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Washington, D.C. 20460

**Docket ID No. EPA-HQ-OW-2008-0692. Drinking Water: Preliminary Regulatory Determination on Perchlorate**

The Massachusetts Department of Environmental Protection (MassDEP) is submitting the following comments in response to the United States Environmental Protection Agency's (EPA's) request for comment on its preliminary determination not to regulate perchlorate in drinking water at a national level, Docket ID No. EPA-HQ-OW-2008-0692 entitled "Drinking Water: Preliminary Regulatory Determination on Perchlorate". These comments were prepared by scientists in the MassDEP Office of Research and Standards (ORS) including Carol Rowan West, MPH, Director, ORS; Tsedash Zewdie Ph.D., Senior Toxicologist, ORS; and C. Mark Smith Ph.D., S.M., Deputy Director, ORS.

**1. A Health Protective National Standard is Needed.** MassDEP disagrees with EPA's draft decision not to regulate perchlorate at the national level and believes that a health protective national drinking water standard for perchlorate is both warranted and necessary to protect the health of our nation's children. Overall, EPA's assessment does not adequately support its determination to not regulate perchlorate for a sizeable number of United State' citizens, by

disregarding elevated exposures and potential developmental effects in the neonate. This decision is inconsistent with basic precepts of public health protection.

**2. EPA's HRL Is Not Sufficiently Health Protective.** MassDEP continues to believe that EPA's Reference Dose (RfD) and the associated Health Reference Level (HRL) for drinking water for perchlorate are insufficiently health protective of neonatal exposures. There is compelling evidence to support a national drinking water standard for perchlorate at a value well below EPA's HRL of 15 ppb.

- Literature publications (Zoeller and Rice, 2004; Zoeller, 2006; Ginsberg et al., 2007) and state agency risk assessments (MassDEP, 2006; CA, 2004) support a more health protective RfD and drinking water value. EPA's HRL of 15 ppb is 7.5 times higher than MassDEP's drinking water standard of 2 ppb and 2.5 times higher than California's standard of 6 ppb. EPA's evaluation includes no discussion of these alternative assessments.
- The results of Blount et al (2006) and Steinmaus et al (2007) demonstrate thyroid effects associated with a dose of 0.06 ug/kg/day in iodide insufficient women, which is well below, and calls into question the protectiveness of, EPA's RfD of 0.7 ug/kg/day.
- Although acknowledged in EPA's evaluation, potential interactive effects between thiocyanate, a metabolite of cyanide found in tobacco smoke and some common foods, and perchlorate, were not accounted for. Such interactions heighten concern regarding perchlorate induced thyroid hormone effects in women with serum iodine levels < 100 ug/L.
- Use of a more appropriate and health protective RfD would lower the acceptable drinking water limit for perchlorate, resulting in a substantial increase in the total number of citizens exposed to unacceptably high levels of this toxicant from drinking water. This would clearly create a "meaningful opportunity for health risk reduction" through a national perchlorate drinking water regulation under the Safe Water Drinking Act.

**3. Infant Exposures at the HRL Exceed EPA's Insufficiently Protective RfD.** EPA's calculations (Table 8, Federal Register publication) demonstrate that perchlorate intake by

nursing and bottle-fed infants and children to 2 years of age, attributable to the consumption of drinking water at 15 ug/L (and not even considering other dietary sources of exposure) would substantially exceed EPA's insufficiently health protective RfD value. Based on EPA's own calculations, a bottle-fed infant would receive a dose of perchlorate 5 times higher than EPA's RfD and 50 times higher than MassDEP's RfD. Consistent with EPA's assessment, in a study conducted in Texas Dasgupta et al. (2008) also showed that the majority the infants (9 out 13 infants) in their study ingested perchlorate at a level that exceeds the EPA reference dose. Furthermore, this study indicates that breast milk iodide concentrations decrease as perchlorate levels increase in breast milk (Dasgupta et al., 2008), potentially raising risks to nursing infants. Due to potential impacts on children's health, this data alone justifies the establishment of a lower, more appropriately health protective HRL for perchlorate. By discounting this information in the evaluation, EPA is de facto adopting an even higher, less protective RfD for these sensitive subgroups. EPA's explanation for discounting these findings- that the model's predicted iodide uptake inhibition (IUI) level at 15 ppb would be insignificant- is unjustified for at least three reasons.

- a. The predicted IUI in these groups is very uncertain due to model limitations.
- b. Although EPA indicates that iodide uptake inhibition of 2.2% is non-adverse, no objective data exists to support this determination and no objective safe level of IUI, especially in the neonate, has been established. In fact, the Blount et al. (2006) and Steinamus et al. (2007) studies indicate that 2.6 ug/L of urinary perchlorate (which equates to an approximate dose level of 0.06 ug/kg/d in iodine deficient women was associated with decreased T4 and increased TSH levels, consistent with the mode of action of perchlorate. Iodide uptake inhibition at this dose level would be predicted by the model to be very small suggesting either that the model is inaccurate; the effect is not solely due to IUI or low levels of IUI are adverse.
- c. Allowing up to 2.2% iodine uptake inhibition also exceeds NRC's hypothesized non-adverse effect level of 1.8% IUI (NRC, 2005) although 1.8% IUI is considered an adverse effect level by many scientists (US EPA 2002; Ginsberg and Rice, 2005; and MassDEP, 2006).

**4. The PBPK Model is Uncertain Especially for Iodine Insufficient Women.** Instead of using the standard approach of comparing estimated doses to the RfD to determine safe drinking water levels, EPA is instead relying on physiologically-based pharmacokinetic (PBPK) modeling to predict IUI. MassDEP believes that the PBPK modeling has a number of limitations and may be less reliable. For example, the PBPK modeling does not adequately address effects in iodide insufficient populations and is very uncertain with respect to predicted breast milk perchlorate concentrations, effects on neonates and impacts during early fetal development. Empirical data on these issues is sparse, limiting model construction and evaluation. More robust uncertainty analysis and evaluation of model outputs is needed.

**5. EPA Needs to Better Assess and Present PBPK Model Uncertainties.** Since EPA relies heavily on the outputs of the PBPK model to predict breast milk perchlorate levels, a more thorough presentation of the model, model uncertainties and its outputs, in particular for breast milk perchlorate concentrations and neonatal exposures under differing maternal exposure scenarios is needed. This information should be provided to the public for review and comment, in addition to a scientific peer review session. These are uncertain because the PBPK model relied on rat data for several key parameters that influence breast milk perchlorate concentrations. Furthermore, the model was only evaluated against limited human data derived from populations in Chile (Tellez et al., 2005).

**6. US Data Indicates the PBPK Model May Underestimate Breast Milk Perchlorate.** Due to differences in dietary iodide intake rates, which are likely to be much higher in Chile, as well as other factors, breast milk data from US populations with lower levels of iodine intake, such as from the Boston study (Pearce et al., 2007), should also be used for model evaluation. Based on the Pearce et al., study, MassDEP is concerned that the model may significantly underestimate perchlorate breast milk concentrations in US women. Table 1, compiled by MassDEP, compares observed perchlorate and iodide concentrations in breast milk and perchlorate in urine from the Chilean and Boston study populations. These data are consistent with higher dietary iodide intake levels in the Chilean populations compared to the Boston area. The US data also exhibits a higher breast milk to urine perchlorate concentration ratio compared to those observed in the Chilean study groups - a factor of 4 for the Boston data vs. a range of only 0.33 to 2 for the

Chilean populations. This suggests that the Boston women, perhaps due to lower iodide intake, may have partitioned a greater fraction of perchlorate dose into breast milk than predicted by the model. This would result in even higher neonatal exposures than predicted by EPA at a maternal drinking water concentration of 15 ug/L, which as noted above, already exceeds the RfD.

Table 1. Lactational Perchlorate and Iodide levels in Urine and Breast Milk

Sample type	N	Antofagasta (ClO <sub>4</sub> <sup>-</sup> H <sub>2</sub> O conc. <4 µg/L)	N	Chanaral (ClO <sub>4</sub> <sup>-</sup> H <sub>2</sub> O conc. 5.8 µg/L)	N	Talatal (ClO <sub>4</sub> <sup>-</sup> H <sub>2</sub> O conc. 114 µg/L)	N	Boston  ClO <sub>4</sub> <sup>-</sup> source unknown
Tellez et al. 2005							Pearce et al., 2007	
Urine ClO <sub>4</sub> <sup>-</sup> (µg/L) (mean)	6	22.3 ± 23.8	4	17.5 ± 10	16	49.1 ± 35.2	56	8.2 ± 19
Breast milk ClO <sub>4</sub> <sup>-</sup> (µ g/L) (mean)	13	7.7 ± 7.5	16	18.3 ± 17.7	25	95.6 ± 54.6	49	33 ± 77
Breast milk iodine (µ g/L) (mean)*	14	454 ± 374	16	325 ± 150	25	384 ± 154	57	205 ± 271
ClO <sub>4</sub> <sup>-</sup> Breast milk/to ClO <sub>4</sub> <sup>-</sup> urine Ratio		0.35		1.04		2.0		4.0

\* Note: The Pearce et al., paper states that the Boston population breast milk iodine concentrations were higher than in the Chilean populations. This is an apparent error as the concentration units were not adjusted to account for the fact that the Boston results were presented in units of ug/L vs. ug/dL in the Chilean populations.

**7. The PBPK Model is Deficient for Early Developmental Periods.** Emerging data now indicate that thyroid hormone deficiency during early gestation causes neuronal toxicity (Sinah et al., 2008). The EPA has acknowledged that the lack of biological information during early fetal development limits the applicability of the PBPK modeling of the fetus and thus can not make meaningful predictions regarding early fetal IUI.

**8. The PBPK Model Does Not Consider Other Potential Mechanisms of Toxicity.**

Additionally, the model only addresses iodide uptake inhibition. However, perchlorate not only inhibits iodide uptake but also promotes the discharge of endogenous iodide, which is not addressed in EPA's assessment. The thyroid gland possesses two kinds of iodide. The first is the iodide which is accumulated into the thyroid by an active transport mechanism, the so-called "transported iodide". The second source is the iodothyronins which are derived by hydrolysis from thyroglobulin and rapidly deiodinated within the gland to yield the so-called "endogenous iodide". It is believed that both iodide sources are used within the thyroid gland for the synthesis of hormones. Rosenberg et al., 1961; Isaacs et al., 1966; Greer et al., 1969 showed that

perchlorate discharged endogenous iodide in animals, and Burgi et al.(1974) confirmed this phenomenon to occur in humans. Wolff (1974) has attempted to propose mechanisms by which perchlorate accomplishes the discharge of stored thyroidal iodide, but how this process affects thyrocytes upon short- and long-term exposure is not well understood and is not covered by the PKPB modeling.

**9. MassDEP Believes That a National Perchlorate Drinking Water Standard Provides a Significant Risk Reduction Opportunity.** Table 2 of the Federal Register publication provides information on the occurrence and population estimates for perchlorate above various thresholds. The table shows that up to 2.0 million people would be provided drinking water above 15 ppb, a value that, based on EPA's own estimates, is not protective of the breast or bottle fed infant, yet which is EPA's proposed HRL. EPA does not explain in the Federal Register how it reached its conclusion that protecting up to 2.0 million people is not a meaningful opportunity for risk reduction for persons, in particular infants, served by public water systems.

**10. EPA Underestimates Numbers of At Risk Citizens.** Due to the fact that MassDEP believes the HRL should be 2 ppb we conclude more than 16.6 million people are exposed to unsafe levels of perchlorate in their drinking water, and that this is a significant national public health issue.

In conclusion, EPA's determination that a national drinking water is not warranted is based on an incomplete assessment of the data and will place many of the nation's most vulnerable citizens, our newborn children and fetuses at an early stage of development, at risk. MassDEP believes that there is compelling evidence to support a national drinking water standard for perchlorate at a value well below EPA's HRL of 15 ppb.

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