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March 9, 2009

Office of the Inspector General
United State Environmental Protection Agency
Washington, D.C. 20460

[Perchlorate comments for OIG@EPA.gov](mailto:Perchlorate_comments_for_OIG@EPA.gov)

Dear Inspector General:

We are submitting the following comments on the USEPA Office of the Inspector General's *Scientific Analysis of Perchlorate (External Review Draft)*, dated December 30, 2008. Respondents include toxicologists and public health scientists at the Massachusetts Department of Environmental Protection (MassDEP), who participated in the development of the first state drinking water standard for perchlorate.

Overall comments relating to the draft report's preparation, release and conclusions are presented first, followed by a more specific discussion highlighting some of the technical limitations and uncertainties in the assessment. We believe these issues seriously undermine the draft report's analysis and conclusions.

Overall Comments. Although several of the technical aspects of the OIG assessment have merit, the overall document is, in several aspects, seriously flawed. In addition we are troubled by elements of the process followed in the preparation and release of this draft report.

Comment 1: The use of ICF Incorporated (Inc.) to provide technical review of this document prior to its release is troubling. ICF Inc. has provided considerable consulting services on perchlorate to at least one organization, the National Aeronautics and Space Administration, potentially subject to any USEPA regulatory determinations regarding this drinking water contaminant. This raises the appearance of a potential conflict of interest. In light of allegations of regulated industries' influence on certain USEPA policy and regulatory deliberations and decisions (e.g. as reported with respect to the Clean Air Mercury Rule), and in order to maximize process transparency, the USEPA should make the draft documents submitted to ICF Inc., as well as all comments and input provided by ICF Inc., available to the public.

Comment 2: It also appears that this document was rushed “out the door”, as appropriate editing and review were clearly not completed. The report is often inconsistent and self contradictory; contains numerous distracting grammatical errors and several technical misstatements; and is incomplete with respect to discussion of scientific uncertainties. For example:

- The document incorrectly states that a reference dose (RfD) is “derived from a dose associated with an adverse effect” (pg. 43). In fact many RfD values are derived from “no adverse effect level” doses.
- The document also states that the USEPA perchlorate RfD was derived from a biological response (iodide uptake inhibition (IUI)) “several steps before the adverse effect (hypothyroidism) (pg. 45) but then subsequently demonstrates, compellingly, that adverse neurodevelopment outcomes in children are in fact associated with thyroid effects well prior to overt hypothyroidism. Indeed the OIG document makes a strong case that IUI is penultimate, rather than several steps upstream, to effects directly associated with adverse neurodevelopmental outcomes.
- Grammatical and typographical errors exist throughout the report.

Comment 3: While cumulative effects on the thyroid gland are a valid issue to address, applying a new cumulative assessment methodology for determining an appropriate drinking water standard for perchlorate significantly deviates from longstanding USEPA protocols. Other drinking water standards and guidelines do not consider cumulative impacts nor has USEPA established a specific protocol for doing so. Is perchlorate an exception to the rule for standard setting or will the OIG recommend that USEPA consider cumulative effects for all other drinking water standards and health advisories? As a result of application of the cumulative effect approach, OIG appears to discount the need for a low perchlorate standard. Instead, OIG considers reassessing the nitrate drinking water standard, but favors adding iodine to prenatal vitamin supplements as the better alternative. However, protocols for these types of exposure standard tradeoffs and risk mitigation measures through dietary treatments do not exist, have never been vetted publically and have not been used with other chemicals. For example, calcium and iron have a protective effect with respect to lead exposures. Will OIG argue for a higher drinking water standard for lead with dietary supplementation with calcium and iron as an alternative? Due to these issues we believe such new protocols should be developed through a public process prior to their application on a chemical with such nationwide significance to public health. We recommend that USEPA’s protocol for assessing mixtures to evaluate risks of multiple chemicals acting via the same mechanism of action be used to address perchlorate within a mixture of thyroid toxicants in water supplies, which would support a lower, more protective standard for perchlorate as discussed in comment 4.

Comment 4: Although OIG’s use of a cumulative effect approach may have merit, it is inappropriately used to argue against a protective drinking water value for perchlorate. In our view, from a public health perspective and a desire to protect children’s health, exposures to multiple thyroid toxicants should lower the acceptable exposure value for any single toxicant not the other way around. OIG’s conclusion that reliance on iodide supplementation through vitamins is an adequate public health response to contaminated drinking water supplies inappropriately shifts the responsibility for protecting public health from the polluter to the individual. It also affords those most at risk, the fetus and neonate, with no ability to protect their own health. Under this intervention approach, protection of infants from adverse health effects

attributable to contaminated water supplies is completely dependent on the mother's ability to obtain necessary iodide supplementation and then to follow the recommended supplementation regimen, which may not always be possible due to individual circumstances and variability in the actual iodide content of vitamins, as has recently been reported (Boston Globe, 03/02/09)

Comment 5: OIG's conclusion that "the most effective and efficient approach for reducing health risks of permanent mental deficits in children from low maternal thyroid iodide uptake during pregnancy and nursing is to add iodide to all prenatal vitamins". One water supply in MA had perchlorate at a concentration of 1300 ppb. At this level, iodide supplementation is not likely to protect public health.

Additional Technical Comments.

Comment 6: The OIG assessment relies upon the Clewell *et al.* physiologically based pharmacokinetic (PBPK) model to predict iodide uptake. The uncertainties and limitations of this model were not considered despite the fact that questions have been raised regarding aspects of the model, in particular its applicability to the fetus and neonate, the groups of most concern.

Comment 7: The OIG assessment assumes a constant proportionality between thyroidal iodide uptake and concentrations in the serum/urine as advanced by Tonacchera *et al.* (2004). Although this assumption may be appropriate for the *in vitro*, petri dish experiments performed by Tonacchera *et al.*, this is an oversimplification that ignores adaptive responses which occur *in vivo*, as well as uncertainties regarding the cumulative impacts of exposures to sodium iodide symporter (NIS) inhibitors on the thyroid and other tissues expressing this protein. Specifically, the OIG document used the *in vitro* study of Tonacchera *et al.* (2004) to estimate the interaction and total amount of iodide uptake inhibition in the thyroid caused by perchlorate, thiocyanate, and nitrate. This analysis was described as a dose addition method. However, the simple kinetic equations used in the document (pg. 39, 72, 132, etc.) which were derived from the Tonacchera *et al.* *in vitro* lab study on Chinese hamster ovary cells expressing human NIS, do not adequately represent the *in vivo* workings of the hypothalamic-pituitary-thyroid axis. This approach does not account for the complex regulatory mechanisms involved in the modulation of iodide absorption, thyroid uptake, use and disposition. None-the-less, OIG based their analysis and conclusions on this *in vitro* approach with little discussion of the model's limitations and uncertainties. Reliance on such a simplistic approach to predict responses of such a complex system is fraught with uncertainty. Furthermore, even assuming that the Tonacchera model is accurate in predicting serum perchlorate equivalent concentrations (SPECs) in adults, the risk numbers derived by OIG based on the various studies and the derived SPECs are not themselves protective of the most sensitive subgroup, the neonate and the fetus.

The limitations of simple modeling approaches are further evidenced by the National Research Council (NRC) Perchlorate Committee (2005) use of Michaelis-Menton competitive inhibition equations to estimate the iodide uptake inhibition induced by perchlorate at various concentrations of perchlorate and iodide. They concluded that humans who have serum iodide concentrations of 0-1000 ug/L would be equally sensitive to perchlorate's effects on thyroid iodide uptake. However, studies conducted by Blount *et al.* (2006) and Stienmou *et al.* (2007) are inconsistent with this conclusion, as their results indicate that people with urine iodide levels

less than 100 ug/L (assuming urine levels represent serum levels at steady state) are more sensitive to perchlorate's effect than people who have urine levels of iodine greater than 100 ug/L.

Comment 8: OIG also downplayed important results by Steinmaus (2007). This well designed human study, which was conducted in the US, received only cursory review in Appendix A of the document while other human studies conducted in Chile and elsewhere were extensively reviewed in the body of the document. Stienmaus *et al.* concluded that thiocyanate and perchlorate, at a relatively low level, interact in affecting thyroid function in women with low urinary iodine. Thiocyanate alone at urine concentrations about 2000 times that of perchlorate was not associated with altered thyroid hormone levels in women with low urinary iodine levels, but significantly altered hormone levels were observed when perchlorate exposures were also considered. This interactive effect was observed at perchlorate and thiocyanate exposure levels documented to be occurring in the US.

Comment 9: The OIG document also relied on the Tonacchera *et al.* model (pg 133) to justify the NRC (2005) statement that "To cause declines in thyroid hormone production that would have adverse health effects iodide uptake must likely be reduced by at least 75% for months or longer". In the OIG assessment the thyroid iodide uptake (TIU) that is associated with hypothyroidism ($TIU_{\text{hypothyroidism}}$) is calculated as the ratio of the urinary iodide concentration (UIC) associated with severe iodine deficiency (20 ug/L urine iodide) to the median UIC in healthy adults (150 ug/L urine iodide). On this basis OIG argues that the $TIU_{\text{hypothyroidism}} = 20 \text{ ug/L} / 150 \text{ ug/L} \times 100\% = 13.3\%$ of the "normal" uptake, which is equated to an 86.7% inhibition of iodide uptake. However, this calculation is overly simplistic as thyroid function is a complex process involving the up and down regulation of iodide uptake. The amount of iodide excreted in the urine in iodine deficient diets is relatively less than that in iodine sufficient diets, indicating that urinary iodide levels in iodine deficient individuals are not representative of ingested iodine levels or iodide uptake as suggested by the OIG document. It is also important to note that, although NIS up-regulation increases iodide uptake in iodine deficient animals, it does not necessarily prevent hormone alterations (Schroder-Van Der Elst *et al.* 2005), especially in fetuses. Therefore, the ratio determined in the previous paragraph is not a good measure of iodide uptake inhibition or its potential to cause adverse neurodevelopment effects in children.

Comment 10: Although the OIG's use of thyroid effect data attributable to other NIS inhibitors is with merit and could provide useful information regarding effect levels, the assessment appears biased. The OIG report provides little evaluation of the limitations of the various epidemiological studies addressing other NIS inhibitors, which compromise their ability to accurately detect and estimate effects. In addition the RfD derivation using data from nitrate exposed populations inappropriately considered the enlarged thyroid effects observed to be non-adverse. This outcome should be considered an adverse health effect, which would lower the associated RfD for perchlorate to a value well below that derived by NRC/EPA.

Comment 11: The OIG interpretation of the data in Braverman *et al.* (2005) is also incomplete. OIG assumed that the increased urinary iodide observed during perchlorate exposure compared to pre-exposure levels was due to increased ingestion of iodide during exposure and adjusted the calculations accordingly. Braverman *et al.* noted that the urinary iodine excretion among

employees during perchlorate exposure was approximately 55% higher than in the pre-exposed state and stated that they found it unlikely that this was attributable to a short-term dietary change. Rather the authors suggested that the thyroid may be concentrating less of the dietary iodide during perchlorate exposure. Schroder-Van Der Elst *et al.* (2005) have also reported an increase in serum levels of iodide in perchlorate exposed rats.

Conclusion. In conclusion, the OIG assessment contains several technical limitations and inadequately considers the many scientific uncertainties involved in predicting thyroid iodide uptake and inhibition and risks of adverse neurodevelopmental effects in children. Due to these deficiencies, as well as the issues previously noted in the first section of these comments, the OIG's conclusions are questionable. Given widespread contamination of drinking water supplies and food items with perchlorate and other thyroid toxicants, MassDEP continues to believe that perchlorate levels in drinking water should not exceed 2 parts per billion in order to protect the fetus and neonate.

Sincerely,

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Citations:

Blount BC, Pirkle JL, Osterloh JD, Valentin-Blasini L, Caldwell L 2006b. *Urinary Perchlorate and Thyroid Hormone Levels in Adolescent and Adult Men and Women Living in the United States*. Environmental Health Perspectives 114(12): 1865-1871.

Braverman LE, XueMei H, Pino S, Cross M, Magnani B, Lamm SH, Kruse MB, Engel A, Crump KS, Gibbs JP 2005. *The Effect of Perchlorate, Thiocyanate, and Nitrate on Thyroid Function in Workers Exposed to Perchlorate Long-Term*. Journal of Clinical Endocrinology & Metabolism 90(2):700-706.

NRC 2005. *Health Implications of Perchlorate Ingestion*. The National Academies Press, Washington, DC, 2005, (ISBN 0-309-09568-9).

Schroder-van Der Elst JPN, Van Der Heide D, Kastelijn J, Rousset B, *et al.* 2005. The expression of the sodium/iodide symporter is up-regulated in the thyroid of fetuses of iodine-deficient rats Endocrinology 142:3736–3741.

Steinmaus C, Miller MD, Howd R 2007. *Impact of Smoking and Thiocyanate on Perchlorate and Thyroid Hormone Associations in the 2001-2002 National Health and Nutrition Examination Survey*. Environmental Health Perspectives 115(9):1333-1338.

Tonacchera M, Pinchera A, Dimida A, Ferrarini E, Agretti P, Vitti P, Santini F, Crump K, Gibbs J, 2004. *Relative Potencies and Additivity of Perchlorate, Thiocyanate, Nitrate, and Iodide on the Inhibition of Radioactive Iodide Uptake by the Human Sodium Iodide Symporter*. Thyroid 14:1012-1019.