Review of the California Public Health Goal for Perchlorate in Drinking Water

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This review was prepared with the understanding that the manuscript addresses public health concerns alone, and that any cost/benefit analyses are to be considered elsewhere. In addition to the review prepared by the State of California, the comments of interested parties have also been noted. A number of comments addressed economic concerns, which are important but rest outside the boundaries of a Public Health Goal (PHG). Others sought to reduce attention to perchlorate as a public health issue by emphasizing the significance of other environmental contaminants. The exposure of people to one chemical cannot be used as a reason to downplay the importance of exposure to another. The authors have prepared an extensive review of the literature and have evaluated and expressed continuing uncertainty about the safety of perchlorate in drinking water, the possible increased impact due to co-exposures to other thyroid-disrupting agents, and concerns about iodine intake. The OEHHA has requested review of some specific issues that are new to this 2011 Draft Perchlorate PHG. These will be addressed first, followed by review of major issues that have been carried over from the 2004 review. California law specifies that the PHG be set in accordance with certain criteria. The last section of this review consists of comments pertaining to the degree to which these criteria have been met.

Issues New to the 2011 PHG.

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

The reviewer is familiar with sensitivity of infant neurodevelopment to thyroid hormone, with studies associating small decreases in thyroid hormone with reduced IQ and increased risk of ADHD-like traits, with studies indicating that neonates have minute stores of thyroid hormone and may be especially vulnerable to low iodine intake or impaired iodine uptake during early life. Recent studies have found many human milk samples are low in iodine and relatively high in perchlorate, possibly placing breastfed infants at increased risk of sub-optimal development. It is agreed that infants, along with fetuses, are uniquely sensitive to the effects of thyroid hormone insufficiency, and thus to the effects of perchlorate. Therefore it is also agreed that application of a ten-fold uncertainty factor and upper-level

confidence limits for the protection of infants is appropriate. **OEHHA's use of updated data from the USEPA on typical drinking water intake rates in the U.S.**

Use of the EPA data on water consumption among lactating and pregnant women and infants not available for the 2004 PHG is appropriate. Use of the upper 95th percentile of water consumption obviously protects the large majority of consumers.

2. **Use of newly available data on perchlorate exposure from food**.

Many studies of perchlorate in food have been published since the previous PHG of 2004 and these should be considered for the 2011 PHG. The Draft document states that the PHG uses concentrations of perchlorate in infant formula as the basis for the relative source contribution for water for infants, which was set at 0.73. Infant formula is fairly low in perchlorate, and formula is fortified with iodine, which should be protective. Perchlorate concentrations are substantially higher in breast milk. Why was human milk not used as the basis for the public health concentration, since breastfed infants may be most vulnerable to perchlorate, given evidence of low iodine in many human milk samples? One strategy might have been to estimate what concentration of perchlorate in drinking water would result in a concentration of perchlorate in breast milk that would pose no risk to infants.

The PHG also uses information from the FDA's Total Diet Survey to calculate a relative source contribution of .27 for food (and the same 0.73 for water derived for infants), although it also states on (page 110) that "food is the primary source of perchlorate for the general population." The FDA's Total Diet Survey relies on four different area market baskets that are defined as "North East, South, West and North Central." Some of the sites have been located in California, but contaminant levels do not seem to have been reported on a regional basis. Is a relative source contribution of 73% water reflective of California, especially given the high likelihood of use of perchlorate-contaminated irrigation water relative to the rest of the country? Of course it is possible that foods are so widely distributed that local conditions do not matter, but it seems that this is an area of uncertainty. It is hoped that the conservative approach used by OEHHA would more than cover any errors or uncertainties in relative source contribution.

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

   Consideration of studies published since the 2004 perchlorate PHG has been undertaken in a conservative and accurate manner. A number of these studies indicate that infants may be at elevated risk of perchlorate exposure and/or associated risks, and justifies their inclusion as a vulnerable population. There are at least two studies which do not appear to have been included in the PHG (Cao et al. 2010 and Valentin-Blasini 2011) which would provide additional support for the argument that infants are a vulnerable subpopulation.

4. **OEHHA's decision not to base the PHG on the Tonacchera et al. 2004 *in vitro* study.**

   It is agreed that *in vitro* studies are poor models of human exposures. However, the Tonacchera[1] study does provide an indication of the potential potency of perchlorate as an iodine-uptake inhibitor for humans and is especially relevant to the hypothesis that neonates, with their small thyroidal reserves, are more vulnerable to the effects of perchlorate than healthy adults. The argument that perchlorate exposure is unimportant, because other chemicals also pose risks to human health, is irrelevant. This is analogous to claiming one should not be concerned with cars while crossing the highway because buses are bigger.

Major issues unchanged from the 2004 PHG that have already been reviewed.

1. **Use of a five percent decrease in iodide uptake at the thyroid as the critical effect for establishing the PHG.**

   The five percent decrease in iodide uptake is appropriate and reasonable. Selection of this critical effect provides consistency among regulatory agencies, is consistent with common practice in risk assessments, and is in accordance with effects observed in the study used for calculating the benchmark dose. Using inhibition of iodide uptake as the critical event is appropriate since this is the first step in perchlorate toxicity, and any other effects would follow subsequently.

2. **Use of the clinical human dosing study (Greer et al. 2002) as the source data for calculation of the benchmark dose.**
   Using the human dosing study by Greer et al.[2] remains the best strategy at present. It is most appropriate of those available, given its use of human subjects and multiple defined dosing levels which allowed construction of confidence intervals for perchlorate exposure and inhibition of iodide uptake. OEHHA has chosen to use an estimated dose believed to result in a 5% reduction in iodide uptake as the benchmark dose. A 5% reduction in iodide availability was deemed unlikely to harm healthy adults with an adequate intake of iodine, and this seems reasonable.

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

   Use of the BMD approach is preferable given the limitations of the Greer study and is consistent with OEHHA protocol.

The literature review is quite thorough, although a few recent studies may have been overlooked or were published past the date of this manuscript's submission. Among these are Cao et al.,[3] which would have provided additional evidence that perchlorate alters thyroid hormone levels in infants, and Valentin-Blasini et al. 2011,[4] which provides some interesting information on infant exposures not previously available. The literature review, however, makes it clear that the extant ecological studies are flawed and in conflict, that we do not know the level at which no adverse effects on health will occur, and that therefore, a value must be derived which will protect public health until more is known about a number of issues, including iodine intake among vulnerable populations, the significance of co-exposures, and the importance of sub-clinical hypothyroidism among pregnant women and infants.

The PHG has attempted to obtain a reasoned safe exposure level through reliance on data from the 2002 Greer et al. study, as described previously. Further reductions were made from this point to protect vulnerable populations for whom data on dose/response relationships are unavailable. Use of an uncertainty factor of ten is standard practice for risk assessments in which data from one group (in this case healthy adults) is applied to another (in this case pregnant women, infants, breastfed infants and those suffering from thyroid disorders.) This uncertainty factor was appropriately selected by the authors. The authors also chose the 95th percentile for the ratio of body weight to water consumption (BW/WC) for the group with the highest such ratio: infants age zero to six months. This is a reasonable approach in that it offers additional protection to infants, a proportion of which will consume soy formula,

and/or whose mothers smoke, who are exposed to higher levels of thiocyanate, and thus at greater risk of adverse effect from impaired iodine assimilation.

The authors have considered additive effects from co-exposures to nitrate and thiocyanate, and have identified co-exposed individuals as vulnerable populations. The uncertainty factor of 10 used to calculate the PHG has been applied, in part, for their protection. This presumably covers those exposed to other thyroid-disrupting agents such as PCBs, etc. Future research on the impact of contaminants with similar modes of action (nitrate and thiocyanate) or similar targets seems prudent. It is possible that nitrate, as well as perchlorate exposure should be reduced. This does not imply that perchlorate is unimportant relative to other goitrogens, or that perchlorate should be disregarded because there are other environmental agents that also pose risk to developing infants or others.

The most vulnerable sub-group identified by the PHG are infants. Given the small thyroidal reserves of neonates and the possible need for an uninterrupted supply of iodine, this seems to be a reasonable change from the previous PHG's focus on pregnant women, whose fetuses may be protected by larger maternal stores.

OEHHA has considered perchlorate exposures with potential to alter function or structure, and addressed the issue through selection of a level of exposure at which 5% inhibition of iodine uptake would occur. This is a reasonable point of departure, although it is not clear that this (5% inhibition) would be the same level for individuals across the board, regardless of the level of iodine intake. It is agreed that perchlorate poses little risk as a carcinogen. Any PHG that protects individuals from iodine uptake inhibition should also protect against development of thyroid tumors. There appears to be an adequate margin of safety. Hopefully continuing research on iodine nutrition, and better understanding of how subtleties of variations in thyroid hormones affect infant development, will shed more light on risks posed by environmental exposures to perchlorate (as well as other chemicals).

There is not currently a demonstrated safe dose-response threshold for this contaminant. While there are a number of epidemiology studies showing no associations between perchlorate exposure (or presumed exposure) and thyroid hormone parameters they are not sufficiently strong to justify their use in determining a safe dose. The Brechner study,[5] showing a positive association, is limited in the same way. The Blount[6] and Pearce[7] studies, showing associations between direct measures of perchlorate exposure and direct measures of thyroid hormones, are quite interesting and highlight the need for continued research in this area.

Given how little we know about the sensitivity of infants, particularly neonates, to thyroid hormone disruption or about iodine intake among pregnant women and breastfed infants it seems reasonable to be cautious about exposing them to thyroid-hormone disrupting agents. Defining what degree of thyroid hormone change will result in a change of clinical significance and what degree or reduction of iodine availability would be needed to bring about a clinically significant change would reduce uncertainty about perchlorate exposures.

Conclusion.

The authors have provided a thorough critical review of current literature and strong rational for a conservative approach to regulation of perchlorate in California drinking water. Heightened focus on iodine nutrition, especially among pregnant women and infants will do much to protect people from perchlorate and other iodine uptake inhibitors. More information on the vulnerability of fetuses, neonates and infants to TH-disruption would be key to developing a more precise estimation of a safe exposure level for perchlorate. In the interim, a drinking water concentration of 1 ppb is likely protective to the population. Concentrations of perchlorate in water used for irrigation should also be addressed.

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[1] Toncchera M, Pinchera A, Dimida A, et al. 2004. Relative potencies and additivity of perchlorate, thiocyanate, nitrate and iodide on the inhibition of radioactive iodide uptake by the human sodium iodide symporter. Thyroid. 14: 1012-1019.

[2] Greer MA, Goodman G, Pleus RC et al. 2002. Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans. Environ Health Perspect. 110(9): 927-937.

[3] Cao Y, Blount B, Valentin-Blasini L, Bernbaum J, Phillips T, Rogan W. 2010. Goitrogenic Anions, Thyroid-Stimulating Hormone, and Thyroid Hormone in Infants. Environ Health Perspect. 118(9):1332-1337.

[4] Valentín-Blasini L, Blount B, Otero-Santos S, Yang C, Bernbaum J, Rogan W. 2011. Perchlorate Exposure and Dose Estimates in Infants. Enviro Sci Technol45(9): 4127-4132

[5] Brechner RJ, Parkhurst GD, Humble WO et al. 2000. Ammonium perchlorate contamination of Colorado River drinking water is associated with abnormal thyroid function in newborns in Arizona. J Occup Environ Med. 42: 777-787.

[6] Blount BC, Valentin-Blasini L, Osterloh JD, et al. 2006. Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. Environ Health Perspect. 114(12): 1865-1871.

[7] Pearce EN, Lazarus JH, Smyth PP et al. 2010. Perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant women. J Clin Endocrinol Metab. 95: 3207-3215.