would cause greater effects on this outcome than the two week exposures used by Greer *et al.* (2002).

SENSITIVE POPULATIONS

Comment 15: OEHHA relies heavily on ecologic studies to support using infants as a susceptible population. Ecologic studies have weaknesses that limit their use and these studies cannot be used to determine causality. (Southern California Water Committee)

Response: OEHHA does not rely solely on ecologic epidemiological studies to justify classifying infants as a susceptible population. The ecologic epidemiological studies support the possibility that perchlorate may decrease thyroxine and increase thyroid stimulating hormone levels, both of which are effects consistent with the known mechanism of perchlorate. Many arguments could be made about the strengths and weaknesses of these studies, and OEHHA's PHG document includes a lengthy discussion of the issues that potentially affect interpretation of these studies (pages 60-91). Most importantly, while these studies provide evidence linking perchlorate exposure during pregnancy with changes in thyroid hormone levels in the newborn, they were not critical to the PHG calculation.

California Health and Safety Code section 116365.2 requires that OEHHA, in reviewing and revising PHGs, assess "exposure patterns, including, but not limited to, patterns determined by relevant data, among bottle-fed infants and children that are likely to result in disproportionately high exposure to contaminants in comparison to the general population." Pursuant to section 116365.2, OEHHA took the higher drinking water intake rates in infants and children into consideration in the PHG calculations. A major reason why infants and children are considered potentially susceptible to perchlorate is that their intake of drinking water on a per body weight basis is substantially greater than that in adults. This is a well-documented finding that is completely independent of the ecological studies referred to above. The importance of this finding is that if infant intake of drinking water is greater on a body weight basis, then exposure to a given concentration of a chemical in that drinking water will result in greater intake of the chemical on a per body weight basis. As stated in the PHG document, drinking water intake rates were based on data from the Continuing Survey of Food Intake of Individuals (CSFII), not on the results of the ecological epidemiological studies referred to in this comment. The CSFII was a large multistage probability sample collected by the U.S. Department of Agriculture (USDA). Additional reasons for identifying infants as the most sensitive subpopulation are described on pages 154-156 of the PHG document.

OEHHA agrees that in many instances ecologic studies may not be helpful in assessing causality. However, this is not always the case. There are some circumstances where ecologic studies can provide valuable information for evaluating causal inference. For example, the original classification of arsenic in drinking water as a human carcinogen by the International Agency for Research on Cancer, the National Academy of Sciences' (NAS) National Research Council (NRC), and other authoritative bodies was based on ecologic data (IARC, 2004; NRC, 1999; U.S. EPA, 2001).

Comment 16: Table 13 [Table 29 in final document] creates an erroneous impression of the weight-of-evidence in support of OEHHA's argument. It is inappropriate for OEHHA to present the re-analyses of data from some studies in Table 13 while citing the original authors. The conclusions of several of these studies, as portrayed by OEHHA, are contrary to the conclusions stated by the study authors. There are a number of other studies that demonstrate no association between environmental perchlorate exposure and thyroid effects and these are not presented in Table 13. (California Manufacturers andTechnology Association, Intertox)

Response: Many of the perchlorate-thyroid hormone studies referred to in this comment were not included in Table 13 (final version Table 29) because the focus of this table was on newborns, and these other studies were done in adults or older children. These other studies are discussed in detail throughout the PHG document (pages 60-112).

Several of the data points presented in Table 13 were calculated by OEHHA using the data presented by the original authors in the tables of their publications. OEHHA believes it is appropriate to examine the data in the tables of the publications OEHHA evaluates, and not simply rely on the authors' conclusions. The analyses referred to in this comment are based on the actual data presented by the original authors. In addition, authors' conclusions don't take into account subsequent research (such as later studies finding associations in younger infants). While OEHHA does consider the authors' conclusions in its evaluations, they are not the sole determinants of the PHG evaluation.

Table 13 (final version Table 29) is only one of over 40 tables in the document, and for the reasons described above it would be inappropriate to place undue emphasis on this single table. Table 13 was created because it shows the fairly remarkable consistency of the findings in those studies that evaluated perchlorate-thyroid hormone associations in newborns. As seen in this table, all five studies that evaluated these associations showed some evidence for an effect. OEHHA feels this is an important finding since it shows the marked consistency across these studies, despite the differences in populations, methods, and researchers. This type of consistency is important since it is a key element of causal inference (Hill, 1965). The importance of evaluating consistency is discussed on page 75 of the PHG document.

To avoid any confusion with regard to the recalculations, several changes have been made to Table 13 (final version Table 29). The PHG document now states, "Table 29 summarizes data from the most relevant studies of perchlorate exposure and newborn thyroid hormone levels. In several studies, the authors did not specifically present results for the early newborn period, but provided data that OEHHA used to perform its own evaluation of possible associations for this period. These are clearly marked in Table 29 under the heading 'Source of data and results.' It should be noted that the data points calculated by OEHHA are not based on the original study authors' conclusions and most represent unadjusted estimates. Any conclusions drawn from this table should be interpreted in light of these facts." The original sources of the data are still cited since it would be inappropriate not to do so. References to the methods

used are now given in the table and further data on these calculations are provided in the document (e.g., Table 25).

Comment 17: The thyroxine data presented in Table 13A [Table 29 in final document] using the data from the Kelsh *et al.* (2003) and Brechner *et al.* (2000) studies is not based solely on samples collected within the first 24 hours. (Partnership for Sound Science in Environmental Policy)
Response: The odds ratios involving these data have now been moved to another column in Table 13 (final document Table 29) labeled "Summary notes regarding confounding and other related findings," and it is now stated that they both include all ages.

Comment 18: Blount *et al.* (2006) showed a negative association between urine perchlorate and serum thyroxine, but this study did not show that perchlorate lowered serum thyroxine concentrations to levels below normal reference ranges (Blount *et al.,* 2006). (Association of California Water Agencies)
Response: This commenter referred to a 2008 comment in response to OEHHA's initiation of the update of the 2004 perchlorate PHG. In the PHG document, OEHHA reviewed a large number of studies that suggest that even changes in thyroid hormone levels ***within*** normal reference ranges can be associated with important adverse outcomes including adverse impacts on cognitive development and increases in cardiovascular risks factors (pages 44-58).

Comment 19: A perchlorate PHG higher than 1 ppb is not adequately protective of vulnerable populations. Research since Blount (2006), by the Centers for Disease Control and Prevention and Pearce (2007), demonstrate that exposure can interfere with thyroid hormone production, a substantial portion of the population is vulnerable to health risks associated with exposure, and the prevalence of iodine deficiency puts breast feeding babies at risk. (Clean Water Action-California)
Response: OEHHA has carefully examined all of these sources and updated the PHG based on an upstream effect, the inhibition of iodide uptake by the thyroid gland. The data are limited for estimating the concentration and fraction of perchlorate in breast milk that results from drinking water exposure, and for explicitly calculating risk for iodine-deficient infants. The PHG includes an uncertainty factor of 10 that takes into account interindividual variability that may result from a number of exogenous and endogenous factors, including added possible sensitivity of the breastfed iodine-deficient infant.

Comment 20: OEHHA cites studies involving newborn TSH measurements collected within the first 24 hours of birth as justification for classifying the infant as a susceptible population, but TSH readings during this period are unstable and unreliable. A complicating trend in labor and delivery on measured TSH levels is the reduced time of hospital stay: the trend is strongly toward early discharge of mothers and infants (before 48 hours of age). (Western Growers Association, Intertox)

Response: OEHHA agrees that short hospital stays after birth are a potentially complicating trend in using TSH screening data to evaluate possible relationships between perchlorate exposure and thyroid function. However, most healthy children will be discharged within 48 hours of birth. As such, infants with TSH measurements collected after 48 hours could represent those children who remain in the hospital for medical conditions or birth complications. Since many of these conditions could affect TSH levels, they could affect the ability of a study to identify perchlorate-TSH associations. Because of this, evaluations that only include TSH measurements collected before 48 hours of birth may represent more valid analyses.

OEHHA also agrees that TSH levels are relatively unstable during the first 24 hours after birth. However, this instability would most likely bias results towards the null, not towards the positive associations identified. Additionally, OEHHA agrees that under the proper circumstances, TSH levels collected after 24 hours of birth are probably a more reliable predictor of congenital hypothyroidism than TSH levels collected earlier. However, OEHHA is not aware of data to suggest that TSH measurements collected in the first 24 hours after birth cannot be used for identifying strong perchlorate-TSH relationships. Research has shown that altered thyroid hormone levels before birth are associated with adverse impacts on brain development (detailed in the PHG document), and thus OEHHA believes that high TSH levels immediately following birth could be associated with similar effects. Thus any significant change in thyroid hormone levels during fetal or childhood brain development (including those within 24 hours of birth) should be considered a potentially adverse effect. The studies on TSH collected within the first 24 hours are only a part of OEHHA's overall much larger assessment of infant susceptibility, and there were several other factors identified that provided evidence that this group may be particularly susceptible to perchlorate (e.g., low stores of thyroid hormone, high drinking water intake rates, period of rapid brain development).

Comment 21: Guidelines in the State of Washington and California suggest that TSH readings collected in the early newborn period should not be used for screening purposes or need to be adjusted for age. (Intertox)

Response: The TSH screening programs in these states are designed to screen for a very serious condition: congenital hypothyroidism. This outcome is associated with extremely large changes in TSH and severe physical and neurological effects. Because this is a severe condition and its associated TSH levels are extremely high, the TSH cutoff points for defining a "high" TSH in these programs are set fairly high. These cutoffs were not designed to detect outcomes that may be less severe than congenital hypothyroidism, such as the changes in thyroid hormones associated with 5-10% declines in IQ and other cognitive measures reviewed in the PHG document (beginning on page 44). In addition, the cutoff points used by these programs were not designed to evaluate whether neonatal TSH levels are different in perchlorate-exposed communities compared to unexposed communities. As such, these cutoff points were not used as the basis of OEHHA's evaluations. It should also be noted that the positive perchlorate-neonatal findings reported by Steinmaus *et al.* (2010) were closely adjusted for by age (i.e., hours post-partum).

Comment 22: The natural surge in TSH levels collected within the first 24 hours would dwarf any subtle environmental effect of perchlorate, even if one exists. (Intertox)
Response: Since the surge occurs in both perchlorate-exposed and unexposed groups, it would not necessarily hide an impact of perchlorate. In addition, increased variability from the surge would most likely bias results to the null rather than create the positive associations identified.

Comment 23: The inability to adequately control for the increase and decrease in TSH levels within the first 24 hours likely requires more sophisticated statistical techniques (e.g., spline regression). (Intertox)
Response: OEHHA is not aware of any evidence that regression splines or other complex statistical modeling would increase the validity of these analyses or that they would not introduce their own bias or error. A further discussion of this issue can be found in the review by Greenland (1998).

Comment 24: The draft PHG does not take into consideration the work of Bruce *et al.* (2012), which demonstrates that the conclusions reached in the Blount *et al.* (2006) and Steinmaus *et al.* (2007) studies upon which the draft PHG does rely, are not reproducible. (Partnership for Sound Science in Environmental Policy, Southern California Water Committee, Western Growers Association)
Response: The analyses of Bruce *et al.* (2013) rely on the relative potencies of perchlorate, nitrate, and thiocyanate reported in the Tonacchera *et al.* (2004) study of human NIS transfected into Chinese hamster ovary cells discussed above. For the reasons discussed above, these relative potencies (and the Bruce *et al.* results) were not used as the basis of the perchlorate PHG, and the Bruce *et al.* (2013) results do not affect the interpretation of Blount *et al.* (2006) and Steinmaus *et al.* (2007), which were not based on the Tonacchera *et al.* (2004) study.

Comment 25: OEHHA's statement that "…human data show that perchlorate can interact with other contaminants to produce a greater effect than that caused by perchlorate alone…" is misleading. First, these studies, based on the National Health and Nutrition Examination Survey (NHANES) 2001-2002, do not report data on infants or young children. Second, these references are superseded by a study that utilizes better and more complete thyroid measures (Bruce *et al.,* 2013). (Intertox)
Response: OEHHA is not aware of any evidence or logical reason to believe that additive effects or interactions occurring in adults would not also occur in infants. On pages 4 and 155 of the PHG document, the sentence has been reworded to state, "Human data suggest that perchlorate can interact with other contaminants to produce a greater effect than that caused by perchlorate alone (Blount *et al*., 2006; Steinmaus *et al.*, 2007), and infants are exposed to these same contaminants." The findings of the Bruce *et al.* (2013) study are now described on pages 110-111. However, these findings are completely dependent on the study in Chinese hamster ovary cells discussed above. As stated above, OEHHA does not feel there is adequate evidence

that the effects that occur in these cells and laboratory conditions are the exact same effects that occur in people.

Comment 26: Non-differential misclassification of exposure in the epidemiologic studies of perchlorate may not always bias results towards finding no association. (Intertox)
Response: OEHHA agrees and the discussion of this issue has been reworded throughout the document to make it clear that the *most likely* direction of this bias is towards the null.

Comment 27: OEHHA evaluates the possible impacts of confounding using the methods presented by Axelson (1978). However, Axelson discusses confounders in the context of a disease that is strongly associated with an occupational exposure, while perchlorate in OEHHA's analysis is only weakly associated with thyroxine. (Intertox)
Response: The methods presented by Axelson (1978) can be used to evaluate the potential for confounding regardless of whether the strength of the association between the main exposure and outcome of interest is strong or weak.

Comment 28: Table 14 [Table 31 in the final document] presents mean thyroxine (T4) levels for a "perchlorate-unexposed group" from the NHANES 2001-2002 dataset. However, there is no "perchlorate-unexposed group." (Intertox)
Response: These groups are now labeled as "lower" and "higher" perchlorate exposure (page 81). These changes do not affect OEHHA's analyses or conclusions regarding these studies.

Comment 29: In the evaluation of thiocyanate as a potential confounder (page 57-8 [pages 79-82 in the final document]), there is no group "unexposed" to thiocyanate in the NHANES 2001-2002 dataset, and the differences in thiocyanate exposure between the groups are relatively minor. Some other potential confounders were not evaluated. (Intertox)
Response: The fact that there is no group that is unexposed to thiocyanate would not affect these analyses. The thiocyanate categories in this analysis were selected based on the results of Steinmaus *et al*. (2007). This is now stated (page 80). OEHHA examined a large number of potential confounders, but focused its detailed quantitative analyses on those factors which would most likely cause confounding and bias, including those factors most commonly referred to in the perchlorate literature. This is now stated (page 80 of the PHG document).

Comment 30: Based on its evaluation of thiocyanate as a confounder, "OEHHA suggests that the effect of thiocyanate on T4 is 'weak' and that the 'decrease is small.' However, if we [Intertox report dated Jan 22, 2013] examine the dataset based on urinary perchlorate tertials [*sic*] for the same population, mean T4 values for the low, mid, and high urinary perchlorate concentration tertials are 8.70 µg/dL, 8.49 µg/dL, and 8.45 µg/dL, respectively (corresponding to maximum perchlorate concentrations within each tertial of 2.4 µg/L, 5 µg/L, and 100 µg/L, respectively). In other words, the decrease in T4 across tertials is nearly identical

to (or even smaller than) that across the urinary thiocyanate tertials. If the effect of thiocyanate is considered 'weak' the effect of perchlorate is clearly 'weak' as well. (Intertox)
Response: OEHHA cannot evaluate the results presented by the commenter since the full methods are not provided. Importantly though, other peer-reviewed analyses of these data show evidence of perchlorate-T4 effect sizes that are much larger than those presented by the commenter (Blount *et al,.* 2006; Steinmaus *et al.,* 2007).

Comment 31: The authors of the Crump *et al.,* (2000) study caution that the reports on familial history of thyroid issues were not verified, there may have been recall bias, and it may represent historical variations in iodine supplementation. (Partnership for Sound Science in Environmental Policy)
Response: The possibility of recall bias and the lack of verification of records are now noted on page 64 of the PHG document. The changes in iodine supplementation in Chile were already noted (page 64) but OEHHA is not aware of any clear evidence that iodine supplementation patterns were different in perchlorate-exposed and unexposed areas. In addition, OEHHA notes that it would be highly unusual for recall bias in this situation to cause an odds ratio near 5.

Comment 32: In Brechner *et al.* (2000) follow-up testing of TSH was done only in infants with the lowest 10% of T4 concentrations, and perchlorate exposures were not directly measured in infants' mothers or during the same time frame as when the thyroid hormone levels were measured. In addition, the NAS explained that the "apparently" positive association in Brechner *et al.* (2000) was explainable by other factors (NRC 2005). (Intertox)
Response: The lack of perchlorate exposure data during the time frame in which thyroid hormones were measured and the fact that TSH levels were only assessed in those with low T4 levels are discussed on pages 67 and 88 of the PHG document, respectively. These TSH measurements can be informative in that they allow for an examination of a potentially important group: those with both a low T4 and an elevated TSH. The NAS raised the possibility that the Brechner *et al.* (2000) findings may have been due to other factors (e.g., differences in altitude between cities), but they did not present evidence that this was the case. OEHHA's evaluations also found no strong evidence that the Brechner *et al.* (2000) findings were due to these other factors (pages 67-68 and 84).

Comment 33: In its justification for choosing the infant as the most susceptible population, OEHHA cites studies of low iodine in breast-fed infants. Formula is fortified with iodine and an exclusively formula-fed infant would receive middle to higher iodine levels through formula and would not be expected to be iodine deficient (Schier *et al.,* 2009). (American Chemistry Council, Intertox)
Response: As discussed, low iodine intake was not the only reason why infants were considered potentially susceptible to perchlorate. Other reasons were also cited (rapid brain development, increased water intake, low stores of thyroid hormone…) (pages 146 and 155 of the PHG document). These other reasons would still apply to formula-fed infants. In addition, low iodine levels in breast milk may impact those children who are both formula- and breast-fed.

Comment 34: OEHHA's statement that "…young infants have low stores of thyroid hormone (less than one day's worth, compared to several weeks' worth in adults)…" is misleading. If the point of departure is a NOEL for a non-adverse effect, the amount of thyroid hormone storage is immaterial. (Intertox)
Response: This statement was not made in reference to the NOEL, but rather to the potential susceptibility of infants to perchlorate (pages 4, 146, and 155 of the PHG document).

Comment 35: Clearance rates of other chemicals in infants and young children are the same as, or greater than, those of adults. This would lead to a shorter half-life in infants and young children. (Intertox)
Response: The comment is incorrect. A number of drug clearance studies have shown that infants have lower clearance rates than older children and adults (see for example Ginsberg *et al.*, 2002; Hattis *et al*., 2003). Further, PBPK modeling of a number of environmental chemicals by OEHHA (OEHHA, 2008), indicates higher "Area Under the Curve" (AUC) for many chemicals in infants and young children than in adults. The relative clearance rates of perchlorate in infants and in adults are unknown. Clearance rates can vary dramatically from chemical to chemical, so, the relevance of clearance rates of other chemicals to perchlorate is unknown.

Comment 36: Utilizing perchlorate exposure data from California Department of Public Health files (as was done in Steinmaus *et al.,* 2010 and Buffler *et al.,* 2006) is not appropriate because in many instances they do not incorporate blending of different water sources, water treatment, or other factors. This was referring to a comment made in 2011. (Association of California Water Agencies)
Response: These issues are acknowledged in the discussion of the Steinmaus *et al.* (2010) study on pages 70-71, and it is noted that the most likely bias resulting from these issues is towards finding no effect, not towards the associations identified in this study.

Comment 37: OEHHA relied on its own studies and claims about other research that are contrary to the findings of the original study authors. (Western Growers Association)
Response: Much of OEHHA's re-analyses of published data have undergone peer-review in the scientific literature. The complete PHG document underwent external peer review convened by the University of California, and the independent reviewers did not challenge or reject the analyses performed by the author of the PHG document.

CALCULATING THE PHG

Comment 38: Increasing the uncertainty factor in infants from 3 in the 2004 PHG to 10 in the current PHG seems unwarranted and arbitrary. (Association of California Water Agencies)
Response: The uncertainty factor of 10 is not arbitrary. It is consistent with the uncertainty factor of 10 recommended by the NRC for the derivation of the perchlorate

reference dose for U.S. EPA (NRC, 2005) and has been used in other OEHHA PHGs. In addition, it is in agreement with the NRC's statement that, "In the absence of data on the range of sensitivity among humans, a default uncertainty factor of 10 is typically applied" (NRC, 2005). OEHHA has identified a number of reasons why infants are likely to be more susceptible to perchlorate than healthy adults, and these are reviewed on pages 146 and 155 of the PHG document. The previous variability factor of 3 to account for differences between infant population and healthy adults was increased to 10 for a number of reasons. This includes the evidence on the effects seen in several new epidemiologic studies and several new analyses of existing studies linking perchlorate to altered thyroid hormone levels in infants and adults (Kelsh *et al.,* 2003; Buffler *et al.,* 2006; Steinmaus *et al.,* 2010; Li *et al.,* 2000; Crump *et al.,* 2000; Blount *et al.,* 2006; Steinmaus *et al.,* 2007; Mendez and Eftim, 2012; Steinmaus *et al.,* 2013 [pages 60-110]), and in several new studies linking small changes in thyroid hormone levels or deficiencies in iodine levels during pregnancy to significant decrements in cognitive function or changes in brain development in the offspring (van Wijk *et al.,* 2008; Gilbert and Sui 2008; Kooistra *et al.,* 2006; Bath *et al.,* 2013) [pages 40-53].

Comment 39: The PHG calculations do not account for differences in absorption, distribution, or excretion between adults and infants. (Intertox)
Response: Adequate data on age-related differences in the absorption, distribution, and excretion of perchlorate are not available from human studies. In the absence of these data, OEHHA uses uncertainty factors to account for the toxicokinetic differences among humans, including those related to age. Some indirect or animal data on these factors are available, but their use would require significant assumptions.

Comment 40: The U.S. EPA Science Advisory Board (SAB) recommended that U.S. EPA employ scientific modeling techniques - in particular Physiologically Based Pharmacokinetic (PBPK) modeling - in which actual experimental data are used in a model designed to simulate animal or human response to perchlorate exposures. There are more sophisticated, science-based approaches available based on its mode of action involving pharmacokinetic/pharmacodynamics modeling. (Association of California Water Agencies, Health Risk Strategies)
Response: OEHHA evaluated several existing PBPK models (Clewell *et al.,* 2003; Clewell *et al*., 2007; Lumen *et al*., 2013; Merrill *et al*., 2003; Merrill *et al*., 2005; U.S. EPA, 2009) and found that they required a large number of assumptions that could cause substantial uncertainty in the exposure and risk estimates they were used to generate.

Comment 41: One alternative approach would be the use of the 2006 Centers for Disease Control and Prevention (CDC) study by Blount *et al.* (2006), rather than the Greer *et al.* (2002) study, as the basis for the calculation. (Environmental Working Group)
Response: This was done and is presented in the Appendix of the PHG document.

WATER CONSUMPTION BY INFANTS

Comment 42: There are three points in the PHG calculation in which OEHHA states it is accounting for uncertainty: its use of the lower 95th confidence interval of the benchmark dose, the uncertainty factor of 10 for intraspecies variation, and the 95th percentile of the drinking water intake rate for infants. The cumulative effect of these multiple adjustments is overly conservative, especially since the critical effect is a non-adverse effect (iodide uptake inhibition). (Intertox)
Response: The comment is incorrect. The public review draft only refers to two points of uncertainty. Each of these three issues was incorporated into the PHG calculations for different reasons. The first accounts for the uncertainty in the dose-response estimate (i.e., the fact that the Greer *et al.* (2002) study included a relatively small sample size, that is, relatively small numbers of people in each dose group). The second one is a factor that accounts for human variability and the possibility that some people are likely to be much more susceptible than others. This uncertainty/variability factor is not intended to account for drinking water rates and estimating actual exposures. The NRC used this same uncertainty factor for human variability. The fact that infants have higher intakes of drinking water on a per body weight basis than the adults in the Greer *et al.* (2002) study and the fact that some infants, for example bottle-fed infants receiving formula reconstituted from water and powder, drink more water than others is not an uncertainty. It represents available data. Failure to account for any one of these factors could lead to a PHG that is not adequately protective for all groups.

Comment 43: The body weights used by OEHHA are lower than those reported in 1996-2000 NHANES, as presented by U.S. EPA in the Child Specific Exposure Factors Handbook (U.S. EPA, 2008d) and may not be representative of the general population. (Western Growers Association)
Response: The data on drinking water intake rates (intake per body weight) were derived from data from the Continuing Survey of Food Intake of Individuals (CSFII). The intake rates were normalized to individual body weights reported in CSFII. This survey was conducted by the U.S. Department of Agriculture (USDA) and designed to collect dietary and water intake information from nationally representative samples of non–institutionalized persons residing in U.S. households. Households were sampled from the 50 states and Washington, D.C. The survey was conducted according to a stratified, multi–area probability sample organized using estimates of the U.S. population, and stratification accounted for geographic location, degree of urbanization, and socioeconomics. Because of this design, OEHHA believes that this survey provides a representative sample and does not underestimate body weights.

Comment 44: The USDA CSFII study used by OEHHA to develop the drinking water intake rates for infants is a recall study and errors leading to an overestimation of true drinking water intake rates are possible. (Herwig Opdebeeck)
Response: It is possible intake is overestimated in some people, and underestimated in others. It is also possible that these errors balance each other out. Although their true

impact is unknown there is no reason to believe they were large. This is now mentioned on page 148 of the PHG document.

Comment 45: The drinking water intake rates used for infants are exceptionally high as noted by one of the peer reviewers. (Intertox)

Response: One of the peer reviewers questioned OEHHA's use of the 95th percentile estimated water intake rate for infants 0-6 months old rather than their median intake rate (or its 90 percent confidence interval), and questioned whether this level of intake might be associated with water intoxication. OEHHA has chosen to use the 95th percentile drinking water intake rate rather than the median drinking water intake rate because the California Safe Drinking Water Act (Health and Safety Code Section 116365) requires OEHHA to take into consideration the existence of groups in the population that are more susceptible to the adverse effects of contaminants than a normal healthy adult when establishing its PHGs. At a given chemical concentration in water, people who drink more water on a body weight basis (like infants) will have an overall increased intake of that chemical contaminant on a per kilogram body weight basis, and thus may be at greater risk from any harmful effects caused by that chemical. OEHHA's decision to use the 95th percentile drinking water intake rate rather than the 50th percentile is designed to help protect those people who drink more water on a body weight basis than the normal healthy "median" adult or even the normal healthy "median" infant. This is consistent with OEHHA's mandate to consider groups in the population (heavy water drinkers, in this case) who may be at greater risk than the average or median person.

There are several reasons why OEHHA believes the 95th percentile water intake rate used in the PHG calculation represents an accurate estimate of the true 95th percentile intake of children ages 0-6 months in the U.S. population and is not consistent with water intoxication. First, the data used to estimate the 95th percentile intake were derived from the USDA's CSFII, a large multistage probability sample involving more than 20,000 individuals from all age groups from throughout the U.S. The very large sample size of this survey helps to ensure the precision of its results, including those results at the tails of the distribution. It also helps ensure that a small number of outlying values, although they might affect the mean, would have only small effects on the 95th percentile.

Second, drinking water intake data in the CSFII were collected from each subject on two non-consecutive days, 3-10 days apart. Because multiple samples were collected from each person, the issue of "regression to the mean" should be less of a problem in this dataset than in other surveys that assessed drinking water intake on only a single day. OEHHA evaluated the possible magnitude of the impact of collecting drinking water data on two days versus only one day by comparing the distributions of the drinking water intake measured on day one of the CSFII to those of the two-day averages. If "regression to the mean" is a major problem one would expect the 95th percentile of the two-day average to be closer to the mean value than the 95th percentile of the day one-only measurements. Table 1 below shows the results of this analysis of the CSFII data for various age groups. As seen, the two-day average 95th percentiles were closer to the mean than the 95th percentiles from the day one-only measurements, but this effect

was relatively small: 9.7 percent for all age groups combined and essentially zero for children < age 1. These results suggest that regression to the mean may not be a major source of bias in this dataset. The reason for this is unknown although it is likely related to the fact that unlike intake of many individual foods, a consistent intake of water is necessary for life and good health.

Table 1. Comparing CSFII Drinking Water Intake Rates (ml/kg-day): Day One Intake Versus Two Day Average

	Day One			Two Day Average			Difference[b]	
	Mean	95th perc[a]	Diff[a]	Mean	95th perc	Diff[a]	Absolute	%
All	23.0	56.0	33.0	21.8	51.6	29.8	3.20	9.7%
Age < 1 year	86.0	200.1	114.1	84.4	198.8	114.4	-0.30	-0.3%
Age 1-6	33.5	84.7	51.2	31.4	74.4	43.0	8.20	16.0%
20+ males	20.5	46.8	26.3	19.4	43.3	23.9	2.40	9.1%
20+ females	22.2	49.5	27.3	21.4	45.4	24.0	3.30	12.1%
Pregnant	22.4	45.4	23.0	20.7	44.5	23.8	-0.80	-3.5%
Age 55+	21.4	43.5	22.1	21	40.7	19.7	2.40	10.9%

[a]Diff, Difference (95th percentile minus the mean); Perc, percentile
[b]Two Day Average difference minus Day One difference

The third reason why OEHHA concludes that the intake rate used to calculate the PHG represents the true 95th percentile is that while the 95th percentile water intake rate for infants 0-6 months old is almost 2-fold higher than the median intake, a greater ratio is seen in all other age groups (see Table 2 below). It seems unlikely that these 95th percentiles would be associated with water intoxication in every age group. This similarity across age groups provides additional evidence that the 95th percentile intakes measured in infants is valid and is not consistent with water intoxication.

Table 2. Ratio of the Median Drinking Water Intake Rate to the 95th Percentile by Age Groups

Age group	Median	95th percentile	Ratio: 95th percentile to median
0-6 mo.[a]	123	237	1.93
1-3 years	20	68	3.40
4-6 years	18	63	3.50
7-10 years	13	40	3.08
11-14 years	10	36	3.60
15-19 years	9	32	3.56
20+ years	13	39	3.00
20-24 years	11	39	3.55
25-54 years	13	40	3.08
55-64 years	14	38	2.71
65+ years	16	37	2.31
All ages	13	44	3.38

[a] Values are from OEHHA, 2012; remainder of drinking water intake rates are from U.S. EPA, 2004

Fourth, other sources of infant water intake data suggest that a water intake of 237 ml/kg-day is a reasonable estimate of the true 95th percentile water intake in infants. In an OEHHA analysis of two studies which longitudinally assessed infant breast milk intake, the 95th percentile intake was estimated to be 167 ml/kg-day (OEHHA, 2012). Although this is below 237 ml/kg-day, it seems unlikely that the 70 ml/kg-day difference would be enough to lead to water intoxication and death. The OEHHA estimate is also consistent with data from the large evaluation of U.S. water intake rates by Ershow and Cantor (1989). This evaluation used data from the 1977-78 Nationwide Food Consumption Survey (NFCS), a stratified random sample of over 30,000 people designed to represent the non-institutionalized U.S. population. Based on dietary and water intake records for three days, the 95th percentile intakes for ages 0-6 months in this survey were 353 ml/kg-day for total water intake and 155.6 ml/kg-day for tap water intake. OEHHA's estimate of 237 ml/kg-day (direct and indirect water in community water consumers) is within the range of these values.

Finally, OEHHA reviewed the published literature on water intoxication and found little evidence that overall water intake of 237 ml/kg-day would cause water intoxication. Most reports of water intoxication appear to involve total water intakes of well over 300 ml/kg-day (Corneli *et al*., 1985; David *et al.,* 1981; Keating *et al*., 1991; Medani, 1987; Rodriguez-Soriano *et al*., 1981). For example, in a case series of 34 infants (average age = 4.2 ± 2.1 months) treated for water intoxication at the St. Louis (Missouri)

Children's Hospital between 1975 and 1990, Keating *et al.* (1991) estimated a water intake rate of 7.5 L/m^2 prior to hospitalization. In a 6-kg four-month-old child, this corresponds to a water intake rate of approximately 390 ml/kg-day, well above the 237 ml/kg-day value used in OEHHA's calculations. Using data on maximal free water clearance by the kidneys in infants provided by Rodriquez-Soriano *et al*. (1981), Medani (1987) estimated that children with normal filtration and diluting capacity should be able to excrete more than four liters of free water per day. In a 6-kg child, this would correspond to an intake rate of more than 600 ml/kg-day, again, much higher than 237 ml/kg-day. In conclusion, OEHHA found little evidence that a drinking water rate of 237 ml/kg-day would cause water intoxication in most children. Based on this finding, combined with the other evidence presented above, OEHHA concludes that a drinking water intake rate of 237 ml/kg-day provides a valid representation of the true 95th percentile intake in California infants.

Comment 46: OEHHA chose to use drinking water intake rate data for consumers of tap water only, yet individuals commonly use water from other sources. (Intertox)

Response: OEHHA agrees that some individuals commonly use water from other sources. However, some people do not. OEHHA chose to use tap water consumers since these are the people most likely to have the greatest exposures from local public drinking water sources for which the PHG is intended. This is mentioned on page 148 of the PHG document.

RELATIVE SOURCE CONTRIBUTION: ADDRESSING PERCHLORATE EXPOSURE FROM OTHER SOURCES

Comment 47: Schier *et al.* (2009) [*sic*] study does not account for any potential health effect, particularly in light of the iodine sufficiency provided by commercial formula. OEHHA's reliance on Schier *et al.* as a basis for the relative source contribution (RSC) is therefore misplaced. (Intertox)

Response: The aim of the Schier *et al.* (2010) study was to measure perchlorate concentrations in infant formula, and the authors of the publication did not provide a full review of the potential health effects of perchlorate. OEHHA agrees that this study does not account for any potential health effect. Because of this, OEHHA only used it to assess perchlorate exposure, which is very clear in the PHG document (page 150).

Comment 48: U.S. Environmental Protection Agency's (U.S. EPA) Office of the Inspector General's (OIG) 2010 report on perchlorate used data from the 2008 U.S. Food and Drug Administration (FDA) Food Dietary Study in 6- to 11-month-old infants and estimated a lower relative source contribution than that used by OEHHA. (Western Growers Association)

Response: Direct comparisons cannot be made between the RSC estimated by the U.S. EPA OIG and the one estimated by OEHHA since the FDA analysis involved infants ages 6-11 months while RSC estimates in the PHG document involved infants <6 months of age. In addition, the FDA data involves all infants, including those receiving breast milk (Murray *et al.,* 2008). Rather than using an RSC estimate for all infants OEHHA chose to use one for formula-fed infants since their perchlorate intake

from the formula could be higher than that in breast-fed infants. Failure to consider this higher intake could have resulted in a PHG that was not adequately protective for formula-fed infants. This is now stated on page 150 of the PHG document.

Comment 49: Some studies (e.g., Huber *et al.* (2011)) suggest that food is a much greater source of perchlorate exposure than drinking water (Huber *et al.* 2010). (American Chemistry Council)
Response: OEHHA agrees that some data show that food is the major source of perchlorate exposure in some people. However, this does not apply to everyone. In people with elevated perchlorate concentrations in their drinking water, water will likely be a more important source of perchlorate exposure than food.

COMPARISON WITH OTHER AGENCIES

Comment 50: The NAS concluded that "in healthy subjects, a dose of 0.007 mg/kg-day has no effect on iodide uptake." (California Manufacturers and Technology Association)
Response: The exact wording in the NAS document (NRC, 2005; page 66) is, "Those results [the five experimental studies of perchlorate and radioactive iodide uptake and thyroid hormone levels] have been analyzed in multiple ways, but the experimental results are clear: in healthy subjects, a dose of perchlorate of 0.007 mg/kg per day has no effect on thyroid radioiodide uptake or any other measure of thyroid function…" Thus, this statement only refers to healthy adults. It is possible and likely that this dose will still have an effect in susceptible populations or in people who are not healthy. In addition, this statement refers only to the five human experimental studies reviewed by the NAS (Brabant *et al.,* 1992; Braverman *et al.,* 2004; Greer *et al.,* 2002; Lawrence *et al.,* 2000; Lawrence *et al.,* 2001) and is not an overall conclusion based on the entirety of the evidence. The NAS report agrees with the findings of OEHHA that some people may be more susceptible to perchlorate than normal healthy adults (NRC, 2005). The NAS, consistent with OEHHA's approach, applied a factor of 10 to address interindividual variability among humans in sensitivity to perchlorate exposure when developing their reference dose.

Comment 51: The NAS stated that it would take a dose of perchlorate sufficient to inhibit iodide uptake by 75% over an extended period of time (measured in months) to lead to an adverse effect. They also noted 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. (California Manufacturers and Technology Association)
Response: These conclusions are based on a limited number of clinical studies in healthy adults or a limited number of studies in adults being given very high doses of perchlorate to treat clinical hyperthyroidism (NRC, 2005). They are not based on studies in susceptible groups like infants, pregnant women, children, and people with low iodide uptake or pre-existing thyroid dysfunction.

Comment 52: OEHHA applies the benchmark dose method to a no observable effect level (NOEL), which is a departure from the accepted practice of applying

this method only to lowest observed adverse effect levels (LOAELs) or no observed adverse effect levels (NOAELs). According to the National Academy of Sciences (NAS), the use of a non-adverse effect that is upstream of adverse effects is a conservative, health protective approach to perchlorate risk assessment. (Association of California Water Agencies, California Manufacturers and Technology Association)

Response: The comment conflates two distinct procedures in risk assessment. The benchmark dose approach estimates the dose for a specified response rate in the study population using regression models and the dose-response data from the study. In this way the benchmark dose approach considers the trend of all the data in response to exposure. The NOAEL approach is a totally separate method that simply identifies the highest dose in the study at which statistically significant effects were not observed based on a pairwise analysis. Thus, the benchmark approach is not as stated in the comment applied to a LOAEL or NOAEL, and there is no departure from accepted practice.

In regard to the comment's assertion that inhibition of iodide uptake by the thyroid is a "non-adverse effect," as discussed in the PHG document, inhibition of iodide uptake by the thyroid was selected as the key biochemical event because this is the primary mechanism of perchlorate toxicity and when severe enough, leads to reduced thyroid hormone production. As reviewed in the PHG document, even small reductions in thyroid hormone have been associated with increased cardiovascular disease risk factors, abnormal fetal brain development, and altered childhood cognition. The purpose of this PHG is to help prevent perchlorate-related reductions in thyroidal iodide uptake and any subsequent decreases in thyroid hormone production and related adverse effects. This is explained on pages 1-2 of the PHG document.

The expert committee of the NAS reached a similar conclusion regarding the use of iodide uptake inhibition as the key event for perchlorate risk assessment. In their 2005 document (NRC, 2005), they state, "…the committee recommends that inhibition of iodide uptake by the thyroid in humans, which is the key biochemical event and not an adverse effect, should be used as the basis of the risk assessment. Inhibition of iodide uptake is a more reliable and valid measure, it has been unequivocally demonstrated in humans exposed to perchlorate, and it is the key event that precedes all thyroid-mediated effects of perchlorate exposure."

Comment 53: Other agencies used a No Observable Effect Level (NOEL) approach rather than the Benchmark Dose (BMD) approach used by OEHHA. (International Formula Council)

Response: OEHHA used the BMD approach rather than the NOEL approach for a variety of reasons, which are detailed on pages 137-138 of the PHG document. Briefly, the advantages of the BMD approach are that it uses all the data points in the selected study rather than just one, it incorporates the precision of each data point, and it incorporates the shape of the dose-response curve. In contrast, the NOEL approach is limited to just one of the doses in the study and thus is highly dependent on the dose levels selected by the investigators. In addition, this approach does not account for the

shape of the dose-response curve, and does not account for the precision of each data point, including the one selected as the NOEL.

Comment 54: It remains unclear why OEHHA feels compelled to deviate so dramatically from an authoritative reference dose (that produced by the NAS in 2005) based on a universally recognized non-adverse effect. (Western Growers Association)
Response: OEHHA's approach is the same as that used by the NAS to develop their reference dose in several key areas: the use of iodide uptake inhibition as the key effect; the use of the Greer *et al.* (2002) study as the critical study; and the use of a 10-fold uncertainty factor to account for intra-species variability. The only difference is OEHHA's use of the benchmark dose approach, which is discussed in Comment 53.

Comment 55: OEHHA staff assured the Association of California Water Agencies that the work conducted by OEHHA and U.S. EPA on perchlorate health effects would reach similar conclusions. (Association of California Water Agencies)
Response: OEHHA closely follows and takes into account the work of the U.S. EPA on perchlorate but cannot assure that the two agencies will reach the exact same conclusions.

Comment 56: The NAS (National Academy of Sciences (2005)) committee, formed at the request of the EPA and other agencies, has evaluated more than 60 years of science over a 15-month period. NAS took two unusual steps where they based their determination on a non-adverse effect and derived a reference dose. IUI is the only observed effect at levels above 245 ppb and at lower levels, there were no measurable effects of any kind. The NAS reference dose-24.5 ppb- is protective of even the most sensitive subpopulations. (Western Growers Association)
Response: The NAS (2005) did not conclude that IUI is the only observed effect at levels above 245 ppb. The NAS did not conclude that the reference dose was 24.5 ppb or that 24.5 ppb is protective of even the most sensitive subpopulations. Instead, NAS concluded that IUI is the most appropriate effect to use in perchlorate risk assessment. The NAS used the same uncertainty factor of 10 to account for variability between individuals. The NAS calculated a reference dose of 0.0007 milligrams of perchlorate per kilogram of body weight per day. The NAS did not recommend a drinking water level. To do so would have required them to estimate water consumption, and consider other exposure sources as is required in setting drinking water goals.

OTHER COMMENTS

Comment 57: The most direct approach to reducing risk of perchlorate exposure in an individual is to ensure adequate iodine intake. (Health Risk Strategies)
Response: Assuring adequate iodine intake is beyond the scope of this PHG.

Comment 58: Resetting the PHG at the proposed level could result in severe collateral damage to the agricultural interests in California including higher costs and lower confidence in the safety of California fresh fruits, vegetables and dairy

products. There is concern that lowering the PHG will cause activist organizations to assert, and the media to report, that consumption of foods containing perchlorate creates a substantial risk of adverse health effects. (Western Growers Association)
Response: The PHG is solely designed to evaluate perchlorate in drinking water and it would be inappropriate to use it to make conclusions regarding food. In the first paragraph of the preface of the document OEHHA states, "The PHG is a drinking water goal only; therefore, this document does not evaluate the safe levels of perchlorate in foods or other sources."

Comment 59: The state might consider an exemption for drinking water supplies with a naturally occurring iodine concentration above a certain level. (Health Risk Strategies)
Response: Determining methods for how the State of California regulates perchlorate concentrations is beyond the scope of the PHG.

Comment 60: OEHHA continues to dismiss the practical realities of establishing a lower perchlorate PHG for millions of water users who already face the prospect of rapidly increasing water rates. (California Manufacturers and Technology Association)
Response: This is outside the scope of the PHG. State law does not allow OEHHA to consider economic impacts when it develops a PHG. The State Water Resources Control Board (SWRCB) considers impacts on water rates and other economic criteria when it develops regulatory Maximum Contaminant Levels.

Comment 61: California is rapidly moving into uncharted territory in terms of water supply predictability. We cannot afford to sacrifice additional drinking water sources to well-meaning but unnecessary drinking water standards. If OEHHA revises the PHG downward to 1 ppb, the California Department of Public Health will be under significant pressure to reset the maximum contaminant level (MCL) at or near 1 ppb. We are concerned that such action could have serious implications with regard to the provision of safe, clean, affordable and accessible water supply. (California Building Industry Association and other California Building Trade Associations)
Response: See OEHHA's comment above regarding the purpose of the PHG. OEHHA agrees that an accessible and affordable drinking water supply is vitally important to California but these types of economic issues are beyond the scope of this PHG. The SWRCB considers economic and water-supply issues when it promulgates MCLs (formerly the responsibility of the California Department of Public Health).

Comment 62: Dr. Steinmaus has served both a central role in developing the science and in providing the regulatory analysis supporting the PHG and this may be a conflict of interest. (California Manufacturers and Technology Association, Southern California Water Committee, Western Growers Association)
Response: OEHHA disagrees with the statements in this comment. Dr. Steinmaus developed some of the science presented in the PHG document and subjected that

science to additional peer review in the scientific literature. The publication of Dr. Steinmaus' evaluations of perchlorate data in the peer-reviewed literature provides the opportunity for greater scrutiny and discussion of the PHG analysis. While it is not required that OEHHA publish the findings in highly regarded scientific journals, OEHHA often does so to obtain additional peer review from the scientific community.

Comment 63: The 2012 draft PHG document is essentially the same as the draft PHG document released in 2011. (Intertox)

Response: Numerous changes were made to the 2011 draft document in response to the peer reviewers and the public comments. These comments were helpful in that they brought up several issues that needed further explanation. However, they did not necessitate changing the key study (Greer *et al*., 2002) or other key data (e.g., the use of water intake rates in infants), so they did not change the proposed PHG. Much of the document did not change because the very large majority of it describes previous research wherein interpretations and descriptions did not change and were not commented on by the public or the peer reviewers.

2011 Comments Received on the First Draft PHG Document

HEALTH IMPACTS FROM PERCHLORATE

Comment 1: The National Academy of Sciences (NAS) recommended that chemical testing and risk assessment should be based on preventing perturbation of 'toxicity pathways,' rather than endpoints. This approach is public health-protective and OEHHA made an appropriate decision to use iodide [uptake] inhibition as the pathway of interest. (National Resources Defense Council, Center for Public Environmental Oversight)
Response: This is consistent with the perchlorate PHG. The NAS (NRC, 2007) report that is being referred to here cited perchlorate as an example of how such an approach should work. The perchlorate PHG is based on preventing significant perturbations of iodide uptake that in turn can lead to neurological or other impairments.

Comment 2: 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 iodide uptake can be linked to thyroid dysfunction. (Partnership for Sound Science in Environmental Policy)
Response: The PHG is based on the Greer *et al*. (2002) study where subjects were given known concentrations of perchlorate which resulted in iodide uptake inhibition. An analysis of the relationship between blood levels of perchlorate and iodide uptake inhibition was not presented in this study.

Comment 3: Perchlorate inhibits the uptake of iodide (IUI) into the thyroid. IUI is a common and non-adverse biological event. (Perchlorate Study Group)
Response: As discussed in the PHG document, inhibition of iodide uptake by the thyroid was selected as the key biochemical event because this is the primary mechanism of perchlorate toxicity and when severe enough, leads to reduced thyroid hormone production. Even small reductions in thyroid hormone have been associated with increased cardiovascular disease risk factors, abnormal fetal brain development, and altered childhood cognition. The purpose of this PHG is to help prevent perchlorate-related reductions in thyroidal iodide uptake and any subsequent decreases in thyroid hormone production and related adverse effects. This is explained on pages 1-2 of the PHG document. The original 2004 PHG for perchlorate also was based on inhibition of iodide uptake by the thyroid.

The expert committee of the NAS reached a similar conclusion regarding the use of iodide uptake inhibition as the key event for perchlorate risk assessment. In their 2005 document (NRC, 2005), they state, "…the committee recommends that inhibition of iodide uptake by the thyroid in humans, which is the key biochemical event and not an adverse effect, should be used as the basis of the risk assessment. Inhibition of iodide uptake is a more reliable and valid measure, it has been unequivocally demonstrated in humans exposed to perchlorate, and it is the key event that precedes all thyroid-mediated effects of perchlorate exposure."

Comment 4: Nowhere in OEHHA's document does it show that California's current perchlorate standard is not health protective or that lowering the public health goal from 6 ppb to 1 ppb will offer additional health benefits. (Perchlorate Study Group)

Response: OEHHA is not required to make such a determination. The purpose of this updated PHG is to identify a level of perchlorate in drinking water that prevents perchlorate-related reductions in thyroidal iodide uptake and subsequent decreases in thyroid hormone production that may be associated with adverse health effects. The updated PHG incorporates new data on infants and helps ensure that infants are protected from adverse health effects from perchlorate in drinking water.

HEALTH VALUE FROM THE GREER ET AL. STUDY

Comment 5: The Greer *et al.* (2002) study is far from an ideal basis for calculation of a PHG due to a small study population and considerable variability in the response to perchlorate among the subjects, which is not well-understood. It is also reasonable to use more than one study as the basis for the PHG. (Environmental Working Group, National Resources Defense Council, Center for Public Environmental Oversight)

Response: All of the published clinical dosing studies were evaluated and are discussed in the PHG document (pages 91-97). Consistent with OEHHA, the NAS also selected the Greer *et al.* (2002) study as the key study for its perchlorate risk assessment (NRC, 2005). Like the NAS, OEHHA found no major weaknesses in the Greer *et al.* (2002) study that precluded it from being used in the PHG calculations. Human variability in response was addressed by applying a factor of 10. Variability in response within the Greer *et al.* study subjects themselves was addressed by using the lower 95% confidence interval of the benchmark dose. For comparison purposes, a benchmark dose analysis using the data from Blount *et al.* (2006) is also presented in the PHG document (see Appendix).

Comment 6: The draft document treats the point of departure (POD) for perchlorate as if it were an adverse effect. This is not scientifically defensible, nor has it been supported by other expert risk assessments. (Perchlorate Study Group)

Response: OEHHA treats iodide uptake inhibition as it would an adverse event because it is in the direct causal pathway between perchlorate exposure and several important adverse events. OEHHA states on page 2 that, "The perchlorate PHG of 1 ppb is intended to help prevent any perchlorate-related decrease in iodide uptake by the thyroid that could lead to decreased thyroid hormone production and that could disrupt the important functions of this hormone." Both the 2004 PHG for perchlorate and the National Academy of Sciences' review of perchlorate (NRC, 2005) selected iodide uptake inhibition as the key biochemical event for use in risk assessment.

SENSITIVE POPULATIONS

Comment 7: Any use of ecological studies (Steinmaus *et al.* 2010, Buffler *et al.* 2006, etc.) in OEHHA's analysis is inappropriate because these studies are greatly flawed in their analysis. (Association of California Water Agencies, Riverside Public Utilities Department, Perchlorate Study Group)
Response: The ecological studies were not critical to the PHG calculation. OEHHA evaluates studies of all designs, including ecological studies, in its risk assessments, as is done by other scientific bodies (IARC, 2013). The strengths and weaknesses of each relevant study and its design are evaluated by OEHHA in its review of the scientific literature. Some ecologic studies are "greatly flawed," while others are not, and the same is true for any study design.

Comment 8: The departure from prior positions on the most sensitive population is based principally on one study which is not in concurrence with the preponderance of scientific evidence on the health effects of perchlorate, all of which suggests a 6 ppb or higher level as more than sufficiently protective for all populations including infants. (Agricultural organizations consortium)
Response: OEHHA's conclusion that infants are one of several susceptible groups is not based on one study, but rather on several sources of evidence. This includes epidemiologic evidence linking relatively low perchlorate exposures to changes in thyroid hormone levels in infants (reviewed on pages 60-91 of the PHG document); the finding that infants have very low reserves of thyroid hormones compared to adults; the fact that early childhood is a period of brain and neurodevelopment, processes that are critically reliant on adequate supplies of thyroid hormone; and the data showing that drinking water rates per unit body weight in young children are much higher than those of adults. These factors are reviewed on pages 154-156 of the PHG document.

Comment 9: It should not be a priority for California to reduce the public health goal. The change is based on a new position that infants are a sensitive population. (Agricultural organizations consortium)
Response: OEHHA must review the public health goal at least once every five years based on availability of new scientific evidence (HSC 116365(e)). OEHHA is also required to follow HSC 116365.2 in conducting the periodic review and revision of public health goals. This provision requires OEHHA to "assess all of the following, to the extent information is available:

> (1) Exposure patterns, including, but not limited to, patterns determined by relevant data, among bottle-fed infants and children that are likely to result in disproportionately high exposure to contaminants in comparison to the general population.
>
> (2) Special susceptibility of infants and children to contaminants in comparison to the general population."

Thus, OEHHA must consider any available information on the special susceptibility of infants relative to the general population. In reviewing the literature, OEHHA determined that infants, along with pregnant women and the fetus, are likely to have increased susceptibility, which should be considered in the assessment. OEHHA also determined that the bottle-fed infant, because of its greater water intake per body weight, has disproportionately higher exposure compared to the general population.

Comment 10: The commenter urged consideration of several new papers, including one by Cao *et al*. (2010) with "measurements of thyroid function for individual infants and their urinary levels of perchlorate, thiocyanate, and nitrate." (Department of Defense Region 9 Environmental Coordinator)
Response: The commenter specifically mentions five publications: Cao *et al.* (2010), Blount *et al.* (2010), Gold *et al.* (2010), "Rogan *et al.* (2010)", and Tarone *et al.* (2010). The studies by Cao *et al.* (2010), Blount *et al.* (2010), and Gold *et al.* (2013) are reviewed in the PHG document. For the reasons given in the PHG document, none of these had a major impact on the PHG calculations. The commenter's reference to Rogan *et al.* (2010) is probably an error since the commenter cites the same journal, volume, and page numbers for this publication as Cao *et al.* (2010) (and Rogan is a co-author of the Cao *et al.* paper). OEHHA performed a literature search but found no relevant article with Rogan as the first author published in 2010. The article by Tarone *et al.* (2010) is a review and does not include any new data or any important new insights that were not already considered or discussed in the PHG document.

Comment 11: The draft PHG uses the neonate for the exposure assessment, as contrasted with the 2004 draft that used the pregnant woman and her exposed fetus. While references are provided that the neonate may be sensitive, our review could not establish that the neonate is more sensitive than the fetus in utero. (Department of Defense Region 9 Environmental Coordinator)
Response: The PHG risk assessment documents that the fetal and infant periods are sensitive exposure windows for neurological development and for the potential impact of perchlorate. The PHG derivation does not state that the neonate is more sensitive than the fetus. It does however find that on a per body weight basis, the amount of water consumed by the infant is greater than that consumed by a pregnant woman. This is well established by surveys of water consumption as reported in OEHHA (2012), and in the PHG document.

Comment 12: "Studies from California and elsewhere provide evidence that thyroid hormone levels in infants were adversely affected by perchlorate at exposure levels that were much lower than the levels shown to cause no effects in healthy adults (Kelsh *et al.,* 2003; Brechner *et al*., 2000; Buffler *et al*., 2006; Steinmaus *et al.,* 2010; Li *et al*., 2000a; Crump *et al*., 2000)." We suggest this statement (page 3, paragraph 2) include past and recent findings that demonstrate no effect, or effects only in infants with significant iodide deficiencies. We further suggest the term "adverse" be eliminated. (Department of Defense Region 9 Environmental Coordinator)
Response: Studies that demonstrate no effect or effects only in infants with low iodine status are thoroughly described throughout the PHG document. Regarding the word

"adverse," OEHHA believes that a change in hormonal status can be an adverse effect, particularly for the young in the case of thyroid hormone.

Comment 13: The author of the draft PHG has published his conclusion that the effects estimated are not known to result in adverse health effects. This conclusion should either be more clearly reflected in the analyses presented in the PHG or the PHG should explain this apparent inconsistency (page 46, paragraph 2). (Department of Defense Region 9 Environmental Coordinator)
Response: The following sentence has been added to page 71 of the PHG document: "This study only evaluated TSH levels and it is currently unknown whether the effects seen here cause actual impacts on health and development."

Comment 14: Referring to the Steinmaus *et al.* study, we recommend that regulatory values be based on analyses that use standard criteria for normal and abnormal ranges for physiological parameters. (Department of Defense Region 9 Environmental Coordinator)
Response: As reviewed in the PHG document, changes in thyroid hormones, even those that fall within "normal" ranges, have been linked to cognitive declines in children and increases in cardiovascular disease risk factors in adults (page 39-58). Also, the OEHHA PHG is an advisory level, not a regulatory value.

Comment 15: In discussing the Buffler *et al.* (2006) study, limiting TSH samples to less than 24 hours following birth is inadequate given the dynamics of the post-birth TSH surge. The authors have no way of knowing where on the curve individual measurements lay, or if hospital policies can skew the results for a given location. The limitations of the studies upon which the calculations in the PHG depend should be clearly and concisely presented in the PHG so that stakeholders using this document understand its limitations (Page 46, paragraph 2). (Department of Defense Region 9 Environmental Coordinator, Perchlorate Study Group, Exponent)
Response: OEHHA found no evidence that, and sees no logical reason why, hospital policies should vary between perchlorate-exposed and unexposed areas. If a difference did occur, it most likely would relate to differences in the age of collection. However, this was adjusted for in the Steinmaus *et al.* (2010) analysis of the Buffler *et al.* (2006) data and shown to make little difference in perchlorate-TSH associations. In addition, as explained in the PHG document, TSH samples collected within the first 24 hours of birth may be the most appropriate for assessing perchlorate-thyroid hormone associations in studies like Buffler *et al*. (2006). Pages 59-60 of the PHG document state, "…most of the human studies on newborn thyroid function and maternal perchlorate exposure categorized exposure based on the concentration of perchlorate in the mother's residential drinking water *during* pregnancy, not on the actual perchlorate intake of the newborn *after* birth. This is important since the half-lives of both perchlorate and thyroid hormones in newborns are fairly short (less than 24 hours) (Greer *et al*., 2002; Van den Hove *et al*., 1999). As such, any effect that the mother's perchlorate exposure during pregnancy might have on the fetal thyroid should be seen within the first 24 hours after birth (e.g., within the thyroid hormone and perchlorate half-lives). But, they may not be seen at a later time if perchlorate exposure changes at

birth. For example, the newborn may be fed an infant formula with a different perchlorate concentration than that of the drinking water used by the mother during pregnancy. Perchlorate exposure may also change after birth in breast-fed infants if the mother uses water from the hospital or bottled water that has a different perchlorate concentration than the residential water used before birth.

The exposure to the infant might also be affected by the different kinetics of transplacental versus breast milk transfer of perchlorate. Since most of these studies based exposure status solely on the water source used by the mother before birth, any change in exposure in the child after birth could lead to a misclassification of exposure that would bias results towards the null and could cause any true effect to appear to diminish relatively soon after birth. Since the half-life of thyroid hormone in the child is short, this bias would most likely begin to occur within 24 hours after birth and become stronger thereafter. Because of this potential bias, our evaluation of these studies adds an additional emphasis on thyroid hormone measurements collected within the first 24 hours after birth."

Comment 16: Steinmaus *et al*. are equating clinically insignificant changes in TSH to small changes in thyroid hormones, which were not measured in the data set. It is unknown if these "high" TSH levels resulted in differences in thyroid hormones so we recommend the regulatory values not to be based on inferences from surrogates that may not correlate directly with the parameter of interest. (Department of Defense Region 9 Environmental Coordinator)

Response: OEHHA did not use the TSH findings from Steinmaus *et al.* (2010) as the basis of the perchlorate PHG. Rather, the PHG is based on changes in iodide uptake inhibition observed in the Greer *et al.* (2002) study. This is the same study that formed the basis of the original 2004 PHG for perchlorate. Inhibition of iodide uptake by the thyroid was selected as the key biochemical event because this is the primary mechanism of perchlorate toxicity and when severe enough, leads to reduced thyroid hormone production. As reviewed in the PHG document, even small reductions in thyroid hormone have been associated with increased cardiovascular disease risk factors, abnormal fetal brain development, and altered childhood cognition. The purpose of this PHG is to help prevent perchlorate-related reductions in thyroidal iodide uptake and any subsequent decreases in thyroid hormone production and related adverse effects. The expert committee of the NAS reached a similar conclusion regarding the use of iodide uptake inhibition as the key event for perchlorate risk assessment. In their 2005 document (NRC, 2005), they state, "…the committee recommends that inhibition of iodide uptake by the thyroid in humans, which is the key biochemical event and not an adverse effect, should be used as the basis of the risk assessment. Inhibition of iodide uptake is a more reliable and valid measure, it has been unequivocally demonstrated in humans exposed to perchlorate, and it is the key event that precedes all thyroid-mediated effects of perchlorate exposure."

Comment 17: To the extent surrogates are used (e.g., confounders are adjusted), we recommend that they be as specific as possible. (Department of Defense Region 9 Environmental Coordinator)

Response: The PHG document includes additional discussion on this subject when discussing the human data on associations of perchlorate exposure and thyroid hormone markers.

Comment 18: We suggest that the PHG address the result in the Steinmaus *et al*. (2010) paper: that mean TSH levels were higher in… Asians (4.40 µU/mL) than other ethnicities (4.01 to 4.15 µU/mL). It appears to contradict the fundamental assumption that the drinking water is the primary source of exposure to perchlorate. Specifically, the bias-to-the-null assumption that is fundamental to the evaluation of the PHG would suggest this finding is particularly robust. If missing and inferred data, e.g., the relationship between TSH levels and T4 levels, is biased, then bias toward the null is assumed. If bias toward the null is assumed, then the results that contradict the assumptions that tap water is the relevant source of perchlorate exposure for these neonates needs to be explained. (Department of Defense Region 9 Environmental Coordinator)
Response: Many things affect TSH levels, including ethnicity, genetics, and diet. The finding that Asians have a higher mean TSH than other ethnicities did not impact the association identified between perchlorate exposure and TSH levels in Steinmaus *et al.* (2010). As stated in the PHG document (page 82), the Steinmaus *et al.* (2010) results were adjusted for ethnicity and this adjustment had little impact on the perchlorate-TSH relationships identified.

Comment 19: OEHHA uses cross-sectional studies, and inappropriately uses analyses of the NHANES data to support a causative relationship between iodine, perchlorate, and thyroid hormone levels. The studies do not support a change to infants as the sensitive population and do not support a change in the PHG. OEHHA focuses on six studies as their basis for focusing on infants. (Partnership for Sound Science in Environmental Policy)
Response: The potential weaknesses commonly associated with cross-sectional studies (like NHANES) were addressed in the PHG document. One commonly cited potential weakness is the lack of information on temporality. That is, since perchlorate and thyroid hormones were measured at the same time in these studies, some uncertainty may arise as to whether perchlorate led to lower thyroid hormone levels or whether lower thyroid hormone levels led to increased urinary perchlorate concentrations. Given the known mechanism of perchlorate, the former was judged to be much more likely (page 106). The other major issue with NHANES is the potential for exposure (perchlorate) or outcome (thyroid hormones) misclassification. However, as discussed throughout the document, these misclassifications would likely bias results towards the null, not towards the positive effects identified in the NHANES studies. OEHHA identified several studies which reported associations between perchlorate exposure and thyroid hormone levels in infants, but these were not the sole basis for considering infants in the PHG calculations. Other factors (low thyroid hormone stores, rapid neurologic development, increased water intake per body weight) were also considered (reviewed on pages 3-4 of the PHG document).

It is important to point out that OEHHA did not make “a change to infants as the sensitive population.” Rather, infants are not “the” sensitive population but one of

several sensitive populations, and this was not a "change" since they were also identified as a sensitive population in the 2004 PHG document.

Comment 20: OEHHA relies heavily on analyses using the NHANES data without addressing its limitations. OEHHA inappropriately uses the urinary iodine levels as an indicator of individual iodine nutritional status. (Partnership for Sound Science in Environmental Policy)

Response: The limitations are discussed in the PHG document in the section, "Analysis of Blount *et al*. (2006) and Steinmaus *et al*. (2007)." In addition, see the discussion of cross-sectional studies and the NHANES studies in Comment 19. Regarding urinary iodine levels, as discussed in the PHG document, single spot iodine measurements (the type used in NHANES) correlate fairly well with 24-hour urine iodine measurements (the common method for assessing iodine status) (Table 41). In addition, any errors that result from using a single spot urinary iodine measurement as a metric for long-term iodine status would most likely bias results to the null, not towards the associations identified in the NHANES analyses (pages 104-105).

Comment 21: Animal study data and physiologically-based pharmacokinetic (PBPK) modeling do not demonstrate that the neonate is more susceptible. Clewell *et al.* (2003) developed a PBPK model to reproduce measured perchlorate distribution in the lactating and neonatal rat and predict resulting effects on iodide kinetics from competitive inhibition at the NIS. The neonate shows less perchlorate-induced inhibition of thyroid iodide uptake compared to the other life stages in the rat. (Perchlorate Study Group, p.35)

Response: OEHHA evaluated several existing PBPK models (Clewell *et al.,* 2003; Clewell *et al.,* 2007; Lumen *et al.,* 2013; Merrill *et al.,* 2003; Merrill *et al.,* 2005; U.S. EPA, 2009) and found that they required a large number of assumptions that could cause substantial uncertainty in the exposure and risk estimates they were used to generate.

Comment 22: Blount *et al.* (2009) published another study that was not cited in OEHHA (2011b) that evaluated the association between maternal (urine, serum) and fetal (cord blood) levels of perchlorate, thiocyanate, nitrate, and iodide compared to infant body weight, body length, and head circumference. They report no association between perchlorate, nitrate, and thiocyanate in cord blood and fetal birth weight, head circumference, and birth length. (Perchlorate Study Group, p. 35)

Response: This was a small study (n≈130) so only very large changes in birth weight, length, and head circumference would be detectable with sufficient statistical power. In addition, the outcomes assessed (statistically significant changes in birth weight, length, and head circumference) are indicative of effects that are likely much more severe than one would expect from the fairly low perchlorate exposures seen in this study (median urine perchlorate = 2.76 µg/L; 90^{th} percentile = 4.35 µg/L). Finally, urine, rather than blood, is the most common matrix used to assess perchlorate exposure, but urine perchlorate was only measured in 34 of the women and analyses of associations between maternal urinary perchlorate and birth weight, length, and head circumference were not presented. These issues are discussed in the PHG document (page 74).

Comment 23: Other studies have not shown the effects reported by Blount *et al.* (2006) and Steinmaus *et al*. (2007) on T4 at the perchlorate levels measured in the NHANES study. Furthermore, T4 measurements alone may be insufficient to assess thyroid effects. (Perchlorate Study Group, p. 38 and p. 44)
Response: At the time these reports were published, no previous study had the statistical power (i.e., a large enough sample size) to detect the level of effect identified in these two studies. In addition, most previous studies did not assess effects in potentially susceptible populations. After these two studies were published, two separate analyses of data from a more recent NHANES (2007-2008) (described on pages 109-110 of the PHG document) both reported evidence of associations between perchlorate and thyroid hormone levels (Mendez and Eftim, 2012 and Steinmaus *et al.,* 2013). Decreases in T4, even without changes in TSH, are a common effect of adverse impacts on the thyroid, including the effect caused by iodine deficiency (Obregon *et al.,* 2005).

Comment 24: Referring to Blount *et al.* (2006) and Steinmaus *et al*. (2007), spot urine samples do not support identification of iodine deficient individuals and are unreliable indicators of longer term perchlorate exposure status. (Perchlorate Study Group, pp. 39-42)
Response: As reviewed on page 104 of the PHG document, studies have shown that iodine concentrations measured in spot (single) urine samples are fairly well correlated with concentrations measured in 24 hour urine samples, the preferred method of assessing iodine status. In addition, there is no reason to believe that any errors that may occur from using spot urine iodine concentrations to assess long-term iodine status are associated with thyroid hormone levels. Thus, these errors are most likely non-differential and would most likely bias the findings of the Blount *et al.* (2006) and Steinmaus *et al.* (2007) analyses towards finding no effect, not towards the associations identified. Similar effects would be caused by any misclassification of true perchlorate exposure due to the use of spot urine concentrations of perchlorate. In addition, Mervish *et al.* (2012) have shown that concentrations of perchlorate in spot urine samples can be used to reliably place subjects into categories of longer-term perchlorate exposure.

Comment 25: In Blount *et al.* (2006) and Steinmaus *et al*. (2007), perchlorate did not lower (nor was it associated with) thyroid hormone levels outside the normal range of values. In fact, the perchlorate exposure levels considered in these studies are below those that caused measurable IUI in other studies. (Perchlorate Study Group, p. 41).
Response: As discussed above and throughout the PHG document, many of the other studies likely had insufficient sample sizes, poor exposure data, or did not assess potentially susceptible populations. And, as discussed on pages 39-58 of the PHG document, changes in thyroid hormone levels within normal reference ranges have been linked to adverse impacts on cognitive development in children and adverse impacts on cardiovascular disease risk factors in adults.

Comment 26: OEHHA ignores or discounts the results of several studies that conflict with the findings of Blount *et al.* (2006) and Steinmaus *et al.* (2007). (Perchlorate Study Group)
Response: Study results that conflict with Blount *et al.* (2006) and Steinmaus *et al.* (2007) are discussed in detail (e.g., Pearce *et al.,* 2010 and Bruce *et al.,* 2013). However, OEHHA relies on the Greer *et al.* (2002) study to establish the PHG using standard risk assessment methods as applied to protect infants and children.

Comment 27: The OEHHA interpretation of the epidemiologic data is not considering the complete set of studies 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). (Exponent)
Response: Table 13B (Table 30 in the final PHG document) identifies the excluded studies and reasons for their exclusion. In addition, a review of the strengths and weaknesses of each of the studies cited in this comment are discussed in the text of the PHG document.

Comment 28: The OEHHA odds ratio calculated for T4 for the community studied by Kelsh *et al*. (2003) and Buffler *et al.* (2006) 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). (Exponent)
Response: The PHG document now states on page 61, "The Colorado River is one of the water sources of Riverside County, so the water serving some of the "unexposed" comparison group may have been contaminated with perchlorate. Perchlorate exposure in the comparison areas would most likely bias any true associations towards the null." It would not likely cause the associations identified.

CALCULATING THE PHG

Comment 29: We agree with OEHHA's assertion that infants are particularly vulnerable to perchlorate exposure and that a revision of the PHG to adequately protect them is necessary. We also agree with the PHG of 1 ppb and the adjustment of the RSC (relative source contribution). (Clean Water Action)
Response: OEHHA acknowledges the comment.

Comment 30: Setting the PHG to 1 ppb is accomplished by weaving together several epidemiological studies, changing the sensitive life stage from pregnant women to infants, and making use of the 95% confidence interval of infant drinking water intake. OEHHA should reconsider basing their PHG on associations found in epidemiological studies and use causal relationships replicated by science. (Department of Defense Region 9 Environmental Coordinator)
Response: The PHG is based on Greer *et al.* (2002), which is a clinical study in humans who were given known doses of perchlorate. The same study formed the basis

of the original 2004 PHG for perchlorate. Also, OEHHA used the 95th percentile water intake rate in its PHG calculations, not the 95% confidence interval.

Comment 31: It is appropriate to calculate a PHG based on infant exposure to perchlorate, however OEHHA does not appear to have calculated infant exposure from breast milk. (National Resources Defense Council, Center for Public Environmental Oversight)
Response: The data are limited for estimating the concentration and fraction of perchlorate in breast milk that results from drinking water exposure. The PHG includes an additional factor of 10 that takes into account interindividual variability that may result from a number of exogenous and endogenous factors, including added possible sensitivity of the breastfed infant.

Comment 32: The use of an uncertainty factor (10) is reasonable, but the complete removal of the 3-fold database UF seems rash in light of the fact that the Greer study has been criticized for numerous deficiencies. (National Resources Defense Council, Center for Public Environmental Oversight)
Response: An uncertainty factor of 3 for database uncertainty was not used in deriving the PHG in 2004. The factor of 3 used in the 2004 PHG and the factor of 10 now used in the updated PHG was/is to account for interindividual differences. While the Greer *et al.* (2002) study has limitations, it is a clinical study in humans, with known doses of perchlorate, and data on a sensitive endpoint.

Comment 33: OEHHA's new analysis of existing data should not be used in the development of a PHG without formal peer review. They do not support a change to focus on infants in the proposed PHG. (Partnership for Sound Science in Environmental Policy, Perchlorate Study Group)
Response: Much of OEHHA's re-analyses of published data have undergone peer-review in the scientific literature. The complete PHG document underwent external peer review convened by the University of California, and the independent reviewers did not challenge or reject the analyses performed in the PHG document. The analyses support inclusion of infants among the populations to consider. Nevertheless, the Acceptable Daily Dose level has not been changed from the value used in 2004. Rather, the two major changes were: 1) OEHHA increased the uncertainty factor applied to infants from a factor of 3 to a factor of 10. As discussed above, this is the same uncertainty factor recommended by the NAS. 2) OEHHA now uses new drinking water consumption rates for infants. These rates are based on new methodology developed by OEHHA (2012) that considers the water used to reconstitute infant formula. These new rates are higher than those used in the 2004 PHG document.

Comment 34: There is no justification for raising the uncertainty factor in the 2011 draft to 10. (Perchlorate Study Group)
Response: The 2004 PHG applied an uncertainty factor of 10 to address differences in susceptibility between healthy adults and several sensitive groups (e.g., pregnant women) and a factor of 3 for human variability between healthy adults and infants. The increase to 10 was done for a number of reasons. This includes the evidence on the effects seen in several new epidemiologic studies and several new analyses of existing

studies linking perchlorate to altered thyroid hormone levels in infants and adults (Kelsh *et al.,* 2003; Buffler *et al.,* 2006; Steinmaus *et al.,* 2010; Li *et al.,* 2000; Crump *et al.,* 2000; Blount *et al.,* 2006; Steinmaus *et al.,* 2007; Mendez and Eftim, 2012; Steinmaus *et al.,* 2013 [pages 60-110]), and in several new studies linking small changes in thyroid hormone levels or deficiencies in iodine levels during pregnancy to significant decrements in cognitive function or changes in brain development in the offspring (van Wijk *et al.,* 2008; Gilbert and Sui 2008; Kooistra *et al.,* 2006; Bath *et al.,* 2013) [pages 40-53]. It is consistent with the uncertainty factor of 10 recommended by the National Research Council (NRC) for the derivation of the perchlorate reference dose for U.S. EPA (NRC, 2005) and has been used in other OEHHA PHGs. This is in agreement with the NRC's statement that, "In the absence of data on the range of sensitivity among humans, a default uncertainty factor of 10 is typically applied" (NRC, 2005).

Comment 35: Applying the explicit 10-fold variability factor and the 95th percentile water consumption rate is redundant and clearly reflects some double-counting for inter-individual variability. (Exponent)

Response: The 10-fold factor and drinking water consumption rates account for two different things and therefore are not related and are not double-counting. The 10-fold factor for human variability is standard in risk assessment and accounts for the fact that some members of a population may be more sensitive to an exposure than others because of differences in pharmacokinetics and pharmacodynamics. The use of the 95th percentile water consumption rate accounts for the fact that some people drink more water than others, and thus would have a greater internal dose or exposure at a given perchlorate concentration in drinking water.

Comment 36: There is a failure to account for ubiquitous exposure to nitrate and thiocyanate, which have the same biological mode of action as perchlorate, in setting the PHG. Establishing a PHG for perchlorate should account for both aggregate and cumulative exposures to goitrogens with the same mode of action. (Health Risk Strategies)

Response: The effect of exposure to nitrate, thiocyanate and other inhibitors of iodide uptake by the thyroid were extensively considered in the analysis of the epidemiological literature, both as possible confounders and as possible effect modifiers (pages 79-86). It was noted that some groups of people exposed to high levels of these and other types of thyroid-active contaminants like polychlorinated biphenyls may be especially susceptible to perchlorate. The interindividual factor of 10 is expected to take into account this range of susceptibility and protect those who may be more susceptible to perchlorate because of concomitant exposures to other goitrogens.

Quantitatively accounting for exposure to other chemicals acting through the same mode of action is difficult because data are limited. There are *in vitro* (cell-culture) studies (Tonacchera *et al.* (2004)) of similarly acting chemicals but the relevance of these data to actual conditions in humans is unknown. Further discussion of this issue is provided in response to Comment 7 on the December 2012 draft document. As stronger data emerge on these or other chemicals that work by the

same mode of action as perchlorate, OEHHA would formally assess them pursuant to Health and Safety Code 116365.2 b(4):

> "(b) In preparing and publishing risk assessments pursuant to subparagraph (C) of paragraph (1) of subdivision (c) of Section 116365 that involve infants and children, the office shall assess all of the following, to the extent information is available:
> … (4) The interaction of multiple contaminants on infants and children."

WATER CONSUMPTION BY INFANTS

Comment 37: Since OEHHA dramatically increased the infant drinking water intake per body weight in its analysis, it is inappropriate to increase the uncertainty factor for infants when so much uncertainty was already accounted for. (Association of California Water Agencies, Perchlorate Study Group)
Response: The PHG calculation reflects the fact that infants consume more water per unit of body weight than adults, and therefore will have greater exposure to any perchlorate that is in drinking water. This is simply an estimate of exposure, rather than an uncertainty factor. The 10-fold factor for human variability used in the perchlorate PHG is standard in risk assessment and accounts for the fact that some members of a population may be more sensitive than others to a chemical due to pharmacokinetic and pharmacodynamics differences. The NAS, in its report, *Health Implications of Perchlorate Ingestion* (NRC, 2005), also used a factor of 10 for human variability in deriving its reference dose. Application of the acceptable daily dose, which is essentially the same as the reference dose, then requires consideration of drinking water exposure rates in calculating the PHG.

Comment 38: We support the approach taken by OEHHA to base its proposed goal on the body weight and water consumption of infants, rather than pregnant women, the subpopulation that forms the basis of the current California PHG set in 2004. (Environmental Working Group)
Response: OEHHA acknowledges the comment.

RELATIVE SOURCE CONTRIBUTION: ADDRESSING PERCHLORATE EXPOSURE FROM OTHER SOURCES

Comment 39: We suggest that the use of an RSC of 73% be reconsidered in light of the fact that the effects are unlikely to be primarily due to exposure to perchlorate, in drinking water, as well as other publications and analyses that suggest that tap water is not the primary source of exposure to perchlorate. (Department of Defense Region 9 Environmental Coordinator)
Response: The RSC is addressing effects potentially resulting from a person's perchlorate intake that comes from water. While it may be possible that food is the predominant source of perchlorate in many people, this may not apply to all people. In many people, especially those who have water supplies that are moderately or highly contaminated with perchlorate, water could be the predominant source of perchlorate exposure. This is especially true for infants, who are the sensitive subpopulation on which this PHG update is based. An infant consuming powdered formula reconstituted

with tap water in an area with high drinking water perchlorate levels could have a much higher intake of perchlorate from water than from food.

Comment 40: A study in the Journal of Exposure Science and Environmental Epidemiology suggests that food is the predominant source of perchlorate intake with a contribution of 86 percent while the contribution from water is 14 percent (Huber 2010). A calculation based on OEHHA's other assumptions but incorporating an RSC of 14 percent would result in a PHG of 0.2 ppb. (Environmental Working Group)
Response: Please see the response to the preceding comment.

Comment 41: The application of an RSC to an ADD based on the Greer *et al.* (2002) study is not appropriate, since the people used in the study would have been exposed to perchlorate in their diet in addition to the doses administered in the study. (Exponent)
Response: The Greer *et al*. (2002) study measured the increase in iodide uptake inhibition by the thyroid after subjects were given a known dose of perchlorate. This known dose was on top of the background intake of perchlorate that subjects were receiving in their normal diet. The individuals in the Greer *et al.* study served as their own controls. Consequently, the results of the Greer *et al.* study are the incremental change in iodide uptake associated with the incremental increase in perchlorate exposure during the study.

COMPARISON WITH OTHER AGENCIES

Comment 42: OEHHA selectively excludes information and recommendations from expert bodies, including the National Academy of Sciences (NAS), the American Thyroid Association (ATA), and published literature. OEHHA should defer to expert bodies and to peer reviewed literature. (Partnership for Sound Science in Environmental Policy)
Response: OEHHA considered information from the NAS, the ATA, and from a very large volume of the published literature. References from the ATA, the NAS, and over 200 studies from the published literature are cited and used in the PHG document (please see the reference section).

Comment 43: The NAS concluded there is no evidence that perchlorate doses below 245 ppb (40 times greater than the current PHG) will have *any* health effect- much less an adverse effect- in humans. (Perchlorate Study Group)
Response: The NAS calculated a reference dose of 0.0007 milligrams of perchlorate per kilogram of body weight per day (NRC, 2005). They did not calculate or make any conclusions regarding a specific perchlorate concentration in drinking water below which adverse effects would not occur in susceptible populations.

Comment 44: No new science has emerged that changes the fundamental toxicology and pharmacology of perchlorate; therefore the findings of the 2005 NAS comprehensive review of the science on perchlorate and human health effects remain valid today. (Perchlorate Study Group)
Response: The updated PHG incorporates new data on infants that helps ensure that infants are protected from adverse health effects from perchlorate in drinking water.

Comment 45: OEHHA's identification of the infant as the most susceptible population contradicts the assessments of many other authoritative bodies, including the National Academy of Sciences, National Research Council (NRC), the Centers for Disease Control (CDC), the Agency for Toxic Substances and Disease Registry (ATSDR), and the U.S. EPA Office of the Inspector General (OIG), which concluded the most susceptible population is the pregnant woman and her fetus. (Perchlorate Study Group)
Response: In reviewing the literature, OEHHA determined that infants are likely to have increased susceptibility, and therefore should be considered in the assessment. The PHG does not assume infants have greater sensitivity than the pregnant woman and her fetus, but rather that they are one of several potentially sensitive groups. In addition, OEHHA concluded that infants consume more water on a per body weight basis than pregnant women, and this higher intake rate was incorporated into the PHG calculations.

OTHER COMMENTS

Comment 46: Lowering the PHG for drinking water will lead to other concerns such as levels in food and in irrigation water. (Agricultural organizations consortium)
Response: Pursuant to HSC section 116365, the PHG risk assessment is solely designed to evaluate the health effects of perchlorate in drinking water and it would be inappropriate to use it to make conclusions regarding food. In the first paragraph of the preface of the document OEHHA states, "The PHG is a drinking water goal only; therefore, this document does not evaluate the safe levels of perchlorate in foods or other sources."

Comment 47: We support the draft of the PHG of 1 ppb. The State of Wisconsin proposed rules for contaminants and their enforceable groundwater standard of 1 ppb for perchlorate became law in January 2011. (Citizens for Safe Water Around Badger, Clean Water Action)
Response: OEHHA acknowledges the comment.

Comment 48: The perchlorate risk assessment should compare the microbiological risks mitigated by current disinfection practices with the risk associated with the introduction of perchlorate from sodium hypochlorite storage. It should also evaluate the threats to public safety by switching back to gaseous chlorine. (East Bay Municipal Utility District, Association of California Water Agencies)

Response: This is outside the scope of the PHG risk assessment, which by law consists only of a risk assessment of perchlorate in drinking water. Factors such as risk-risk tradeoffs are taken into account by the State Water Resources Control Board (SWRCB) in establishing maximum contaminant levels. A discussion of the development of MCLs by the SWRCB is available on the board's website at: http://www.swrcb.ca.gov/drinking_water/certlic/drinkingwater/Chemicalcontaminants.shtml.

Comment 49: The table titled, "Major changes from the 2004 PHG," presented in the Perchlorate Workshop on February 23, 2011, should be included in the press release and in the Summary of the PHG report. (Golden State Water Company)
Response: The PHG now contains a full discussion of the major changes in the Summary of the report.

Comment 50: We would be supportive of instituting a plan that suggests testing of the analyte in areas with known perchlorate plumes. Until DPH changes the MCL, we will not change our current perchlorate enforcement policies. (San Bernardino County Department of Land Use).
Response: OEHHA acknowledges the comment, however the comment is beyond the scope of the PHG.

Comment 51: Perchlorate is both a naturally occurring and human made chemical. (Perchlorate Study Group)
Response: The fact that perchlorate occurs naturally does not negate the importance for setting a protective public health goal.

Comment 52: Relative exposure to other iodide uptake inhibitors is likely much greater than perchlorate and findings reported by Blount *et al.* (2006) are inconsistent with the literature. (Perchlorate Study Group, p. 43)
Response: As discussed above, the hypothesis that common exposures to other iodide uptake inhibitors (e.g., nitrate and thiocyanate) should have greater impacts on thyroid iodide uptake than common exposures to perchlorate is mostly based on the effects seen in Chinese hamster ovary cells, not in actual human studies. OEHHA decided not to use these Chinese hamster ovary cell findings as the basis of the PHG for the reasons discussed above (response to Comment 7 on the second draft PHG document).

Comment 53: The Amatai *et al.* (2007) study particularly points out that mothers with adequate intake of iodine may not be susceptible to the effects of perchlorate, again suggesting the need for a discussion of this relationship in the document. (Exponent)
Response: The assessment of iodine in this study was minimal, and an assessment of high versus low iodine status was not done. Therefore, it is OEHHA's judgment that this study does not provide any valuable evidence regarding the effects of high or low iodine.