Charge to EPA Science Advisory Board

LIFE STAGE CONSIDERATIONS AND INTERPRETATION OF RECENT EPIDEMIOLOGICAL EVIDENCE TO DEVELOP A MAXIMUM CONTAMINANT LEVEL GOAL FOR PERCHLORATE

Background

On February 11, 2011 (U.S. EPA, 2011a), EPA published a determination to regulate perchlorate under the Safe Drinking Water Act (SDWA) because:

- perchlorate may have an adverse effect on the health of persons;

- perchlorate is known to occur or there is a substantial likelihood that it will occur in public water systems with a frequency and at levels of public health concern; and,

- in the sole judgment of the Administrator, regulation of perchlorate presents a meaningful opportunity for health risk reduction for persons served by public water systems.

EPA has initiated the process to develop a Maximum Contaminant Level Goal (MCLG) and National Primary Drinking Water Regulation (NPDWR) for perchlorate. The MCLG is a non-enforceable goal defined under the SDWA (§1412.b.4.B) as *the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety.* For perchlorate, the NPDWR will likely specify an enforceable Maximum Contaminant Level (MCL) and monitoring and reporting requirements for public water systems. The SDWA (§1412.b.4.B and D) specifies that the enforceable MCL be set as close to the MCLG as feasible using the best available technology, treatment techniques, and other means (taking cost into consideration).

The regulatory schedule established by SDWA requires EPA to publish a proposed MCLG and NPDWR within 24 months of making a determination to regulate a contaminant and promulgate a final regulation within 18 months of the proposal. As part of this proposed rulemaking, EPA also must develop a Health Risk Reduction and Cost Analysis that includes an assessment of the quantifiable and non-quantifiable health risk reduction benefits likely to occur as a result of treatment to remove the perchlorate. SDWA further requires that when proposing any NPDWR that includes an MCL, the Administrator must analyze "*[t]he effects of the contaminant on the general population and on groups within the general population such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subpopulations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population[1].*"

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[1]SDWA uses the term subpopulation to refer to groups within the general population such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other groups that can be identified and characterized and are likely to experience elevated health risks. In 2005 EPA started using the term life stages to refer to age-defined groups. All life stages are subpopulations but not all subpopulations are life stages. In this document, the term life stage is used predominantly because of the focus on infants and very young children.

In 2005, at the request of EPA and other federal agencies, the NRC published a comprehensive report "*Health Implications of Perchlorate Ingestion*" (NRC, 2005). The NRC concluded that perchlorate can affect thyroid function because it is an ion that competitively inhibits the transport of iodide into the thyroid by a protein known as the sodium (Na)/iodide (I) symporter (NIS). Significant inhibition of iodide uptake results in intra-thyroid iodine deficiency, decreased synthesis of key thyroid hormones (Triiodothyronine, T3 and Thyroxine, T4), and increased thyroid stimulating hormone or thyrotropin (TSH). The NRC also concluded that a prolonged decrease of thyroid hormone is potentially more likely to have adverse effects in sensitive populations (people with thyroid disorders, pregnant women, fetuses, and infants).

The NRC recommended the use of a precursor, non-adverse effect (i.e., inhibition of iodide uptake) to derive a reference dose (RfD) for perchlorate. An RfD is defined by EPA as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." The NRC identified a clinical study involving 37 healthy men and women by Greer *et al*. (2002) as the critical study and determined an RfD of 0.7 µg/kg/day for perchlorate. The RfD was based on the No Observed Effect Level (NOEL) of 7 µg/kg/day corresponding to a radioactive iodide uptake (RAIU) inhibition of 1.8 percent and application of an intraspecies uncertainty factor (UF) of 10 to account for differences in sensitivity between the healthy adults in the Greer *et al.,* (2002) study and the most sensitive population, fetuses of pregnant women who might have hypothyroidism or iodide deficiency. The NRC also acknowledged that the RfD may need to be adjusted upward or downward on the basis of future research. The RfD of 0.7 µg/kg/day was adopted by EPA in 2005 (U.S. EPA, 2005a). EPA believes that this RfD is the most scientifically defensible endpoint available at this time for assessing risk from perchlorate exposure.

In October 2008, EPA published a preliminary determination not to regulate perchlorate in drinking water using a health reference level (HRL) of 15 µg/L, which was derived from the RfD of 0.7 µg/kg/day, using a default body weight (70 kg), a default drinking water consumption rate (2 L/day), and a perchlorate-specific relative source contribution (RSC) of 62% for a pregnant woman (U.S. EPA, 2008). The RSC is the percentage of the RfD remaining for drinking water after the other sources of exposure to perchlorate (e.g., food) have been considered. In January 2009, EPA issued an interim health advisory (15 µg/L perchlorate in drinking water) to provide guidance to state and local officials in their efforts to address perchlorate contamination while EPA was continuing to review scientific issues (U.S. EPA, 2009a).

In August 2009, EPA published a supplemental request for comment with a new analysis that derived potential alternative HRLs for 14 life stages, including infants and children. The analysis used the RfD of 0.7 µg/kg/day and life stage-specific body weight and exposure information (i.e., drinking water intake, RSC) (U.S. EPA, 2009b). The HRLs ranged from 1 µg/L to 47 µg/L. In February 2011, EPA published the Final Regulatory Determination to regulate perchlorate under SDWA. The Final Regulatory Determination stated that EPA was

evaluating the potential alternative HRLs and considered them to be levels of public health concern for the purposes of final determination (U.S. EPA, 2011a).

Charge to the SAB

The purpose of this white paper is to seek guidance from the SAB on how best to consider and interpret the life stage information, the epidemiologic and biomonitoring data since the NRC report, physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive an MCLG for perchlorate.

Specific Charge Questions

Issue I - Sensitive Life Stages

While studies directly demonstrating the adverse effects of perchlorate in humans are not available, potential effects can be inferred from the mode of action for perchlorate and the literature on thyroid hormone decrements and neurological deficits in various life stages. Perchlorate blocks the transport of iodide into the thyroid gland leading to iodide deficiency and decreased synthesis of thyroid hormones, T3 and T4. Transfer of iodide from blood into the thyroid gland is essential for the synthesis of the thyroid hormones. In its deliberations on the health effects of perchlorate in drinking water, the NRC committee considered pregnant women who might have hypothyroidism or iodide deficiency and their fetuses to be particularly sensitive populations to perchlorate mediated health effects (NRC, 2005).

Based on the discussion in Section IV of the white paper, pregnant women and their fetuses, neonates, infants (breast-fed and bottle-fed) and young children have been identified as life stages of concern for adverse effects due to perchlorate. Significant thyroid perturbations *in utero* are well known to cause neurological deficits in infants and children (NRC, 2005). High turnover rate of thyroid hormones, and low storage capacity in the fetus and neonate make these in particular, sensitive life stages for thyroid hormone perturbations. Furthermore, infants and children, in general, are more susceptible to xenobiotics effects because of low urinary clearance of contaminants, and higher food consumption and drinking water intake per body weight relative to adults (USEPA, 2011b). As in the thyroid gland, perchlorate is actively taken up into mammary tissue via NIS. Perchlorate also competitively inhibits the uptake of iodide into the mammary gland, reducing the amount of available iodide in breast milk. Therefore, breast-fed infants also represent a population of particular concern as they experience a double hit – exposure to perchlorate accumulated in breast milk in addition to a deficiency of iodine in the breast milk. (Kirk *et al.*, 2005; Dasgupta *et al.*, 2008; Valentin-Blasini *et al.*, 2011).

There are currently no data available to directly link perchlorate to neurobehavioral effects in infants and children. How should EPA consider the following life stage factors in deriving an MCLG?

- **Life stage specific differences in body weight and food and drinking water intake;**

- **Differences in greater severity and permanence of potential adverse effects in neonates, infants and young children compared to adults;**

- **Shorter half-life and lower reserves for thyroid hormone in infants compared to adults; and**

- **Intrauterine exposure to perchlorate and impact on thyroid status in fetuses.**

Issue II - Physiologically-Based Pharmacokinetic Evidence

The NRC relied on information on inhibition of RAIU in a small group of healthy, iodine sufficient, adults, similar data are not available for other life stages. With the development of the PBPK model (U.S. EPA, 2009b), it is now possible to provide estimates of the effect of perchlorate on RAIU in different life stages as outlined in white paper Section VI.

The PBPK model predictions can be evaluated in two different ways. The first application is based on a comparison of the relative RAIU inhibition sensitivity at a fixed dose (point of departure, POD of 7 µg/kg/day identified by NRC) for different life stages. One exception in the first application scenario with regard to dosing is that the breast-fed infants received a dose higher than the POD, but lactating mothers received a dose equivalent to the POD. The second application involves comparing RAIU inhibition at a fixed drinking water exposure level (15, 20 and 24.5 ppb) with and without perchlorate contribution via food for various life stages. Thus, the doses for different life stages varied in the second application scenario.

The findings from the first application indicate a greater sensitivity for RAIU inhibition for fetuses and breast-fed infants compared to other life stages/sub populations (Table A-3 of the White Paper). The findings from the second application indicate a RAIU inhibition of 2.2% or less for all life stages when they are exposed to drinking water containing 15 µg/L perchlorate in addition to perchlorate in food (Table A-4 of the White Paper). In the context of significance of RAIU inhibition, NRC determined 1.8% RAIU inhibition was not significant at the POD/NOEL of 7 µg/kg/day for healthy adults, but recommended that a 10-fold uncertainty factor be applied to the POD to protect the fetus of the pregnant woman who might have hypothyroidism or iodine deficiency. However, the doses infants receive when exposed to 15 µg/L perchlorate in water and perchlorate in food are up to 5 times higher than the RfD.

- **How should EPA consider PBPK modeling to derive an MCLG for perchlorate?**

- **What are the strengths and limitations of the two PBPK model results described in this effort?**

Issue III – Epidemiological Evidence

Since the NRC report (2005), a number of epidemiological studies have investigated the association between perchlorate exposure and thyroid hormone perturbations. None evaluated the neurodevelopmental outcomes. The studies reported findings for sensitive life stages of concern: pregnant women, neonates and infants. Several of these studies investigated the association between perchlorate exposure in drinking water and thyroid hormone levels in the US, Israel and Chile (Tellez *et al*., 2005, Amitai *et al*., 2007, Steinmaus *et al*., 2010). The study

in Chile (Tellez *et al*., 2005) reported urinary and serum perchlorate levels in women during pregnancy and post partum (a longitudinal cohort study). However, perchlorate assignment to subjects was based solely on geographical location. Other studies that examined the association between perchlorate and thyroid hormone levels included urinary perchlorate concentrations as biomarkers of exposure (Blount *et al*., 2006; Pearce *et al*., 2010, 2011). Using NHANES 2001-2002 data, Blount *et al*. (2006) demonstrated a perchlorate-related increase in TSH and decrease in T4 in women >12 years of age with urinary iodide <100 µg/L. Pearce *et al*. (2010, 2011) did not find an association between urinary perchlorate and thyroid hormone perturbations in first trimester pregnant women. Differences in study designs, numbers and age of subjects, exposure assessment approaches, and statistical methods may explain the mixed findings among these studies. The studies published in the literature since the NRC (2005) review are described in Section VII and Table A-5 of the white paper. The new epidemiological evidence may inform bounding of the possible life stage-specific MCLG estimates derived in the White Paper (Table-1).

- **How should EPA consider the post-NRC epidemiology data in deriving an MCLG?**

Issue IV – Integration of Information

The primary action of perchlorate exposure is on the thyroid gland, where perchlorate inhibits the transport of iodide from the blood into the thyroid gland which in turn can lead to perturbations in the synthesis of thyroid hormones. Perturbations in thyroid hormones during critical stages of development lead to permanent neurological deficits in children (NRC, 2005). EPA generally derives an MCLG on the basis of the RfD. EPA believes that the NRC derived RfD of 0.0007 mg/kg/day (0.7 µg/kg/day) for perchlorate is the most scientifically defensible endpoint available at this time for deriving an MCLG. In deriving the RfD, the NRC applied an intraspecies factor of 10x to protect the fetuses of pregnant women who might have hypothyroidism or iodide deficiency. The UF 10 can be further subdivided into a $UF_{TK} = 10^{1/2} = 3.16$ (generally rounded to 3) to account for differences in internal dosimetry due to toxicokinetic differences, and a $UF_{TD} = 10^{1/2} = 3.16$ (generally rounded to 3) to account for differences in toxicodynamics. This convention is used by EPA in the absence of compound-specific data as is the case with perchlorate.

At a fixed dose of 7 µg/kg/day, the first application of PBPK model findings indicate 6.7x, 2.6x, 7.8x, and 1.1x greater sensitivity for RAIU inhibition for GW 40 fetuses,7 day breast-fed infants, 7-day bottle-fed infants and children from 6 months to 2-years, respectively, as compared to adults (Table A-3 of the White Paper). It was not possible to estimate sensitivity in younger than term fetus. The second use of PBPK modeling indicates a RAIU inhibition of 2.2% or less for all life stages when they are exposed to drinking water containing 15 ug/L perchlorate in addition to perchlorate in food (Table A-4 of the White Paper). In the context of significance of RAIU inhibition, NRC determined 1.8% RAIU inhibition not significant for healthy adults. However, the doses infants receive when exposed to 15 ug/L perchlorate in water and perchlorate in food are up to about 5 times higher than the RfD.

As discussed previously the mixed pattern of observations in the epidemiologic studies which investigated the association between perchlorate exposure and thyroid perturbations since

the 2005 NRC review is not surprising in light of their different study designs, numbers and age of subjects, exposure assessment approaches, and statistical methods. In an ecological study, Steinmaus *et al*. (2010) found increased TSH levels in neonates when the mothers were exposed to perchlorate concentrations above 5 µg/L in drinking water. Using 2001-2002 NHANES data, perchlorate-related increases in TSH and decreases in T4 were demonstrated in women >12 years of age with urinary iodide <100 µg/L (Blount *et al*., 2006). The changes in thyroid hormone levels in the NHANES analyses were observed at a mean perchlorate intake level of approximately 0.1 µg/kg/day (including food and drinking water) reported by Huber *et al*. (2011) for the NHANES populations, suggesting thyroid hormone perturbations at a perchlorate intake level less than the RfD determined by NRC (2005). The perchlorate dose estimated from Huber *et al*. (2011) is consistent with that reported from other biomonitoring studies and analyses reported in Section VIII and Table A-6 of the White Paper. Other studies of pregnant women or neonates did not report associations between residence in a city with perchlorate in drinking water supplies or between urinary perchlorate at similar or higher exposure levels than those estimated for Blount *et al*. (2006) (Tellez *et al*., 2005; Amitai *et al*., 2007; Pearce *et al*., 2010, 2011). Together the results of these studies may serve as a means to bound the drinking water exposure range of concern, and assist in determining where within the range of potential MCLGs an appropriate regulatory value can be set.

- **How can EPA best use the total body of information to derive a health protective MCLG, while considering the results of epidemiology and biomonitoring data in establishing bounds on potential values?**

- **How can EPA use the available data to estimate reductions in adverse health effects (i.e., dose response) that are likely to result from reducing perchlorate levels in drinking water?**