Three Scientific Peer Reviews Of The Office Of Environmental Health Hazard Assessment's December 2002 Draft Public Health Goal (PHG) Document On Perchlorate In California Drinking Water

(in alphabetical order)

Jerome M. Hershman, MD
Professor of Medicine
UCLA School of Medicine
Endocrinology and Diabetes Division

Robert I. Krieger, PhD
Extension Toxicologist
Department of Entomology
University of California, Riverside

Craig M. Steinmaus, MD, MPH
Assistant Adjunct Professor
School of Public Health
University of California, Berkeley
Division of Occupational and Environmental Medicine
University of California, San Francisco

January 2004

Under terms of an agreement signed in September and October of 2003 by representatives of the Office of Environmental Health Hazard Assessment (OEHHA) and the University of California, the University agreed to select reviewers and to administer a peer review of OEHHA's December 2002 draft Public Health Goal document on perchlorate in California drinking water.

This report compiles three peer reviews. In accordance with the agreement the identities of the reviewers have not been previously disclosed nor are the comments in this report attributed to specific reviewers. The enclosed report is not a consensus document. The report and the reviews represent the individual work and opinions of the three reviewers.

Peer Review #1

Peer Review

A Draft Public Health Goal for Perchlorate In Drinking Water

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

January 6, 2004

This commentary primarily concerns review of a Draft document, "Public Health Goal for Perchlorate In Drinking Water." The occurrence of perchlorate and other potential inhibitors of the sodium iodide symporter (NIS) responsible for the entry of iodide into the thymus were of particular concern. Some preliminary original data concerning perchlorate levels in produce are contributed. Based upon consumption data, lettuce contribute even less perchlorate than water at 4 ppb to potential exposure. Attention is also drawn to thiocyanate and nitrate, other anions known to inhibit NIS. Perchlorate exposure studies in environmental settings are dominated by work in settings where persons are marginally iodine deficient. Elevated perchlorate exposures of the workforce are not linked with adverse health effects. Data are lacking to indicate that iodine deficiency is public health issue in California. Trace levels of perchlorate in water may prompt a functional or adaptive response, but higher levels are necessary to cause an adverse effect. The threshold adverse effect level for perchlorate in drinking water is signaled by a decrease in serum T4. The human study of Greer et al. study (2002) is well suited for establishment of a Public Health Goal for perchlorate.

A Draft Public Health Goal for Perchlorate In Drinking Water (PHG) prepared by the Pesticide and Environmental Toxicology Section, Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency (December, 2002). The Draft was submitted to the University of California, Office of the President, and Office of Research for additional peer review. This review concerns some scientific issues related to the Draft document.

The OEHHA authors of this Draft are commended for the breadth, depth, and clarity of the Draft document. OEHHA staff that have made informative public presentations in the process of clarifying the regulatory process are applauded.

Materials included for the review were the Draft Public Health Goal for Perchlorate In Drinking Water and a series of Comments on the OEHHA Draft. These materials including letters, publications, and preprints were provided as a tabulated notebook for University reviewers. I am pleased to have had opportunity to review these materials and to learn more about technical aspects of the overall perchlorate ingestion issue, and to offer some technical comments concerning the content of the DRAFT document.

Subject of Review

From the Preface of the Draft the nature of Public Health Goals is specified. "PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime."

"The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365), amended 1999, requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and publish PHGs for contaminants in drinking water based exclusively on public health considerations."

Selected topics include the following:

1. From the Preface: Interactions
    - 1a. Trace levels (parts per billion) of perchlorate may be accumulated by produce
    - 1b. Preliminary measurements of perchlorate in produce
    - 1c. Other chemicals in the diet and water
2. Range of perchlorate exposures
    - 2a. Occupational Exposure
    - 2b. Human environmental perchlorate exposures
3. Estimation of human perchlorate exposure derived from water
4. Iodine status of Californians
5. Critical effect associated with perchlorate ingestion

1. From the Preface: Interactions

"To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants."

The thyroid acquires iodide from a complex chemical milieu in plasma. Most of the ingested iodides that are absorbed from the gastrointestinal tract are excreted by the kidneys after about 20% enter the thyroid. The NIS actively (requiring energy) provides iodide to the follicular cells of the thyroid for the biosynthesis of thyroid hormones. Under normal conditions thyroid gland will contain 30-times more iodide than blood.

The NIS is not a specific iodide transport system. Perchlorate is a competitive inhibitor of iodide uptake and the site of action is the sodium iodide symporter (NIS), a membrane-bound protein. Perchlorate like other chemicals absorbed in sufficient amounts into the circulation (including nitrate, chlorate, bromate, fluborate, thiocyanate, chloride, bromide, iodide, and other anions) can cause a transient decrease in synthesis and secretion of thyroid hormone synthesis and a compensatory increase in TSH (Capen, 1997). These chemicals are not new to human environments and they may act additively, synergistically or not at all on thyroid function. The possibility has not been adequately considered.

1a. Trace levels (parts per billion) of perchlorate may be accumulated by produce

Draft, line 543 (page 13)
There are preliminary results showing that some vegetables (e.g., lettuce) may bioaccumulate perchlorate.

Draft, line 2947 (page 85)
There are preliminary results showing that some vegetables (e.g., lettuce) may bioaccumulate perchlorate. In a recent greenhouse study, U.S. EPA (2001) reported that lettuce irrigated with 10 µg/ml perchlorate exhibits a perchlorate content of about 300 µg/g on a wet mass basis.

The initial reports of perchlorate in produce represented test conditions that would not occur in production agriculture. Perchlorate accumulation potential is low and represents amounts of exposure that will not contribute substantially to risk assessments based upon adverse effects. The occurrence of perchlorate residues on produce has had an unfortunate negative impact on some person's perception of wholesomeness of produce.

1b. Preliminary measurements of perchlorate in produce

Pilot studies (Krieger and Sanchez, 2003; Tables 1, 2 and 3) and Environmental Working Group (EWG) data (2002) have been used to estimate potential produce perchlorate exposures from water and produce (lettuce). The exposure attributable to water using the OEHHA standard of 4 ppb was 0.12 ug/kg-day for a 70 kg person. The potential exposure at 1 ppb in drinking water is also listed. Pilot data resulting from measurements of perchlorate in lettuce produced in the Colorado River Valley yielded a potential dosage of 0.02 ug/kg-day, or 0.17 x the potential water dosage derived from drinking water. A virtually identical perchlorate levels was found in

10 leaf lettuce samples (29 ppb; none detected to 70 ppb) to yield an estimated exposure potential of 0.02 ug perchlorate/kg-day.

It is also of interest to compare the potential perchlorate exposures from lettuces featured in an earlier Environmental Working Group report (2002). If an exposure estimate is constructed from all lettuce samples, not just positive samples, the weighted perchlorate average potential exposure is 1.4 ug/person-day and the potential dosage is 0.02 ug/kg-day, also below the level resulting from a 4 ppb water standard and equal to the preliminary data of Krieger and Sanchez (2003; Table 3).

There are now additional unpublished perchlorate residue data for lettuce that indicate a mean field residue level of 11 ug/kg head lettuce (11 ppb) produced in areas irrigated by waters of the Colorado River (Krieger and Sanchez, 2003). Analysis of 24 samples of lettuce revealed 21 ppb perchlorate in the above-ground parts of the plant. The samples included wrapper leaves (not consumed) containing 55 ppb and the edible trimmed heads that contained 11 ppb. This level will make a minimal 0.62 ug perchlorate (11 ug/kg produce x 0.056 kg produce/day) contribution to individual daily perchlorate exposure. The dosage for a 70 kg male would be 0.62 ug/70 kg = 0.009 ug/kg. The corresponding dosage for a 70 kg male who consumed 2L water that contained 4 ppb perchlorate would be 8 ug/70 kg = 0.11 ug/kg (Table 3). The lettuce dose would represent less than 10% of the Draft PHG perchlorate level and less than 0.2% of a PHG adjusted to 200 ppb perchlorate in water.

These estimates must be considered preliminary and the data do not sufficiently define the exposure potential of produce since they represent small samples in both time and space. Manuscripts have not been submitted for peer review and publication. Those limitations aside, potential lettuce exposures are less than default exposures developed for drinking water (4 ppb perchlorate, 2 L/day, 70 kg body weight) and miniscule relative to levels linked to adverse effects.

1c. Other chemicals in the diet and water

Perchlorate like other chemicals absorbed into the circulation (including nitrate, chlorate, bromate, fluborate, thiocyanate, chloride, bromide, iodide, and other anions) can cause a transient decrease in synthesis and secretion of thyroid hormone synthesis and a compensatory increase in TSH (Capen, 1997). Perchlorate and other substances to which humans are commonly exposed are competitive inhibitor of iodide uptake and the site of action is the sodium iodide symporter (NIS), a membrane-bound protein

Several important dietary chemicals must also be considered inhibitors of NIS. For example, the amount of perchlorate in lettuce is dwarfed, and probably made quantitatively insignificant, relative to the amount of nitrate (ca. 50 ppm), also an NIS inhibitor, that is also present in lettuce and in some California water supplies. Preliminary perchlorate analyses reveal that the nitrate: perchlorate ratio in lettuce is about 7,300:1 (mole ratio). This estimate is presently not suitable for anything but a back-of-the-envelope estimate of NIS inhibitor exposure. Most importantly the nitrate:perchlorate ratio urges caution in the assignment of biological or toxicological significance to ingestion of trace levels of perchlorate or any other NIS inhibitor in food or water. This issue may be critical to establishment of a PHG.

Consideration of other sources of NIS inhibition including nitrate and thiocyanate should occur under the charge to OEHHA "to consider possible synergistic effects." For example, thiocyanates derived from cassava *Manihot esculenta* (a valuable starch source consumed by

millions of people) and cigarette smoking are important in the etiology of human thyroid disease *in iodine deficient populations*. There is also a substantial literature on laboratory and accidental animal poisoning by both nitrate and thiocyanate (see Kingsbury, *Poisonous Plants of the United States and Canada*, 1964) that is relevant to NIS inhibitor exposure. Given the lack of widespread thyroid disease in California, such a review could considerably inform OEHHA scientists of the significance of naturally-occurring iodine uptake inhibitors including nitrate and thiocyanate.

The potential for interactions including synergism and antagonism has not been adequately explored. Recognition of the occurrence of NIS inhibitors and of possible interactions is of importance for risk assessment and risk communication.

2. Range of perchlorate exposures

Draft, line 2868 (page 83)
Potassium perchlorate has been used to treat Graves' disease in humans, and most of the high-dose toxicity data on humans are obtained from clinical studies. At the 10-20 mg/kg-day range…

Dosages used to treat Graves' Disease are vastly greater than perchlorate levels that occur in drinking water. To acquire a dosage of 10 to 20 mg/kg-day, a 70 kg person would have to consume over 100,000 liters of water in one day, a useful point for risk communication with a wary public. Citation of such a dose in the context of determining a PHG serves to document the safety of trace levels of perchlorate exposure.

Exposure-dependent responses to ingested perchlorate have been studied in humans and experimental animals. Stanbury and Wyngaarten (1952) and Wyngaarten et al. (1952) reported that perchlorate inhibited iodine entry and retention by the human thyroid. Their observations served as foundation for the therapeutic use of perchlorate in large doses (600 mg/day to 1400 mg/day for months) in treatment of thyrotoxicosis (particularly Graves' disease). Later after aplastic anemia was associated with in this high dose regimen, lower doses (40 mg/day to 200 mg/day) were used in humans for periods of 2 years or longer (Connell, 1981; Wenzel, 1984). These and additional therapeutic uses described by Dollarhide et al. (2003) demonstrate therapeutic uses of mg/kg dosages of perchlorate in humans.

Potential occupational and environmental exposures would be of much lower magnitude. For example, assuming that a 70 kg adult, consumed 2L of water at 4 ppb perchlorate, the perchlorate dosage would be (4 ppb x 2 L)/70 kg or 0.11 ug/kg or 0.00011 mg/kg (Table 3).

2a. Occupational Exposure

The discussion of OEHHA (2002) is full and complete concerning an occupational study by Lamm et al. 1999) and it is reiterated here *in toto*.

> "Inhalation of airborne perchlorate particles could be an important exposure route in occupational settings. Lamm *et al*. (1999) studied a group of workers in a perchlorate production plant and reported that there was a correlation between airborne perchlorate dust concentration and the amount of perchlorate excreted in urine.

> As described above, 95 percent of a dose of sodium perchlorate administered orally to human subjects was eliminated in the urine by 48 hours after administration (Durand, 1938). Lamm *et al*. (1999) monitored urinary perchlorate levels of two workers during three days with measurable occupational perchlorate exposure and during the subsequent three days without known perchlorate exposure. The perchlorate body burden, as indicated by urinary perchlorate concentration, increased over the three days of work exposure, with a decrease between the 12-hour work shifts. The elimination of perchlorate after the last exposure period appeared to follow a first-order kinetics pattern. The average perchlorate elimination half-lives measured for the two workers was 7.9 hours and 8.2 hours."
> The OEHHA Draft document summarizes the results of a study of occupational exposure. "Lamm *et al*. (1999) conducted a cross-sectional study of two similar worker populations from the same industrial complex: ammonium perchlorate production workers and sodium azide production workers. A total of 37 workers were exposed to airborne ammonium perchlorate, 35 males and two females. Twenty-one workers from the azide production plant served as the control group.
>
> Perchlorate exposure was measured using full-shift breathing zone personal air samplers for total as well as respirable perchlorate particles. Urinary perchlorate concentration was assessed at the beginning and end of the 12-hour shift in which the perchlorate exposure was measured. Lamm *et al*. (1999) reported that there were no differences in thyroid function tests between workers in the azide and perchlorate plants or between the azide workers and any of the three perchlorate-exposure groups (Table 14). Based on these data, a NOAEL of 0.48 mg/kg-day (33.6 mg/day divided by 70 kg) can be estimated. However, it should be noted that this data set has several limitations: (a) small sample size, (b) high dietary iodine intake among the workers, and (c) given the short biological half-life of perchlorate (approximately 8 hr), the exposed workers might recover from the effects of perchlorate during off-shift hours. Using the medical examination and questionnaire findings, Lamm *et al*. (1999) reported that worker exposures to perchlorate in the plant were not found to be associated with thyroid abnormalities (OEHHA Draft, 2002)."

Utilization of worker experience in risk assessment provides investigators opportunity to study higher-level exposures than occur in the general public. Capture and utilization of these real time dosage-response data should be given great importance in public health decision-making.

2b. Human environmental perchlorate exposures

Kelsh et al. (2003) focused analysis on overt disease, primary congenital hypothyroidism (PCH), and TSH in a community where perchlorate was detected in ground water in concentrations ranging from 4 ug/L to 130 ug/L. The TSH findings were similar to earlier studies in California and Nevada counties with elevated perchlorate in water (Lamm and Doemland, 1999). Similar findings were reported in another study in Nevada (Li et al., 2000).

Brechner et al. (2000) compared TSH levels among infants from Yuma and Flagstaff, AZ. Median TSH levels were higher for infants from Yuma where perchlorate was present in the water supply than for infants from Flagstaff who did not have perchlorate exposure. Variation in blood collection time may have compromised the work (Goodman, 2001). Epidemiological support for this possibility is the critical finding of Kelsh et al. (2003) that the age of newborns at the time of screening was the most important predictor of TSH.

Environmental studies concerning marginally iodine deficient populations are difficult to relate to concerns about persons consuming trace levels of perchlorate and the remaining chemicals in the environmental array of NIS-inhibitors. The concern about exposure is heightened when perchlorate levels in drinking water are assumed, rather than measured concurrently.

3. Estimation of human perchlorate exposure derived from water

The equation that follows and its associated definitions is a well-proven means to calculate water concentrations of chemicals of concern. OEHHA used the following equation (p. 83, line 2723) to estimate health-protective water concentrations (C, in mg/L) for various sub-populations (adults, pregnant women, lactating women, and infants).

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

$$= \frac{0.0037 \text{ mg/kg-day} \times 0.8 \times (25.2 \text{ kg-day/L})}{30}$$

$$= 0.00249 \text{ mg/L (rounded to 0.002 ppm)}$$

Where:

BMDL = the lower limit of a one-sided 95 percent confidence interval of a perchlorate dose that reduces mean thyroidal iodide uptake by five percent;

RSC = relative source contribution; a default value of 80 percent is used for pregnant women because the major source of exposure to perchlorate is through drinking water;

(BW/WC) = the ratio of body weight (kg) and tap water consumption rate (L/day); the ratio for the 95th percentile of the pregnant woman population is estimated to be 0.0252 kg-day/ml or 25.2 kg-day/L (OEHHA, 2000); and

UF = combined uncertainty factor; an uncertainty factor of 30 is used; which includes an uncertainty factor of 10 for inter-individual variability and 3 for limitations of the database.

Relative Source Contribution (RSC) for drinking water will likely be larger than the default 80%. Other sources of perchlorate exposure including diet are very limited, and the potential RSC for produce, in particular, is minimal relative to water. If a higher perchlorate

exposure level (BMDL) associated with an adverse effect is adopted for regulatory purposes the RSC will also be increased.

The Relative Source Contribution (RSC) of water to perchlorate exposure was set at 0.8 in the OEHHA Draft. Concern has been expressed about "field-grown vegetables irrigated with contaminated water" (Sharp, Reference documents, 1/24/03). The potential of lettuce to accumulate perchlorate based upon preliminary data published by the Environmental Working Group has been overstated by media (see 3. above). Current data indicate a potential perchlorate exposure of 0.009 to 0.02 ug/kg from lettuce (Krieger and Sanchez, Table 3). This dosage is less than any perchlorate dosage associated with adverse effects. The dosage represents about 1/5 of the perchlorate dosage attributable to water consumption (4 ppb perchlorate) by a 70 kg person. Additional studies are critical to evaluate the amounts of perchlorate accumulated by produce irrigated with Colorado River Water are in progress. Based upon available preliminary data the RSC is likely to require adjustment (Krieger and Sanchez, Table 3).

An Uncertainty Factor (UF) will be determined based upon the regulatory adverse effect and its associated scientific uncertainties. The magnitude of this factor cannot be forecast lacking determination of a critical factor.

4. Iodine status of Californians

Data are lacking to show that Californians represent an iodine deficient population, and therefore, the potential impact of trace levels of perchlorate may be nil. Although it is clear that perchlorate ingestion can inhibit or reduce iodide uptake by the thyroid, it is much less clear that adverse health effects associated with low-dose perchlorate exposures are similar to those caused by iodine deficiency (after Draft, 1)

"Defined members of the population suffering from iodide deficiency" are not enumerated in the Draft. Three sensitive subpopulations include (1) pregnant women who are marginally iodine deficient, (2) fetuses of those pregnant women, (3) individuals suffering from hypothyroidism. There is little doubt that iodide deficiency is an important global health problem. The World Health Organization (WHO), International Council for Control of Iodine Deficiency Disorders (ICCIDD), has established correlates of iodine deficiency for populations. Spot urine samples have been examined using the following criteria: More than adequate (200-299), normal (100-199 ug iodide/L), mild deficiency (51-100 ug/L), and moderate deficiency (20-49 ug/L), and severe deficiency (<20 ug/L) (International Council for the Control of Iodine Deficiency, WHO, 2001).[1]

There is no data to indicate that human exposures defined by single-digit perchlorate levels in water yield adverse health effects in humans. What data exist concerning the prevalence of iodine deficiency in California? The OEHHA Draft does not establish whether an iodine-deficient sensitive subpopulation exists.

[1] National Academy of Sciences determined an estimated average requirement of 160 µg/day and a recommended dietary allowance of 220 µg/day for pregnant women (NAS, 2001). These values are approximately 50 percent higher than the estimated average requirement of 95 µg/day and the recommended dietary allowance of 150 µg/day determined for adults (age 19 years and older). Inclusion of the iodine margin should be noted in risk assessment and risk communication when potential deficiencies are discussed.

Discussion of the variability of urinary iodine levels provides foundation for acknowledgement of the plasticity of human utilization and excretion of iodine. Diurnal variation of urinary iodide (Rasmussen et al., 1999) and day-to-day variation have been documented (Vought et al., 1963; Rasmussen et al., 1999).

5. Critical effect associated with perchlorate ingestion

Definitions are critically important to distinguishing human responses to chemical stimuli for the risk assessment process. Definitions offered by Dollarhide et al. (2003) are more succinct than some. The *critical effect* (Haber, 2001) is the first adverse effect, or its known precursor, that occurs as dose rate or exposure level increases. An adaptive effect enhances an organism's performance as a whole and/or its attempt to withstand a stressor. An adverse effect is a biochemical change, functional impairment, or pathological change that diminishes an organism's ability to cope or respond to a later challenge (Dollarhide et al., 2003).

OEHHA holds that iodine uptake per se is an adverse effect and, therefore, suitable for use in risk assessment and the determination of PHG. The Draft states, "OEHHA recommends that perchlorate exposure should be kept at a level that does not inhibit iodide absorption by the thyroid."[2]

Greer et al. (2002) has demonstrated that no inhibition of iodine uptake occurs in a euthyroid adult population at about 0.5 mg perchlorate/day (0.007 mg/kg-day). Eighteen (18%) inhibition of iodine uptake occurred at 0.02 mg/kg-day. The equivalent no effect dose (NOEL) of perchlorate ingestion from water would result from ingestion of 2 liters containing 250 ppb perchlorate. This dose would not be associated with adverse thyroid function or iodine metabolism in humans (Greer et al., 2002).

Inhibition of iodine uptake of up to 70% does not reduce T4 levels, even following prolonged exposures (Greer et al., 2002). Clinical studies have shown 50% inhibition of iodine uptake with no effects on T4 or TSH (Abbassi, 2002). On that basis the critical effect of perchlorate exposure is not inhibition of iodine entry, but T4 decrease during pregnancy. Given these data, Greer et al. (2002) suggested the "true no effect level" for iodide uptake inhibition was 0.0052 mg/kg-day to 0.0064 mg/kg-day. These dosages would be equivalent to 180 ppb to 220 ppb perchlorate in the drinking water of a 70 kg person.

[2] In the same vein, would carboxyhemoglobin resulting from either normal intermediary metabolism or low levels of environmental pollution represent an adverse effect of CO exposure in asymptomatic people? I don't think so, and as such it would be classed as an adaptive effect.

Comment concerning the review process

The most cited document in the OEHHA Draft was the 2002 External Review Draft on Perchlorate Environmental Contamination by the U. S. EPA (2002; see inset). Given that there is no public health emergency and that the U. S. EPA (2002) document is an External Review Draft, I am concerned about whether the Draft document represents the most complete scientific review that OEHHA can muster.

> U.S. EPA (2002). Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization (External Review Draft). U.S. Environmental Protection Agency, Office of Research and Development, Washington, D.C. NCEA-1-0503.

Dozens of citations of U.S. EPA (2002) are included in the Draft. The U.S. EPA (2002) document is an External Review Draft (hence peer review not complete). The document was relied upon for much of the material presented in the Draft Public Health Goal for Perchlorate In Drinking Water.

The results of the External Review of U. S. EPA (2002) are apparently not available to OEHHA and citations provided in the Draft do not give any indication of OEHHA review of the original data. Since U. S. EPA and Cal-EPA have selected different critical effects (adverse effects) and each has advocated different standards for perchlorate in water reliance upon "External Review Drafts" and Draft PHGs may not have the permanence expected of the process. No public health emergency is evident in California to drive the rush to regulate trace perchlorate ingestion in drinking water.

It seems reasonable to assume that important in-depth scientific review of U. S. EPA (2002) will be provided by the National Academy of Sciences' Committee to Assess the Health Implications of Perchlorate Ingestion. The Committee's work began in June 2003 and their report is due 15 months later. A recent public meeting at the University of California, Irvine, revealed areas of scientific concern that extended the discussion of U. S. EPA (2002) and the present OEHHA Draft. Important perspective on their review process includes the following: "Specifically, the committee will determine whether EPA considered all relevant literature (both supporting and non-supporting), consistently critiqued that literature, and then used appropriate scientific studies to develop its health risk assessment." The NAS committee will evaluate the animal studies used to assess human health effects from ingestion of perchlorate with particular attention to key endpoints, including changes in brain morphometry, behavior, thyroid hormone levels, and thyroid histopathology.

The current deliberations of the NAS Committee seem to be critically important to the decision-making process given the important role of U. S. EPA reviews in the OEHHA Draft. Lacking precise knowledge of the breadth of the University of California-managed review, the above issues may or may not be important concerns.

Table 1
Distribution of Perchlorate in Lettuce
Pilot Study

Samples	Whole Plant Above-Ground[a]	Total Wrapper Perchlorate	Amount Wrapper-Leaves	Wrapper Leaf Perchlorate	Total Head Lettuce Perchlorate	Amount Trimmed Head	Head Lettuce Perchlorate
24	1285 g	538,000 ng	487 g	15-102 ppb	287,000 ng	798 g	28 ppb

Krieger and Sanchez, 2003

Total perchlorate (nanograms)/Amount of sample (grams) = Parts per billion (ppb)

[a] Mass in grams of whole plant (wrapper leaves + head)
[b] Wrapper leaves are removed remain in field after harvest
[c] Trimmed heads are packed and shipped to market

Table 2
What is the potential perchlorate exposure?

Source	Daily Consumption	Level	Dose micrograms	Body weight (kg)	Dosage (ug/kg bw)
Water	2 liters	4 ppb (1 ug/liter)	8	70	0.11
Lettuce	56 g (cup)	28 ppb (ng/g)	1.6	70	0.02

Krieger and Sanchez, 2003

Table 3
Pilot estimates of lettuce and water perchlorate exposures of 70 kg person

Source	Consumption	Potential Exposure (ug/person-day)	Potential Dosage (ug/kg-day)
4 ppb water OEHHA Public Health Guidance	2 liters of water per day	8	0.11
1 ppb water Proposed /EPA		2	0.03
			0.02[a]
			0.056[a]
			0.02[a]

Krieger and Sanchez, 2003

[a] Amount perchlorate/kg-day: (ug perchlorate/kg lettuce x kg lettuce/day)/70 kg/person

Peer Review #2

12/15/03

Review of the OEHHA December 2002 Draft Public Health Goal for Perchlorate in Drinking Water

Introduction

I have been asked by the University of California Office of the President to review the December 2002 draft document, "Public Health Goal for Perchlorate in Drinking Water" from the Office of Environmental Health Hazard Assessment (OEHHA) (1). Although the draft document is very comprehensive, I will attempt to limit this review to my areas of expertise: epidemiology of human health data and the use of epidemiologic data in dose-response assessment and standard setting.

Summary opinions

- The 2002 Greer *et al.* study (2) is the most appropriate currently available study for assessing dose-response and establishing the public health goal for perchlorate.
- Many other studies on the human health effects of perchlorate involve study design issues that may hinder the interpretation of their results and their use in dose-response analyses.
- OEHHA should establish a single value for its PHG rather than a range of values.
- When using data from Greer *et al*., the benchmark dose (BMD) approach is preferred over the NOEAL approach.
- Data on body weight-water consumption ratio of infants should be used in the PHG calculations since this involves the more reasonably conservative approach.
- An uncertainty factor of 10 is appropriate for uncertainty due to inter-individual variability.
- An uncertainty factor of 3, rather than a value of 1 or 10, to account for limitations in the database requires further justification and discussion.
- A PHG of 2 ppb seems reasonably justified. A lower value may be appropriate if there is evidence that chronic exposures could cause significant non-NIS related health effects.
- OEHHA's identification of potentially susceptible populations represents an appropriate interpretation of the current literature.

Choice of the Greer *et al*. study

There is abundant evidence that thyroid deficiency can have severe health impacts, including important neurological effects in the developing fetus and infant (3-8). Although iodine deficiency may not be the only cause of hypothyroidism, and while the exact level of iodine deficiency that is required to cause thyroid disorders in different susceptibility groups may be subject to debate, iodine deficiency is clearly a risk factor for hypothyroidism.

It also seems clear that the major health effects of perchlorate are related to its effects on the thyroid gland, and inhibition of iodine uptake appears to be a critical early step in the mechanism by which perchlorate may cause adverse health effects. For this reason, it seems

appropriate to use studies of iodine inhibition in efforts to determine the levels of perchlorate consumption that are likely to pose no risk.

In my opinion, the 2002 Greer *et al.* study is the most appropriate for establishing the dose-response relationship between perchlorate and inhibition of iodine uptake (2). The advantages of this study are: 1. It takes place in humans rather than in laboratory animals, so extrapolations and uncertainty factors related to interspecies variation are not needed to predict human effects, 2. A clear and easily defined dose-response relationship is present in the Greer *et al.* data on iodine inhibition, 3. Given the clinical nature of the study, exposures are relatively well controlled and well described, and important potential confounding variables can be measured and controlled, and 4. The results presented in the Greer *et al.* study are consistent with those of other studies. In particular, the two studies by Lawrence *et al.* support the findings of Greer *et al.* (9, 10). For example, in Lawrence *et al.* 2000, subjects received 10 mg of perchlorate per day. This is roughly equivalent to 0.14 mg/kg-day given an average weight of 70 kg. Iodine uptake inhibition was 38%, which is reasonably close to the 45% inhibition seen in 0.1 mg/kg-day group of the Greer study. When plotting the dose-response curves of these studies, the dose-response curve of the subjects from the two Lawrence *et al.* studies appears to be a little higher than that of Greer *et al*. This is shown graphically in Figure 5 of the Greer *et al*. paper (2). However, it is important to note that the Lawrence *et al.* and Greer *et al.* studies involved different study subjects, as well as differences in dosing regimens, study personnel, and study facilities. Given these differences, the results of these two studies seem to be markedly consistent. The discussion by Greer *et al*. regarding the *ad libitum* consumption in Lawrence *et al.* seems to be a reasonably valid explanation for the relatively small difference seen in the results of these two studies. As a whole, it is my opinion that the Lawrence *et al.* studies are generally supportive of the dose-response findings of Greer *et al.*.

One of the primary disadvantages of using the Greer *et al.* study is the somewhat small sample size and low study power, although the size of this study is certainly comparable to many similar clinical investigations in humans. Another disadvantage of using this study is the need to extrapolate findings or add uncertainty factors to account for differences in susceptibility between healthy adults and potentially susceptible subpopulations. In my opinion, the advantages discussed above outweigh these disadvantages.

Many other studies have attempted to provide useful information on the dose-response relationship of perchlorate-related health effects. Several ecological studies have compared perchlorate levels in large public water supplies to thyroid testing results in newborns (11-15). However, based on the results of occupational, clinical, and animal studies, the exposure levels in most of the ecological studies seem much too low to expect to find effects using ecological exposure analyses. For example, in the study by Li *et al.*, perchlorate exposure in Clark County is described as 4.1 to 15 ppb during part of the study period and below 4 ppb during other parts of the study period (11). Exposure information is not described in any more detail than this. Individual exposure information was not collected. Thus, no information is known about individual drinking water consumption rates, use of bottled water, the use of water outside of the area of residence, or the use of private wells or other water sources that may or may not have perchlorate. Given the dose-response relationships seen in clinical and animal studies, the levels of exposure in this study are very low. Since non-differential errors in exposure assessment will generally bias results towards the null, one would expect that highly detailed information on exposure would be needed to detect any effect at these levels (16). Thus, given the use of

ecological exposure data, the large potential for exposure misclassification, and the relatively low levels of exposure, the negative findings in this study and similar investigations add little to our knowledge of perchlorate. On a side note, it would be interesting to see the details of the statistical power calculations that were performed in the planning stages of these studies.

The findings of the two low-dose population studies that did identify effects are also difficult to interpret. Questions have been raised about bias relating to the timing of thyroid testing and control for ethnicity in the Brechner *et al.* study (1, 14). The Schwartz study identified effects on T4 at exposures greater than 13 ppb and a possible dose response relationship at lower doses (13). This study is also not conclusive given the ecological exposure analyses and possible confounding.

Several occupational studies have also failed to identify links between perchlorate and potential health effects (17, 18). These studies provide some reassurance that occupational perchlorate exposures may not be causing detectable adverse health effects in most healthy workers. However, they provide no information on actual iodine inhibition and little information on health effects in potentially susceptible subgroups.

In summary, I feel that the Greer *et al.* study is currently the most appropriate database for dose-response analysis and agree with the OEHHA choice of this study in their PHG draft document. However, I think it is important to note that in both the Greer *et al*. and Lawrence *et al.* studies, subjects were normal healthy adults and did not include potential susceptible subpopulations.

Benchmark dose approach versus NOEAL approach

OEHHA provides two general methods for assessing dose-response and establishing a public health goal and uses these two methods to develop a PHG that involves a range of values from 2 to 6 ppb. I agree with the public comment from the Anaheim Public Utilities Department (comment #6) that a range of values could potentially lead to confusion among consumers and added difficulties for water agencies. The publication of a single number would be more appropriate and practical. For this reason, I feel that OEHHA should define a single risk assessment methodology to use in developing their final PHG. The most important factors with which to make this decision should be scientific validity and standard administrative policy. In my reading of the OEHHA PHG draft document, I did not see a thorough explanation of OEHHA policy or precedent on the use of the NOEAL and benchmark dose approaches. If such a policy or precedent is available, a little more discussion of this issue in the document is warranted.

Although I will not comment on the general scientific validity of the benchmark dose versus the NOEAL approaches as used by OEHHA, I think it is important to note a few important aspects of these approaches with regards to perchlorate and the Greer *et al.* data. That is, I do not agree with OEHHA's use of the 0.007 mg/kg-day dose as a NOAEL. One important finding from the Greer *et al*. study is the clear dose-response trend seen in iodine uptake inhibition. I don't believe it can be stated with any certainty that the lower dose in this study represents a NOAEL. At this exposure level for both the 8 and 24-hour uptake measures, iodine uptake on day 14 is lower in the 0.007 mg/kg-day dose group than in the control group. This is true when looking at the raw percentages as well as the percent of baseline. Granted, these differences are not statistically significant. However, given the obvious dose-response trend seen overall, this lack of statistical significance in the lowest exposure group is very likely a matter of

inadequate sample size and statistical power. The benchmark dose approach offers the advantage of taking into account information from all dose levels and the shape of the dose-response curve. The use of this approach also lessens the impact of sample size, dose selection, and variability compared to the NOEAL approach (19). The benchmark dose approach may be a little more difficult for the lay person to understand and reproduce. However, it is my opinion that, given the uncertainty in establishing a NOEAL from the Greer *et al*. study, and the added information on dose-response provided by the benchmark dose approach, the benchmark dose approach is the more valid method in this situation. This does not mean that other approaches should not be assessed. I feel OEHHA's presentation of a variety of approaches is very appropriate, and a failure to discuss and compare alternative methods would result in an incomplete assessment. However, it is my opinion that for the reasons given above, the benchmark dose approach is the more valid method and the NOEAL approach should be presented in the context that it is for comparison purposes only.

Regarding the specifics of the benchmark dose approach as used by OEHHA, I agree with the level of five percent inhibition as the BMD given the level of responses seen in the Greer *et al.* study. I also believe it is appropriate to use the 95% lower confidence interval of the BMD as the BMDL given the precedent for its use in many other risk analyses. The Hill model appears to fit the Greer *et al.* data well, although I would suggest a little more discussion on its selection and would consider presenting a comparison of this model with other models.

Body weight-water consumption (BW/WC) data

I commend OEHHA for presenting calculations using several different values for body weight-water consumption ratio. This is valuable for comparison purposes. However, I believe that it could be misleading to use the data in Table 29 to state "health-protective water concentrations derived from various exposure scenarios tend to converge around 2 ppb." The health-protective water concentrations for infants would be 0.74 ppb if the uncertainty factor for inter-individual variation were not decreased in this calculation. The explanation for lowering the uncertainty factor for inter-individual variation in the calculations for infants does not seem to be adequately justified. This may give some readers the perception that this factor was lowered simply to make the health-protective water concentration for infants consistent with that for pregnant women and lactating mothers. It may be that by using the BW/WC of infants, some of the uncertainty relating to intra-individual variation has been removed. But, how much? Is OEHHA attempting to state that by using the BW/WC of infants we have removed 67% [(10-3)/10 = 67%] of the uncertainty present in the calculations involving pregnant or lactating women? If so, this should be justified in a more thorough discussion.

In summary, I think reasonably good arguments could be made for using the BW/WC ratio for pregnant women, lactating women, or infants in determining the final PHG. My recommendation would be to use the value for infants (5.99 kg-day/L) since this is more reasonably conservative number. Regardless of which value is used for BW/WC however, I would recommend the uncertainty factor for inter-individual variation remain at 10 unless further justification is provided for using a different number based on established policy or scientific validity.

Uncertainty factors

Whenever reasonable, uncertainty factors should be based on formal written policy. This adds consistency, reproducibility and validity to standard setting processes.

The Greer *et al.* study involved healthy adults and therefore the results of this study may not represent the effects that may occur in susceptible subgroups. For this reason, I agree with OEHHA's application of an uncertainty factor of 10 for inter-individual variability. I do not however, see adequate justification for the additional uncertainty factor of 3 for database limitations. This factor is presumably applied to account for uncertainty in the use of subchronic exposure data to estimate effects that may be caused by more long-term intake. On page 80 of the draft document, it is stated that, "There is a possibility that long term adverse health effects not related to the NIS inhibition effect of perchlorate were not observed in the studies because of the short exposure and observation periods." If OEHHA has evidence to support this possibility, this research should be referenced in this section of the document. I am not an expert on immunotoxicity; however, based on the discussion presented on pages 29, 30 and 42 of the draft document, the evidence for a link between long-term low doses of perchlorate and significant immune effects is not convincing.

With regards to NIS-related health effects, in the 2002 EPA External Review Draft on perchlorate, it is noted on page 7-18 that BMDL estimates based on animal data decreased with duration over a 90 day period (20). This does suggest that the risks of certain health effects caused by perchlorate could become greater as the duration of exposure increases. However, it should be noted that the BMDL estimates referred to in the EPA document are based on effects such as colloid depletion and hypertrophy, not on inhibition of iodine uptake, the presumed precursor event (20). In contrast, the OEHHA risk assessment is based on a study of iodine uptake. For this reason, when assessing the impact of exposure duration on uncertainty in perchlorate dose-response assessment, the question is not whether the risk of an adverse effect such as colloid depletion or hypertrophy is associated with duration of exposure. Rather, the question is whether the inhibition of iodine uptake is related to exposure duration. There is some evidence in Greer *et al.* that iodine inhibition from short-term exposures is similar to that of longer-term exposures. That is, at all dose levels, inhibition on day 2 was similar to inhibition of day 14. This suggests that iodine uptake is inhibited very quickly after exposure begins and inhibition does not worsen as exposures continue. As noted in the EPA document, the health effects associated with this inhibition may worsen as exposure is prolonged and compensatory mechanisms begin to fail. But, presumably, if we can prevent the precursor event, iodine uptake inhibition, then we can prevent the subsequent health effects. Importantly, we do have data from occupational cohorts who have been exposed for many years. Although these studies involve healthy adult workers and not susceptible subgroups, they provide at least some evidence that long-term cumulative exposures do not lead to tremendously high risks of thyroid-associated disease.

As a whole, there appears to be at least some evidence that protective standards based on preventing the subacute effects on iodine uptake inhibition, as seen in the Greer *et al.* study, will prevent significant perchlorate-caused health effects. This would suggest that no additional uncertainty factor is needed for extrapolating from short-term to long term exposures. On the other hand, if OEHHA has evidence that long-term exposure may cause greater inhibition of iodine uptake than short-term intake, or that chronic exposure is related to non-NIS related health effects, this evidence should be referenced and an uncertainty factor should be applied. In this

case, I would recommend a factor of 10 based on precedent (19). If a factor of 3 is used, I would recommend that OEHHA reference a formal written policy, research on the scientific validity of this value, or adequate precedent.

There was some mention in the public comments about applying an additional uncertainty or safety factor of 10 given the potential neurological effects in children and the tremendous impact these types of effects could have on children and society as a whole. I agree that the effects of hypothyroidism on fetal and infant development are extremely important and well documented. However, I believe this additional factor is probably not needed. By using the Greer *et al.* results, the calculation of the PHG in the OEHHA document is based on an effect that is not a direct adverse health event, but rather a precursor to an adverse health event. Based on the literature I have reviewed, it appears that there may be a substantial gap between the lowest level of perchlorate that inhibits iodine uptake and the level that will lead to hypothyroidism. Granted, this gap may be larger in some people than others, this is why the uncertainty factor of 10 has been applied for inter-individual variation. Regardless, whatever gap does exist between inhibition of iodine uptake and the development of disease offers at least some additional conservatism in the PHG calculations by OEHHA. Others areas of conservatism in the OEHHA PHG are the use of the 95% BMDL, the use of the BMD_{05} rather than a BMD_{10} or a standard deviation approach, the use of the 95^{th} percentile for the WC/BW in susceptible populations, and the rounding down of the final health protective water concentration number.

In summary, in my opinion, there is adequate precedent for using an uncertainty factor of 10 for inter-individual variability. In addition, there appears some evidence that the effects from long-term and shorter-term exposures on iodine uptake inhibition are similar and OEHHA should consider removing the second uncertainty factor of 3. If there is evidence of greater effects on iodine uptake inhibition as exposure duration continues past 14 days, this evidence should be presented in this context. If an uncertainty factor is applied for database limitations or sub-chronic to chronic exposures, further justification for a factor of 3 should be given or an uncertainty factor of 10 should be considered.

Justification for a PHG of 2 ppb

Based on the discussion presented above, I feel there is adequate justification for a PHG of 2 ppb. As presented in the OEHHA draft document, a dose-response analysis based on the Greer *et al.* data can be used to estimate a BMDL of 0.0037 mg/kg-day. Using an uncertainty factor (UF) of 10 for inter-individual variation and the BW/WC of 5.99 kg-day/L for infants:

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

$$C = \frac{0.0037 \text{ mg/kg-day} \times 1.0 \times 5.99 \text{ kg-day/L}}{10}$$

C = 2.2 mg/L, rounded to 2 ppb

I think it is important to note that given the uncertainty factor of 10 applied for interspecies uncertainty in the EPA external review document on perchlorate, a PHG of 2 ppb is very close to the hypothetical EPA DWEL calculated using a weight of evidence approach and animal data

(20). The calculation of a similar numbers using dramatically different data and dramatically different methods strengthens the validity of this value.

Several of the public comments I reviewed referred to possible biases relating to differences between coronal and sagittal cuts in the data on brain morphology used in the EPA risk assessment on perchlorate. While I am not an expert in this area, I think it is important to note that the EPA risk assessment is not based on one single outcome measure, but on a variety of different outcomes and effects. I am also not an expert on the absorption of chemical agents into food and therefore do not feel qualified to comment on the relative source contribution figures used by OEHHA or the US EPA study of perchlorate levels in food.

Susceptible sub-populations

In the draft document, OEHHA identifies three potentially sensitive sub-populations: 1. Pregnant women who may be iodine deficient, 2. Fetuses of these pregnant women, 3. Individuals suffering from hypothyroidism. I agree with the OEHHA interpretation of the data on the increased potential for perchlorate toxicity in these groups. Based on my review of the relevant literature, there is clear evidence that perchlorate inhibits iodine uptake, iodine deficiency causes hypothyroidism, and mild to moderate hypothyroidism can cause important neurological effects in the developing fetus and infant. Thus, there is a high degree of biologic plausibility that perchlorate could cause or worsen hypothyroidism and lead to neurodevelopmental effects in humans. In the public comments I have reviewed, it has been argued that the levels of perchlorate that cause mild to moderate inhibition of iodine uptake are substantially lower than those that might cause hypothyroidism and subsequent neurodevelopmental effects. While this may or may not be true, given the seriousness of the effects being discussed (decreased IQ, for example) it seems prudent to allow a wide margin of safety when setting drinking water goals for perchlorate. Given the logical connection between perchlorate, diminished iodine uptake, hypothyroidism, and thyroid-related health effects, it also seems reasonable to assume that people who are iodine deficient or clinically or subclinically hypothyroid may be more susceptible to the effects of perchlorate than people who are healthy. For this reason, I agree with OEHHA's interpretation of the current literature in defining susceptible subpopulations.

In several of the public comments, it has been argued that the United States is not an iodine deficient population. These comments appear to be based primarily on the results of urinary iodine excretion from NHANES III (21). In this study, 11.7 percent of subjects had urinary iodine levels in spot samples of less than 5 ug/dl. Based on the large intra-individual variability of urinary iodine excretion and the WHO criteria for defining iodine deficient populations, it has been argued in several of the public comments that the United States is not an iodine deficient population. In my opinion, this argument is irrelevant. I agree that spot urine samples can not be used to determine the exact proportion of iodine deficient people in a particular community. The paper by Andersen *et al.* provides an example of the large intra-individual variation that can occur in iodine excretion (22). However, the Andersen *et al.* results were based on only sixteen healthy men in a somewhat narrow age window (ages 24-53). It seems likely that in a much larger study, one in which there was greater variability in health status, gender, age, diet, and other lifestyle factors among study subjects, the variability in both spot samples as well as daily average levels would also become greater. I agree that given the variability in urinary iodine excretion over time, we can not say that 11.7 percent of the population are iodine deficient. However, population averages or percentiles are not a direct

reflection iodine status of each individual within the population. Thus, we can not say that based on the NHANES III data that each and every person in this country has an adequate iodine intake. More likely, at least some fraction of our population is iodine deficient, and this fraction probably lies somewhere between 0 and 11.7 percent. It was also implied in at least one of the public comments that iodine deficiency is not seen in pregnant women in this country due to the widespread use of prenatal nutritional supplements. I agree that the percentage of pregnant women in this country on prenatal vitamins is probably very high, but I have not seen convincing data that it is 100%.

While on the topic of iodine deficiency, I think it is important to note that there was a 50% fall in mean urinary iodine excretion in the twenty-year period between NHANES I and NHANES III. Four times as many people had urinary iodine levels below 5 ug/dl in NHANES III (14.9%) than in NHANES I (3.9%) (21). In pregnant women, these percentages were 6.9% in NHANES III and 1.0% in NHANES I. Although there is some evidence from NHANES 2000 that this downward trend has ended (23), the overall decline in the last few decades raises concern that a fairly large number of people in the US may be iodine deficient. It has also been reported using NHANES III data that 4.3 percent of the US population may be subclinically hypothyroid (24). While the majority of these cases may not be due to iodine deficiency, these data provide additional evidence that a large population of potentially susceptible people could exist in this country.

According to the draft document, OEHHA must consider the existence of groups in the population that are more susceptible to adverse effects of contaminants than a normal healthy adult. In my opinion, the dramatic decrease in iodine excretion over the last two decades and the large fraction of subjects identified in NHANES who have subclinical hypothyroidism raises concern that the number of people that may be susceptible to the inhibitory effects of perchlorate on iodine uptake is not trivial.

Summary

In conclusion, overall, I believe that the revised risk assessment is based on sound scientific knowledge, methods and practices. For the reasons given above, I agree with OEHHA's choice of the Greer *et al.* study and the benchmark dose approach for dose-response analysis. I also believe that OEHHA's identification of potentially susceptible populations represents an appropriate interpretation of the current literature. I recommend that OEHHA should choose a single value for its public health goal rather than a range of values. Using the more conservative body weight-water consumption ratio and an uncertainty factor of 10 for inter-individual variation, the BMDL based on the Greer *et al.* data corresponds to a health protection concentration of 2 ppb. It is my opinion that this value is consistent with the principles of a PHG as defined by the California Safe Drinking Water Act of 1996 (Health and Safety Code, Section 116365c).

References

1. Office of Environmental Health Hazard Assessment. Public Health Goal for Perchlorate in Drinking Water (Draft): Pesticide and Environmental Toxicology Section. California Environmental Protection Agency, 2002.

2. Greer M, Goodman G, Pleus R, Greer S. Health effects assessment for environmental perchlorate contamination: the dose-response for inhibition of thyroidal radioiodine uptake in humans. Environ Health Perspect 2002;110:927-37.
3. Pop V, Kuijpens J, van Baar A, et al. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol 1999;50:149-55.
4. Pop V, Brouwers E, Vader H, Vulsma T, van Baar A, de Vilder J. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol 2003;59:282-8.
5. Rovet J, Ehrlich R, Sorbara D. Intellectual outcome in children with fetal hypothyroidism. J Pediatr 1987;110:700-4.
6. Haddow J, Palomaki G, Allan W, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. New Engl J Med 1999;341:549-55.
7. Klein R, Sargent J, Larsen P, Waisbren S, Haddow J, Mitchell M. Relation of severeity of maternal hypothyroidism to cognitive development of offspring. J Med Screen 2001;200:18-20.
8. Glorieux J, Dussault J, Morissette J, Desjardins M, Letarte J. Follow-up at ages 5 and 7 years on mental development in children with hypothyroidism detected by Quebec Screening Program. J Pediatr 1985;107:913-8.
9. Lawrence J, Lamm S, Braverman L. Low dose perchlorate (3 mg daily) and thyroid function. Thyroid 2001;11:295.
10. Lawrence J, Lamm S, Pinto K, Richman K, Braverman L. The effect of short-term low-dose perchlorate on various aspects of thyroid function. Thyroid 2000;10:659-63.
11. Li Z, Li F, Byrd D, et al. Neonatal thyroxine level and perchlorate in drinking water. JOEM 2000;42:200-5.
12. Li F, Byrd D, Deyhle G, et al. Neonatal thyroid stimulating hormone level and perchlorate in drinking water. Teratology 2000;62:429-31.
13. Schwartz J. Gestational exposure to perchlorate is associated with measures of decreased thyroid function in a population of California neonates (thesis). Berkeley: Unviversity of California, 2001.
14. Brechner R, Parkhurst G, Humble W, Brown M, Herman W. Ammonium perchlorate contamination of Colorado River drinking water is associated with abnormal thyroid function in newborns in Arizona. JOEM 2000;42:777-82.
15. Crump C, Michaud P, Tellez R, et al. Does perchlorate in drinking water affect thyroid function in newborns or school-age children? JOEM 2000;42:603-12.
16. Rothman K, Greenland S. Modern Epidemiology. Philadelphia: Lippencott-Raven, 1998.
17. Lamm S, Braverman L, Li F, Richman K, Pino S, Howearth G. Thyroid health status of ammonium perchlorate workers: a cross sectional occupational health study. JOEM 1999;41:248-60.
18. Gibbs J, Ahmad R, Crump K, et al. Evaluation of a population with occupational exposure to airborne ammonium perchlorate for possible acute or chronic effects on thyroid function. JOEM 1998;40:1072-82.

19. Crump K, Allen B, Faustman E. The Use of the Benchmark Dose Approach in Health Risk Assessment. Washington DC: Risk Assessment Forum. Environmental Protection Agency, 1995.
20. EPA. Perchlorate Environmental Contamination: Toxicological Review and Characterization. External Review Draft. Washington DC: Environmental Protection Agency, 2002.
21. Hollowell J, Staehling N, Hannon W, et al. Iodine nutrition in the United States. Trends and public health implications: iodine excretion data from National Health and Nutrition Examination Surveys I and III (1971-1974 and 1988-1994). J Clin Endocrinol Metabol 1998;83:3401-8.
22. Andersen S, Pedersen K, Pedersen I, Laurberg P. Variations in urinary excretion and thyroid function. A 1-year study in healthy men. Eur J Endocrinol 2001;144:461-5.
23. NHANES 2000. http://www.cdc.gov/nchs/products/pubs/pubd/hestats/iodine.htm.
24. Hollowell J, Staehling N, Flanders D, et al. Serum TSH, T4, and thyroid antibodies in the United States population (1988-1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metabol 2002;87:489-99.

Peer Review #3

Review of the Revised Draft Public Health Goal Document for Perchlorate in Drinking Water.

I have reviewed the document prepared December, 2002 by OEHHA. I also reviewed the other material provided to me including the extensive statements by various interested parties. I read carefully all of the source material which I cite below. Please note that there is redundancy in the charge given to me for my review that is shown in the headings in **bold type** below. As a consequence, there is some redundancy in my statements, although I tried to limit it.

I obtained additional background material during my recent participation in the Perchlorate Symposium (Sept. 29-Oct.1, 2003) organized by the University of Nebraska Center for Toxicology. My role was to be an expert reviewer.

I have no financial or other ties with industry or with environmental groups in regard to perchlorate or related issues. The views expressed below are my own.

1. **Review of the information presented, including but not limited to data on perchlorate toxicity, thyroid hormone regulation, and effects of iodine deficiency on pregnant women and their fetuses.**

The Introduction is an excellent summary of thyroid physiology relevant to maternal-fetal relationships and effects of thyroxine deficiency on the fetus. The material on perchlorate pharmacokinetics and toxicology provides an appropriate background for developing policy on the public health goal (PHG). Table 6, page 32 provides typical relevant data showing the inhibitory effect of perchlorate on iodide uptake in rats. The studies of the Argus Research Lab in regard to neurotoxicity have been severely criticized in comments by interested parties and in the University of Nebraska Perchlorate Symposium. However, many studies show that induction of hypothyroidism in animals can lead to detrimental alterations in brain morphology in rats. It is likely that perchlorate in suitable doses could result in the same detrimental effects.

The section on carcinogenicity does not provide any convincing data that perchlorate is a carcinogen. Follicular cell hyperplasia is a consequence of a TSH-stimulated thyroid gland secondary to iodine deficiency. Thyroid gland enlargement, including benign adenomas, is a consequence of TSH stimulation secondary to hypothyroidism induced by chronic perchlorate treatment in animals. Benign adenomas are not precursors to carcinomas. In essence, no data are presented that show perchlorate, by itself, is a carcinogen.

The various studies of thyroid function in newborns, based on T4 and TSH screening data in infants born to mothers in areas with different perchlorate exposure, yield contradictory results and have many flaws, in part because they are all retrospective. The Schwartz data shown on page 37, based on her M.S. thesis, are not published in a peer-reviewed journal. The correlation

of low T4 with increasing perchlorate exposure is impressive, but the fact that perchlorate measurements were not made at the time of gestation is a serious flaw.

Another positive study by Brechner (2000), who found higher TSH in newborns in Yuma with high perchlorate exposure compared with Flagstaff that has lower exposure, has been criticized because of possible sampling issues and lack of direct perchlorate measurements. This work is balanced by the negative studies of Li and Lamm in Nevada who found no association of low newborn blood T4 level with perchlorate exposure. However, low T4 is probably a less sensitive indicator of minimal hypothyroidism than is serum TSH.

The study of Crump et al (2000) showed that there was no alteration of thyroid function or incidence of congenital hypothyroidism in Taltal, Chile where the tap water contained 100-120 ppb perchlorate compared with two other regions of Chile with low or no perchlorate in the water. The draft omits the data of Table 2 in the paper which reported that urine iodine is 947 mcg/g creatinine in Taltal and similar in the comparison areas. These urine iodine data indicate that iodine intake was very high, about 5-fold increased compared with urine iodine in the United States. Such a high iodine intake would overcome the potential effect of perchlorate on inhibition of thyroid function.

Older studies showed that perchlorate in doses of 100 to 1000 mg significantly lowered thyroid radioiodine uptake in humans. Doses in this range controlled the hyperthyroidism of Graves' disease. In the last few years, studies with smaller amounts of perchlorate have been performed to determine the threshold for its effect on reducing radioiodine uptake. Doses of 3 mg or 1.4 mg in adults had significant but small effects. Extrapolation of the dose response data in the Greer study (2002), regarded as the best study, showed a no-effect dose of ~6 mcg/kg/day or 420 mcg in a hypothetical typical adult. The study of Greer (2002) showed that the results with two days of perchlorate were similar to those with 14 days of perchlorate treatment. Presumably a longer duration of perchlorate ingestion would not result in a greater effect in regard to inhibition of thyroid uptake. This work and a similar study showed no effect of perchlorate on serum TSH or T4, but the duration of these studies is insufficient to deplete the thyroid gland's store of thyroid hormone in euthyroid individuals.

The draft contains an excellent summary of the literature on thyroid function in pregnancy, pointing out the dangers of low iodine intake in pregnancy that could result in maternal goiter and hypothyroxinemia. There are appropriate summaries of the relevant rat data from the Escobar group. However, the excellent studies of Hetzel on low iodine intake in pregnant sheep resulting in altered brain morphology of the fetus and newborn are not described:

Potter BJ, Mano MT, Belling GB, McIntosh GH, Hua C, Cragg BG, Marshall J, Wellby ML, Hetzel BS. Retarded fetal brain development resulting from severe dietary iodine deficiency in sheep. Neuropathol Appl Neurobiol. 1982 Jul-Aug;8(4):303-13.

Hetzel BS, Chavadej J, Potter BJ. The brain in iodine deficiency. Neuropathol Appl Neurobiol. 1988 Mar-Apr;14(2):93-104. Review.

The review of human data showing that maternal hypothyroidism can result in reduced thyroid function is appropriate. The data of Haddow (1999) are especially important. The work of Pop et al (1999) has recently been extended in a new study showing that children of women who had low free T4 at 12 and 24 weeks gestation had developmental delay at 2 years of age (Clinical Endocrinology (2003; **59:** 282–288).

2. **The appropriateness of the approach used in developing the revised draft PHG, including but not limited to: (a) identifying the pregnant women and their fetuses, and people with compromised thyroid function as the sensitive sub-populations; and (b) identifying the inhibition of thyroid iodide uptake in human studies as the critical end-point for both non-carcinogenic and carcinogenic health effects.**

The most vulnerable population is the fetus. The fetal thyroid gland does not begin to function until 10 to 12 weeks of gestation. During the second trimester, the fetal thyroid is functioning, but maternal thyroxine also plays a significant role in the fetus. During the third trimester when the fetal nervous system continues to develop, thyroxine production by the fetus is the main source for its thyroid hormone. To synthesize thyroid hormone, the fetus obtains iodide transported across the placenta from the mother. During the second and third trimesters, perchlorate ingestion by the mother along with low iodine intake could subject the fetus to the consequences of insufficient thyroid hormone. Unfortunately, there are no human prospective studies that directly study this problem. However, there are extensive animal studies, as noted above, and studies in human populations with severe iodine deficiency that support these conclusions.

A study of deceased preterm and term infants showed that their thyroid glands have only small stores of thyroxine in thyroglobulin, the storage protein in the colloid of the thyroid gland (van den Hove MF, Beckers C, et al. Biochimie 1999; 81: 563-70). These investigators estimated that the turnover of the thyroxine pool of these thyroids is 100%/day. Because of high turnover within the fetal preterm and term thyroid, iodide depletion could lead to deficient hormone secretion very readily compared with the adult. (Note that the adult human thyroid in regions of iodine sufficiency has a two to three month reservoir of thyroid hormone.) Depletion of fetal thyroxine could result in deficient neurological and cognitive development.

See the comment in 1 on the lack of data showing carcinogenic effects of perchlorate. It is not a carcinogen.

3. **Data evaluation and interpretation: Identification of key studies and the use of human data in dose-response assessment. Do the data support the conclusions?**

In the discussion of dose-response assessment and the iodine intake in pregnancy, the review of Glinoer in Thyroid 2001 is cited appropriately. The NHANES 3 study shows that there is iodine deficiency in women of the age for pregnancy in the USA. Although I am not familiar with the BenchMark Dose Software or the Hill model, the BMD and the BMDL seem

reasonable and provide a significant safety factor by exaggerating this lower limit. The discussion of potential carcinogenic effects is appropriate for "completeness", but is not meaningful, as noted above. Carcinogenic effects are not a basis for calculation of a PHG for perchlorate.

In regard to the calculation of the PHG, I agree with the use of BMDL. The relative source contribution (RSC) of 80% allows for 20% intake of perchlorate through possible foodstuffs which seems to provide another safety factor that is reasonable. The body weight/water consumption (BW/WC) of 25.2 kg/day/L for ratio of body weight and water consumption is at the 95th percentile, and thus again provides a safety margin.

The rationale for the uncertainty factor (UF) of 30 is not effectively justified. I think it is more reasonable to use a factor of 4 for inter-individual variability in a human database. Since data are available for this calculation, I see no rationale for adding another factor of 3 for limitations of the database. Therefore, I recommend using a UF of 4. The PHG calculation then becomes 3.7,kg-day x 0.8 x 25.2 kg-day/L x 1/4. **This leads to a concentration of 18.6 mcg/L as the PHG.**

4. **The appropriateness of identifying pregnant women and their fetuses, and people with compromised thyroid function as the sensitive sub-populations. Are there other sub-populations that may be equally or more sensitive to perchlorate exposure than those identified?**

I believe that the fetus represents the most vulnerable segment of the population. This implies that pregnant women are the target population for the PHG. The basis for this conclusion is that hypothyroidism in the mother may result in reduced cognitive function of the child. Therefore, maternal hypothyroidism and low iodine intake must be avoided.

In regard to other potential vulnerable populations, none have been clearly identified. The effect of perchlorate is likely to be much stronger in regard to depletion of iodide stores in individuals with low iodine intake. Although the USA is not a region of low iodine intake, there are individuals with marginal iodine intake, as identified in NHANES 3 (see above).

In theory, patients with compromised thyroid function, such as those with untreated subclinical hypothyroidism, may be affected more readily by significant perchlorate ingestion. This size of this group increases with aging and becomes 5 to 15% of the elderly population. Exacerbation of the thyroid condition could lead to adverse consequences, such as the development of overt hypothyroidism with increased cardiac morbidity and mortality. However, worsening hypothyroidism in this group could be detected by screening and corrected with thyroxine therapy, thus avoiding the consequences. The adverse effects of hypothyroidism occur slowly in adults and can be corrected completely. Therefore, I consider that the consequences of perchlorate exposure in this population are not as severe as those in the fetus.

5. **Other major and critical information that needs to be considered which might affect the estimates of impacts on public health.**

The NHANES 3 study documented that a small proportion, about 6%, of pregnant women have a low iodine intake (Hollowell, 1998). Public health measures should also include adequate iodine intake during pregnancy, preferably a supplement of 200 micrograms iodine per day. This should negate any potential effect of perchlorate on inhibition of thyroxine synthesis in both mother and fetus. It is likely that maternal ingestion of 30 liters of water containing perchlorate at 15 mcg per liter would be overcome by the additional iodine intake because this intake of perchlorate is below the BMDL cited above. It should be noted that patients with excessive water intake due to untreated diabetes insipidus do not ingest even half of this volume of water/day.

6. The appropriateness of identifying and quantifying the uncertainties in the PHG calculation.

Because the fetal thyroid gland has only a small reservoir of thyroid hormone, it is more vulnerable to iodine depletion than the adult thyroid. Adequate maternal iodine ingestion provides the fetus with iodine. I have noted above the issues that require assuring the fetus has adequate iodine intake and that thyroid hormone production in pregnant women is not compromised. It is reasonable that safety factors be built into the PHG. The use of a BMDL calculation is an attempt to make sure that a significant quantity of perclorate will not be ingested. The RSC has a safety factor by assuming that perchlorate can be ingested in food rather than water alone. The BW/WC is set for 95th percentile of tap water intake despite the extensive use of bottled water in the population currently.

The uncertainty factor consists of two components. First, a component of 10 for inter-individual variability. The principal rationale for this, as I see it, is that pregnant women were not studied in the benchmark study of Greer (2002). Pregnant women have increased renal iodide excretion so they are more vulnerable. This vulnerability is far less than would be accounted for by a factor of 2. Including another factor of 2 provides an additional safety margin. Therefore, a UF of 4 seems reasonable.

The second component of UF accounts for limitations of the database. Although ideal studies have not been performed yet and additional studies are highly desirable, especially long-term human studies, there are data in prospective short-term human and longer-term animal studies that are not widely discrepant. The retrospective epidemiologic data are discrepant, but do not clearly show significant consequences of perchlorate exposure. Because of these reliable, short-term human and animal prospective studies, I do not believe that an additional uncertainty factor of 3 is justified.

Using the parameters noted above, the calculation results in a PHG perchlorate of 18.6 mcg/L (see section 3, also).