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September 17, 2009

Docket ID No. **EPA-HQ-OW-2009-0297**
Drinking Water: Perchlorate Supplemental Request for Comments
U.S. Environmental Protection Agency

We highly commend the U.S. Environmental Protection Agency's (EPA) decision to reconsider its approach to analyzing scientific data related to perchlorate in drinking water. The Wednesday, August 19, 2009 Federal Register announcement includes a summary of the major comments EPA received regarding its October 10, 2008 preliminary regulatory determination to not regulate perchlorate in drinking water. This includes comments on why the proposed 15 ppb health advisory is not protective of children's health. These comments provide a strong basis for EPA's appropriate decision to consider a broader range of alternatives for interpreting the health data, the level of health concern, the frequency of occurrence of perchlorate in drinking water, and the opportunity for health risk reduction through a national primary drinking water standard. The Commonwealth of Massachusetts' Department of Environmental Protection (MassDEP) is pleased to provide comments on several of the issues that are the focus of this Federal Register announcement and is available to further consult with you or answer any questions you may have on our comments. Our comments are organized by issues described in specific sections of the Federal Register.

Section II: Background

MassDEP supports EPA's opinion that further review by the National Research Council (NRC) will delay regulatory decision-making and supports EPA's current plan to publish alternative approaches to interpreting the data on perchlorate and to consider public comments towards making a regulatory decision on perchlorate in drinking water.

Section III Alternative Approaches to Analyzing Scientific Data Related to Perchlorate in Drinking Water

For a number of reasons we do not believe that sodium iodide symporter (NIS) inhibition predictions based on Physiologically-Based Pharmacokinetic (PBPK) modeling should, at this time, be relied upon to establish or justify a perchlorate reference dose (RfD) nor to evaluate relative sensitivities between life-stages. Although the PBPK model previously relied upon, but now under reconsideration by EPA, provides a valuable exploratory research tool and is a potentially useful predictor of perchlorate distribution and NIS effects in the adult, it is highly uncertain regarding the fetal and neonatal life-stages of most concern and may not reflect perchlorate effects on thyroid function. Our view on this issue is based on the following observations:

1) In response to peer review comments on the PBPK models, EPA noted that "the models have not been specifically parameterized to describe hypothyroid or iodine deficient individuals." In other words the model does not take into account responses in those with insufficient iodine intakes, the very group of most concern with respect to perchlorate exposures. In other documents EPA has also noted that the PBPK model did not account for within group variability in pharmacokinetics; uncertainty in several model parameters, including fetal and neonatal values derived from rodent models, and differences in adaptive responses. Although peer reviewer comments recommended that a much more robust uncertainty analysis be preformed on the model, EPA concluded that this was beyond the scope of the current effort and would be difficult to conduct due to data gaps. However, such an assessment is critical to determining the ultimate usefulness of the model predictions.

2) The perchlorate associated thyroid hormone alterations reported in Blount et al. 2006 and Steinmaus et al. 2007 in women with urinary iodine < 100 µg/L highlight some of these uncertainties, as they suggest that either the model estimates of iodide uptake inhibition (IUI) at low perchlorate intake levels are inaccurate; that unexpectedly small increments in IUI may cause thyroid effects; and/or that perchlorate may act through additional mechanisms not captured in current models. Although NIS inhibition has been viewed as perchlorate's primary mode of action, other possible mechanisms that could contribute to its toxicity have been suggested. Based on a biologically-based dose response model of the hypothalamus-pituitary-thyroid axis and PBPK modeled perchlorate distribution and inhibition of thyroid iodide uptake, a recent assessment concluded that IUI was insufficient to explain observed changes in rat thyroid hormone levels attributable to perchlorate (McLanahan et al. 2009). These results suggest either that an additional mechanism of action exists, perhaps attributable to perchorate uptake into the thyroid and interference with other targets involved in hormone synthesis and release or that the PBPK modeling is inaccurate.

3) Although the impact of thyroid toxicants on the fetus can be buffered by the thyroid hormone synthesis and reserve capacities of the mother, iodide insufficiency and pregnancy-related stresses on maternal thyroid function increase the potential for perchlorate effects during fetal development (Glinoer 2001; Ginsberg et al. 2007). These are factors that the PBPK modeling does not adequately account for and could lead to a significant underestimate of NIS inhibition.

4) Available data indicate that neonatal exposures to perchlorate in breast milk are significant. The median perchlorate exposure to two week old nursing infants in the U.S. was predicted to be

0.206 µg/kg/day (95th percentile = 0.744 µg/kg/day) (Ginsberg et al. 2007). Other data indicate that nursing infant perchlorate exposures in the U.S. can be even higher. Based on a breast milk intake rate of 0.172 L/kg/day and reported median breast milk perchlorate concentrations (Kirk et al. 2005 and 2007; Pearce et al. 2007a), we estimate that nursing infant perchlorate intakes in three U.S. cohorts ranged from 0.56 to 1.57 µg/kg/day. Dasgupta et al. (2008) estimated breast milk perchlorate intake rates ranging from 0.3–2.1 µg/kg/day, with intakes of 9 of 13 infants exceeding the National Research Council's (NRC) RfD (NRC 2005) (Dasgupta et al. 2008).

Due to the significance of this exposure pathway, PBPK modeled estimates of perchlorate and iodide concentrations in breast milk warrant close scrutiny and additional validation. In response to peer review comments, EPA added section 4.1.1 to the May 2009 report, "Inhibition Of The Sodium-Iodide Symporter By Perchlorate: An Evaluation Of Life Stage Sensitivity Using Physiologically Based Pharmacokinetic (PBPK) Modeling." This section includes several informative comparisons of model predictions with published data but no comparison of predicted human breast milk perchlorate concentrations with published data. A comparison of breast milk data from Pearce et al 2007; Kirk et al 2005 and 2007 etc. combined with estimated US median perchlorate intakes (Blount et al 2006) should be completed, as this would provide important insight into model uncertainty regarding this critical exposure pathway.

Section III(B): Comments on Alternative Approaches for Calculating Health Reference Levels (HRLs)

1) MassDEP recommends that EPA use the approach to setting HRLs as shown in Section III, Subsection B-3.

2) We support EPA's reassessment of exposure assumptions for life stages, including fetuses of gestation week 40, infants and developing children. Application of EPA's Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants is appropriate along with application of EPA's Guidance for Risk Characterization to convey the variability in risk levels experienced by different individuals in the population. In doing so, EPA has appropriately taken into account specific and appropriate exposure values for many but not all potentially sensitive life stages. Because of the potential sensitivity of the early neonatal period from birth to several days thereafter, we believe that exposures to the bottle-fed 7-day old should also be considered. In EPA's Interim Drinking Water Health Advisory for Perchlorate, the 7-day old bottle-fed infant was estimated to have the highest perchlorate exposure per body weight.

3) Other sensitive populations should not be forgotten when EPA is addressing levels of health concern and potential numbers of people exposed to perchlorate in drinking water. Other sensitive subgroups not explicitly addressed include individuals with low iodine intake, untreated thyroid conditions, those suffering from cardiovascular and renal diseases (Miller et al. 2009; Iglesias and Diez 2009), individuals exposed to mixtures of other thyroid stressors, the elderly who are often prone to thyroid problems, and people with thyroid cancer. The results of Blount et al 2006 also indicate that women should be considered a sensitive group, certainly at the current RfD.

4) MassDEP supports setting the HRL on the basis of the life stage(s) with highest exposure and risk with a 90% percentile ingestion rate, which is standard practice. Based on Table 2, this would support an HRL of 2 ppb (or perhaps somewhat lower depending on the exposure estimate for the 7-day old). It is worthwhile to note that the alternative HRLs calculated using the 95th percentile exposure values for early life stages are not very different than the HRL values estimated using the 90th percentile ingestion rates, especially considering the rounding involved in the final calculation of the HRLs. Although EPA's concern about sample size and aggregation of life stages is legitimate, the aggregation of life stages in the current document (birth to < 6 months) yield closely similar HRL values derived for life stages birth to < 1 month, 1 to < 3 months, and 3 < 6 months and birth < 6 months and therefore appear to be reasonably stable estimates (Table 2).

5) Although the HRL of 2 ppb recommended above is numerically similar to the maximum contaminant level adopted by MassDEP and protective of the sensitive segment of the population, the RfDs used by the two agencies as the bases to derive the drinking water levels are different. MassDEP concluded that the National Research Council's (NRC) RfD is not protective of public health (Zewdie et al. 2009). Although uncertain, the EPA's modified PBPK analysis presented in Table 1 for a 7-day-old healthy infant supports this position. In this analysis, the infant gets about 3 times the maternal dose through breast milk at the dose equal to the point-of-departure (POD) in the NRC RfD derivation. This translates to a 7-day infant receiving about 20 µg/kg/day (0.02 mg/kg/d) dose of perchlorate through breast milk from a mother ingesting 7 µg/kg/day. This dose level is equivalent to the exposure level that resulted in significant inhibition (17 %) of iodide uptake in healthy adults in the Greer et al. (2002) study, suggesting that the factor of 10 applied to the POD by the NRC to protect sensitive individuals is insufficient. An additional uncertainty factor is required to extrapolate from LOAEL to NOAEL as 0.02 mg/kg/day is an effect level. Efforts to determine populations at risk based on the NRC RfD will yield significant underestimates of those at risk. MassDEP can support EPA's decision to not re-evaluate the NRC RfD at this time, if EPA adopts an HRL of 2 ppb or lower.

6) We believe that EPA has used the best available exposure data for deriving the HRLs. Use of the 90% percentile ingestion rate addresses uncertainties regarding the issue of minimum data set deficiencies for ingestion rates.

Section III C: Occurrence Analysis

4(a)) EPA's proposal to use a Bayesian model to estimate the number of public water systems, and populations served by such systems, with sample detections at various levels appears to be a reasonable approach. Further details regarding the specific model inputs are, however, needed in order to assess the usefulness of the model. MassDEP will provide U.S. EPA with Massachusetts perchlorate monitoring data to assist in this effort. However, we wish to note that the sampling results and data distribution for MA may not reflect the situation in other states. We also wish to note that the population estimates in column 5 of Table three would be likely to underestimate those exposed in MA, and quite likely other states, due to mixing of supplies from multiple entry points.

4(b)) EPA requested comments on using US Census data to estimate the portions of the population that are sensitive at any one time to perchlorate in drinking water. This analysis is used as one factor in EPA's decision-making on the need for a drinking water standard for perchlorate, based on the number of people in the U.S. who would be at risk. MassDEP believes that it is inappropriate to consider sensitive groups one-by-one using census or any other data. EPA should certainly consider perchlorate exposures to fetuses, infants and young children up to 2 years of age. However, EPA should also, for several reasons, consider the entire population's exposure. . First, Blount et al. (2006) and Steinmaus et al. (2007) reported an association between perchlorate exposure and decreased T4 and increased TSH in iodine deficient adult women and increased TSH in all women. As such, we believe that all women should be included in EPA's analysis as a sensitive subgroup. Secondly, as previously noted, there are other sensitive members of the population beyond fetuses, infants and women, and they should also be factored into EPA's framework for considering the extent of the population at risk to perchlorate exposures from drinking water. Lastly, because significant exposures to other thyroid toxicants are known to occur, other members of the population may also be at increased risk. Thus, any estimate derived based on exposures to the fetus, neonate and women as a group will still be an underestimate of those actually at risk.

We appreciate the opportunity to comment. For further information please contact Carol Rowan West at 617-292-5510 (Carol.RowanWest@state.ma.us), C. Mark Smith at 617-292-5509 (C.Mark.Smith@state.ma.us) or Tsedash Zewdie at (617) 292-5842 (Tsedash.Zewdie@state.ma.us).

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