March 8, 2006

Stephen L. Johnson, Administrator
United States Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

RE: Perchlorate PRG and water contamination

Dear Administrator Johnson:

The Children's Health Protection Advisory Committee (CHPAC) is writing to express concern over a recent assessment guidance issued by the U.S. EPA, Office of Solid Waste & Emergency Response (OSWER). The OSWER guidance creates a groundwater preliminary remediation goal (PRG) for perchlorate at Superfund sites that is not protective of children's health. The new PRG is not supported by the underlying science and can result in exposures that pose neurodevelopmental risks in early life. The new PRG can lead to exposures that are well above USEPA's IRIS RfD for perchlorate. The CHPAC finds it disturbing that this change in the PRG was made without dissemination of a decision support document or any opportunity for public input. We recommend that OSWER lower the PRG, taking into account infant exposures and susceptibility. We also recommend that USEPA's Office of Ground Water and Drinking Water (OGWDW) develop a Maximum Contaminant Level (MCL) for perchlorate, and in the interim, issue a health advisory for potable water that takes into account early life exposures.

Background

On January 26, 2006 OSWER released a PRG that would allow remediation of perchlorate at Superfund sites to a higher level (24.5 μg/L) than the previous screening level (4-18 μg/L). This establishes a potable water PRG, which is a critical starting point for site cleanup. USEPA is required to develop PRGs in a health protective manner to enable broad future use of the site, with site-specific factors enabling the risk manager to adjust the cleanup target.

Risk of neurodevelopmental toxicity can occur from perchlorate exposure because perchlorate impairs the uptake of iodide by the thyroid, which can decrease thyroid hormone production and affect brain development. This is especially important in infants because they do not have stores of thyroid hormone, and are no longer supported by maternal thyroid hormone following birth. What may be considered by some to be a precursor effect in normal adults (inhibition of iodide uptake by the thyroid) may be an adverse effect during this sensitive life stage, especially in concert with exposure to other thyroid toxicants (e.g., PCBs, PBDEs) and because perchlorate may decrease iodine levels in human milk.

The CHPAC acknowledges that EPA's RFD incorporates a ten-fold uncertainty factor to protect the fetuses of pregnant women who might have hypothyroidism or iodide deficiency. This factor was used to account for interindividual differences that lead to uncertainty in assessing perchlorate risk. However, the uncertainty factor does not cover the types of exposure differences across life stages discussed in this letter.

The OSWER Perchlorate PRG Does Not Protect Infants and Should be Lowered

Perchlorate is a well-recognized endocrine disruptor at sufficiently high doses, targeting the thyroid and thus creating risk of neurodevelopmental toxicity. A key concern is the nursing infant because of the potentially high exposure rate associated with this pathway, and the high susceptibility at this life stage. The following points highlight the fact that nursing infants could receive daily doses that are greater than the RfD if the mother is exposed to 24.5 μg/L perchlorate in tap water. The supporting calculations are provided in the appendix to this letter.

Infant Exposures

- Perchlorate is actively transported into human milk leading to nursing infant exposure to perchlorate; current data suggest this is associated with concomitant lowering of iodide in human milk (Kirk, et al., 2005; Tellez, et al., 2005, see Appendix to this letter). Both of these factors increase the risk of neurodevelopmental toxicity due to perchlorate anti-thyroid effects occurring in the susceptible postnatal period.
- The current PRG (24.5 μg/L) would allow a nursing mother to ingest approximately 54 μg of perchlorate per day. Based upon the Chilean three-cities database (Tellez, et al., 2005), this would yield a human milk perchlorate concentration of 28 to 46 μg/L.
- **This would lead to a nursing infant exposure that is approximately 5 to 10 times higher than the perchlorate RfD.**
- This analysis does not account for variability in perchlorate exposure. Assessment of the entire population distribution would identify high-exposure individuals that would be at greater risk than currently estimated.
- Bottle-fed babies can also receive perchlorate exposure above the RfD through tap water used to reconstitute formula and juices, or directly fed to the infant. This perchlorate exposure may not be quite as high as in breast-fed infants; however, it is still a concern.

Infant are a Susceptible Population

Not only are infants more exposed, they are also susceptible to the neurodevelopmental effects of perchlorate because of the following early life factors:

- The central nervous system (CNS) is still developing but the maternal supply of thyroid hormone that was present *in-utero* is no longer available; thyroid hormone does not transfer into breast milk in significant amounts.
- The developing CNS in infants is sensitive to small deficits in thyroid hormone levels as evidenced by later indices of neurocognitive function (Oerbeck, et al., 2003; Heyerdahl and Oerbeck, 2003; Rovert and Daneman, 2003);
- Infants are not born with adequate thyroid hormone reserves and so must make new thyroid hormone on a continual basis to meet the demands of brain growth (Delange, 1998; van den Hove, et al., 1999).
- Immaturities in renal function at birth may lead to slow clearance of perchlorate, as urinary excretion is the major elimination pathway. Data from rats on perchlorate toxicokinetics in neonates (Clewell, et al., 2003) may not be highly relevant (see Appendix).

These factors, coupled with the infant exposure estimates, indicate that the PRG of 24.5 μg/L in drinking water is not protective. The PRG would produce above-RfD perchlorate exposure in infants who are susceptible to endocrine disruption and adverse neurodevelopmental impacts. While RfDs are generally considered chronic toxicity values, applying the perchlorate RfD to a shorter, critical window of susceptibility and high exposure in infancy is warranted. The OSWER cleanup PRG should apply the RfD to infants just as it is applied to pregnant women.

Lack of Consideration of an RSC

Groundwater cleanup targets are normally based upon the chemical's RfD and a relative source contribution (RSC) factor. The RSC accounts for that part of the exposure that comes from non-drinking water sources. The OSWER PRG is set without accommodation for other exposure sources. This is an obvious concern given the recent widespread detection of perchlorate in lettuce and milk (USFDA, 2004). Drinking water standard setting for perchlorate in New Jersey and Massachusetts has used an RSC of 0.2 (20% from water) while the California RSC is 0.6 (NJ Drinking Water Quality Inst., 2005; Ting, et al., 2006).

Use of an appropriate RSC could lower the PRG to a range that would ensure maternal intake of perchlorate is below a level which poses a risk of adverse neurodevelopmental outcome for the fetus and nursing infant.

The CHPAC recommends that OSWER lower the PRG considering the following points:

- The OSWER PRG ignores the higher exposure and susceptibility of infants, and could lead to nursing and bottle-fed infants being exposed to daily doses

that are well above the perchlorate RfD; the PRG needs to protect this susceptible population.

- The OSWER PRG does not account for perchlorate exposures from foods, which are in addition to drinking water. By omitting the RSC and not accounting for infant exposure, the PRG now allows for greater-than-RfD doses to the mother and her developing fetus and to nursing infants. OSWER should lower the PRG with an appropriate RSC and adjustment for exposure to infants.

The scientific issues discussed above are also central to the ongoing OGWDW deliberation of whether to set a Maximum Contaminant Level (MCL) for perchlorate. The CHPAC has been closely monitoring this deliberation for the past year and is concerned that there is still no decision about a perchlorate MCL.

OGWDW Regulatory Determination on Perchlorate

The CHPAC encourages OGWDW to establish a national drinking water standard for perchlorate, and in so doing, to fully consider both the prenatal and postnatal exposures and risks. Perchlorate has been known to contaminate groundwater at over 400 locations nationwide (GAO, 2005) and biomonitoring data demonstrate widespread exposure (Valentin-Blasini, 2005). We encourage the Agency to fully consider the particular susceptibility of the fetus as well as the infant who may be exposed through breastfeeding or reconstituted formula. We believe that technology (e.g., cleanup methods) exists to protect infants from perchlorate exposure.

Setting a federal MCL will greatly facilitate the discovery and control of drinking water contamination by this pervasive chemical. It would also help decrease a key uncertainty identified by the CHPAC: we do not know the perchlorate level in pre-constituted infant formula and other drinks. The water that goes into ready-to-use formulations is not currently required to be tested for perchlorate, although we are aware that manufacturers may purify water that goes into pre-constituted formula. Setting a federal MCL would require widespread testing of water supplies and thus provide greater confidence that both commercial and home-reconstituted infant formulations are made with water free of perchlorate contamination.

We recognize setting an MCL can be a lengthy process. In the interim, it is important for OGWDW to develop a drinking water health advisory for perchlorate. Such advisories normally factor in the RSC and can account for early life windows of high intake rate and susceptibility. A drinking water health advisory can inform the many state and federal programs that may detect perchlorate in drinking water supplies and need a public health protective guideline. The OSWER PRG is not intended for this purpose, but some risk managers may extend its use to such applications. This would be most unfortunate given the concerns expressed above that the current PRG is not protective of infants. Therefore, it is especially important for OSWER to lower the PRG and for OGWDW to develop an interim health advisory for perchlorate.

Summary and Recommendations

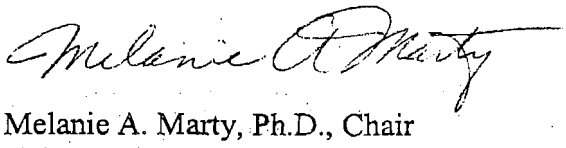
Perchlorate is an important endocrine toxicant because of widespread exposure and the potential for impairment of the thyroid during critical stages of brain development. The risk posed by this environmental agent is preventable by appropriate Agency action.

The CHPAC recommends that:

- OSWER lower the perchlorate PRG, using a more comprehensive risk assessment that includes postnatal exposures and health risks.
- OSWER use an RSC factor of less than 100% to account for the non-drinking water sources of perchlorate.
- OGWDW set an MCL for perchlorate that protects both the pre-and post-natal exposure periods.
- OGWDW develop an interim health advisory that addresses the early life exposure and susceptibility issues raised above.

We would be happy to discuss any of the points or recommendations raised in this letter with you or your staff. We would also like to be informed of the Agency's progress in protecting the public from perchlorate and to be provided with the documentation for any future guidance on perchlorate remediation. We thank you in advance for your consideration of these issues.

Sincerely,



Melanie A. Marty, Ph.D., Chair
Children's Health Protection Advisory Committee

Cc: Susan Bodine, Assistant Administrator, OSWER
Barry Breen, Deputy Assistant Administrator, OSWER
Benjamin Grumbles, Assistant Administrator, OW
Michael Shapiro, Deputy Assistant Administrator, OW
William Sanders, Interim Director, OCHPEE
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Appendix

1) Relationship between iodide and perchlorate levels in human milk.

A sodium iodide transporter protein akin to that in the thyroid exists in mammary tissue. It transports iodide into human milk, and perchlorate id able to take iodide's place and be selectively pumped into milk (Clewell, et al., 2003). This can lead to nursing infant exposure to perchlorate, while at the same time leading to lower levels of iodide in milk. Kirk, et al. (2005) demonstrate an inverse correlation between perchlorate and iodide concentrations in human milk in a small number of US samples that were over 10 μg/L perchlorate. Tellez, et al. (2005) did not see a correlation, inverse or otherwise, between perchlorate and iodide concentrations in human milk across three Chilean cities with widely differing concentrations of perchlorate in drinking water. However, there does seem to be a factor that depresses iodide levels in human milk in these Chilean cities relative to the U.S. On average, Chilean human milk iodide concentrations were 40% lower than in US women in spite of the fact that iodide intake rates are known to be higher in these Chilean cities than in the US (Tellez, et al., 2005; Kirk, et al., 2005). The factor responsible for the lower-than-expected human milk iodide in Chile may be perchlorate intake as baseline (dietary) exposure to perchlorate is approximately 3 times higher in Chile as compared to the US. This is seen by comparing perchlorate biomonitoring data in Atlanta against the three Chilean cites (Valentin-Blasini, et al., 2005). The reason the Chilean cross-sectional study did not find an inverse correlation between human milk levels of perchlorate and iodide is unclear but comparisons are available only on the basis of group mean (Tellez, et al., 2005); regression analysis of the entire dataset would be a more sensitive method to determine whether there is a significant relationship between these human milk parameters in Chile. Evidence in rats for an inverse relationship between maternal perchlorate exposure and iodine levels in breast milk (Clewell, et al., 2003) supports the evidence for such a relationship in human milk.

2) Calculations of nursing infant perchlorate dose stemming from the OSWER cleanup target (24.5 μg/L) and comparison to the EPA RfD:

Nursing Infant Dose (μg/kg/d) = (μg/L in human milk/ug perchlorate ingestion-day)*[(24.5 μg perchlorate/L water)* (L water ingested/day) + (baseline US dietary ingestion rate, μg/d)]*(L human milk ingested/day/infant body weight)

Parameter values:

a) Relationship between human milk perchlorate and maternal perchlorate intake:

i) μg/L in human milk – data for the 3 Chilean cities (Tellez, et al., 2005)
Antofagasta: Cannot use the data due to extreme outlier and high variability;
Chanaral: **Mean = 18.3 μg/L**; SD = 17.7
Taltal: **Mean = 95.6 μg/L**; SD=54.6

ii) μg perchlorate excreted/g creatinine:
Antofagasta: Min: 2.9; 10th%: 8.64; 25th%: 12.96; Med: 22.7; 75th%:43.2; 90th%: 59.4; Max:: 75

Chanaral: Min: 12; 10th%: 17; 25th%: 27; Median: 37; 75th%:63; 90th%: 155; Max: 210
Taltal: Min: 20; 10th%: 45; 25th%: 70; Median: 120; 75th%:190; 90th%: 295; Max: 395

iii) μg perchlorate excreted /day = above #'s * creatinine excretion/d (1.08 g/d) (Tellez, 2005; Knuppel, 1979)
Antofagasta: Min: 3.1; 10th%: 9.3; 25th%: 14; Median: 24.5; 75th%:46.7; 90th%: 64; Max: 81
Chanaral: : Min: 13; 10th%: 18.4; 25th%: 29.2; **Median: 40**; 75th%: 68; 90th%: 167; Max: 227
Taltal: Min: 21.6; 10th%: 48.6; 25th%: 75.6; **Median: 129.6**; 75th%:205; 90th%: 319; Max: 427

Assume μg excreted/day = μg intake/day

Estimate of relationship between μg/L human milk to μg ingested/day is thus:
Chanaral: 18.3 μg/L / 40 μg/d = **0.458 (units of d/L)**
Taltal: 95.6 μg/L / 129.6 μg/d = **0.737 (d/L)**

b) Lactating mother water ingestion rate (ml/d): mean = 1189 ml/d, SD=699; 50th percentile = 1063; **90th% 2191**; 95th% = 2424 (from CSEFH, USEPA, 2000, Table 4-13)

c) Dietary perchlorate ingestion rate per day from food and other baseline sources in US (Atlanta data – Valentin-Blasini, et al., 2005)
μg perchlorate excreted/g creatinine:
Atlanta: Min: 2.5.; 10th%: 3.1; 25th%: 4.8; **Median: 7.8**; 75th%:10.0; 90th%: 16.2; Max: 20
μg perchlorate excreted /day = above #'s * creatinine excretion/d (1.08 g/d) (Tellez, 2005; Knuppel, 1979)
Atlanta: Min: 2.7; 10th%: 3.35; 25th%: 5.2; **Median: 8.4;** 75th%:10.8; 90th%: 15; Max: 21.6

d) Infant human milk consumption rate at 2 wks of age: **634 ml/d**, SD = 149.5; range = 416-922. (CSEFH, 2000; page2-4)

e) Infant body wt at 2 weeks age (kg): avged across sex:
5th% = 2.76; 25th%= 3.34; **Median = 3.69**; 75th%=4.07; 95th%=4.57

Exposure and Risk Calculations:
Nursing infant exposure dose = (0.458 or 0.737 d/L) *[(24.5 μg/L * 2.191 L/d) + 8.4 μg/d] * (0.634 L human milk/d) / 3.69 kg body wt) = **4.9 – 7.9 μg/kg/d**

RfD = 0.7 μg/kg/d

Nursing infant Hazard Index = 4.9 or 7.9 / 0.7 = 7 to 11

Note: Hazard Index is influenced by the way in which the milk to perchlorate intake ratio was calculated. The cited literature reports the mean human milk concentrations and the median urinary perchlorate; it will take a full distributional analysis to calculate the mean urinary perchlorate; this will enable the construction of a mean milk to mean intake ratio. This ratio may be slightly lower than the mean milk to median intake ratio presented above. Therefore, we round our estimate of nursing infant hazard index downward to **5 to 10 fold** pending further analysis.

3) Perchlorate Toxicokinetics in the Neonate

Perchlorate is cleared primarily via the urine with protein binding tending to retain perchlorate in serum and retard its excretion (Clewell, et al., 2003). Human infants have immature renal function and less urinary clearance of many water soluble chemicals (Morselli, 1989; Kearns and Reed, 1989, Ginsberg, et al., 2002), suggesting that slow clearance is another infant susceptibility factor to perchlorate. Rat toxicokinetic data show that in spite of higher dose rate from nursing, pups had lower perchlorate serum concentration than adult rats (Clewell et al., 2003; NAS, 2005, Appendix E). These data are of questionable relevance to human infants given the variety of cross-species differences in the ontogeny of toxicokinetic systems (Ginsberg, et al., 2004). Other factors also affect the utility of neonatal rat data from this study (Clewell, et al., 2003): a) rat dams drink 80% of the daily output of pup urine which inflates the adult dose and serum level of perchlorate relative to the neonate; b) lactating dams and pups were dosed with radioactive iodide which may affect perchlorate toxicokinetics, especially with regards to competition for serum binding sites in the neonate which has limited binding capacity. These factors discourage the use of nursing rat pup data (Clewell, et al., 2003) to describe the toxicokinetics of perchlorate in human infants.