University of Massachusetts-Amherst

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US Environmental Protection Agency
Office of Water Docket (Mailcode: 2822T)
1200 Pennsylvania Avenue, NW
Washington, DC 20460

RE: Comments on Regulatory Determination on Perchlorate
Docket EPA-HQ-OW-2008-0692

Drs. Carol Bigelow, Larry Schwartz, and R. Thomas Zoeller are pleased to submit comments to the US EPA on Docket ID No. EPA-HQ-OW-2008-0692, entitled "Drinking Water: Preliminary Regulatory Determination on Perchlorate". In brief, the authors of docket ID No. EPA-HQ-OW-2008-0692 propose that there be ***no*** national primary drinking water regulation, the rationale being that such would not present a *"meaningful opportunity for health risk reduction for persons served by public water systems"*. EPA's proposal not to regulate perchlorate in public water systems:

(1) Lacks the requisite scientific basis. Specifically, EPA regularly cites the nearly 4 year-old NAS report (NRC, 2005) without a critical evaluation of the science underlying the document and how new information should be integrated into it. This issue is most germane in the emphasis on the pregnant woman and fetus as the most sensitive population to perchlorate exposure. EPA fails to consider published, peer-reviewed data demonstrating that the current RfD for perchlorate exposure is not protective of neonates and infants (Ginsberg and Rice, 2005; Ginsberg et al., 2007).

(2) Lacks critical evaluation of the literature employed to justify its decision. Methodologically sound research indicates an association between perchlorate exposure and thyroid function in adult women with low iodine intake (Blount et al., 2006a; Steinmaus et al., 2007). If infants are no more sensitive to perchlorate than adult women, brain damage will occur at the median level of perchlorate exposure, according to published data (reviewed by (Ginsberg et al., 2007)). Thus, the CDC study should reasonably replace the 6 year-old "Greer Study" (Greer et al., 2002) as the point of departure for RfD development.

(3) Fails to critically evaluate the reliability of null findings. EPA justifies ignoring the Blount Study using a series of studies that identify no relationship between perchlorate exposure and thyroid function in humans. However, EPA is apparently unaware of published data describing the variability of serum thyroid hormone measures in adults (Andersen et al., 2002; Andersen et al., 2003) and in neonates (Herbstman et al., 2008a; Herbstman et al., 2008b). It is our opinion that critical analysis of the null findings employed by EPA to justify ignoring the findings in the Blount Study will

demonstrate that these null findings cannot be interpreted to indicate no relationship between perchlorate exposure and thyroid function.

(4) Relies on a PBPK model parameterized with weak data. It is discouraging that EPA went to the effort of obtaining the code for the Clewell et al. PBPK model and modified it without critically evaluating the data employed to parameterize the model.

Considering these 4 points, it is our opinion that a scientifically valid RfD and HRL will be significantly lower than that the current proposal. Moreover, the data are available to scientifically defend a return to EPA's draft RfD of 2002.

Perchlorate interferes with thyroid function in both animals and humans. A consideration of known differences in thyroid physiology between adults and neonates/infants supports the conclusion that the neonate and infant are the most "at risk" population.

Three important differences in thyroid physiology between adults and neonates/infants supports the conclusion that this population is the most vulnerable to perchlorate exposure (reviewed by (Ginsberg et al., 2007)):

1) Serum half-life of the thyroid hormone T_4 is substantially longer in the adult relative to the neonate (7-10 days (Chopra and Sabatino, 2000)) versus 3 days (Lewander et al., 1989; van den Hove et al., 1999). This means that for adults, serum thyroid hormone levels are stable in the face of the daily fluctuations in perchlorate exposure and iodine uptake that might arise from drinking water contaminated with perchlorate. In contrast, the shorter serum half-life of T_4 in the neonate means that there will be a much more rapid response to the inhibition of iodine uptake by perchlorate.

2) The adult thyroid gland stores a considerable amount of hormone, possibly enough for several months of normal secretion (Greer et al., 2002). Consequently, adults can presumably function normally without new hormone synthesis for extended periods. In contrast, the neonatal thyroid gland contains essentially no extra hormone and the amount of thyroid hormone in the neonatal gland represents a single day's worth of hormone (van den Hove et al., 1999). Therefore, the neonate must generate new hormone on a daily basis and perturbations in iodine uptake can have significant consequences.

3) The adult thyroid system can compensate for low thyroid hormone levels and the consequences of low thyroid hormone are likely to be reversible. This is in contrast to the neonatal thyroid gland which does not readily compensate for low thyroid hormone (reviewed by (Ginsberg et al., 2007)), and the consequences of low thyroid hormone at this time are not reversible (reviewed by (Rovet, 2002; Zoeller and Rovet, 2004).

Thus, neonates and infants represent unique "at risk" populations in the matter of perchlorate exposure and its effects on public health.

Thyroid hormone insufficiency in the neonate and infant leads to irreversible health consequences. Defects in thyroid hormone regulation negatively impact brain development and may contribute to a cluster of irreversible neurological defects that includes autism. This literature – completely ignored by EPA's analysis – is compelling public health rationale for regulating perchlorate exposure.

Perhaps the best examples of infants' unique sensitivity to thyroid hormone insufficiency are the studies of infants with congenital hypothyroidism (CH) (for review, see (Zoeller and Rovet, 2004)). These studies are particularly useful because subjects are under continuous medical surveillance so there is good documentation of the relationship between endogenous thyroid hormone, levels of hormone supplementation, and developmental outcome (Heyerdahl and Oerbeck, 2003). The neuropsychological outcome of children diagnosed with CH at birth is associated with both the severity of CH and early treatment factors (how soon T_4 was administered, starting dose and serum T_4 levels during the first two years of life). These T_4 parameters were highly correlated with verbal IQ at age 20, and children with CH who ultimately completed high school had a significantly higher T_4 starting dose than those who did not (Oerbeck et al., 2003). Strikingly, the difference in mean starting dose between these two groups was a modest 2.1 µg/kg-day. Because iodine represents 65% (w/w) of T_4, the amount of iodine associated with that T_4 difference was only 1.37 µg/kg-day. Independent studies were consistent in their findings. In Selva et al. (2002) and Selva et al (2005), a difference in starting dose of only 12.5 µg/day (8.13 ug/day iodine equivalent or 2.3 ug/kg/d) was associated with a significant difference in full scale IQ of 11 points (Selva et al., 2002; Selva et al., 2005). Thus, small differences in available thyroid hormone (and the iodine associated with it) during the first few weeks of life can have significant lifetime consequences including, especially, reduced IQ.

In addition, the experimental literature clearly demonstrates that specific neurodevelopmental events are irreversibly damaged by marginally-low thyroid hormone. These include neuronal migration (Lavado-Autric et al., 2003; Auso et al., 2004), synaptic function (Gilbert and Sui, 2006, 2008), white matter development (Sharlin et al., 2008), and the development of nodular heterotopias (Goodman and Gilbert, 2007). Each of these developmental events will have cognitive and neurological sequelae in humans.

In its unsupported reliance on the NAS report of 2005 (NRC, 2005), EPA did not focus their analysis on the relevant vulnerable groups, the neonate and infant. In this regard, EPA failed to employ one of the largest, and critically relevant, data sets relating thyroid hormone to health consequences – that of neonates and infants (see (Chan and Rovet, 2003; Zoeller and Rovet, 2004)). The superficial reference EPA makes to the infant is wholly inadequate in the current version of this document and should take into consideration the issues developed above and expanded previously (Ginsberg et al., 2007). In addition, EPA should review the issue of genetic factors that may impact individual sensitivity to perchlorate exposure (Scinicariello et al., 2005). Due consideration to this published literature will dramatically change the EPA's analysis.

The analyses that form the basis of docket ID No. EPA-HQ-OW-2008-0692, entitled "Drinking Water: Preliminary Regulatory Determination on Perchlorate" err significantly in the omission of critically relevant data sources. At a minimum, a critical evaluation of Blount et al (2006a) should be incorporated into the docket and the conclusions drawn therein should be revised accordingly.

Another key data source that was omitted from consideration by the EPA is the relationship between perchlorate exposure and thyroid function identified by Blount et al. (Blount et al., 2006a). Blount et al., (2006a) results are consistent with a causal relationship between perchlorate exposure and thyroid function as follows:

a. The strength of the relationship between urinary perchlorate and serum total T_4 and serum TSH was greater in women with low urinary iodide (>100 µg/L).

b. The strength of the relationship between urinary perchlorate and serum total T_4 and serum TSH was greater in women who smoked (Steinmaus et al., 2007).

c. Significant relationships with other ions known to affect iodide uptake were not observed.

d. Given the known variability in urinary perchlorate levels (Blount et al., 2006b) and in T_4 and TSH levels (Andersen et al., 2002; Andersen et al., 2003), a very large sample size would be required to identify these relationships.

EPA cites the NAS report of 2005 (NRC, 2005) as indicating that epidemiological studies cannot identify a causal relationship between perchlorate exposure and thyroid function. However, the CDC study of 2006 represents a verification that known and predicted relationships between perchlorate exposure and thyroid function are occurring at environmental levels of perchlorate exposure in the human population. EPA must consider the statistical power of the CDC study to identify relationships of interest. These findings, furthermore, indicate that the high-dose, short-term studies of Greer and others do not provide relevant information about the life-time low-dose exposure to perchlorate. Therefore, in the absence of a rational alternative to epidemiological studies to identify such relationships of interest in humans, EPA must employ the best available science – that of the Blount study.

We also found critical errors in the selection, design and interpretation of the studies that were included in docket ID No. EPA-HQ-OW-2008-0692. The irrelevant studies should be dropped from the docket, the flawed interpretations of the remaining studies should be corrected, and the conclusions drawn revised.

Several studies reported in docket ID No. EPA-HQ-OW-2008-0692 are either inappropriate for inclusion, or erred in their design or interpretation. Most significant in this regard is the population that was emphasized by the EPA in citing the NAS report of 2005 (NRC, 2005): pregnant adults. EPA provided no scientific justification for this emphasis. Moreover, the emphasis on the pregnant adult illustrates the mistake of public health recommendations by persons who are *not* at significant risk. As we've noted above: *"the adult thyroid system appears capable of significant compensation for low thyroid hormone levels, and the consequences of low thyroid hormone are likely to be reversible."*

Also lacking in the science presented in docket ID No. EPA-HQ-OW-2008-0692 are the power considerations necessary to inference making that is precise. Indeed, several of the studies relied upon by the US EPA lacked the statistical power needed to rule out a non-null association.

EPA has failed to address key questions regarding the studies it uses to defend ignoring the CDC study. Specifically, *given the known variability in measures of thyroid function* (Andersen et al., 2002; Andersen et al., 2003) and *maternal, infant and delivery factors on neonatal and thyroid status* (Herbstman et al., 2008a; Herbstman et al., 2008b), *to what extent do epidemiological studies exploring the relationship between perchlorate and thyroid function provide reliable evidence of a null relationship?* Andersen et al. (Andersen et al., 2003) discuss the sources of variability in measures of thyroid hormone in adults. These are critical considerations to employ in estimating the ability of epidemiological studies to identify relationships of interest between perchlorate and thyroid function. Moreover, Andersen et al. (2002) found that to identify the homeostatic set-point within 5% precision required 85 individual measures of TSH and 25 of total T_4. Given this degree of variation, studies comparing average measures of thyroid function and proxy measures perchlorate exposure have little – if any – ability to identify relationships of interest. Therefore, EPA is required to determine which of the epidemiological studies it used in its analysis had the potential to identify a relationship between perchlorate exposure and thyroid function, and the degree to which null findings are meaningful.

Considering that the Blount study (Blount et al., 2006a) is the only study available to the EPA that had the ability to identify a relationship between life-time, low-dose perchlorate exposure and thyroid function, this study should supercede the Greer 2002 study for the derivation of the RfD. This study demonstrates that, in women with low urinary iodide, perchlorate exposure at the 50th percentile is associated with a 1.06 µg/dL reduction in serum total T_4. While this may be of uncertain clinical significance to adult women, it is clinically significant to an infant during highly sensitive periods of postnatal brain development. In addition, the EPA would then be in a stronger position because it would be regulating on hormone reduction, rather than iodide uptake inhibition. Moreover, it is now conclusively shown that perchlorate is transported by the sodium/iodide symporter (NIS) (Dohan et al., 2007) and is found at high levels in human milk (Kirk et al., 2007; Pearce et al., 2007). Thus, the US EPA should recalculate the RfD and HRL based on the CDC study as the point of departure.

*Accordingly, docket ID No. EPA-HQ-OW-2008-0692 should **not** form the basis for national primary drinking water regulation.*

Considering these issues, we conclude that EPA has based its argument for not regulating perchlorate contamination in public water systems on a literature that is both limited and ill focused. We believe that EPA has not performed a sufficiently "thorough review" of the literature, that it has omitted important information, and that it has failed to perform its due diligence in the interpretation and analysis of the information that it did present. To correct this, EPA must employ the CDC study (Blount et al, 2006a) as the point of departure for RfD determination, and must focus on the neonate and infant as the most sensitive population.

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