Public Health Goal for Perchlorate in Drinking Water

Review of the draft technical support document of the proposed Public Health Goal for perchlorate. October 14, 2011

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Issues that are new to the 2011 draft document

1. The identification of infants as one of the groups that may be particularly sensitive to the effects of perchlorate

Infants are more sensitive to the effects of perchlorate, not so much because perchlorate has a different or more "potent effect" in infants as compared to children or adults, but more because the stakes are higher during this critical stage of brain development. Perchlorate acts as a competitive inhibitor of uptake of iodide by the thyroid gland. If the intake of perchlorate is high enough to interfere with iodide uptake, production of thyroid hormone will be reduced. The brain has a critical dependence on thyroid hormone for the first two to three years of life; thyroid hormone deficiency during this time will injure brain development. The need for adequate thyroid hormone begins during fetal life. In the first trimester of pregnancy, prior to its own production of thyroid hormone, the fetus depends on transfer of maternal thyroid hormone. In the second and third trimester, the fetal thyroid is developed and able to produce increasing amounts of thyroid hormone. Fetal thyroid hormone production depends on adequate transfer of maternal iodine. For these reasons, guidelines recommend an increase in iodine intake during pregnancy, and guidelines also recommend an increase in thyroid hormone dosing of hypothyroid women during pregnancy. The critical dependence of the developing brain on thyroid hormone is the rationale behind screening newborn infants for congenital hypothyroidism; early detection and treatment results in normal or near-normal neurological development. By way of contrast, the effects of hypothyroidism on the brain after age 3 years appear to be reversible with treatment.

More specifically, preterm infants (<37 weeks gestation) are the subgroup most at risk for impairment in thyroid hormone production with any reduction in uptake of iodine. In general, individuals are able to adjust to a reduction in iodide uptake, by relying on thyroid hormone already formed and stored, by the compensatory ability to increase uptake of a smaller pool of iodine, and by hyperplasia and hypertrophy of the thyroid gland, all driven by increased TSH levels. Studies estimate that a term infant has enough intrathroidal store of thyroid hormone for one day, compared to several days in an adult (Vulsma 1991). The intrathyroidal iodine in a preterm infant, however, is approximately one-fifth that of a term infant (van den Hove 1999). In addition, preterm infants have immature pituitary-thyroid function, with degree of immaturity in proportion to degree of prematurity. Further, preterm infants lose the contribution of maternal thyroid hormone that crosses the placenta. Preterm infants often have immature gastrointestinal function, and so are not able to take enteral feeds right away, a factor which reduces the availability of iodine (unless it is supplied parenterally). All of these factors contribute to reduced serum T4 levels in preterm infants. It is worth noting that there has been an increase in

the percentage of infants born preterm in the United States, from ~7% in the 1990s to ~12% at present (Guyer 1996, Mathews 2011).

To turn to the studies that investigate a link between perchlorate exposure and thyroid function in infants, the majority of these studies looked for a difference in the incidence of congenital hypothyroidism or changes in thyroid function tests carried out as part of newborn screening programs in populations born in higher vs. lower perchlorate levels in drinking water. None of the studies reported a higher incidence of congenital hypothyroidism in a population of neonates born in a higher vs. lower perchlorate exposure. If perchlorate has an effect on neonatal thyroid test results, it could be manifested by either an increase in the TSH level or decrease in the T4 level. Some studies did not find a significant difference in the TSH level, but re-analysis of the data in the draft technical support document or by other investigators reported a significant difference. An example is the study of Kelsh et al. 2003. In a comparison of a birth population in Redlands (high perchlorate) vs. San Bernadino/Riverside (low perchlorate), Kelsh reported the odds ratio (OR) for a high TSH = 1.24 in all newborns screened, and n newborns with samples after 18 hrs of age, an OR = 0.69. Kelsh concluded that "residence in a community with potential perchlorate exposure has not impacted …newborn thyroid function". The draft technical support document, however, re-analyzed the data of Kelsh and found an OR = 1.57 ($p<.0001$) for a high TSH when obtained at <18 hrs of age (pg 40 and Table 8). In a similar vein, Buffler et al. 2006 in a study of birth populations from communities in California with perchlorate levels >5 ppb and <5 ppb reported an OR = 0.73 for a TSH >25 mU/L in specimens obtained after 24 hrs of age. A re-analysis by Steinmaus et al. 2010, however, reported an OR = 1.53 ($p<.0001$) for a TSH >25 mU/L in specimens collected <24 hrs of age. Brechner et al 2000 reported higher TSH levels in the birth population from Yuma (high perchlorate) as compared to Flagstaff (low perchlorate), TSH 19.9 vs. 13.4 mU/L, respectively. A re-analysis by Lamm 2003 concluded that this difference may have been due to other differences between Yuma and Flagstaff, including a higher Hispanic ethnicity in Yuma vs. Flagstaff (59% vs. 13%) and altitude differences between Yuma and Flagstaff (138 ft. vs. 7,000 ft elevation, respectively). Other reports, including those of Li et al. comparing Las Vegas (high perchlorate) vs. Reno (low perchlorate) did not find a difference in T4 levels (2000a) or TSH levels (2000b), nor did Amitai et al 2007 in three birth populations in Israel. Lastly, studies from 3 cities in Chile with high (Taltal), medium (Chanaral) and low (Antofagasta) perchlorate levels in drinking water did not report differences in neonatal TSH or T4 levels (Crump et al 2000, Tellez Tellez 2005). However, again, re-analysis in the draft technical support document came to a different conclusion, finding "45% higher mean TSH" in infants born in Taltal, the city with high perchlorate in the drinking water (pg 50, Table 13).

While these studies attempt to answer the question about an effect of perchlorate exposure on thyroid function in infants, there are shortcomings in essentially all of them. None of the studies was designed prospectively to investigate the effect of perchlorate on neonatal thyroid function. In general, perchlorate was not measured in the study subjects (i.e., mothers or newborns), but rather data on perchlorate levels in drinking water samples was used as a surrogate for estimates of perchlorate intake. None of the studies was able to control for all the variables known to affect thyroid function tests in newborns. The results of the studies are only meaningful if perchlorate is the only variable, with all other variables known to affect levels either similar between the birth populations being compared, or undergoing multivariate analysis to examine for an effect of

potential confounders. Examples of variables that influence neonatal thyroid function tests include birth weight and gestational age, postnatal acute illness (e.g., respiratory distress), certain drugs, and age that the newborn screening specimen is obtained. There is a dramatic rise in serum TSH following delivery, increasing from a cord level of 6-10 mU/L to a peak of 60 mU/L at 30 minutes, and then falling to <10 mU/L by age 5 days. Thus, a difference in the age of sample collection of even a few hours during the first 24 hours of life can make a significant difference in TSH levels. For this reason, the authors of several studies cited above chose not to look at results from specimens obtained in the first 24 hours of life. On the other hand, the draft technical support document chose to specifically look at results in the first 24 hours, arguing that this was the time period perchlorate most likely might impact neonatal thyroid function test results. While it makes sense that results in the first 24 hours reflect maternal and therefore fetal/neonatal iodine uptake and thyroid test levels, if some factor, e.g., perchlorate exposure, causes an elevated TSH or decreased T4 level, I would expect most likely it would persist and so be found in specimens obtained after 24 hours of age. Infants with high TSH or low T4 levels tend to track higher or lower, respectively, recovering to the reference range in a week or two after birth. I think these are some of the reasons that "experts" in this field have not reached a consensus on this issue, and that considerable difference of opinion remains on whether there is a "cause and effect" relationship between perchlorate levels in drinking water and neonatal thyroid function. It is worth noting that the "critical" study by Greer et al. 2002 found an effect on decreased uptake of I-123 starting at a dose of 7 ug/kg-day (though not statistically significant until 20 ug/kg-day), but they did not find an effect on serum thyroid function tests except at a dose of 500 ug/kg-day (=3,500 ug/day in a 70 kg adult) – and this effect was a lower TSH level. Thus, it seems a stretch that intake of perchlorate in drinking water as low as 5-20 ug/L (or 5-20 ppb) in a mother would impact neonatal thyroid test results.

The draft technical support document notes that perchlorate exposure is more likely to cause a problem in the face of low iodine intake. This was one of the significant findings of the study of Blount et al. 2006, investigating the correlation of urinary perchlorate levels and serum TSH and T4 levels in samples obtained as part of the National Health and Nutrition Examination Survey (NHANES). Urinary perchlorate correlated positively with serum TSH and negatively with T4 in women with low urinary iodine (<100 ug/L), while it correlated only with TSH in women with normal urinary iodine (>100 ug/L). Women with low iodine intake would potentially put their breast-feeding infant at risk for reduced thyroidal uptake of iodine. The finding of Pearce et al. 2007 that 47% of lactating women in Boston (n=57) had insufficient breast milk iodine reinforces the vulnerability of infants.

For all of the reasons summarized above, I concur that infants, and more specifically preterm infants, are more sensitive to the effects of perchlorate than any other age group. As such, it makes sense that, if an "uncertainty factor" of 10 is deemed appropriate for susceptible groups such as pregnant women, the fetus, and individuals with thyroid disease, this uncertainty factor of 10 should also apply to infants.

2. OEHHA's use of updated data from the U.S. EPA on typical drinking water intake rates in the U.S.

The crux of this issue is the intake of drinking water for an infant, both because the infant has been identified as more sensitive to the effects of perchlorate, and because an infant has the highest intake of drinking water on a weight basis. Thus, in the calculation of the proposed public health-protective concentration of perchlorate, the drinking water rate of an infant is used in the formula: C = ADD x RSC divided by the drinking water rate.

The 95th percentile estimated water consumption rate for an infant 0-6 mo is reported at 0.234 L/kg-day, or 234 mL/kg daily (U.S. EPA, 2008b). Maintenance fluid rates for infants from 0-10 kg is 100 mL/kg-day (Nelson Textbook of Pediatrics 2011). An intake of 234 mL/kg-day might be necessary with excessive losses, e.g., with an an acute illness, excessive heat and sweating, etc. It is hard to imagine ongoing, continuing intake at 234 mL/kg-day in an otherwise healthy infant. Such a continuing intake in a healthy infant might be dangerous, e.g., lead to "water intoxication". Thus, while I understand and concur with the use of a "safety factor" in calculating the proposed public health-protective concentration of perchlorate, ongoing intake of 234 ml/kg-day seems excessive. The 50th percentile estimated direct and indirect total water ingestion for infants <1 mo to 6 mo is 75-89 mL/kg-day (90% CI 64-114) (Kahn & Stralka 2009). I would think using the upper 90% CI for this estimate (e.g. 114 mL/kg-day) would be more realistic.

3. The use of new data on perchlorate consumption from foods.

Data presented shows an estimated contribution of perchlorate from water of 73%, leaving 27% coming from other sources, i.e., mostly food. I concur with this estimate.

4. The accuracy of the information presented regarding the new studies published since the 2004 perchlorate PHG.

Brief comments on studies published since the 2004 perchlorate PHG:

- **Braverman 2005 & 2006:** The 2005 publication examined the effect of exposure to perchlorate in industrial workers; the RAI uptake decreased from 21.5% in pre-shift workers to 13.5% in post-shift workers (consistent with the findings of **Greer 2002**). Despite this decrease, there was no change in serum TSH levels, and T4 and T3 levels were minimally increased. The 2006 publication did not find an effect of long-term (6 mo) ingestion of two doses of perchlorate (0.5 mg/day and 3.0 mg/day) on RAI uptake or serum thyroid function tests. These results are difficult to reconcile with the reduced RAI uptake found by **Greer 2002.** The authors speculated that chronic exposure to perchlorate may "upregulate" the sodium-iodide symporter (NIS), overcoming the effect of perchlorate.
- **Kirk 2005:** Reported detection of perchlorate in nearly all samples of cow's milk, and found an inverse relationship between perchlorate and iodine levels in human breast milk.
- **Blount 2006:** As noted in comments above (end of 1.), the finding from NHANES specimens that urinary perchlorate correlated positively with serum TSH and negatively with serum T4 in women with low urinary iodine raises concern about the potential impact on fetal and neonatal thyroid function. It should be noted that a re-analysis of this data, but now using creatinine-adjusted urinary iodine levels, did not find a negative correlation of urinary perchlorate with serum T4 in women of childbearing age and low

urinary iodine (**Lamm 2007**). Arguments can be made pro and con as to which results carry more credence; in general, creatinine-adjusted measurements are thought to correct for day-to-day variations in measured analytes.

- **Steinmaus 2007:** Demonstrated that the association of urinary perchlorate with decreased urinary iodine was increased in by other factors, such as high cotinine, history of smoking, and thiocyanate.
- **Gibbs & Landingham 2008:** In an analysis of pregnant women from the 3 cities in Chile (see **Tellez Tellez 2005**), these investigators found no association between urinary perchlorate, iodine and serum TSH and free T4 levels.
- **Lao 2010:** Found that urinary perchlorate "weakly" correlated with an increase in urinary TSH levels in infants with low urinary iodine levels; also correlated with increased urinary T4 levels.
- Note: I previously commented on the publications of **Tellez Tellez 2005, Pearce 2007, Pearce 2010, and Steinmaus 2010** (1. above).

In summary, several studies published since the 2004 perchlorate PHG offer evidence in support of the effect of perchlorate on RAI uptake, which in turn could affect thyroid function. At the same time, it needs to be disclosed that some of the studies do not, including **Braverman 2006** which did not find an effect of chronic perchlorate intake on RAI uptake and the re-analysis by **Lamm 2007** which appears to refute some of the findings of **Blount 2006.**

5. OEHHA's decision not to base the PHG on the Tonacchera *et al.* (2004) *in vitro* study in Chinese hamster ovary cells.

Tonacchera et al. investigated the relative potency of perchlorate to inhibit I-125 uptake in Chinese hamster cells expressing the sodium-iodide symporter (NIS). On a molar basis, the relative potency of perchlorate was found to be 15, 30, and 240 times that of thiocyanate, iodide (non-radioactive), and nitrate, respectively. The effect of each chemical was additive; no synergism was found.

Although this study confirms that perchlorate is a competitive inhibitor of iodide uptake in the thyroid gland, and provides a comparison of *in vitro* potencies, I agree that there are better methods to base the PHG of perchlorate on. While the ingestion of thiocyanate and nitrate may be additive to perchlorate, recommendations regarding these two chemicals were beyond the scope of the draft technical support document.

<u>Major issues that have not changed from the 2004 perchlorate PHG document that was competed following public comments and UC peer review.</u>

1. The use of a five percent decrease in iodide uptake by the thyroid as the critical effect for establishing the PHG.

A five percent decrease in iodide uptake was selected because this is "near the level recommended by the U.S. EPA as a bench mark response for risk assessments involving continuous variables", per the draft technical support document. A five percent decrease also was selected, as it is "the lowest level of effect that is commonly detectable with statistical

significance", and it is "within the range of effect levels identified in the critical study by Greer *et al*, 2002". Using the data from the **Greer 2002** study, OEHHA then used the "Hill model" to plot percent inhibition of thyroidal uptake vs. perchlorate dose (pg 103 of the draft technical support document). The best fit curve showed the five percent decrease in iodide uptake to correspond to a dose of 0.0068 mg/kg-day (Benchmark Dose [BMD]) and the lower 95% CI = 0.0037 mg/kg-day (BMDL). As noted, this was the perchlorate dose used in the calculation of the PHG perchlorate level in the 2004 report.

While I find the assumptions reasonable and calculations used to arrive at this dose accurate, I think it is important to bear in mind that the Greer study did not find a statistically significant decrease in iodide uptake at 0.007 mg/kg-day (the lowest dose used in the study); a statistically significant decrease was seen at the next higher dose, 0.020 mg/kg-day. Further, the Greer 2002 study did not find an effect on thyroid function test results even at the highest dose used, 0.500 mg/kg-day. Thus, the 0.0037 mg/kg-day dose would appear to incorporate a significant margin of safety.

2. The use of the clinical human dosing study Greer *et al.* 2002 as the source of data for calculating the benchmark dose.

Greer 2002 is a prospective study of the effect of increasing doses of perchlorate on inhibition of iodide uptake (I-123) by the thyroid gland in healthy adult human volunteers. I concur that the data from this study are the best available to evaluate the effect of perchlorate, i.e., the "critical study". No comparable data exists for infants or children (for obvious reasons), but based on thyroid physiology, I would expect the effect of perchlorate to have a similar effect on inhibition of iodide uptake in these age groups as it does in adults.

I think it is worth pointing out that the study of **Braverman 2006** did not confirm a decrease in iodide uptake, as seen in the **Greer 2002** study. The main difference between the two studies is that Greer administered perchlorate for 14 days, while Braverman administered it for 6 months. As noted above, one possible explanation is that chronic exposure to perchlorate may "up-regulate" the NIS, overcoming the effect of perchlorate. If correct, based on thyroid physiology, I would expect this compensation to work best in healthy adults, perhaps somewhat less well in young children, and perhaps not as well in infants.

3. Use of the benchmark dose (BMD) approach for establishing the point of departure for the Acceptable Daily Dose (ADD) and the PHG calculations.

While I find arguments to use BMD over "No Observable Adverse Effect Level" (NOAEL) method to make sense, if the "critical study" chosen uses doses close to that calculated for BMD, it would seem that both methods should arrive at a similar ADD number. In fact, **Greer 2002** state that, "based on the dose response for inhibition of the 8- and 24- hr RAIU on E14 in all subjects, we derived estimates of the true no-effect level: 5.2 and 6.4 ug/kg-day, respectively". These figures are essentially identical to the 0.0068 mg/kg-day (=6.8 ug/kd-day) BMD estimated to cause a five percent reduction in iodide uptake, arrived at using the Hill model.

The Big Picture

a. In reading the technical report, are there any important scientific issues relevant to the proposed PHG that have not been addressed in the response to the points listed above?

Overall, in my opinion the draft technical support document does an excellent job of identifying and presenting the scientific publications relevant to the impact of perchlorate on thyroid function and necessary to calculate the PHG for the perchlorate level in drinking water. The major new issue is the identification of infants as a population group that may be particularly sensitive to the effects of perchlorate. As noted in my comments, I concur that infants deserve this designation, not because there is evidence that perchlorate has a more potent effect on iodide uptake and thyroid function in infants, but because the stakes are higher during this stage of brain development, which is dependent on normal thyroid hormone levels. Preterm infants are likely the most at-risk subgroup, a point worth making as the percentage of infants born preterm in the U.S. has increased over the last two decades.

The other main new issue is the use of updated data from the U.S. EPA on typical drinking water intake rates in the U.S. The designation of infants as a group more sensitive to perchlorate leads to the use of the intake of drinking water for infants 0-6 mo in the calculation of the PHG for the acceptable concentration of perchlorate in drinking water. As the infant has the highest intake of water on a weight basis, this change has a dramatic effect on the calculation of the PHG. As noted in my comments (see 2., above), intake at the 95th percentile estimated water consumption rate of 0.234 L/kg (234 mL/kg-day) is more than twice the intake of daily maintenance fluids for a healthy infant (100 mL/kg-day). I would expect such high rates to be temporary, not continuous. In my opinion, the U.S. EPA 50th percentile estimated direct and indirect total water ingestion for infants, which is 75-89 mL/kg-day, then using the 90% CI = 114 mL/kg-day, is a more realistic estimate of chronic water intake.

b. Taken as a whole, are the document and the proposed PHG based on sound scientific knowledge, methods, and practices?

As a whole, in my opinion the use of the benchmark dose (BMD) approach for establishing the acceptable daily dose (ADD) and the public health goal (PHG) calculation are based on sound scientific knowledge, with the exception of the use of the 95th percentile of estimated water consumption for infants, 234 mL/kg-day. I think it is worth pointing out that safety margins have been incorporated for each factor used in calculating the PHG, summarized as follows:

1. The estimated BMD corresponding to a 5% reduction in thyroidal iodine intake = 0.0068 mg/kg-day perchlorate
2. Use of the lower 95% CI for the BMD, or BMDL = 0.0037 mg/kg-day
3. Designation of infants as a susceptible population group, deserving the higher "uncertainty factor" = 10
4. Use of the 95th percentile estimated water consumption rate for an infant 0-6 mo = 234 mL/kg-day (=4.3 kg-day/L).

I believe the use of the 90% CI for average water intake is a more realistic estimate of chronic water intake in an infant, and still preserves the concept of a safety margin for this factor. If one uses this figure, 114 mL/kg-day (=8.8 kg-day/L), the calculation of the health protective concentration would be:

$$C = \frac{BMDL \times (BW/WC) \times RSC}{UF}$$

$$C = \frac{3.7\ ug/kg\text{-}day \times 8.8\ kg\text{-}day/L \times 0.73}{10} = 2.4\ ug/L, \text{ rounded to } 2\ ug/L\ (=2\ ppb)$$

New References (all others will be found in the draft technical support document)

Guyer B, Strobino DM, Ventura SJ, MacCorman M, Martin JA (1996) Annual summary of vital statistics. Pediatrics 98:1007-1019.

Kahn HD, Stralka K (2009) Estimated daily average per capita water ingestion by child and adult age categories based on USDA's 1994-1996 and 1998 continuing survey of food intake by individuals. J Expo Sci Environ Epidemiol 19:396-404.

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Matthews TJ, Minino AM, Osterman MJ, Strobino DM, Buyer B (2011) Annual summary of vital statistics 2008. Pediatrics 127:146-157.

Nelson Textbook of Pediatrics (2011) RM Kliegman, BF Stanton, JW St. Geme III, NF Schor, RE Berhman, eds. 19th Ed. Elsevier Saunders, Philadelphia: Maintenance and Replacement Therapy, pg 243.

Vulsma T (1991) Etiology and Pathogenesis of Congenital Hypothyroidism. Evaluation and Examination of Patients Detected by Neonatal Screening in the Netherlands. Academisch Proefschrift, Rodopi,Amsterdam, pp 63.