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Specialists in Occupational & Environmental Health

May 20, 2008

Honorable James M. Inhofe
Ranking Member,
Senate Committee on Environment and Public Works
United States Senate
Washington, DC 20510-6175

Dear Senator Inhofe:

Thank you for your letter of May 15, 2008 in which you asked me to comment on current concerns and debates regarding the health effects of perchlorate, particularly with respect to its presence in the nation's water supplies.

Allow me first to introduce myself. I am Clinical Professor of Epidemiology & Public Health and Associate Clinical Professor of Medicine at the Yale University School of Medicine and director of Yale's Interdisciplinary Risk Assessment Forum. I am a member of the Editorial Boards of *Journal of Occupational and Environmental Medicine*, *Journal of Occupational and Environmental Hygiene*, and *Occupational Medicine*. I have published numerous books, book chapters and research papers on the toxicology of environmental contaminants. I have written, spoken and taught on the science of perchlorate for the past six years in the context of my university activities and as a paid advisor to the Perchlorate Study Group and its member companies. My full CV is attached to this letter.

Please note that this letter is a response to your request for information; I do not mean to advocate whether or how perchlorate should be regulated. My hope is that by correcting some often repeated errors concerning the findings of recent scientific research, my comments can help to clarify some of the perchlorate-related confusion and misinformation about which you wrote. The information presented below is not a matter of opinion, but of established and reviewable scientific fact. I have provided the necessary links and references so that the factual correctness of my statements can be independently verified.

1. The Perchlorate database. There is an unusually extensive database on the health effects of perchlorate, reflecting the fact that it has been used medicinally at high doses for more than 50 years. That database has been the subject of recent, critical reviews by a panel of the National Academy of Sciences (NAS) and by the Agency for Toxic

Substances and Disease Registry (ATSDR).^{1,2} The NAS and ATSDR conclusions remain current and relevant today; the more recent reports summarized below affirm and expand those conclusions.

2. The recent FDA report on perchlorate in food. Recent public statements have erroneously characterized the findings of a 2008 report by FDA scientists who measured the content of perchlorate and iodine in US diets.³ Some have claimed that the FDA data show that perchlorate exposure from food, combined with exposure from water, exceeds established safe levels. The facts indicate otherwise. The FDA study, which considered food intake of Americans from 6-months to greater than 75-years of age, provided no evidence that anyone is exposed to unsafe perchlorate levels from food; a recent EPA study provided complementary evidence for drinking water.

- In 2005, a panel of the National Academy of Sciences (NAS) concluded that perchlorate caused no observable health effects, adverse or otherwise, at levels as high as 0.007 mg/kg/day, equivalent to drinking water levels of 245 parts per billion (ppb). To ensure an adequate margin of safety for even potentially vulnerable subpopulations (e.g., pregnant and nursing mothers and their children) the NAS panel applied a ten-fold safety factor, resulting in a perchlorate Reference Dose of 0.0007 mg/kg/day, equivalent to a drinking water level of 24.5 ppb. That Reference Dose was subsequently adopted by EPA⁴ and ATSDR,⁵ and endorsed as “conservative” by FDA.⁶ I regard the Reference Dose as a conservative, health-protective exposure limit.
- That Reference Dose was based on perchlorate doses administered to study subjects over-and-above whatever background exposures they had from diet and drinking water. In other words, study subjects almost certainly had total perchlorate exposures greater than the doses administered in that study. Thus the

¹ National Research Council: *Health Implications of Perchlorate Ingestion*. National Academy Press, 2005. (http://books.nap.edu/catalog.php?record_id=11202).

² ATSDR: *Toxicological Profile for Perchlorates (Draft for Public Comment)*, 2005. (<http://www.atsdr.cdc.gov/toxprofiles/tp162.html>)

³ CW Murray et al: US Food and Drug Administration’s Total Diet Study: Dietary intake of perchlorate and iodine. *J Expo Sci Environ Epidemiol*, 2008. (<http://www.nature.com/jes/journal/vaop/ncurrent/pdf/7500648a.pdf>).

⁴ EPA: *Integrated Risk Information System*, 2005. (http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showQuickView&substance_nmbr=1007)

⁵ ATSDR has adopted this Reference Dose as its chronic oral MRL. *Minimal Risk Levels for Hazardous Chemicals*, 2008. (<http://www.atsdr.cdc.gov/mrls/>).

⁶ “NAS Committee ... recommended a perchlorate reference dose ... the reference dose is conservative.” FDA: *Perchlorate Questions and Answers*, 2007. (<http://www.cfsan.fda.gov/~dms/clo4qa.html>).

Reference Dose derived from the study findings incorporates an even larger and more health-protective margin of safety than that specifically described by NAS and EPA. That extra margin of safety is an additional reason that I regard the Reference Dose as conservative and health-protective.

- The FDA study measured the perchlorate contents of a broad selection of foods comprising the US diet. In turn, upper bound estimates of perchlorate intake were determined for infants, children and adults. For all age/sex groups, the FDA estimated that daily dietary perchlorate intake was well below the Reference Dose.
- In a complementary study, EPA reported tests of 34,193 water samples from US public water systems; only 637 samples (1.86%) had perchlorate levels ≥ 4 ppb.⁷ Half of those 637 samples (i.e., 319) were in the range of 4-6.4 ppb. Thus, perchlorate levels were ≤ 6.4 ppb in over 99% of water samples; the distribution of samples with more than 6.4 ppb perchlorate was not described.
- Total perchlorate intake reflects both diet and drinking water ingestion. EPA has described the interdependence of those two exposure sources and the likelihood that combined exposures would exceed the perchlorate Reference Dose (see Exhibit 6.9.f in ⁽⁷⁾). In light of the FDA findings, it is probable that even if drinking water perchlorate levels exceeded 12-20 ppb, total perchlorate exposures would not exceed the Reference Dose.

Taken together, the results of the FDA diet study and the EPA water study provide no evidence that individuals ingest perchlorate at daily doses exceeding the Reference Dose and they further indicate that there is little or no likelihood that such ingestions would occur.

3. The recent FDA report also evaluated the iodine content of the US diet. The FDA study findings indicate that dietary iodine consistently exceeded current Estimated Average Requirements. This is of particular importance because FDA has also determined:

“the impacts of perchlorate exposure will vary depending upon an individual's iodine sufficiency.”⁸

⁷ Office of Water: *The Analysis of Occurrence Data from the First Unregulated Contaminant Monitoring Regulation (UCMRI) in support of Regulatory Determinations for the Second Drinking Water Contaminant Candidate List* (EPA 815-D-06-008); EPA, 2006.
(http://www.epa.gov/safewater/ccl/pdfs/reg_determine2/report_ccl2-reg2_ucmr1_occurrencereport.pdf).

⁸ US FDA: *2004-2005 Exploratory Survey Data on Perchlorate in Food* (Update 2007).
(<http://www.cfsan.fda.gov/~dms/clo4data.html>).

In other words, the impact of perchlorate is reduced in individuals with sufficient iodine intake. The FDA findings emphasize that the US diet is iodine sufficient, which is consistent with recent CDC findings.⁹ The FDA study also found that most perchlorate-containing foods contain relatively higher levels of iodine. Accordingly, it can be expected that anyone eating a perchlorate-rich diet would also ingest higher than usual levels of iodine, thus ensuring both relative and absolute iodine sufficiency.

These findings provide additional reassurance that there is little or no likelihood that dietary perchlorate intake could result in adverse effects.

4. The “CDC Study.” A study published in late 2006 by Blount and colleagues,¹⁰ sometimes referred to as the “CDC study”, has been often misrepresented in the public debate on perchlorate. Some have wrongly asserted that this study found perchlorate caused adverse effects on human health; that is not correct. I discuss below three key points that should govern how it is considered and discussed in the context of perchlorate regulation:

- The Blount study neither found nor discussed a causal link between perchlorate exposure and abnormal thyroid function. The terms “cause” and “causal” are not used anywhere in the text. Instead the authors repeatedly refer to “associations”, i.e., statements indicating a statistical relationship of uncertain direction and relevance.¹¹
- None of the subjects in the Blount study had abnormal thyroid function. Subjects with a history of thyroid abnormalities and those with abnormal thyroid tests were specifically excluded. Thus, the study did not (and could not) comment on thyroid dysfunction.
- The results of the Blount study are inconsistent with accepted principles of thyroid science. Perchlorate is only one of a number of molecules that exert similar effects upon the thyroid, i.e., competitive inhibition of iodine uptake by the Sodium/Iodide Symporter (NIS). Other such molecules include nitrate and thiocyanate. The effects of these molecules have been shown repeatedly to be similar in direction and additive in magnitude. In the Blount study, however,

⁹ National Center for Health Statistics: *Iodine Levels, United States, 2000*; CDC, 2007. (<http://www.cdc.gov/nchs/products/pubs/pubd/hestats/iodine.htm>)

¹⁰ BC Blount et al: Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. *Environ Health Perspect* 114:1865-1871, 2006. (<http://www.ehponline.org/members/2006/9466/9466.pdf>).

¹¹ The distinction between causation and association is a critical concern of epidemiology. (e.g., KJ Rothman, S Greenland: *Modern Epidemiology*; Lippincott-Raven, 1998, pp. 7-28).

thyroid effects attributed to these molecules were different and inconsistent, a fact the authors described as “unexpected ... the explanation for this is unclear”. I agree that the reported associations are inconsistent, contradictory, and not explicable by known physiology. Because of such inconsistency, these study data must be viewed with caution.

- I am not alone in raising concerns about the Blount study. The American Thyroid Association, for example, concluded that the study findings were “intriguing”, but limited in their application to the setting of exposure standards.¹² A particular issue of concern was the inexplicable finding that perchlorate-associated effects were not seen for the other goitrogens included in the study.

The Blount study raises interesting hypothesis, but it is not adequate to test those hypotheses, it does not document any adverse effects, and it is inconsistent with well-accepted principles of the relevant physiology.

5. Children’s Health Protection Advisory Committee (CHPAC) letter. The CHPAC letter reviewed a number of perchlorate-related issues of potential relevance to nursing infants. However, that letter was written more than two years ago and it necessarily fails to consider more recent reports and data relevant to its concerns.

- Consider the statement that “perchlorate may decrease iodine levels in human milk”, which is further discussed in Appendix 1 of the letter. That statement is based on the findings of one small study of milk samples from 23 women.¹³ Moreover, the conclusion of an inverse relationship between perchlorate and iodine levels derived from an analysis of only six of those 23 samples (see Figure 4). By contrast, a reanalysis of those data that was subsequently published found that iodine levels were actually greater in the 12 milk samples with highest perchlorate, as compared to the 12 milk samples with lowest perchlorate.¹⁴ In other words, there was apparently no inverse relationship between breast milk perchlorate and iodine. That reanalysis was not cited in the CHPAC letter.
- Likewise, the CHPAC letter did not consider the 2007 findings of a study that measured perchlorate and iodine levels in the milk of 57 lactating Boston-area women.¹⁵ No correlation was found between breast milk perchlorate and iodine

¹² ATA Public Health Statement: *Update on the Question of Perchlorate Exposure and Potential Effects ...*; 2006. (http://thyroid.org/professionals/publications/statements/06_12_13_perchlorate.html).

¹³ Kirk et al: Perchlorate and iodide in dairy and breast milk. *Environ Sci Technol* 39:2011-2017, 2005.

¹⁴ Lamm S et al.: Comment on “Perchlorate and iodine in dairy and breast milk”. *Environ Sci Technol* 39:5900-5901, 2005.

¹⁵ Pearce EN et al: Breast milk and perchlorate concentrations in lactating Boston-area women. *J Clin Endo Metab* 92:1673-1677, 2007.

Hon. James M. Inhofe
May 20, 2008
Page 6 of 7

levels. Such a lack of correlation seemingly corroborates the Chilean findings reported earlier by Tellez et al.,¹⁶ which were discounted in the CHPAC letter.

Unfortunately, the CHPAC letter only came to my attention in the last few days and I have not had sufficient time to research and update the various other issues that it raises. It is apparent that although the letter may have fairly reflected the science when it was written, it is now out-of-date. Perhaps I will be able to augment my comments at some future time, when it has been possible to more carefully review and update the relevant details.

6. Perchlorate does not cause cancer in humans. I am aware that some individuals have proposed that perchlorate exposure causes various types of human cancer, but I am aware of no evidence that supports such claims. To the contrary, the weight of evidence argues that perchlorate is not a human carcinogen.

The possibility that perchlorate might be carcinogenic in humans was comprehensively reviewed by the NAS, which found insufficient epidemiological evidence to support that possibility. I am not aware of any evidence to the contrary that has been published since the report. Moreover, the NAS found that the evidence was not sufficient to suggest that a link between perchlorate and human cancer was even plausible.¹⁷

“The committee questions the biologic plausibility of thyroid cancer as a likely outcome of perchlorate exposure.”

EPA reached similar conclusions:¹⁸

“EPA thus concludes that perchlorate is not likely to be carcinogenic to humans, at least at doses below those necessary to alter thyroid hormone homeostasis.”

ATSDR cited the above NAS and EPA statements and affirmed that there is no evidence of perchlorate-induced human cancers:¹⁹

“Cancer has not been reported in humans with exposure to perchlorate.”

¹⁶ Tellez et al: Long-term environmental exposure to perchlorate through drinking water and thyroid function during pregnancy and the neonatal period. *Thyroid* 15:963-975, 2005.

¹⁷ National Research Council: *Health Implications of Perchlorate Ingestion*. National Academy Press, 2005. (http://books.nap.edu/catalog.php?record_id=11202), p.10.

¹⁸ EPA: *Integrated Risk Information System*, 2005. (http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showQuickView&substance_nمبر=1007).

¹⁹ ATSDR: *Toxicological Profile for Perchlorates (Draft for Public Comment)*, 2005. (<http://www.atsdr.cdc.gov/toxprofiles/tp162.html>); p. 114.

Hon. James M. Inhofe
May 20, 2008
Page 7 of 7

Notwithstanding the claims that have sometimes been made, there is no scientific evidence that perchlorate exposure causes human cancer.

In Summary

The ongoing public debate about environmental perchlorate exposure has led to misstatements and misinterpretations of the relevant scientific findings. The current state of knowledge should be clear:

- There is no evidence of excessive perchlorate in the US diet and little likelihood that routine perchlorate ingestion would exceed the EPA and NAS Reference Dose.
- There is no evidence that perchlorate is a human carcinogen.
- There is evidence that the US diet contains sufficient iodine, and sufficient iodine intake is protective against effects that might result from perchlorate excess.

In short, there is no evidence that environmental perchlorate exposure causes human injury. Likewise, I am not aware of any evidence that environmental perchlorate exposure causes abnormal human development. This does not mean that concerns for its potential harms are wrongheaded. To the contrary, it is appropriate that public health concerns be voiced and it is necessary that public health agencies evaluate and monitor exposures that are perceived as potentially serious threats to the public health.

On the other hand, such concerns do not justify misinterpretation or misrepresentation of scientific findings and evidence. Unfortunately, such misinterpretations and misrepresentations have sometimes characterized the ongoing perchlorate debate.

I hope that you find the information presented above to be responsive to your request. Please do not hesitate to contact me if I can be of further assistance to you or the committee.

Yours truly,

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