

POSITION PAPER OF THE PERCHLORATE STUDY GROUP¹ CONCERNING
REVISION OF THE PERCHLORATE PUBLIC HEALTH GOAL
TO ADOPT SCIENTIFIC FINDINGS OF THE NATIONAL ACADEMY OF SCIENCES

This paper is submitted by the Perchlorate Study Group, to present views regarding revisions to the Perchlorate Public Health Goal to adopt scientific findings of the National Academy of Sciences Report on the Health Effects of Perchlorate.

In March 2004, The Office of Environmental Health Hazard Assessment (“OEHHA”) issued a Public Health Goal (“PHG”) Support Document. OEHHA prefaced its discussion of the support document with a statement that the evaluation of perchlorate risk by an expert committee of the National Academy of Sciences (“NAS” or “NAS Committee”) -- then ongoing -- was “an important undertaking that may help guide efforts to study the health effects of perchlorate.” Recognizing that the NAS Committee’s conclusions should resolve some existing uncertainties, OEHHA committed to “carefully review the NAS conclusions . . . and revise the PHG as necessary” when the NAS evaluation was completed, citing its obligations under Health and Safety Code section 116365(e)(1). That code section defines the criteria to be used in setting a PHG.

The NAS Committee’s Report, “Health Implications of Perchlorate Ingestion” (“NAS Report”) was published in January 2005.² Although the NAS Report was directed to a review of

¹ Participating in this position paper are the member companies of the Perchlorate Study Group, with the exception of Lockheed Martin Corporation.

² The NAS Committee was made up of 15 of the country’s leading authorities in the field, including experts in toxicology, teratology, veterinary pathology, neurotoxicology, reproductive toxicology, biological monitoring,

the United States Environmental Protection Agency (“EPA”)’s perchlorate risk assessment, not OEHHA’s, it necessarily addressed the same issues faced by OEHHA in developing a PHG for perchlorate. In fact, NAS endorsed a number of OEHHA’s decisions, including important issues on which OEHHA had diverged from EPA’s risk analysis.³ However, in a few important respects, the NAS Committee differed with OEHHA’s analysis.⁴ In addition, as anticipated, the NAS report resolves a number of scientific issues existing at the time OEHHA issued its PHG. The resolution of these issues has provided greater certainty about application of the statutory criteria for setting a PHG.

The Perchlorate Study Group therefore respectfully requests that: (1) OEHHA now revise its PHG to reflect the NAS Report’s findings; and (2) requests that OEHHA, in accordance with its prior public commitment, look to the conclusions of the NAS in applying the statutory criteria of Health and Safety Code section 116365. Application of the NAS findings to the statutory criteria would, after adjustment for source contribution, result in a revised PHG of 236 ppb (the no effect level minus source contribution).⁵ No further adjustment for sensitive subpopulations or variation in body weight is legally or scientifically justified given the highly health protective

statistics, epidemiology, pediatric endocrinology, pediatrics, medical endocrinology and biostatistics. It conducted four public hearings around the country, at which it heard testimony from additional experts and from the public. In reaching its conclusions, it evaluated all of the current science.

³ Among the points on which the NRC Committee and OEHHA approaches agree are 1) rejection of the animal studies relied upon by U.S. EPA; 2) a preference for human over animal data for estimating human health risks from perchlorate; 3) reliance on Greer *et al.* (2002) as the critical study; and 4) the scientific judgment that the most sensitive population is the pregnant woman and her fetus.

⁴ Significant differences between the two assessments include: 1) OEHHA used a point of departure corresponding to an estimated five percent chance of a five percent decrease in mean radioactive iodine uptake by the thyroid, based on the lower limit of a one-sided 95 percent confidence interval on the benchmark dose (BMD), a dose approximately one-half as great as the no observable effect level (NOEL) dose from the Greer *et al.* study; 2) OEHHA describes iodide uptake inhibition as an “undesirable” effect, a term without meaning in regulatory toxicology; 3) OEHHA in fact interprets this “undesirable” effect as an adverse effect, while the NRC Committee concludes that, “inhibition of iodide uptake by the thyroid clearly is not an adverse effect” and states that “if it does not occur, there is no progression to adverse health effects...”, NAS Report p. 111; and 4) OEHHA considers transient changes in thyroid hormone as adverse effects, while the NRC Committee clearly concluded that transient changes in serum thyroid hormone or TSH concentrations are not adverse health effects but normal adaptive phenomena. NAS Report p. 8.

⁵ See pages 12, 13, *infra* for discussion of derivation of source contribution.

basis for the 236 ppb number. Nevertheless, if such further adjustments were made, a calculation based on actual source and weight/consumption data would produce a PHG of 167 ppb, while alternatively, adjustment based on application of the super-protective 10-fold safety factor used by NAS would produce a PHG of 16 ppb.

OVERVIEW OF PERCHLORATE

Perchlorate is both a naturally occurring and man-made ion used to form a variety of salts. Ammonium perchlorate (NH_4ClO_4), the most common form, has been widely used for decades as a constituent of propellants. Perchlorate production continues today, primarily for use as an oxidizer in solid rocket fuel and other propellants. Other forms of perchlorate have been used as fertilizers and growth promoters in leguminous plants. Perchlorate is often present in Chilean nitrate fertilizer, which has been used more recently in cultivating organic produce. Perchlorate salts are also components of air bag inflators, certain fabrics and dyes, and have been used in rubber manufacture and in the production of paint and enamels. Medically, perchlorate is used to diagnose defects in thyroid hormone synthesis.

Perchlorate is also believed to occur naturally in the United States and around the world. It has been detected in groundwater aquifers in the United States (*e.g.*, west Texas) at concentrations approaching 40 ppb, despite the absence of an industrial, Department of Defense, or agricultural source. Furthermore, perchlorate is being found in food or beverage products, such as bottled water,⁶ even though there is no source link between these products and perchlorate makers or users.

⁶ United States Food and Drug Administration, Center for Food Safety and Applied Nutrition, Perchlorate Questions and Answers, available at <http://vm.cfsan.fda.gov/~dms/clo4qa.html>.

STATUTORY BASIS FOR DEVELOPMENT OF PUBLIC HEALTH GOALS

The process and criteria for setting a PHG is specifically described in the California Safe Drinking Water Act. Cal. Health & Safety Code §§ 116365 *et seq.* In most significant part:

- OEHHA is required to “conduct a risk assessment using the *most current principles, practices and methods* used by public health professionals who are experienced practitioners in the fields of epidemiology, risk assessment and toxicology.” (emphasis added). Cal. Health & Safety Code § 116365(c).
- OEHHA must determine the level of the contaminant in drinking water that is not anticipated to cause or contribute to adverse health effects, or that does not pose a significant risk to human health.
- It must consider susceptible subgroups such as children and contributions from other sources.
- Finally and most importantly, the statute unambiguously specifies the level at which the PHG is to be set after taking these factors into account:

“If adequate scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the public health goal should be set at that threshold.”

APPLYING THE NAS FINDINGS TO OEHHA’S RISK ASSESSMENT AND PHG

California Health and Safety Code section 116365(c)(1)(D) specifies that “if adequate scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the public health goal should be set at that threshold.” The NAS Report authoritatively and clearly identifies the level at which there is no adverse effect (“NOAEL”) based on “the most current principles, practices and methods used by public health professionals who are

experienced practitioners in the fields of epidemiology, risk assessment and toxicology.” That level is at least 0.4 mg/kg-day.⁷ The NAS Report also identified the level at which there is no effect at all from perchlorate ingestion.⁸ That no effect level (“NOEL”) is 0.007 mg/kg-day.⁹

It is standard risk assessment practice to use the NOAEL, with some adjustment for uncertainty, as the point of departure for deriving the PHG; and that is, as well, what the California Safe Drinking Water Act requires.¹⁰ Indeed, the use of the NOAEL as the point of departure is a well-established tenet of regulatory toxicology.¹¹ EPA’s universal policy for health risk assessment is to derive the reference dose from the NOAEL. OEHHA follows a

⁷ “[I]t is highly likely that in people with a normal iodide intake the dose of perchlorate would have to reduce thyroid iodide uptake by at least 75% for a sustained period (several months or longer) for iodide uptake and thyroid hormone production to decline enough to cause adverse health effects (equivalent to reducing dietary iodide intake by 75%). In adults, that is likely to require sustained exposure to **more than 30 mg of perchlorate per day (0.4 mg/kg per day for a 70-kg person)**, on the basis of the clinical studies in healthy subjects and the studies of long-term treatment of hyperthyroidism, both described in this chapter, and the studies of environmental exposure, described in Chapter 3 (Gibbs *et al.* 1998; Lamm *et al.* 1999; Crump *et al.* 2000).” NAS Report, page 44. “The perchlorate dose required to cause hypothyroidism in adults would probably be more, and substantially more, than .4 mg/kg-day.” Dr. Richard Johnston, Presentation at “Perchlorate Impacts to Water Utilities”, American Water Works Association Webcast (Feb. 9. 2005) Thus, NAS has effectively defined the no adverse effect level for healthy adults at 0.4 mg/kg per day, or 14,000 ppb.

⁸ The NOEL is the highest dose “at which there are no statistically or biologically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control” (ITER 2004). Thus, a NOAEL is based on an adverse effect, and a NOEL is based on a nonadverse effect.” NAS Report p. 113.

⁹ “The study identified a no-observed-effect level (NOEL) for inhibition of iodide uptake by the thyroid at 0.007 mg/kg per day.” NAS Report p. 113. The NOEL value from Greer *et al.* (2002) is consistent with other clinical studies that have investigated iodide uptake inhibition by perchlorate.

¹⁰ EPA defines “point of departure” as the dose selected as the starting point to which uncertainty factors are sometimes applied to derive a “safe” dose. This starting point is typically the no observed adverse effect level (NOAEL) or the lowest observable adverse effect level (LOAEL). A review of OEHHA’s PHGs reveals that the points of departure for all of them is either the NOAEL or LOAELs. It should be noted, however, that PHGs before 1999 were (mis-)labeled by OEHHA as “NOELs,” even though they actually were based on the NOAEL. In 1999, OEHHA decided to use the correct designation, NOAEL, in order to eliminate the internal confusion that had been caused by references to the PHGs as NOELs before 1999, even though they were NOAELs or LOAELs by current standards.

¹¹ Casarett and Doull’s Toxicology (6th ed.) documents standard practice in federal and state regulatory toxicology: the point of departure should be “the significant adverse biological effect that occurs at the lowest exposure level” (p. 92), which it identifies as the No Observed Adverse Effect Level (NOAEL). This is also the standard practice of OEHHA. R. Howd, *Can We Protect Everybody from Drinking Water Contaminants?*, Int’l J. of Toxicol., v.21, pp. 389-95 (2002).

similar policy: In accordance with California law, *all* prior California PHGs have been based on no *adverse* effect levels as points of departure.¹²

Thus, the “safe dose-response threshold” called for by section 116365 is arguably the 0.4 mg/kg-day level identified by NAS as the one at which there is *no adverse effect*. However, the NAS also recognized that, because the 0.4 mg/kg-day level is based on studies of healthy adults, the safe dose for especially vulnerable populations may be lower than the 0.4 mg/kg-day NOAEL identified by NAS; but there is no scientific, logical or legal basis or precedent for setting the safe dose-response threshold below the *no effect* level. Rather, a conservative (highly health protective) view is that the safe dose-response threshold occurs at some point between the NOEL of 0.007 mg/kg-day and, with adjustments for any uncertainties in the data, one tenth of the adverse effect level -- .04 mg/kg-day. Using standard body weight/water consumption assumptions, this translates to a concentration level between 245 ppb and 1,400 ppb. The “safe dose-response threshold” for perchlorate – the level required by California law – cannot be less than 245 ppb, minus potential adjustment for source contribution, as discussed below.

The NOEL identified by NAS is the level at which there is no iodide uptake inhibition (“IUI”). NAS expressly and repeatedly concluded that IUI is not an adverse effect.¹³ Nevertheless, the NAS took the unprecedented step of using the NOEL as its point of departure, recognizing that in doing so it was departing from conventional risk assessment practice.¹⁴ This unusual policy determination was described by NAS Committee Chairman Johnston as “a

¹² It has been suggested that the aluminum PHG was set at a *no effect* level (“NOEL”). However, a review of the Technical Support Document for the Aluminum PHG shows that the PHG is, consistent with OEHHA practice, based on a lowest observable *adverse* effect level (LOAEL) for decreased neurodevelopmental scores in children at 18 months. Public Health Goal for Aluminum in Drinking Water, pp. 50-53 (April 2001); see also footnote 5.

¹³ “Inhibition of iodide uptake by the thyroid clearly is not an adverse effect; however, if it does not occur, there is no progression to adverse health effects....” NAS Report p. 111.

¹⁴ “The committee emphasizes that its recommendations differ from the traditional approach to deriving an reference dose (“RfD”). The committee is recommending using a nonadverse effect rather than an adverse effect as the point of departure for the perchlorate risk assessment.” NAS Report p. 112.

conservative, health protective approach to perchlorate risk assessment.”¹⁵ By starting at a level with no effect of any kind, NAS effectively used a starting point 57 times lower than the no *adverse* effect level -- a substantial margin of safety for any uncertainty in the underlying data. Exposures at or below this level are virtually guaranteed to have no measurable effect at all on adults, including adult women who are pregnant or nursing -- the subpopulation that NAS Committee identified as the *most* sensitive of all subpopulations. This conservative starting point was intended to recognize and make sufficient adjustment for the possibility that the adverse effect level in infants, children and pregnant women may be somewhat lower than the 0.4 or 0.5 mg/kg-day¹⁶ adverse effect level in healthy adults.

The no effect level of .007 mg/kg-day converts to a drinking water concentration of 245 ppb using standard default exposure assumptions (70 kg for body weight and 2L/day for water consumption).¹⁷ Thus, in establishing a reference dose based on the no effect level, the NAS clearly, authoritatively and conservatively defined the basis of the “safe dose-response threshold” for perchlorate as 245 ppb.

When OEHHA published its March 2004 PHG, it recognized that considerable uncertainty remained regarding the adverse effect level, and it identified this as a significant

¹⁵ Dr. Richard Johnston, Presentation at "Perchlorate Impacts to Water Utilities", American Water Works Association Webcast (Feb. 9. 2005)

¹⁶ “The committee notes that effects downstream of inhibition of iodide uptake by the thyroid have not been clearly demonstrated in any human population exposed to perchlorate, even at doses as high as 0.5 mg/kg per day.” NAS Report p. 117. “Furthermore, occupational data suggest that long-term exposure of workers to perchlorate at up to 0.5 mg/kg per day does not have adverse effects on thyroid function.” NAS Report p. 118. “The committee notes that effects downstream of inhibition of iodide uptake by the thyroid have not been clearly demonstrated in any human population exposed to perchlorate, even at doses as high as 0.5 mg/kg per day.” NAS Report p. 118

¹⁷ In developing maximum contaminant level goals (MCLGs are the federal analog of PHGs) for non-carcinogens, EPA’s Office of Ground Water and Drinking Water starts with a reference dose, multiplies that value by the typical adult body weight (70 kg) and then divides by a daily water consumption rate of 2 liters to provide a drinking water equivalent level. EPA Fact Sheet, *Setting Standards for Safe Drinking Water*, available at <http://www.epa.gov/safewater/standard/setting.html>.

piece of missing information.¹⁸ It is now the case, however, even if it was not evident in March 2004, that “adequate scientific evidence demonstrates that a safe dose-response threshold for [perchlorate] exists.” The NAS authoritatively identified the entire dose-response spectrum. It defined the adverse effect: hypothyroidism; it defined the approximate lowest dose that would cause hypothyroidism, the NOAEL (0.4 mg/kg-day); and it defined the NOEL, the level at which there is no effect at all (0.007 mg/kg-day).¹⁹

By describing the dose-response spectrum -- from the very first non-measurable, non-adverse threshold of inhibition of iodide uptake, to the lowest possible dose for an adverse effect²⁰ (the NOAEL) -- the NAS provided OEHHA with a number of possible threshold values and methodological options for deriving a PHG. In effect, the NAS bracketed (or defined the range within which) the safe dose-response level could possibly fall. If OEHHA followed standard practice, it would use the NOAEL of 0.4 mg/kg-day with appropriate uncertainty

¹⁸ OEHHA PHG Response to Major Comments, p. 45, in response to a comment on PHG being set based on a precursor event: “[The] margin of safety is acknowledged but not numerically incorporated into the calculation of the PHG, since the available data are insufficient to delineate the dose-response.” OEHHA PHG Response to Major Comments, p. 61, response to comment on need for UF for intra-species: “There is clearly a negative feedback system in regulating thyroid hormones. However, based on the available human studies, it is not clear what perchlorate exposure level would disrupt this system.” OEHHA PHG Response to Major Comments, p. 63: “Due to the insufficient control of one or more of the parameters, there are no human data available that allow the establishment of a dose-response relationship for these adverse health effects. OEHHA acknowledges there is probably a safety margin between the inhibition of iodide uptake and other more serious thyroid effects, although the magnitude of this margin is not well quantified and is likely to vary among individuals in a population.” OEHHA PHG Response to Major Comments, p. 76: “OEHHA agrees that there is likely a buffer or safety margin between the inhibition of iodine uptake and other undesirable or adverse effects. However, the magnitude of the buffer or safety margin is likely to vary from individual to individual depending on: dietary iodide intake, amount of iodide stored in the thyroid, exposure to other environmental goitrogens, and the capacity of the body to maintain the thyroid hormone balance. At this time, there are no data allowing the characterization of this margin of safety in a population.”

¹⁹ On the basis of the studies of long-term treatment of hyperthyroidism in which patients continued to be given perchlorate after their hyperthyroidism resolved and clinical studies of healthy adults, the perchlorate dose required to cause hypothyroidism in adults would probably be more than 0.4 mg/kg per day, assuming a 70-kg body weight. “[I]t is highly likely that in people with a normal iodide intake the dose of perchlorate would have to reduce thyroid iodide uptake by at least 75% for a sustained period (several months or longer) for iodide uptake and thyroid hormone production to decline enough to cause adverse health effects (equivalent to reducing dietary iodide intake by 75%). In adults, that is likely to require sustained exposure to more than 30 mg of perchlorate per day (0.4 mg/kg per day for a 70-kg person), on the basis of the clinical studies in healthy subjects....” NAS Report p. 44.

²⁰ For adverse health effects to occur in healthy adults, thyroid hormone production must fall substantially and, more

factors to derive the PHG. It might, if it had uncertainty regarding the data, use the NOAEL and benchmark dose analysis with another set of uncertainty factors. In any event, by identifying the no effect level, NAS allowed OEHHA to define a point unquestionably *below* the safe dose-response threshold at which the PHG must be set.

If OEHHA proceeds to set a PHG based on the conservative, indeed unprecedented, use of the no effect level as the point of departure for perchlorate risk assessment, further adjustment through benchmark dose analysis (“BMD”) is completely unjustified and redundant. This conclusion is supported by the Committee’s deliberate decision not to use a BMD-based point of departure in light of its use of the NOEL.²¹ Using a no effect level that is more than two orders of magnitude below the no adverse effect level fully protects against the theoretical possibility that additional studies could produce a somewhat larger range of data points.²²

Similarly, there is no legal or toxicological justification for any further modification for variations in body weight or drinking water consumption. Even where the NOAEL is used as the point of departure, both OEHHA and the EPA use standard default weight/consumption assumptions. For well over 15 years, EPA has selected a drinking water consumption rate of 2 liters per day and an adult body weight of 70 kg. It has applied this default to the NOAEL regardless of the most sensitive subpopulation. EPA has analyzed recent data measuring these parameters and has found the new data not only supports its long-standing default values, but

importantly, must remain low for at least several weeks.

²¹ “The committee concluded that using the NOEL (0.007 mg/kg per day) for iodide uptake inhibition from Greer *et al.* (2002) as the point of departure provides a reasonable and transparent approach to the perchlorate risk assessment.” “[T]he committee reviewed the BMD analyses conducted by EPA (2003), the California Environmental Protection Agency (CalEPA 2004), and Crump and Goodman (2003) on the data from Greer *et al.* (2002).” “Although the committee recognizes that BMD modeling *can be an improvement over the use of the NOAEL or LOAEL as a point of departure*, there appears to be no consensus on the criteria for choosing one BMD approach over another.” The Committee neither suggested nor recognized any validity to the use of a BMD where a *no effect* level was the point of departure. NAS Report p. 113-114.

²² Indeed, four additional clinical studies that investigated iodide uptake inhibition by perchlorate have produced results consistent with the NOEL value from Greer (Brabant *et al.* (1992), Lawrence *et al.* 2000, 2001; Braverman *et*

suggests they are even more conservative than previously anticipated.²³ EPA carefully considered using traditional default values for perchlorate and determined that using such default values are, in fact, adequately protective of children and infants.²⁴

OEHHA too typically uses an adult bodyweight/consumption value to derive a PHG where the risk arises from chronic exposures. Although in some instances OEHHA has used the weight of an adult female (60kg) to derive the PHG, those PHGs have always been based on the no adverse effect level, and not the no effect level. OEHHA's decision to use the weight and consumption of the pregnant woman to derive the March 2004 PHG for perchlorate was the first time it had applied these assumptions to a no effect level. If, as OEHHA and NAS propose, a no

al. 2004)." NAS Report pp. 113-114. These findings suggest that the NAS NOEL is scientifically robust and thus the use of BMD analysis to account for variability in the Greer study population is unnecessary.

²³ EPA has received numerous comments in many rulemakings recommending that these default values be adjusted for particular adverse effects or for sensitive members of the population. For example, in the recent MCL for some disinfection by-products, EPA rejected adding additional safety factors for children or adjusting the standard adult body-weight/consumption parameters. For chlorite, just like perchlorate, the adverse effect of concern was neurodevelopment and the most important exposure was during pregnancy, lactation, and infancy. EPA dismissed the need for adjustments:

EPA disagrees that an additional safety factor should be applied to provide additional protection for children or that drinking water consumption relative to body weight of children should be used in developing the MCLG [maximum contaminant level goal]. The MCLG...presented for chlorite and chlorine dioxide are considered to be protective of susceptible groups, including children, given that the RfD is based on a NOAEL derived from developmental testing.... Additionally, current methods for developing RfDs are designed to be protective for sensitive populations... In addition, the important exposure is that of the pregnant and lactating female and the nursing pup. The 2 liter per day water consumption and the 70 kg body weight assumptions are viewed as adequately protective of all groups. 63 Fed. Reg. 69404-5.

²⁴ EPA has addressed the use of default values (70 kg, 2 liters of water per day) in all of its previous risk assessments on perchlorate, including the most recent document in 2003 (EPA, 1998, 2002, 2003). Also, in EPA's 2003 guidance for perchlorate assessment, the Agency specifically stated that additional exposure adjustments were not necessary:

The uptake and elimination kinetics of perchlorate for children are such that traditional adjustment of exposure based on body weight scaling results in exposure estimates equivalent to those for adults. Concern for increased susceptibility of exposures throughout lifetime are addressed by the uncertainty factors used in arriving at the health risk benchmark. For these reasons, with respect to both a new oral health risk benchmark and the existing provisional clean up range of 4-18 ppb set out in the 1999 Interim Guidance no additional adjustment for childhood exposure is necessary.

See Memorandum from EPA Assistant Administrator Marianne Lamont Horinko to EPA Assistant Administrators and Regional Administrators, "Status of EPA's Interim Assessment Guidance for Perchlorate," p. 2 (January 22, 2003).

effect level is used as the point of departure, there is no need to vary from the 70 kg/2 liter default assumption, inasmuch as the starting point already incorporates a 57-fold margin of safety between the NOEL and the NOAEL. Stated otherwise, if calculation of a PHG based on the no adverse effect level yields a PHG of 10,080 ppb using the pregnant woman's weight/consumption, it is apparent that no such adjustment (for weight/consumption) is needed where the PHG is based on the NOEL -- yielding a PHG of 245 (with further reduction for source contribution). Such an adjustment for weight provides no health benefit inasmuch as the point of departure is below the safe dose-response threshold.

Much the same may well be said of adjustments for source contribution. Although EPA and OEHHA typically do make adjustments for source, these are adjustments made to levels derived using the no adverse effect level as the starting point -- not the no effect level. Thus no further adjustment seems necessary here to achieve a safe-dose response. However, recognizing that adjustment for source contribution is common regulatory practice, we have made such an adjustment, based on recently developed data from the Center for Disease Control and Prevention ("CDC").

At the time that the PHG document was issued, OEHHA was aware that perchlorate had been found in a number of food sources including commercial cows' milk, human breast milk, lettuce, cucumbers, strawberries and blackberries. These data informed OEHHA's relative source contribution estimate of 60% (60% exposure from water and 40% from food and other sources). Moreover, when the PHG document was released in March 2004, most of the perchlorate in U.S. foods was attributed to irrigation with Colorado River water or naturally occurring perchlorate in west Texas. The U.S. Food & Drug Administration data now

demonstrate that perchlorate is widely distributed in regions without known military or industrial sources.²⁵

Subsequent to the 2004 PHG document, several food surveys calculating food contribution to perchlorate exposure have been conducted. Of particular importance in measuring contribution of other sources to perchlorate consumption, is recent data from the CDC demonstrating the current distribution of urinary perchlorate excretion in healthy adults with no known drinking water sources of perchlorate exposure. In a population of 60 adults from Atlanta, median perchlorate excretion was approximately 8 µg/day and the 95th percentile was approximately 20 µg/day.²⁶ The CDC has also analyzed over 2000 frozen urine samples from recent National Health and Nutrition Examination surveys (NHANES) and has found similar distribution of perchlorate excretion.²⁷ These data demonstrate that for the most sensitive population -- the pregnant woman and her fetus -- approximately 9 ppb perchlorate are from sources other than water. Thus, should OEHHA decide to make adjustments for source contribution, important advances in scientific studies subsequent to OEHHA's March 2004 PHG now make it possible to calculate source contribution based on actual data. These data yield a PHG of 236 ppb (the NOEL minus 9 ppb for source contribution).²⁸

In sum, NAS has identified the adverse effect level for healthy adults; it is 0.4 mg/kg-day, arguably the safe dose-response threshold. NAS also identified the level that is, by definition, below the safe dose-response threshold -- the no effect level -- 0.007 mg/kg-day. In what it recognized was an unprecedented step, NAS used that no effect level as its point

²⁵ Data recently released by the University of Arizona not only confirms this widespread distribution, but also demonstrates that organically grown produce has significantly more perchlorate than conventionally grown crops.

²⁶ R. Knuppel, *et al.*, *24-hour Urine Creatinine Excretion in Pregnancy*, *Obstetrics & Gynecology*, v. 54 pp. 327-9 (1979).

²⁷ (Manuscript in press; name and contact information for the CDC study authors have been provided to OEHHA)

of departure for developing a reference dose. Because it was not engaged in a regulatory exercise, NAS did not need or seek to explain how its findings might fit into any particular regulatory framework. However, the relevance and application of the NAS findings to the California Safe Drinking Water Act are clear: the safe dose-response threshold required by California law cannot be less than the NOEL with adjustment for source contribution – 236 ppb.

Arguments Regarding Further Adjustment.

Notwithstanding the unprecedented level of health protectiveness of the NAS analysis, OEHHA has been urged by some to make still further adjustments to account for variation in drinking water and consumption patterns among subpopulations. Such further reduction departs from common regulatory practice and is completely unnecessary, as explained above. Moreover, the specific numerical or formulaic adjustments some have proposed ignore the data, prior conclusions of both OEHHA and the NAS, and are founded on unrealistic assumptions for body weight and drinking water intake. If a further adjustment is made notwithstanding the absence of scientific or legal support, it should at least be correctly calculated. There are two alternative approaches for such adjustment.

1. Adjustment Using Actual Calculation

The conventional regulatory method of deriving a PHG is to use the weight and drinking water consumption rate of a typical adult weighing 70 kg, and consuming 2 liters of water daily. As noted above, EPA's drinking water standards are derived using the 70 kg / 2 L assumption applied to the no *adverse* effect level even where sensitive subpopulations weigh less, as EPA

²⁸ Other recent studies include Data from commercial cows' milk samples collected by the California Department of Health Services ("DHS") around Sacramento in April 2004 and analyses of milk and lettuce surveyed by the FDA

believes they are taken into account in establishing the reference dose. Thus, no further adjustments are necessary when converting this dose to a health protective drinking water standard. OEHHA, too, has used the 70 kg / 2L assumption as the basis for deriving a PHG, addressing uncertainties related to sensitive populations, exposure duration, or other data limitations through the use of composite uncertainty factors.

That said, if OEHHA nevertheless uses the body weight and consumption patterns of the most sensitive subpopulation, it would use the pregnant woman to derive the PHG. NAS has authoritatively determined that this is the most sensitive subpopulation.²⁹ Use of the pregnant woman is also consistent with OEHHA's PHG determination regarding sensitive subpopulations.³⁰ While some critics have suggested using body weight and drinking water consumption patterns of bottle-fed infants, this view misperceives the toxicology and the NAS findings. By deriving a PHG or 'safe' level based on the *most* sensitive subpopulation, all other populations are protected as well. Moreover, the reference dose identified by NAS contemplates the risk of a chronic adverse effect associated with a *lifetime* average daily dose of perchlorate. Indeed, NAS emphasized repeatedly that an adverse effect is produced only where there is "sustained, prolonged" exposure to requisite levels of perchlorate.³¹ To calculate the PHG using

through August 2004 from various regions in the United States.

²⁹ "For the perchlorate risk assessment, . . . the most sensitive population is fetuses, particularly those of pregnant women with hypothyroidism." NAS report p. 115.

³⁰ OEHHA considered four sensitive subpopulations which are identified in this evaluation: (i) pregnant women and their fetuses, especially those who are getting less than a sufficient amount of iodine; (ii) lactating women, especially those who are getting less than a sufficient amount of iodine, (iii) infants, and (iv) individuals with thyroid problems. OEHHA PHG p. 8. OEHHA concluded that a level of protection sufficient for the pregnant woman and her fetus would protect all other populations. *Id.*

³¹ "Thyroid hormone production must fall substantially and, more importantly, must remain low for a prolonged period of time for adverse effects to occur. . . ." NAS Report p. 33. "Given the compensation that is known to occur in people with iodine deficiency, as discussed earlier, it is highly likely that in people with normal iodine intake the dose of perchlorate would have to reduce thyroid iodide uptake by at least 75% for a sustained period (several months or longer) for iodide uptake and thyroid hormone production to decline enough to cause adverse health effects (equivalent to reducing dietary iodide intake by 75%). In adults it is likely to require sustained exposure to more than 30 mg of perchlorate per day (0.4 mg/kg per day in a 70-kg person), on the basis of the clinical studies in healthy adults, and the studies of the treatment of long-term hypothyroidism, both described in this chapter, and the

assumptions of 3 kg infants ingesting 1 L of water over a lifetime dose period simply ignores, among other things, the fact that the dosage and concentrations change throughout the individual's lifespan. In any event, both NAS and OEHHA conclusively established that the developing fetus of a pregnant woman is the most sensitive population.³²

Using OEHHA's default values for a pregnant woman, 65 kg body weight in the first trimester and consumption of approximately 1 liter of water per 25.2 kg body weight, the PHG derived is 176 ppb. Deduction of 9 ppb to account for contribution from non-drinking water sources produces a PHG equivalent to 168 ppb. (See Appendix A for specific calculations).³³

2. Adjustment by Application of a 10-fold Margin of Safety

NAS applied a 10-fold safety factor, describing this additional step as conservative and health protective, especially given that the point of departure is based on a non-adverse effect that long precedes the adverse effect in the continuum of possible effects of perchlorate exposure. Use of this additional ten fold safety factor is not justified for setting the California PHG inasmuch as the NOEL (adjusted for source contribution) already fully satisfies the statutory criteria -- the safe dose-response threshold. Adoption of the additional 10-fold uncertainty factor used by NAS, while unnecessary to public health and scientifically unjustified, completely eliminates any arguments that further adjustments are needed to reflect differences -- actual or potential -- between the study subjects and those potentially exposed. This extremely

studies of environmental exposure, described in Chapter 3." NAS Report p. 43 (section on summary of clinical studies).

³² "For the perchlorate risk assessment, potentially the most sensitive population is fetuses, particularly those of pregnant women who have hypothyroidism or iodide deficiency." NAS Report p. 115.

³³ This calculation has a conservative bias: the weight is a non-pregnant weight, approximately the 75th percentile for reproductive-age women, whereas weight is expected to increase during pregnancy; the default drinking water level is the 95th percentile for pregnant women. Moreover, since the PHG based on 70-kg/2L value and one based on the weight of the pregnant woman are both below the safe level, there is no health benefit.

conservative approach produces an even lower PHG than under scenario 1 above -- approximately 16 ppb (1/10th the NOEL of 245 minus 9 ppb for source contribution).³⁴

Other Considerations

The NAS recognized that using a no effect level as a point of departure for assessment of risk from a chemical in drinking water was unprecedented. The precedential effect of adopting a regulatory standard based on such an analysis has implications far beyond the chemical at issue – implications not considered by the NAS. As stated above, both the EPA and OEHHA have numerous drinking water standards. None are based on a no effect level, to say nothing of one with an additional ten fold margin of safety. At least two OEHHA PHGs – nitrate and thiocyanate --are for other chemicals that inhibit uptake of iodine. They are the same class of goitrogens as perchlorate, and their mechanisms of action, toxicology and health effects with respect to iodide uptake inhibition are identical. Thus, there is no principled basis for using a different starting point for perchlorate than for nitrate or thiocyanate. But, if OEHHA were similarly to set nitrate and thiocyanate PHGs based on IUI as the departure point, the revised nitrate and thiocyanate PHGs would be dramatically reduced -- equivalent to 190 µg/L and 670 µg/L respectively -- far lower than current PHGs, and with significant consequences for the food supply *if* such levels were even attainable. As required by statute, the PHGs for nitrate and thiocyanates are currently based on the *adverse* effect level, and would presumably have to change were a different basis used for perchlorate.

CONCLUSION

³⁴This approach represents more than a 570-fold margin of safety below the no adverse effect level.

Now that NAS has authoritatively addressed perchlorate risk, a PHG of 6 ppb cannot be maintained.³⁵ As OEHHA's 2004 PHG Support Document anticipated, the NAS has provided valuable input to OEHHA's work in developing a PHG and has eliminated prior uncertainty. Other scientific work -- some published in the months since OEHHA completed its March 2004 PHG -- has provided further clarity on relevant issues and, by confirming the Greer study on which OEHHA relied, has reduced uncertainty regarding its data. Thus, OEHHA can now identify the "safe dose-response level" using the "most current principles, practices and methods" used by experts in the field. Cal. Health & Safety Code § 116365(c). As a matter of law, the PHG must be set at that level.

The law requires that the scientific work of the NAS and of OEHHA scientists be applied to the regulatory criteria to derive a PHG. The most conservative possible reading of these regulatory criteria produces a PHG of 236 ppb after adjustment of the NOEL for source contribution. Any further adjustments for body weight and water consumption variation are neither scientifically nor legally supported, given the very conservative basis for the PHG of 236 ppb. Nevertheless, if OEHHA makes these adjustments the resulting PHG would be either 167 ppb (if calculated using actual data) or 16 (if the NOEL were reduced by the additional ten-fold safety factor used by the NAS).

A PHG set at (and certainly below) the NAS-defined no effect level does not provide additional public health protection -- it would ignore the expert conclusions of the NAS as well

³⁵ Even if OEHHA retained all of its assumptions and, ignoring the statutory criteria, did nothing more than adopt NAS' preference for the NOEL of 0.007 mg/kg/day as a point of departure (rather than OEHHA's BMDL of 0.0037 mg/kg/day), it would change the PHG from 6 ppb to 12ppb. If OEHHA were to use a .0007 mg/kg-day reference dose, a pregnant woman weight/water consumption value, and the quantitative source contribution derived from the CDC data in lieu of OEHHA's qualitative 60% assumption, it would produce a PHG of 9 ppb. These approaches maintain every assumption and analysis previously made by OEHHA, the only exceptions being use of the NAS point of departure (and the CDC RSC adjustment in the second scenario) and completely disregard the statute's command that the PHG be set at the safe dose-response threshold. This approach also ignores the substantial safety margin already built into the NAS number.

as much of the work in OEHHA's analytical document; it flies in the face of precedent by adopting an approach that could produce serious practical, economic and even adverse health consequences with respect to other PHGs that OEHHA will have no principled basis for distinguishing from perchlorate; and it diverts both private and public resources away from much more pressing public health and other public needs. We urge OEHHA to recognize the work of its own scientists, the authoritative report by the NAS, and the requirements of its statute by changing the PHG to the safe dose-response threshold described in this position paper.

APPENDIX A

Calculation of the PHG based on 0.007 mg/kg-day as the Reference Dose, Using Pregnant Women to Derive Concentration and Deduction for Source Contribution

1. Assume that the reference dose for perchlorate is 0.007 mg/kg-day, or 7 µg/kg-day
2. According to OEHHA's default values, pregnant women drink 1 liter of water daily for each 25.2 kg body weight.
3. Thus, 7 µg/kg-day x 25.2 kg-day/L = 176 µg/L allowable perchlorate in drinking water *if* that were the only source.
4. From the CDC data, the mean + 2SD (97.5th percentile) perchlorate excretion is 20 µg/gram creatinine. Valentin, L. *et al.*, *Analysis of Perchlorate in Human Urine Using Ion Chromatography and Electrospray Tandem Mass Spectrometry*, Journal of Analytical Chemistry (IN PRESS).
5. Medical literature indicates that on average, pregnant women excrete 1.08 grams of creatinine daily. Knuppel, R. *et al.*, *24-hour Urine Creatinine Excretion in Pregnancy*, Obstetrics & Gynecology, 1979 vol. 54, pp. 327-9.
6. Thus, pregnant women would be expected to excrete 1.08 x 20 = 21.6 ug perchlorate daily, which, because of perchlorate's high solubility and rapid excretion, would represent the upper range of possible perchlorate from daily dietary intake
7. The average pregnant woman in the first trimester weighs 65 kg. Using OEHHA's 25.2 L/kg body weight value, we assume that she will drink 2.58 liters of water daily.
8. Therefore, the 21.6 ug of food perchlorate would be equivalent to 21.6 ug / 2.58 liters = 8.4 µg/L.
9. With 8.4 µg/L associated with food perchlorate, conservatively rounded up to 9 µg/L, the PHG calculated now becomes: 176 µg/L - 8.4µg/L = 167.6 µg/L rounded to 168 ppb.