DEPARTMENT OF DEFENSE
REGIONAL ENVIRONMENTAL COORDINATOR, REGION 9
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February 18, 2011

Michael Baes
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment (OEHHA)
California Environmental Protection Agency
1515 Clay St., 16th floor
Oakland, California 94612

SUBJECT: DOD COMMENTS REGARDING OEHHA'S PROPOSED REVISON TO THE PERCHLORATE PUBLIC HEALTH GOAL

On behalf of the Department of Defense (DoD) Regional Environmental Coordinator in California, I am submitting the enclosed comments on the proposed Public Health Goal (PHG) for perchlorate in drinking water.

These comments are in response to OEHHA's announcement in a public press release of 7 Jan 2011 announcing a proposed PHG of one (1) part per billion (ppb) perchlorate in drinking water instead of the current promulgated PHG of 6 ppb.

My points of contact for this matter are Mr. Baha Zarah at baha.zarah@us.af.mil or (415)977-8843 or Mr. Michael Huber at michael.huber@navy.mil or (619)532-2303.

Sincerely,

C. L. STATHOS
By direction

Encl: (1)DoD REC 9 Perchlorate PHG Comments of 15Feb11

Comments on the CA EPA
"Draft Public Health Goal for Perchlorate in Drinking Water" dated January 2011

Comments submitted by: Department of Defense (DoD) – DoD Regional Environmental Coordinator for Region 9	Date Submitted: 15 February 2011

*Comment Types: Science or methods (S); Policy (P); Editorial, grammar/spelling, clarifications needed (E); Other (O); Major (M), i.e., affects the outcome, conclusions or implementation of the assessment.

Cmt No.	Section	Page & Paragraph (or Global)	Comment	Suggested Action, Revision, and References (if necessary)	Cmt Type*
1		Global	The Department of Defense appreciates the opportunity to provide comments to the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency for their consideration in response to their invitation for public comment on their "*Draft Public Health Goal for Perchlorate in Drinking Water*". We would like to call their attention to recent journal articles that do not appear to have been considered in the draft PHG: 1. Cao et al., 2010. "*Goitrogenic Anions, Thyroid-Stimulating Hormone, and Thyroid Hormone in Infants*," Environ. Health Perspect.118:132-137. 2. Blount et al., 2010. "*Perchlorate, Nitrate, and Iodide Intake through Tap Water*;" Revised manuscript received October 21, 2010. Accepted November 1, Environ. Sci. Technol. 3. Rogan et al., 2010. "*Goitrogenic Anions, Thyroid-Stimulating Hormone, and Thyroid Hormone in Infants*," Environ. Health Perspect. 18:132-137. 4. Gold et al., 2010. "Thyroid Hormones and Thyroid Disease in Relation to Perchlorate Dose and Living Near a Superfund Sits," J. Occup. Environ. Med. 52:653-660. 5. Tarone et al., 2010. "*The epidemiology of environmental perchlorate exposure and thyroid function: a comprehensive review.*" J. Occup. Environ. Med. 52:653-660.	We urge consideration of these new data that include (Cao et al., 2010) measurements of thyroid function for individual infants (neonates to 12 months) and their urinary levels of perchlorate, thiocyanate, and nitrate. We recommend that the decision to develop a PHG for perchlorate in drinking water consider the results of these studies, and the comments that follow.	M, S, P
2		Global	This draft PHG seeks to set the drinking water level for perchlorate in California to 1 ppb. This is accomplished by weaving together several epidemiological studies, each of which has many limitations, to change the sensitive life stage from pregnant women to infants, to make use of the 95% confidence interval of infant drinking water intake.	OEHHA should reconsider basing their PHG on <u>associations</u> found in epidemiological studies and use <u>causal relationships</u> replicated by science.	P
3		Global	The draft PHG uses the neonate for the exposure assessment, as contrasted with the 2004 draft that used the pregnant woman and exposure of her fetus. As the same toxicity data (Greer et al., 2002) were used in both drafts, the change assumes that the neonate is more sensitive than the fetus *in utero*. While references are provided that the neonate may be sensitive, our review could not establish that the neonate is <u>more sensitive</u> than the fetus *in utero*.	If the neonate is retained, we recommend a data summary be added that shows that the neonate is more sensitive than the fetus, <u>especially for exposures to perchlorate.</u> Such an addition would clarify and strengthen this change in the draft PHG.	M, P

ENCLOSURES 1 - 1

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		Global	Cao et al. (2010, op. cit.) studied thyroid status and *"the association of urinary perchlorate, nitrate, iodide, and thiocyanate with urinary T4 and TSH in infants..."* They followed 12 children at weekly intervals from 1 week to 23 weeks of age, and at monthly intervals from 6 months to 12 months of age. They found *"no significant association in either boys or girls between perchlorate and TSH or T_4"*. They also found "a significant increase in TSH in children with lower iodide and high perchlorate" [lower iodide is < 100 μg/L] and *"Unexpectedly, among children with low iodide in urine, the infants with higher perchlorate and TSH do not have lower T_4 levels."*	We strongly recommend that the results of this study be evaluated as part of the reconsideration of lowering the PHG. Unlike previous studies, Cao et al. published results from individual infants with their biomarkers for exposure to three goitrogens, their thyroid hormone levels, and their iodide status. Such data are better than the averages for effects and inferences for exposure that were required to analyze the previous, retrospective studies.	M, S
4	Summary	Pg 3, para 2	"Studies from California and elsewhere provide evidence that thyroid hormone levels in infants were adversely affected by perchlorate at exposure levels that were much lower than the levels shown to cause no effects in healthy adults (Kelsh *et al.*, 2003; Brechner *et al.*, 2000; Buffler *et al.*, 2006; Steinmaus *et al.*, 2010; Li *et al.*, 2000a; Crump *et al.*, 2000)." In epidemiological studies, "adverse effects" are only associations, and additional information is necessary to establish a causal relationship. OEHHA should review the work of Tarone et al. (2010, op.cit.) that evaluates each of the key epidemiological studies listed in the left column, as well as many additional studies. In their review article, Tarone et al. conclude [emphasis added] "There is <u>no epidemiologic evidence</u> that environmental or occupational exposure to <u>perchlorate adversely affects thyroid function</u> in the United States. Even <u>if all perchlorate could be removed from the environment, 99% of the inhibition of iodide</u> uptake in the thyroid resulting from exposure to environmental goitrogens <u>would remain</u>." [This evaluation was conducted by members of the International Epidemiology Institute, Rockville, MD from Vanderbilt	We suggest that the current statement be revised to include the past and recent findings that demonstrate no effect, or effects only in infants with significant iodide deficiencies, in infants or neonates exposed to perchlorate to represent the totality of the literature more accurately. We further suggest that the term "adverse" be eliminated from this sentence, as the changes in thyroid hormone levels, by the published statements of the author of the PHG , are not known to be adverse (see next comment).	S, P

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			University Medical Center. Although funded by Lockheed-Martin Corp., "Lockheed-Martin had no role in the conduct of the review or in the writing or editing of the article."]		
5		Pg 46, para 2	To illustrate some of the issues with reliance on the epidemiological studies cited in the draft PHG, comments # 5 through 9 concern Steinmaus et al. (2010), the most recent study on which OEHHA has focused and authored by the OEHHA official who also wrote the draft PHG. Note that Steinmaus et al. conclude, *"Currently it is unknown whether the effects seen here cause actual impacts on health and development. Further research is needed on this issue, and needed to evaluate the possible role that iodine, thiocyanate, nitrate, and other thyroid-active agents may have played in these findings."*	As mentioned above, the author of the draft PHG has published his conclusion that the effects estimated are not known to result in adverse health effects. This conclusion should either be more clearly reflected in the analyses presented in the PHG or the PHG should explain this apparent inconsistency.	M, S, P
6		Pg 46, para 2	Categorization of TSH levels by <24 hours and >24 hours was also performed in another study on which OEHHA focused (Buffler et al., 2006), i.e., *"the odds ratio for a TSH > 25 μU/mL in the first 24 hours of birth was 1.53 ($p < 0.0001$). For TSH levels collected after 24 hours of birth, the odds ratio for a TSH > 25 μU/mL was similar to that reported in Buffler et al."* Limiting TSH samples to less than 24 hours following birth is inadequate given the dynamics of the post-birth TSH surge. The TSH surge (5-7 times birth levels) peaks at 30 minutes post-birth and falls quickly to 2 times birth levels at 24 hours (Ravel, 1995, "Thyroid function tests." Chapter 29. In: Clinical laboratory medicine: Clinical application of laboratory data. Sixth edition. St. Louis, MO: Mosby, Inc.). The authors have no way of knowing where on the curve individual measurements lay, or if hospital policies can skew the results for a given location. Between 24 and 48 hours, TSH levels fall from 2 times birth levels to equivalent birth levels (Ravel, 1995, op.cit.). Thus, TSH samples taken post-birth are considered screening values and more detailed hormone level measurements would be initiated if a clinical condition is indicated. This is not	The limitations of the studies upon which the calculations in the PHG depend should be clearly and concisely presented in the PHG so that stakeholders using this document understand its limitations.	S, P

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			equivalent to a validated research method. Additionally, assay methods can vary by hospital.		
		Pg 46, para 2	The draft PHG states, *"However, a TSH of 25 μU/mL was the 99.99th percentile of all TSH levels in this age strata and there were very few exposed cases (n = 13)... lower TSH cut-off points were also used to define a "high" TSH in this paper."* Steinmaus and co-authors apparently re-defined the standard criterion for normal TSH levels in newborns, because otherwise very few infants would meet the criteria for abnormally high levels. This indicates that clinically abnormal levels were not prevalent in California during these years. Additionally, since *"90% of California newborns in 1998 with TSH >25 μU/mL in the first 24 hours after birth were not diagnosed with PCH"* (Tarone *et al.*, 2010, op. cit.), Steinmaus et al. are defining as "abnormal" TSH levels that are not recognized by the medical community as anything more than a need to test TSH again when the baby is older.	We recommend that regulatory values be based on analyses that use standard criteria for normal and abnormal ranges for physiological parameters.	M, P
7		Pg 46, para 2	The draft PHG states, *"Because significant neurologic effects have been seen with smaller changes in thyroid hormones (Pop et al., 1999, 2003; Haddow et al., 1999; Klein et al., 2001; Kooistra et al., 2006; Vermiglio et al., 2004), lower TSH cut-off points were also used to define a "high" TSH in this paper."* Steinmaus et al. are equating clinically insignificant changes in TSH to small changes in thyroid hormones, which were not measured in their dataset. It is unknown if these "high" TSH levels resulted in differences in thyroid hormones or even how large or small of a change in thyroid hormones might be seen with these TSH levels, because the data doesn't exist.	We recommend that regulatory values be based on data, not inferences from surrogates that may or may not correlate directly with the parameter of interest and may be influenced by other factors, e.g., hormonal feed-back loops.	M, S
8		Pg 46, para 2	The draft PHG states, *"These analyses adjusted for age of sample collection, gender, mother's age, per capita income, race/ethnicity, birth weight, and feeding type (breast vs. formula)."*	To the extent surrogates are used (e.g., confounders are adjusted), we recommend that they be as specific as	P

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			No epidemiological study can adjust implicitly for confounders. However, *per capita* income has been shown not to be an indicator of prenatal care in California during the time the Steinmaus et al. data were collected (Braveman et al., 2005, Socioeconomic status in health research: One size does not fit all. JAMA. 294:2879-2888). Per capita income combined with education level, however, was a good indicator of prenatal care.	possible.	
9		Pg 46, para 2 Steinmaus *et al.* (2010), pg 1219, para 1	Adjusting for ethnicity did reveal an interesting statistic, i.e., *"Mean TSH levels were higher in … Asians (4.40 μU/mL) than other ethnicities (4.01 to 4.15 μU/mL)"*. The higher number among the Asian population may highlight the importance of diet and thyroid active compounds (e.g., soy products). This ethnic variation raises issues about the assumption (in both the draft PHG and the original paper) that perchlorate in the drinking water is associated with the reported effect, as differences in exposure through drinking water in the U.S. would not be expected to be correlated with ethnicity.	We suggest that the PHG address this result that appears to contradict the fundamental assumption that the drinking water is the primary source of exposure to perchlorate. Specifically, the bias-to-the-null assumption (see next comment) that is fundamental to the evaluation of the PHG would suggest that this finding is particularly robust.	M, S
10		Page 49	The draft PHG states, "*This non-differential misclassification of exposure will generally bias results towards the null. That is, if an association truly exists, non-differential exposure misclassification will cause the magnitude of the observed association to be less than the magnitude of the true association. It will not cause a false association and will not strengthen an association that is truly weak. There are some rare exceptions to this rule, but these exceptions are not likely applicable to the studies in Table 13 (Rothman and Greenland, 1998a). Despite this misclassification bias, which was likely present to some degree in every one of the studies we evaluated, each one of the studies in Table 13 still found evidence of an association.*"	The proof for bias toward the null requires that the uncertainties be unbiased. If missing and inferred data, e.g., the relationship between TSH levels and T_4 levels, is biased, then bias toward the null can not be assumed. If bias toward the null is assumed, then the results that contradict the assumptions that tap water is the relevant source of perchlorate exposure for these neonates needs to be explained.	S

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11		109	The relative source contribution (RSC) used to derive the proposed PHG for perchlorate in drinking water used to account for infant exposure to perchlorate in their diet is 0.73. Blount et al. (2010, op. cit.) found that total tap water intake for 3262 U.S. residents with tap water sampled in conjunction with the 2005-2006 National Health and Nutrition Examination Survey (NHANES) accounted for only a minor percentage of overall perchlorate exposure. As mentioned previously, Tarone et al. conclude, *"Even if all perchlorate could be removed from the environment, 99% of the inhibition of iodide uptake in the thyroid resulting from exposure to environmental goitrogens would remain."*	We suggest that the use of an RSC of 73% be reconsidered, in light of comments 9 through 11 that the effects noted are unlikely to be primarily due to exposure to perchlorate, in drinking water, as well as other publications and analyses that suggest that tap water is not the primary source of exposure to perchlorate.	S, P