COMMENTS IN RESPONSE TO THE EPA NOTICE:
ENVIRONMENTAL PROTECTION AGENCY
[EPA–HQ–OW–2009–0297; FRL–8943–9]
RIN 2040–AF08
DRINKING WATER: PERCHLORATE
SUPPLEMENTAL REQUEST FOR COMMENTS

Prepared for:

PERCHLORATE STUDY GROUP

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EXECUTIVE SUMMARY

On August 19, 2009, the Environmental Protection Agency (EPA) issued a *Federal Register* (*FR*) notice requesting comments on alternative approaches to analyzing data related to EPA's perchlorate regulatory determination (the Notice; U.S. EPA, 2009b). The Notice says that "these additional comments are sought in an effort to ensure consideration of all the potential options for evaluating whether there is a meaningful opportunity for human health risk reduction of perchlorate through a national primary drinking water rule."

The following four points summarize the response prepared by Intertox on behalf of the Perchlorate Study Group (PSG).

1. Interpretation of physiologically-based pharmacokinetic (PBPK) modeling: The use of scientifically derived PBPK models is the best scientific approach among all alternatives for evaluating the relative sensitivity of different life stages, consistent with the conclusions of EPA's peer reviewers and the National Academy of Sciences National Research Council (NRC). The current EPA PBPK model for perchlorate, however, uses values for some key parameters (*e.g.,* urinary clearance) that are not supported by the scientific evidence. The model also does not account for up-regulation of the sodium iodide symporter (NIS). As a result, the model does not provide the best scientific estimates of iodide uptake inhibition (IUI) that would be associated with a particular perchlorate dose, and likely overestimates IUI from perchlorate exposure for various life stages. Further, input parameters are not selected from consistent points within their distributions, such that it is unclear whether the model output represents low, average, or upper-bound estimates of possible IUI. Nonetheless, the predicted levels of IUI in the Notice are low and would be indistinguishable from fluctuations resulting from differences in diet and feeding styles. No adverse health concern at any life stage would be expected based on exposure to perchlorate at the point of departure dose (7 μg/kg-d). EPA should revise this model to represent science-based accurate information on PBPK parameters and use the results to determine whether regulation is necessary.

2. Derivation of alternative Health Reference Levels (HRLs) based upon body weight and water consumption rates for sensitive life stages: The alternative HRL calculation which relies on life-stage specific body weight and water consumption rates is not scientifically justified. Authoritative bodies (*e.g*., NRC, EPA, the Agency for Toxic Substances and Disease Registry, the California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA)) have conducted rigorous scientific assessments and have determined that the fetus of the hypothyroid pregnant woman is the most sensitive to perchlorate's potential health effects, not the infant as suggested by the alternative HRL calculation. The Notice provides no scientific evidence that shows otherwise and offers no justification for basing a HRL on an alternative population that is not the most sensitive. Further, the values given in the Notice for specific exposure assumptions do not meet the Agency's own guidelines for data quality. EPA is justified in making a regulatory determination based upon the current Reference Dose (RfD), which includes a 10-fold uncertainty factor (UF) to account for sensitive life stages; further reductions for sensitive life stages are duplicative and not scientifically justified. Importantly, authoritative bodies concur that the RfD is based on a No Observed Effect Level (NOEL), which is a more conservative approach than EPA's traditional use of a No Observed Adverse Effect Level (NOAEL). In establishing the threshold for IUI—which is defined by the National Academy of Sciences as a nonadverse effect—as the point of

departure, EPA has already ensured that downstream adverse effects due to perchlorate (which to date have not been reported in humans exposed to perchlorate at environmental levels) will not occur (NRC, 2005). Since much information regarding the perchlorate mechanism of action is known, EPA should use PBPK modeling based on the best science rather than the estimations in the alternative HRL calculations.

3. Use of data on perchlorate occurrence in drinking water: The occurrence analysis presented in the Notice relies on data that are nearly a decade old and it assumes exposure to maximum concentrations detected anywhere within a public water system (PWS), even in untreated source water. Therefore, the analysis most likely overestimates concentrations of perchlorate in drinking water. Additionally, the Notice's estimates of populations exposed to perchlorate are overstated because it assumes the entire population served by a PWS is exposed to the maximum concentration, even if the detection was in untreated source water, and it overlooks the steps that have been taken—particularly in California, Massachusetts and New Jersey—that substantially reduce the national population that may be exposed to environmental levels of perchlorate. The process the Notice followed to develop the estimated populations is not transparent, and as a result, it is not possible to independently calculate the estimated values in the Notice based on the information given. Independent calculations resulted in estimated population sizes that are about half of the Notice's estimates, even when conservative assumptions were used. EPA should use more current data to estimate occurrence as levels in drinking water have decreased since UCMR1 monitoring.

4. Science-based considerations: The Safe Drinking Water Act (SDWA) has three requirements—all three of which *must* be met to satisfy the law. The scientific literature addresses these requirements for perchlorate. The science clearly shows EPA's statutory criteria for setting a standard are unmet in this case:

    a) The SDWA requires that the contaminant must have an adverse effect on the health of persons. The weight-of-evidence, after examining the published scientific literature, demonstrates no documented adverse effects in humans exposed to perchlorate at environmental levels.
    b) The SDWA requires that the contaminant must be known to occur in PWSs with a frequency and at levels of public health concern. Where perchlorate is found, it is at levels often an order of magnitude below levels that cause IUI, itself a nonadverse effect. EPA data indicate average perchlorate concentrations in public drinking water systems are <10 parts per billion (ppb), and 99% of samples were <7 ppb. These levels are all below the equivalent concentration corresponding to the RfD, assuming a standard EPA default body weight and drinking water consumption rate, as well as the HRL of 15 ppb proposed by EPA in 2008 (U.S. EPA, 2008a).
    c) The SDWA requires that the regulation of such contaminants must present a meaningful opportunity for health risk reduction for persons served by public water systems. For perchlorate, no possible health benefit can occur when estimated exposure levels are below the NOEL for a nonadverse effect. Further, EPA adjusted the NOEL ten-fold lower to derive the RfD to account for sensitive subpopulations.

EPA, based on a scientific assessment of the literature in 2008, concluded that federal regulation of perchlorate in drinking water is unwarranted. More than 50 years of scientific research and guidelines support the Agency's position.

I. INTRODUCTION

On August 19, 2009, the Environmental Protection Agency (EPA) issued a *Federal Register* (*FR*) notice requesting comments on additional approaches to analyzing data related to EPA's perchlorate regulatory determination (the Notice; U.S. EPA, 2009b). The Notice states that "these additional comments are sought in an effort to ensure consideration of all the potential options for evaluating whether there is a meaningful opportunity for human health risk reduction of perchlorate through a national primary drinking water rule." This document responds to EPA's request for comments on behalf of the Perchlorate Study Group (PSG).[1]

EPA is required by the Safe Drinking Water Act (SDWA) to publish Maximum Contaminant Level Goals (MCLGs) and National Primary Drinking Water Regulations (NPDWR) *if all* the following statutory requirements are met:

> (a) the contaminant may have an adverse effect on the health of persons;
>
> (b) the contaminant is known to occur in public water systems with a frequency and at levels of public health concern; *and*
>
> (c) in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems (U.S. EPA, 1996).

EPA's statutory criteria for setting a standard are unmet in this case. At exposure levels anticipated under the drinking water program, the toxicological literature for perchlorate has demonstrated no adverse effect on human health. Second, data from EPA's first cycle of the Unregulated Contaminant Monitoring Rule (UCMR1) demonstrates that perchlorate does not consistently occur in public water systems at levels that may cause adverse effects in humans. Lastly, because the first two requirements are not met, there is no meaningful opportunity for health risk reduction, the third requirement.

In 2008, EPA concluded that perchlorate did not meet the SDWA requirements and released its preliminary regulatory determination on perchlorate for public comment (U.S. EPA, 2008a). EPA decided not to set an NPDWR for perchlorate as it would not present "a meaningful opportunity for health risk reduction for persons served by public water systems." This decision was based on a Health Reference Level (HRL) for perchlorate in drinking water of 15 ppb, calculated based on an assumed relative source contribution (RSC) for drinking water of 62% of the reference dose (RfD) (U.S. EPA, 2008a).

Data on perchlorate exposure in humans support EPA's preliminary regulatory determination. Any chemical at a sufficient dose will cause an adverse effect. Since the inception of EPA's evaluation of perchlorate and its interim guidance, no evidence of adverse effects from exposure to perchlorate at environmental levels in the U.S. has been presented.[2]

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[1] The PSG member companies include Aerojet General Corporation, American Pacific Corporation, ATK, and Lockheed Martin Corporation.

[2] In 1992, EPA began to address "…concerns about the potential human health effects of perchlorate discovered in drinking water…" and the EPA Superfund Technical Support Center proposed a "provisional" RfD for perchlorate of 0.0001 mg/kg-d which translates to a drinking water equivalent level (DWEL) of 4 ppb (Dollarhide, 1992). In 1995 the provisional RfD was revised by EPA and the National Center for Environmental Assessment (NCEA) to a range that translates from a DWEL of 4 to 18 ppb (Dollarhide, 1995). EPA released a document detailing the derivation of a revised provisional RfD for perchlorate (U.S. EPA, 1998a). In this analysis, EPA focused on potential secondary effects of perchlorate exposure in the developing organism. In 1999, EPA issued was what is referred to as the "1999

50 years of perchlorate toxicological research shows that the scientific weight-of-evidence decidedly supports EPA's preliminary regulatory determination on perchlorate.

A review of the 50 years of perchlorate toxicological research shows that the weight of scientific evidence decidedly supports EPA's preliminary regulatory determination on perchlorate. Furthermore, EPA requested manufacturers and users to fund specific scientific studies on the health effects of perchlorate. As a result, at least 12 animal studies that cover reproductive and developmental toxicity, carcinogenicity, endocrine effects, and other specific toxicological endpoints were funded and conducted.[3] The results of the studies were transmitted directly to EPA for analysis and without review from industry. Vulnerable populations have been considered since the first risk assessment in 1998. All of EPA's interim guidance and the current RfD (which is the basis for the 2008 HRL) are based on the most sensitive subpopulation, the developing fetus.

A small percent of those who commented on EPA's preliminary regulatory determination opined that the infant or child is the most sensitive population to perchlorate health effects; however, experts, including authoritative bodies such as the National Academy of Sciences (NAS) National Research Council (NRC) perchlorate committee as well as federal and state agencies such as the EPA, the Agency for Toxic Substances and Disease Registry (ATSDR), the California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA), and others, conclude that the fetus is the most sensitive population to protect (all others being less sensitive than the fetus are therefore protected). Furthermore, questions about alternative life stages being more sensitive to perchlorate exposure have been addressed in the past; EPA began focusing on the most sensitive life stage as the foundation of health protection as early as 1998 in its first risk assessment (U.S. EPA, 1998a).

In the Notice EPA describes alternative interpretations of health and exposure data for perchlorate that may impact EPA's final regulatory determination for perchlorate. EPA seeks comments on these alternatives in three areas:

- interpretation of physiologically-based pharmacokinetic (PBPK) modeling;
- derivation of alternative health reference levels (HRLs) based on body weight and water consumption rates for sensitive life stages; and
- use of data on perchlorate occurrence in drinking water.

To provide context for these comments, several points regarding the availability of scientific data on perchlorate are important. **First, substantial research and evaluation of the potential health effects of perchlorate have been conducted.** The scientific literature represents more than five decades of scientific inquiry. Since EPA began evaluating

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Interim Guidance" (Noonan, 1999). EPA states, "…the Office of Research and Development (ORD) recommends that the Agency's risk assessors and risk managers continue to use the standing provisional RfD range of 0.0001 to 0.0005 mg/kg-d [4 to 18 ppb equivalent] for perchlorate-related assessment activities." At the same time, the EPA's Office of Water added perchlorate to the Contaminant Candidate List (CCL) and perchlorate was added to the UCMR (U.S. EPA, 1999). In 2003, EPA's Assistant Administrator issued a Memorandum stating, "…we are re-affirming this guidance with an added suggestion to carefully consider the low end of the provisional 4-18 ppb range."

[3] For example, the following animal studies were required by EPA to fill data gaps: Argus Research Laboratories, Inc., 1998; Argus Research Laboratories, Inc., 1999; Kiel *et al.*, 1998, 1999; Argus Research Laboratories, Inc., 2001; Primedica, 2001; Bekkedahl *et al.*, 2000; BRT, 2000a, 2000b; Siglin *et al.*, 2000; York *et al.*, 2001a, 2001b.

perchlorate in the early 1990s, scientists from government, industry, and academia have made important contributions to reducing uncertainties about the risks of perchlorate to public health (see footnote 4). In response to EPA's request for comment on its preliminary determination, Intertox reviewed the existing data (Intertox, 2008).[4] Briefly, these data include:

- the 2005 NRC assessment of perchlorate and update of key studies that have been added to the scientific literature;
- at least twelve animal toxicological studies conducted between 1997 and 2002, all using EPA protocols, including pharmacokinetic, subchronic, developmental, and immunotoxicology studies, and a multigenerational reproductive study, conducted using a range of doses, and evaluated independently by EPA;
- several clinical and occupational exposure studies in humans and a number of epidemiologic and ecological studies between 1997 and 2002, some in occupational settings and some in populations exposed to perchlorate via the community drinking-water supply; and
- additional studies conducted since 2002, adding to the scientific literature.

Other agencies, *e.g.*, the ATSDR (2008), have also conducted rigorous reviews of the scientific literature regarding the potential for adverse health effects from perchlorate exposure and have determined that doses equivalent to the current RfD are health protective.

Second, a no observed effect level (NOEL) has been identified for perchlorate exposure in humans. At the lowest dose of Greer *et al.* (2002) (the basis of the perchlorate RfD), there was no statistical difference in iodide uptake inhibition (IUI), a nonadverse effect, for subjects before and after a dose of 0.007 mg/kg-d (245 ppb assuming default body weight and drinking water intake).[5] As the NRC (2005) states with emphasis, "Inhibition of iodide uptake by the thyroid clearly is not an adverse effect; however if it does not occur, there is no progression to adverse health effects." Use of a NOEL is more conservative than EPA's common approach using the no observable adverse effect level (NOAEL) or the lowest observable adverse effect level (LOAEL).

Third, perchlorate is water soluble, has a half life in humans of approximately eight hours, and does not bioaccumulate. Because perchlorate has a short half life, some have questioned whether exposure to perchlorate might cause an acute effect. Toxicologically speaking, "acute" describes effects seen after one high dose or an exposure of less than 24 hours. No published study has demonstrated an effect after one exposure to perchlorate at environmental levels. The dose required for acute effects would require therapeutic levels; the medical literature reports that doses from 200 mg to over 1 gram given on a daily basis (the equivalent of 100,000 to 500,000 ppb in drinking water using standard EPA default assumptions[6]) are necessary to cause side effects (*e.g.,* nausea and gastrointestinal upset at lower doses to aplastic anemia and agranulocytosis at daily doses of one gram or more) in 5 to 18 percent of study populations (NRC, 2005; Barzilai and Sheinfeld, 1966). At exposures

[4] These comments were in response to the EPA *FR* notice Drinking Water: Preliminary Regulatory Determination on Perchlorate (U.S. EPA, 2008a).
[5] The actual variable measured in Greer *et al.* (2002) was radioactive iodide uptake or RAIU.
[6] 1g = 1,000 mg; Drinking Water Equivalent for 1,000 mg perchlorate / 2 L of water per day = 500 mg/L or 500 ppm or 500,000 ppb; Drinking Water Equivalent for 200 mg would be 100 ppm or 100,000 ppb.

lasting several weeks to months (more commonly termed "subchronic"), the scientific literature does not demonstrate any evidence of adverse effect. Thyroxine (T4) has a half life of 6-8 days and must be sufficiently depleted for developmental effects to occur. A single perchlorate dose in excess of 1 gram per day would most likely cause some frank toxicity, but based on the science to date, will not decrease serum thyroid hormone levels without daily exposure for weeks.

Fourth, the NRC's recommendation to base the RfD on a NOEL was conservative and health protective, as this dose is lower than any dose at which adverse effects may occur. To derive the RfD, the NOEL was divided by an uncertainty factor (UF) of 10 to account for the most sensitive individuals in a population, the hypothyroid or iodine-deficient pregnant women and their developing fetuses. The NRC committee stated that using a NOEL as the point of departure (POD) is a more conservative and health protective approach than EPA's customary approach of using the adverse effect (NRC, 2005). For example, the use of the threshold for IUI as a POD is more conservative and health protective than using changes in thyroid hormones (also a precursor to possible adverse effects) or an adverse effect such as hypothyroidism.

Perchlorate's reversible inhibition of the NIS is documented in many experiments, both *in vivo* and *in vitro*. This interaction exhibits the standard sigmoidal dose-response curve in toxicology and pharmacology—as dose increases, so does the response. There is no scientific evidence to suggest that low doses of perchlorate will cause any other effect. Perchlorate competitively inhibits iodide uptake; it neither mimics a hormone nor directly stimulates a response.

Fifth, the level of IUI that would be associated with exposure to perchlorate at the RfD is minimal compared to the IUI associated with other environmental goitrogens naturally present in many foods. Nitrate and thiocyanate are less potent (Tonacchera *et al*., 2004) but more plentiful inhibitors of NIS activity than perchlorate (Belzer *et al*., 2004). The potency of nitrate and thiocyanate relative to perchlorate has been demonstrated *in vivo* (Wyngaarden *et al*., 1952, 1953; Greer *et al*., 1966; Belzer *et al*., 2004) and *in vitro* (Tonacchera *et al*., 2004). When based on perchlorate equivalence, the effects of perchlorate are much smaller than the effects of either nitrate or thiocyanate (Belzer *et al*., 2004; U.S. EPA, 2008b). The potential for perchlorate to inhibit iodide uptake cannot be distinguished from the effects of other NIS inhibitors (De Groef *et al*., 2006). Because exposure to nitrate and thiocyanate would continue, the premise underlying EPA's attempt to isolate the effect of perchlorate is limited in its ability to provide an actual public health benefit.

II. Responses to Request for Comments on Alternative Approaches To Analyzing Scientific Data Related to Perchlorate in Drinking Water

The Agency's process is not transparent in how it might use any of the three alternative approaches described in the Notice to revise its regulatory determination for perchlorate. For example, the Notice does not remark if it intends to use both the PBPK model and the HRL "model." Further, the Notice is not clear about how the Agency intends to integrate the results of these alternative approaches with existing knowledge about the threshold for IUI in average adults.

Compared to the EPA PBPK model, the alternative HRLs listed in the Notice are not scientifically rigorous.

The comments in this document assume EPA does not intend to apply both the PBPK model and alternative HRLs based on body weight and water consumption. Further, this document assumes that EPA seeks input on whether one approach is scientifically more accurate than the other for extrapolating from a no effect dose measured in adults to sensitive subpopulations. Overall, the scientific community supports the use of PBPK modeling when all parameters are based on scientific experiments (Mager *et al*., 2003). When scientifically validated, PBPK models can be useful to reduce uncertainty about sensitive life stages. In contrast and as will be discussed below, the HRLs based on body weights and water consumption rates do not reflect a similar scientific basis.

It is important to note the difference between the results in Table 1 of the Notice (which presents the PBPK model-predicted RAIU inhibition for each life stage) and Table 2 (which presents the alternative HRLs based on body weight and water consumption). The RAIU inhibition estimates in Table 1 were computed using a dose of 0.007 mg/kg-d, the Greer *et al*. (2002) POD. This dose is equivalent to 245 ppb of perchlorate in drinking water if one uses standard EPA default values for body weight and drinking water consumption.[7] The HRLs in Table 2 are based on the perchlorate RfD which is ten times lower, *i.e.*, 0.0007 mg/kg-d or 24.5 ppb. Therefore, anyone comparing Tables 1 and 2 should recognize a 10-fold difference in the underlying dose assumptions. For example, the highest RAIU inhibition reported in Table 1 is 12.5% for the lactating woman and breast-fed infant exposed to a dose of 0.007 mg/kg-d. At the 10-fold lower RfD in Table 2, the RAIU inhibition for the lactating woman and breast-fed infant would be approximately 2%, a value that would not be significantly different from normal fluctuations because of differences in diet and feeding styles. There is no credible scientific evidence that this effect has any biological significance.

Based on the EPA PBPK model, at the RfD, the RAIU inhibition for the exclusively breast-fed infant would be approximately 2%, a value that would not be significantly different from normal fluctuations due to diet.

A. Interpretation of the Physiologically Based Pharmacokinetic (PBPK) Modeling

Properly conducted, PBPK models provide accurate, peer reviewed scientific information to reduce uncertainty about sensitive life stages. PBPK models for perchlorate have been under development for a number of years. In its 2005 assessment of perchlorate, the NRC identified several subpopulations that are potentially more sensitive

[7] 0.007 mg/kg-d x (70 kg adult / drinking 2 L of water per day = 0.245 mg/L or 0.245 ppm or 245 ppb.

than average adults to thyroid effects from perchlorate exposure, including pregnant women, fetuses, and infants, based in part on perchlorate PBPK models for pregnant and lactating rats and rat pups and adult humans. After the NRC evaluation, the perchlorate PBPK model was improved to include pregnant women, the fetus, lactating women, and the neonate, and was published in the peer reviewed literature (Merrill *et al*., 2005; Clewell *et al*., 2007).

Regarding the preliminary regulatory determination for perchlorate, EPA evaluated published PBPK models for perchlorate "based on their ability to provide additional information surrounding this critical effect for potentially sensitive subgroups and reduce some of the uncertainty regarding the relative sensitivities of these subgroups" (U.S. EPA, 2008a). EPA used public comments on the preliminary regulatory determination, as well as comments from an external peer review (Eastern Research Group, 2008), to further refine the model which is based on both pharmacokinetics and pharmacodynamics (U.S. EPA, 2009a) and used it to predict the relative RAIU inhibition for 17 distinct populations or life stages, including pregnant and lactating women, the fetus, and the neonate, assumed to be exposed to 0.007 mg/kg-d in drinking water. The results of this evaluation are presented in Table 1 of the Notice. From these results, EPA concluded that "by protecting the fetus of the hypothyroid or iodide-deficient woman from the effects of perchlorate on the thyroid, all other life stages and subgroups would be protected."

EPA requested comments on three general questions regarding its use of the PBPK model as an alternative approach to assessing the relative sensitivity of different exposure populations. Responses to these questions follow. Note that the responses to Questions 1 and 2 are combined, as the questions are not substantively different.

1. EPA requests comment on using the PBPK model to evaluate the relative sensitivity of the various life stages to perchlorate exposure in drinking water.

2. EPA requests comment on the utility of the PBPK model for predicting the impact of different perchlorate drinking water concentrations on sensitive life stages to inform HRL selection.

PBPK modeling is valuable as it can integrate dozens of experimentally derived variables drawn from peer reviewed scientific studies to characterize chemical absorption, distribution, metabolism, excretion, and toxicity/effect. PBPK modeling is well established in the pharmacological and toxicological sciences, where it has been used for more than 80 years to understand the action of chemicals in the body. More recently, PBPK models have been used in filling scientific gaps in human health data, especially when conducting animal studies is infeasible, unethical, or impractical.

As stated by Mager *et al.* (2003) in a review of the use of PBPK models:

> The resolution of PK/PD [pharmacokinetic/pharmacodynamic] models and parameters is best achieved by having relevant pharmacokinetics…, an understanding of the mechanism of action of the drug, appreciating the determinants of any time dependence in responses, and collecting a suitable array of experimental measurements as a function of dose and time. When possible, such measurements should be sensitive, gradual, quantitative, reproducible, and meaningful.

This statement reflects scientific consensus about how scientific information should be used in a PBPK model. The EPA PBPK model is for the most part based on this philosophy and can be useful for informing risk management decisions. Not all parameters in this model,

however, meet the criteria required for robust and predictive PBPK modeling. To be useful, the PBPK model inputs should be transparent and scientifically based. This would advance the overarching science policy articulated by the current EPA Administrator, Hon. Lisa Jackson.[8]

While supportive of a science based PPBK model, an evaluation of the EPA PBPK model reveals that model does not produce the best and most scientific estimates of IUI. For example, some components of EPA's PBPK model for perchlorate are not supported by the scientific literature and result in IUI predictions that do not reflect best scientific estimates of IUI associated with a particular perchlorate dose. In particular, EPA's uses values for one of the key parameters in the PBPK model, the urinary clearance of perchlorate, that are not supported by the scientific literature.[9]

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[8] EPA Administrator Lisa Jackson, in her May 9, 2009 memorandum on scientific integrity stated, "While the laws that EPA implements leave room for policy judgments, the scientific findings on which these judgments are based should be arrived at independently using well-established scientific methods, including peer review, to assure rigor, accuracy, and impartiality. This means that policymakers must respect the expertise and independence of the Agency's career scientists and independent advisors while insisting that the Agency's scientific processes meet the highest standards of rigor, quality, and integrity" (http://www.epa.gov/Administrator/scientificmemo.html).

[9] Per EPA's evaluations, perchlorate PBPK model predictions are highly sensitive to urinary clearance rate, such that changes in it significantly impact predicted RAIU inhibition for a particular life stage and perchlorate dose. For each of the 17 distinct populations or life stages evaluated in the model, EPA used one of two different urinary clearance values: 0.05 L/h-kg for the pregnant woman at gestational weeks 13, 20, and 40 (which also impacts the RAIU prediction for the fetus at gestational week 40), and 0.13 L/h-kg for all other populations/life stages.

If one calculates urinary clearance in L/h by multiplying these values by the corresponding scaled body weight, the resulting urinary clearance rates for the pregnant woman are much lower than for all other adults evaluated by the model: urinary clearance rates range from 1.20 to 1.32 L/h for the pregnant woman, 3.21 to 3.28 L/h for the lactating woman, 3.08 L/h for the woman of child-bearing age, and 3.15 L/hr for the average adult. The assumption of reduced urinary excretion during pregnancy, however, is not supported by the bulk of the scientific literature.

The perchlorate urinary clearance rates used in the model are based on data collected in Greer *et al*. (2002). These values were originally described in the Merrill *et al.* (2005) model for adult humans, and were incorporated into the Clewell *et al.* (2003a, 2003b, 2007) models. Per Merrill *et al.* (2005), the 0.13 L/h-kg clearance rate is based on the mean "fit" urinary clearance rate for perchlorate for adult males and females (nonpregnant) in the Greer *et al*. (2002) study; the values for the 23 individuals in that study ranged from 0.06 to 0.24 L/h-kg. According to Clewell *et al*. (2007), the 0.05 L/h-kg urinary clearance value applied to the pregnant woman (and fetus) was selected from the lower bound of this range, in part because this lower value was consistent with data from a study of perchlorate-exposed pregnant women in Chile (Tellez *et al*., 2005). Clewell *et al.* (2007) describes their rationale as follows:

> In the nonpregnant adult model, Merrill and coauthors (2005a) fitted the perchlorate urinary clearance value to each individual for which data were available and noted a marked variation between subjects. Values for urinary clearance (ClUcp) ranged from 0.05 to 0.24 ng/L-h [*sic*], with an average of 0.13 ng/L-h [*sic*]. Using the lower bound of these values (0.05 ng/L) [*sic*], the gestation model predicted serum levels were within the range of the experimental values of Tellez *et al.* (2005)… Since the lower clearance value lies within the range of the normal adult, improves the perchlorate prediction, and yields a more conservative estimate of risk, it was used for all subsequent maternal simulations and dose metric calculations.

Note that the actual lower bound of the perchlorate urinary clearance range from Greer *et al.* (2002) (reported in Merrill *et al*. (2005)) is 0.06 L/h-kg, not 0.05 L/h-kg. Further, this value of 0.06 L/h-kg is for an adult male; no pregnant women were included in the study population, and the lowest reported value for any woman is 0.09 L/h-kg. Clewell *et al.* (2007) indicated the lower-bound value from Greer *et al*. (2002) is consistent with data collected by Tellez *et al*. (2005). Tellez *et al.* (2005) evaluated perchlorate exposure in pregnant women in three cities in Chile exposed to perchlorate in water at average concentrations ranging from 0.5 to 114 µg/L. This paper says that urinary perchlorate was measured during two prenatal visits and one postnatal visit, and reported excretion in units of µg/L and µg/g creatinine. Unfortunately, no data are provided in the paper on time course of excretion, so it is unclear how Clewell *et al*. (2007) established that the lower bound of the urinary clearance rate for these populations was 0.05 L/h-kg.

In selecting a urinary clearance value to use for the pregnant woman, EPA considered two additional values: clearance during pregnancy in the average adult based on Aboul-Khair *et al.* (1964); and clearance during pregnancy equal to nonpregnant average values. Aboul-Khair *et al*. (1964) evaluated urinary clearance of iodide in pregnant women in the United States and reported that "renal (urinary) clearance for iodide is elevated to as much as two times control (nonpregnant) values during pregnancy, and, while clearance then declines fairly rapidly towards control after birth, it is still elevated in the first couple of months" (U.S. EPA, 2009a). EPA assumed that urinary clearance of perchlorate would have the same pregnant to nonpregnant ratio reported by Aboul-Khair *et al*. (1964).

EPA ran the model using all three values. Of these values, the clearance value used by Clewell *et al*. (2007) resulted in the highest predicted RAIU inhibition. For example, at a dose of 7 µg/kg-d (a dose ten times the RfD of 0.7 mg/kg-d), EPA (2009a) reports a RAIU inhibition for the fetus of 11% using the Clewell *et al*. (2007) clearance value, 5.2% using the average non-pregnant adult clearance value, and 3.4% using the Aboul-Khair *et al.* (1964) clearance value. Regarding final selection of this value, EPA (2009a) says:

> Since there are no conclusive human pregnancy data to distinguish which of these alternatives is more likely, EPA selected option 1, the lower clearance value reported in the peer-reviewed paper by Clewell *et al*. (2007) for relative response estimation (life stage sensitivity analysis), since this value leads to the most sensitive predictions… While this analysis uses the lowest urinary clearance value among the alternatives evaluated, it does not provide an overall upper-bound effect estimate because the impact of uncertainty and variability in parameters other than those examined here (*e.g*., uncertainty in thyroid NIS parameters and interindividual variability in urinary excretion) was not evaluated.

Thus, EPA selected a urinary clearance value for this population based on a nonscience consideration that lacked corroborating data in the face of other data supporting a higher value. EPA states that selection of this value is not meant to reflect uncertainty or a bounded estimate. This is inconsistent with the statement in the Notice regarding the use of conservatism in the model (U.S. EPA, 2009a), that:

> The PBPK model for each life stage is presumed to represent a typical or average individual from that life stage. Thus, in evaluating specific PBPK parameter choices, especially for urinary clearance, EPA's objective was to ensure that the values appropriately represented an average or central value for a given life stage and age.

EPA further elaborates (U.S. EPA, 2009a):

> In the case where more than one alternative clearance value appeared to be equally likely (*i.e*., had a similar quality and amount of supporting data), then the more "sensitive" option was selected (*i.e*., the option that leads to predictions of the highest sensitivity to perchlorate-induced RAIU). The overall analysis did not seek to select parameters associated with highest predicted effect and is not intended to represent an upper-bound estimate of the average effect of perchlorate in these populations. Modeling choices are assumed to represent the best or most likely (central) estimate for an average individual within the population. There is uncertainty about the average, and EPA has selected from within the range of uncertainty, but there is still expected to be population variability around the model predictions based on that choice, with the model prediction being near the center of the distribution.

The Notice states that the urinary clearance value was selected to "represent the best or most likely (central) estimate for an average individual within the population." Selecting the lowest urinary excretion value—one that produces the highest estimate of RAIU inhibition—is not the "average." The Notice declares that all three clearance values considered had a similar quality and amount of supporting data; in fact, this cannot be true based on the information presented. The 0.05 L/h-kg value was of low scientific quality (it is not supported by either source EPA cites as its primary basis, *i.e*., Greer *et al*. (2002) or Tellez *et al*. (2005)) and higher values are better supported by the scientific literature, as discussed below.

The scientific literature shows that, although minimal, data are available on perchlorate urinary clearance or excretion rates during pregnancy, but do not suggest lower excretion of perchlorate during pregnancy. In the study of Chilean women, Tellez *et al*. (2005) reported higher urinary perchlorate excretion (measured as µg/g creatinine) during pregnancy relative to postpartum for women in two of the three cities evaluated (Chanaral and Taltal, which had mean concentrations of perchlorate in tap water of 5.8 and 114 µg/L). In the "low perchlorate" city (Antofagasta, with a mean tap water concentration of 0.5 µg/L), excretion was somewhat higher postpartum. Based on urine samples collected during the NHANES 2001–2002 study, Blount et al. (2007) reported higher urinary perchlorate in pregnant women (mean 3.27 µg/g creatinine, n = 115), relative to all women of reproductive age (mean 2.97 µg/g creatinine, n =

In addition to using the best science to support PBPK values, other parameters could be added, such as up-regulation of the NIS. Up-regulation of the NIS represents an adaptive response to iodine deficiency in the thyroid, but EPA (2009b) did not incorporate a mechanism of up-regulation in the EPA model. Incorporation of NIS regulation into the model would more accurately reflect the probable response to perchlorate exposure in the environment.[10]

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662). Interpretation of data on urinary clearance or excretion of iodide is complicated by the iodide status of populations; however, Smyth *et al*. (1997) reported that in an area of moderate iodine intake (median urinary iodide 82 μg/g creatinine), urinary iodide excretion was increased during all three trimesters of pregnancy relative to nonpregnant controls.

EPA's selection of the lowest identified urinary clearance value for the pregnant woman and fetus is inconsistent with the statement in the Notice about the Agency's use of conservatism in the model (U.S. EPA, 2009a):

> The PBPK model for each life stage is presumed to represent a typical or average individual from that life stage. Thus, in evaluating specific PBPK parameter choices, especially for urinary clearance, EPA's objective was to ensure that the values appropriately represented an average or central value for a given life stage and age.

EPA further states, "there is still expected to be population variability around the model predictions based on that choice, with the model prediction being near the center of the distribution," and:

> While this analysis uses the lowest urinary clearance value among the alternatives evaluated, it does not provide an overall upper-bound effect estimate because the impact of uncertainty and variability in parameters other than those examined here (e.g., uncertainty in thyroid NIS parameters and interindividual variability in urinary excretion) was not evaluated.

Nonetheless, in practice, selection of the lowest urinary clearance value for two of the subpopulations renders the RAIU inhibition predictions for these populations more conservative than for other populations, making application of model results to risk assessment difficult to interpret from a purely scientific basis.

[10] Over the past decade, research regarding thyroid autoregulation and the regulation of expression of the NIS has proliferated. Evidence suggests that the NIS is up-regulated in response to iodine deficiency in the thyroid. Up-regulation of the NIS causes the number of NIS membrane proteins to increase; thus, when an individual is iodine deficient, the body increases the number of NIS "pumps" such that the thyroid is more effective at capturing iodide. This is a common adaptive mechanism that many tissues, including the thyroid gland, use to maintain hormone homeostasis. The Draft EPA Office of the Inspector General (OIG) report (U.S. EPA 2008b) appears to consider up-regulation of NIS expression as well.

Earlier versions of the model using the rat did consider up-regulation, and showed no RAIU inhibition in the rat thyroid after 18 days of exposure at perchlorate doses up to 10 mg/kg-d (350,000 ppb assuming default body weight and water intake) (Clewell *et al*., 2003a). Up-regulation was not included in the human model, "based on the fact that up-regulation was not seen in the nonpregnant adult after 2 wk of doses as high as 1 mg ClO_4^- (Merrill *et al*., 2005)" and although "the current simulations cover lifetime exposures rather than a few weeks, the accompanying data on thyroid hormones (TSH, T4) still do not show evidence of thyroidal up-regulation (Crump *et al*., 2000; Tellez *et al*., 2005)" (Clewell *et al*., 2007). The NRC report, however, acknowledges the up-regulation of NIS expression, but did not incorporate it into their risk assessment. NRC (2005) states:

> …rats compensated for the inhibition within 5 days of perchlorate administration, most likely by increasing the expression of NIS in the thyroid. The data suggest that compensation occurs more quickly in rats because rats have a smaller reserve capacity of thyroid hormones than humans.

Dohán *et al.* (2003) provide perhaps the most comprehensive review of the NIS regulation at the time of the NRC report. Dohán *et al*. reported that "up-regulation of thyroid NIS expression and iodide uptake activity by TSH has been demonstrated not only in rats *in vivo* but also in the rat thyroid-derived FRTL-5 [Fisher rat thyroid cell line] cell line and in human thyroid primary cultures. TSH up-regulates iodide uptake activity by an increase in NIS transcription. They say:

Parameters used in the PBPK model were selected from inconsistent points within their distributions. For example, as described above, EPA (2009a) selected a lower bound value to describe the urinary clearance of perchlorate for the pregnant woman and fetus. In contrast, EPA reports that the urinary clearance values it selected for all other population subgroups fall in the middle of the range of possible values (U.S. EPA, 2009a). As a result, it is difficult to interpret the model output because it is unclear whether the output represents lower-, middle-, or upper- bound predictions of possible IUI caused by perchlorate exposure.[11]

3. EPA requests suggestions for ways to use the PBPK modeling analysis to inform the regulatory determination for perchlorate that are different from those described in this notice or the October 10, 2008 notice.

The PBPK model can provide useful information to characterize the relative sensitivity of this life stage if model parameters are scientifically defensible and selected from comparable points within their parameter distributions, and if nonscientific considerations do not introduce unexplained bias into the selection of parameter values. To be most useful, EPA should use probabilistic methods to characterize the uncertainty and variability around parameter distributions and the range and likelihood associated with model-predicted RAIU inhibition for each population or life stage. Use of probabilistic methods is consistent with the Agency's current recommendations for use of probabilistic methods in risk assessment to help inform risk management decisions.[12]

Additional considerations would provide perspective on the significance of the IUI associated with low dose perchlorate exposure. For example, EPA should present the change in RAIU inhibition when the RfD is modeled rather than the Greer *et al*. (2002) POD, which is ten fold higher. Also, multiple chemical agents affect the uptake of iodide into the thyroid in the same way as perchlorate. These goitrogens, which include thiocyanate and nitrate, can be found naturally in common foods, including produce, milk, and cured meats. Incorporation

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Both NIS mRNA and NIS protein levels decreased significantly after either 1 or 6 days of iodide administration. NIS mRNA levels were already significantly reduced at 6 hours following the injected single dose of iodide. In contrast, a significant decrease of NIS protein levels was detected only at 24 hours.

After TSH withdrawal, a reduction of iodide uptake activity is observed in FRTL-5 cells. This is a reversible process, as iodide uptake activity can be restored by TSH. The NIS half-life is approximately 5 days in the presence and approximately 3 days in the absence of TSH (Dohán *et al*., 2003). Other studies support up-regulation of NIS during changing levels of iodine (*e.g*., Eng *et a*l., 1999; Wagner *et a*l., 2002; Merrill et al., 2003; Pedraza *et a*l., 2006; Nordén *et al*., 2007; and Bizhanova and Kopp, 2009).

[11] When conducting calculations to reflect exposure within a population, each parameter can have a range of possible values. In order for PBPK model output to be meaningful, the basis for selection of specific values within the range of possible values should be described and the relationship to the overall distribution for that parameter should be characterized (*e.g*., lower-bound, average, median, upper-bound). Further, in the absence of probabilistic assessment, if point estimates are selected for incorporation in the model, a consistent rationale should be applied in choosing values for the various parameters so that the location of the output within the overall distribution can be approximated. For example, when conducting baseline human health risk assessments for a reasonable maximum exposure (RME) scenario, EPA recommends estimating "a conservative exposure case (*i.e*., well above the average case) that is still within the range of possible exposures," and intake variable values for a given pathway should be selected so that the combination of all intake variables results in an estimate of the reasonable maximum exposure for that pathway (U.S. EPA, 1998a). The objective of evaluating conservative exposures is to generate an upper-bound estimate of exposure below which adverse health effects are unlikely. Note that although EPA presents the impact of alternative urinary clearance assumptions on model-predicted RAIU inhibition in its discussion document on the PBPK model (Table 4-2, U.S. EPA, 2009a), it does not present this information in the Notice.

[12] http://www.epa.gov/fedrgstr/EPA-RESEARCH/2009/August/Day-18/r19755.htm; http://www.epa.gov/raf/prawhitepaper/pdf/pra_mgr_summary_0609.pdf.

of thiocyanate and nitrate exposure into the PBPK model should provide useful information on the relative IUI caused by exposure to these agents and to perchlorate. Thus, daily diets for children and adults including these foods are predicted to have a greater effect on IUI than would result from drinking two liters of water containing perchlorate at environmentally relevant levels (*e.g.*, estimated perchlorate drinking water equivalent concentrations associated with the thiocyanate and nitrate present in these diets are estimated to be at least 1,500 to 29,000 ppb). Based on these data, the contribution of perchlorate in drinking water at a concentration of 20 ppb (assuming consumption of 2 liters per day) to total daily IUI associated with a typical diet would be a fraction of these values.

B. Derivation of Alternative HRLs Based on Body Weight and Water Consumption Rates for Sensitive Life Stages

The NRC panel and subsequent studies consistently identify the fetus as the most sensitive population for perchlorate health effects evaluation.

In October 2008, EPA calculated an HRL for perchlorate in drinking water based on the RfD and a RSC of 62%, and EPA's default body weight and water consumption rates for an adult (U.S. EPA, 2008a). Based on a comment regarding the adequacy of EPA's proposed HRL to be protective of sensitive life stages, EPA presented an alternative calculation of an HRL in the Notice based on weight-normalized water intakes for specific life stages.[13] EPA has not presented any scientific evidence for why its proposed HRL in October 2008 was inadequate to protect other life stages or why it would be necessary to add additional safety factors to the RfD in the form of life stage-specific intake rates. In contrast to the PBPK model, the alternative HRL approach:

- is based primarily on one variable (the water intake rate);
- uses data that are not derived from scientific experiments but from a summary obtained in a survey that relies on subject recall rather than direct measurement;
- relies on methods that are incapable of measuring, estimating, or predicting the effects of a chemical on the body; and
- produces results that are qualitative at best.

In summary, determining the most sensitive life stages based on water consumption rates implicitly makes general assumptions about numerous body functions in lieu of actual scientific data about physiological differences between these population groups. This "model" does not account for absorption, distribution, or excretion, regardless of the individual's state of development. It implicitly assumes that the potential for exposure is directly proportional to body weight, without scientific supporting data.

PBPK modeling provides a more scientifically defensible approach to characterize the relative sensitivity of different life stages to perchlorate exposure. The Notice's alternative HRL calculations are insensitive, duplicative, and not scientifically warranted.

[13] For example, EPA says, "One commenter cites a March 8, 2006, letter from the Children's Health Protection Advisory Committee to the EPA Administrator. The commenter states, "[T]he committee emphasized the higher exposure of infants to perchlorate and greater susceptibility to serious negative effects associated with perchlorate exposure. Neither of these issues, however, was given adequate consideration in the Preliminary Determination."

The Notice should be transparent that the alternative HRL calculation it presents is an arithmetic calculation based on only three variables: the RfD, an RSC, and life stage specific water intake rates. Of these, the only scientifically defensible value is that upon which the RfD is based— the POD derived from Greer *et al.* (2002). The RSC is based on the mean intake of perchlorate from the Food and Drug Administration (FDA) Total Diet Study for the nearest age range, and the 90th percentile intake from a NHANES-UCMR analysis for pregnant women and women ages 15-44 that was conducted for preliminary regulatory determination. Using the 90th percentile is a not a science-driven decision. The water intake by body weight is arbitrarily categorized by age (*i.e.*, what is physiologically unique about 6 months of age versus 5 months of age?). Further, the consumption values for the infant are based on a study in which the study participant had to recall their own (or their infant's) consumption over two non-consecutive days; no direct measurements were taken. Recall studies are subject to error (called recall bias) from lapses in memory on estimations of amounts consumed (*i.e.,* what, when, and how much did I eat or drink?). In addition, the population size in this study does not meet EPA's data quality standards.

The EPA has asked for comment on four general questions regarding the Notice's alternative HRL calculations. Responses to these questions, based on the best available scientific information, follow.

1. EPA requests comment on whether the alternative HRLs described in this notice appropriately take into account specific and appropriate exposure values for all potentially sensitive life stages, including infants, children and the fetuses of pregnant women (rather than the 70 kg body weight and 2 liter per day consumption used for past regulatory determinations).

The HRL methodology that the Notice describes *does not* appropriately account for sensitive life stages for several reasons: (1) the most sensitive population has already been considered in the perchlorate RfD; (2) EPA provides no scientific justification for why this alternative HRL is necessary; and (3) there are no scientific data that meet EPA data quality requirements to substantiate the calculations used to develop these HRLs.

Some have opined that the infant is the most sensitive individual in the population, but no scientific basis for this has been presented. The weight of evidence shows that the fetal brain is more sensitive to hypothyroidism than the neonate or infant brain (Boelaert and Franklyn, 2005). There is no scientific evidence presented in the Notice that demonstrates that other life stages are more sensitive with regard to the development of health protective toxicity guidelines values than the fetus.

The NRC considered all possible sensitive populations in addition to pregnant women and their fetuses; this included infants, developing children, people who have compromised thyroid function, and people who are iodide-deficient, as sensitive to perchlorate exposure. Based on its assessment, the NRC committee states that "…fetuses and preterm newborns constitute the most sensitive populations although infants and developing children are also considered sensitive populations" (NRC, 2005). The purpose of defining an RfD based on "the most sensitive population" is that all other populations, including those that are more sensitive than average (but less sensitive than the most sensitive), would not be expected to have adverse effects, including at doses that exceed the RfD. To date—and with substantial scientific justification—the EPA, ATSDR, the states of California, Massachusetts, and New Jersey all regard fetuses to be the most sensitive population for health effects evaluations.

Reliable scientific studies published since NRC (2005) continue to demonstrate that no observable effect occurs at doses below the RfD. On a weight-of-evidence basis, the scientific literature demonstrates no significant health risk to the most sensitive individuals who consume water on a daily basis over a lifetime at environmentally relevant doses. Overall, these studies demonstrate that perchlorate is a ubiquitous chemical. It is naturally formed and is ubiquitous in the environment (Dasgupta *et al*., 2005), food (Murray *et al.*, 2008), and the human body (Blount *et al.*, 2006; Pearce *et al.*, 2007b).

The RfD is an estimate or a representation of the acceptable level of risk for a lifetime of exposure. It is *not* a threshold above which adverse effects occur.

The RfD is an estimate of the acceptable level of risk for a lifetime of exposure. It is not a threshold above which adverse effects occur. This is particularly true for the perchlorate risk assessment which is based on a NOEL, a more conservative POD than a NOAEL or LOAEL. EPA is correct in setting acceptable exposure levels with margins of safety. This allows, for example, an individual to consume a dose above the RfD on one day and ingest a lower dose on a subsequent day. When considering perchlorate, the issue relative to other chemicals is less of a concern: perchlorate is not metabolized, does not bioaccumulate, and the half-life is approximately 8 hours. Thus, in the rare instance of an exceedence of the RfD over the short term, perchlorate leaves the body quickly. Currently, EPA's use of a ten-fold intraspecies factor in the RfD effectively covers the potential for differences in sensitivity and exposure.

The RfD is based on a NOEL for IUI. IUI is not adverse. It is not scientifically justified to use drinking water rates for specific life stages to lower the HRL when the current RfD already has an UF applied to account for the most sensitive individuals. EPA offers no justification for why other life stages might be currently at risk or why additional protection is needed. EPA remarks "The NRC (2005) identified 'the fetuses of pregnant women who might have hypothyroidism or iodide deficiency' as 'the most sensitive population,' but also identified infants and developing children as additional 'sensitive populations.'" The purpose of defining an RfD based on "the most sensitive population" is that all other populations, including those that are more sensitive than average, would not be expected to have adverse effects, including at doses that exceed the RfD. In addition, reporting that the HRL could be lower in a group that is not the most sensitive without scientific support is not in compliance with the scientific method.

Bereft of scientific evidence, the Notice fails to present justification to alter the HRL based on specific life stages, particularly when the current RfD already has an uncertainty factor applied to account for the most sensitive individuals.

The historic standard procedure for converting the RfD into drinking water equivalent levels (DWELs) assumes 2 liters (67.6 oz) per day of water consumption and a body weight of 70 kg (154 lbs). One important purpose of converting the RfD (in units of mg/kg-day) to a DWEL (in units of µg/L or ppb) is to make it easy to compare water concentrations of contaminants to government guidelines. In doing so, EPA conservatively opts for higher than average intake and lower than average body weight. Thus, these default values are not symmetrically representative of the population. The water consumption (2 liters) default is approximately equal to the 88th percentile water intake for adults aged 20 through 64 (U.S. EPA, 1997). The default body weight of 70 kg is approximately equal to the 27th percentile of the distribution for adult males aged 18-74 and the 70th percentile of the distribution for adult females (U.S. EPA, 1997). Because the conversion uses the ratio of body weight to water intake, the use of lower percentiles in the numerator than are used in the denominator leads to a biased overestimate of the dose.

The purpose of defining an RfD based on "the most sensitive population" is that all other populations, even if they are more sensitive than average, would still be *unlikely* to suffer adverse effects, even at doses that exceed the RfD.

The DWEL is based on the RfD. The RfD is defined as (NRC, 2005):

> …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 risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or BMD, with UFs generally applied to reflect limitations of the data used.

Therefore, by definition, the RfD already accounts for the most sensitive population and lifetime exposures. In the most recent review of the RfD process, the EPA technical committee recommended (U.S. EPA, 2002):

> The intraspecies UF is applied to account for variations in susceptibility within the human population (interhuman variability) and the possibility (given a lack of relevant data) that the database available is not representative of the dose/exposure-response relationship in the subgroups of the human population that are most sensitive to the health hazards of the chemical being assessed. As the reference concentration/dose is defined to be applicable to "susceptible subgroups," this UF was established to account for uncertainty in that regard.

EPA remarks that additional factors should not be applied to determine a MCLG. For example, in the Disinfectant and Disinfection Byproduct rule (enacted during the Clinton Administration), EPA rejected additional safety factors for children or adjusting the default adult body-weight/consumption parameters:

> EPA disagrees that an additional safety factor should be applied to provide additional protection for children or that drinking water consumption relative to body weight of children should be used in developing the MCLG (maximum contaminant limit goal). The MCLG presented for chlorite and chlorine dioxide are considered to be protective of susceptible groups, including children, given that the RfD is based on a NOAEL derived from developmental testing. Additionally, current methods for developing RfDs are designed to be protective for sensitive populations. The 2 liter

> per day water consumption and the 70 kg body weight assumptions are viewed as adequately protective of all groups (U.S. EPA, 1998b).

Lifetime exposure includes exposure during infancy. An RfD that failed to account for exposure during infancy would fail to satisfy the standard definition. Applying life stage specific drinking water values would, in effect, "double count" the UF that has already been applied.

EPA requests comment on the alternative HRLs in Table 2 and which of these values would be appropriate levels of health concern against which to compare the levels of perchlorate found in public water systems.

The calculated values presented in Table 2 are not scientifically justified. Although this table presents levels that have been found in public water systems, there is no health effect associated with the values presented. In fact, every life stage calculation in Table 2 corresponds to a no effect level, based on IUI which is a fully reversible, nonadverse effect that occurs on a routine and daily basis.

The NRC noted that the dose at which perchlorate might cause hypothyroidism is greater than 0.4 mg/kg-d (14,000 ppb using default drinking water and body weight conversions). It states (NRC, 2005):

> On the basis of the studies of long-term treatment of hyperthyroidism in which patients continued to be given perchlorate after their hyperthyroidism resolved and the clinical studies of healthy adults, the perchlorate dose required to cause hypothyroidism in adults would probably be more than 0.40 mg/kg per day, assuming a 70-kg body weight.

Importantly, the NRC (2005) also emphasizes:

> The committee emphasizes that inhibition of iodide uptake by the thyroid has been the only consistently documented effect of perchlorate exposure in humans. The continuum of possible effects of iodide-uptake inhibition caused by perchlorate exposure is only proposed and has not been demonstrated in humans exposed to perchlorate (with the exception that in patients with hyperthyroidism doses of 200 mg daily or higher may reduce thyroid secretion).

The PBPK results, as presented in Table 1 of the Notice, show the 1 week old breastfeeding infant to have the greatest RAIU inhibition when its mother is given a dose 10 times greater than the RfD (*e.g.*, exposure at water concentration of 245 ppb). This assumes that the infant would be exclusively breastfed. In calculating the HRL, the age groups that had the greatest intake per body weight, however, were the youngest infants who are exclusively formula fed. Based on the PBPK model, the bottle fed infant had a 1.5% change in RAIU inhibition, which is well within the normal variation of RAIU inhibition.

2. EPA requests comment on whether EPA used the best available and most appropriate data to estimate alternative HRLs in Table 2 (denoted by footnote c) where the sample size does not meet the minimum data requirements as described in the "Third Report on Nutrition Monitoring in the United States" (LSRO, 1995). Does aggregating life stages (birth to 6 months, and women ages 15-44) address sample size limitation and still provide an accurate representation of the exposure to the most vulnerable life stages?

The drinking water intake rates in the age groups are based on USDA Continuing Study of Food Intakes by Individuals from 1994-1996 and 1998. This was a large study of dietary

recall and was reported by Kahn and Stralka (2008). Although this may be the best study that the Agency could find, it is neither sufficient nor does it meet the scientific standards the EPA's own guidelines demand for a regulatory process.

First, compared to the science-based data used in a PBPK model, water intake is an insensitive variable. It cannot be used for measuring, estimating, or predicting the effects of a chemical on the body. In fact, it does not and cannot estimate or predict any effects in the body. This study is not based on a specific experiment, but a summary of data obtained in a survey based on recall rather than direct measurements. The best and most scientific process would be to measure and record the exact amount of fluid or food intake at the time of ingestion.

Second, as noted by EPA in the Notice, for some life stages, the data do not meet EPA guidelines on data quality.[14] Water intake as the sole variable makes general assumptions about numerous body functions in lieu of actual data. For example, in effect, this calculation does not account for absorption, distribution, or excretion, regardless of developmental state. This calculation implicitly assumes that the body's disposition of perchlorate is directly proportional to body weight. There are no scientific data to support these assumptions.

Third, the study population in Kahn and Stralka (2008) may not be representative of the U.S. population. The body weights presented by Kahn and Stralka (2008) are lower than that found in 1996-2000 NHANES data, as presented by EPA in the Child Specific Exposure Factors Handbook (U.S. EPA, 2008d) and may not be representative of the general population. For one month olds, the Kahn and Stralka (2008) mean, 90th and 95th percentile body weights are 20, 45, and 24% lower than the NHANES 1996-2000 data. A greater body weight will result in a lower total dose, if intake is the same. The comparison body weights for the three youngest age groups are presented in Table 1 in Appendix A.

Fourth, Kahn and Stralka (2008) is a recall study. As noted above, this is a study in which the study participant had to recall their own (or their infant's) consumption over two non-consecutive days. No direct measurements were taken. Recall studies are subject to bias from errors in memory when recalling the amounts consumed (*i.e.,* what, when, and how much did I eat or drink?). For example, it is possible and not unusual that the person reporting the infant intake estimated a high value for intake. If this occurred for one or two individuals in the study, the data would be skewed (as observed by inspection), overestimating the statistical estimation of the 90th and 95th percentile water consumption values.

Furthermore, a dietary recall study should represent the entire population, not just tap water consumers. The water intake from Kahn and Stralka (2008) were calculated based on individual parameters. EPA chose to use the data for consumers of water only, yet individuals commonly use water from other sources (*e.g.*, bottled, in juice or soda). Since the EPA is interested in developing a MCL, sources of water that would be regulated are municipal water systems. One effect of choosing not to use the analysis of all individuals is that the results are higher than what would be reflected if all data were used. That is to say, this would not be a science-

Applying life stage specific drinking water values is, in effect, "double counting" the uncertainty factor that has already been applied.

[14] The Notice states "The sample sizes for the estimates of ingestion rates for these life stages do not meet the minimum data requirements as described in the ''Third Report on Nutrition Monitoring in the United States'' (LSRO, 1995)."

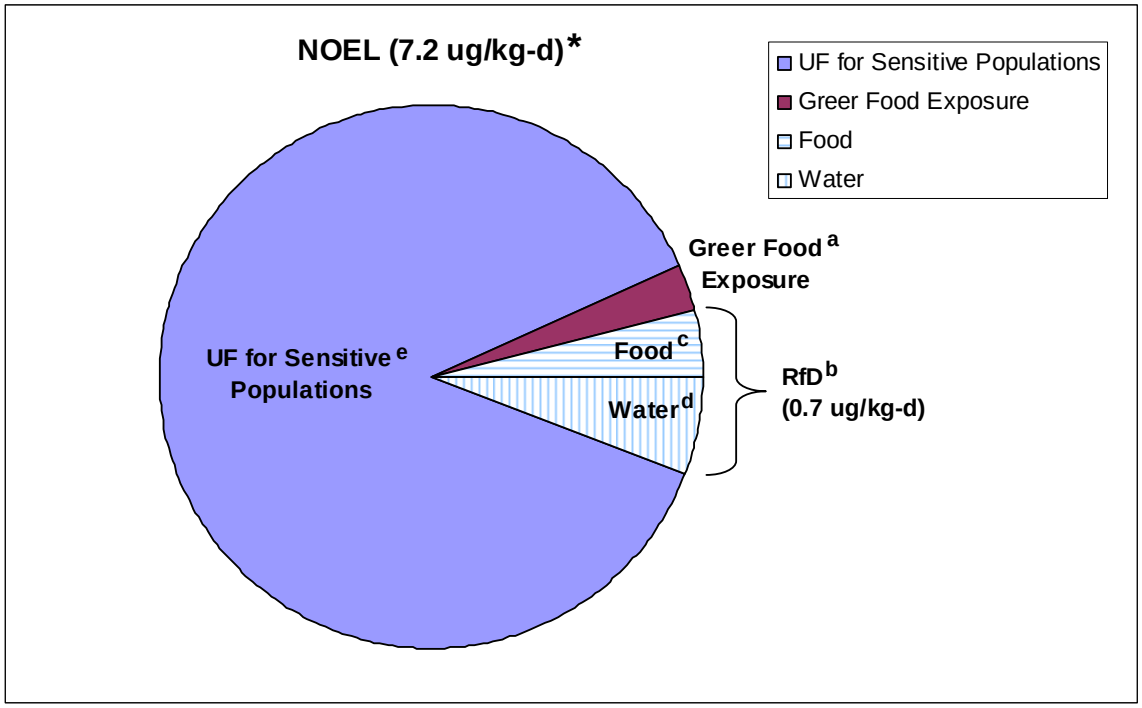
based decision. The results of using ingestion rates from consumer versus all individuals on the alternative HRLs are presented in Table 2 in Appendix A. To illustrate the effect noted above of limiting the population, in infants less than one month of age, the proposed alternative HRL based on consumers only was 3 μg/L; if the value for all individuals is used, the water concentration would be 8 μg/L.

EPA reports intake rates and alternative HRLs based on the mean, 90th, and 95th percentiles. Kahn and Stralka (2008) lack sufficient study size and methodology to reliably inform the science related to the general population, as the Notice acknowledges.

One way to gauge whether the 90th and 95th percentile values suggested in the Notice are statistically unreliable is a simple comparison to blood volume. The average adult has a blood volume of approximately 5 L and drinks approximately 1.4 L/d, or 27% of their blood volume (U.S. EPA, 1997). It is well understood that infants and children consume more than adults when normalized for body weight, but **using the intake rates suggested by EPA, the 95th percentile one month old infant would consume 2.6 L/d or 280% of their blood volume. This is the equivalent of the average adult consuming just under 4 gallons, every day.** Comparisons of water intake to blood volume are presented in Appendix A, Table 3.

The RfD is based on the study by Greer *et al.* (2002) and the researchers in this study did not control dietary intake of perchlorate or other natural agents such as nitrate, thiocyanate, or iodine. Perchlorate has been detected in many foods, including but not limited to milk, lettuce, and cantaloupe (Murray *et al.*, 2008). No perchlorate was reported detected in Portland's city water supply (the location of the study) according to UCMR1. Thus, assuming that Murray *et al.* (2008), is correct, subjects would have received perchlorate from food (See Figure 1). Therefore, the dose of perchlorate that resulted in a NOEL was in addition to the background level of perchlorate ingested through food. If the background dose of perchlorate from all sources was 0.02 to 0.234 μg/kg-d (the 5th and 95th percentile estimated doses from Blount *et al.* (2007)), then all doses in Greer *et al.* (2002) underestimate the true dose by this amount and the RSC has already been considered.

Figure 1. Visual representation of UF, the RfD, and unaccounted for contribution of perchlorate in food are components of the POD dose.



* An upper-bound estimate of a true NOEL for perchlorate. The dose was estimated by summing 7 µg/kg-d from Greer *et al.* (2002) and the background dose from food and water, 0.2 µg/kg-d. Perchlorate was not been detected in Portland's water (area where study participants lived) based on UCMR1 so all background perchlorate was likely due to food intake.

[a] EPA (2008a) presented the mean background perchlorate dose as 0.2 µg/kg-d.

[b] The RfD is 0.7 µg/kg-d based on the low dose from Greer *et al.* (2002) divided by a UF of 10 for intraspecies variability

[c] 62% percent of the RfD defined to account for food exposure (U.S. EPA, 2008a)

[d] 38% "leftover" for water exposure (U.S. EPA, 2008a)

[e] 10 x UF applied to the POD

3. EPA requests comment on the merits of the approach described here of deriving HRLs for sensitive life stages based on the RfD combined with the life stage specific exposure data and whether there are other approaches that may be useful for deriving HRLs.

Given the strength of the underlying science in the EPA PBPK model, the proposed HRLs in the Notice do not address sensitive life stages in a scientifically justified manner.

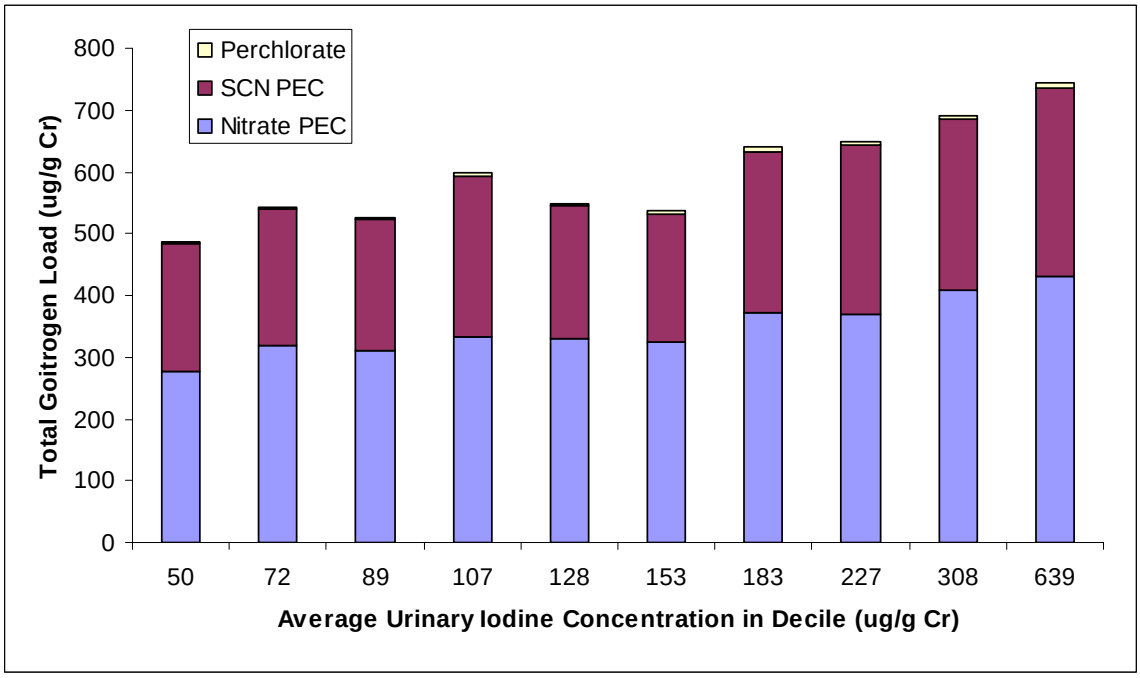
Some have suggested that perchlorate should be regulated differently because its acute effects may be detrimental during sensitive life stages. This assumes that the UF applied to the RfD is not large enough to account for the most sensitive life stage. Such a claim would be not supported by scientific evidence. First, toxicologically speaking, an acute effect is an effect seen after one high dose or an exposure of less than 24 hours. No published study has demonstrated an effect after one exposure to perchlorate at environmental levels. Even if acute is meant to refer to effects over several weeks to months (more commonly termed "sub-chronic") of exposure, no study demonstrates adverse effects at environmental levels, nor would an effect be expected based on the current scientific literature. As the Greer *et al.* (2002) study demonstrated, any IUI at the POD dose is within normal variation and there is

no evidence that any effects, much less any adverse effects, would be expected at doses near the RfD, on a short-term or chronic (lifetime) basis.

One major scientific issue is that the effects of agents that affect IUI in the same way as perchlorate were not considered by the Notice.

Because perchlorate, nitrate, and thiocyanate compete with iodine for uptake by the NIS, the combination of these chemicals in food or water will affect iodine uptake to the thyroid as well as absorption into the body from the gut. The NIS is located in the small intestine and uptake of iodine can be reduced by sufficient doses of perchlorate (Brown-Grant, 1961). In defining a HRL, it is assumed that 100% of an ingested dose is able to reach the thyroid. Of the four chemicals (perchlorate, nitrate, thiocyanate, iodine), perchlorate has the highest affinity for the NIS, however, the other three are more abundant in the diet. In the FDA Total Diet Study, the dose range of perchlorate was 2.4 to 9.1 μg/person-d and the dose range of iodine was 144 to 353 μg/person-d (Murray *et al.*, 2008). Similar to biomonitoring studies (Blount *et al*., 2006) and dose models (Belzer *et al*., 2004), the OIG Draft Report (U.S. EPA, 2008b the results for exposures to nitrate, thiocyanate, and perchlorate found that perchlorate accounted for less than 1% of the predicted IUI in the total goitrogen load. Based on NHANES 2001-2002, the average urinary concentration of perchlorate was 4.8 μg/L, which was much lower than the urinary concentrations of nitrate, thiocyanate, and iodine at 55,017 μg/L, 2,042 μg/L, and 200 μg/L, respectively. Figure 2 demonstrates the relative contribution of perchlorate to total goitrogen load using another set of data, the NHANES 2001-2002 database.

Figure 2. Total goitrogen load in perchlorate equivalence* based on urinary measurements from women ages 12 and older from NHANES 2001-2002.**



* Ability to inhibit iodide uptake
** Approximate population used in Blount *et al.* (2006), n =1162
SCN: thiocyanate
PEC: Urinary perchlorate equivalence (SCN PEC = thiocyanate / 8.8; Nitrate PEC = nitrate / 150)

One characteristic of this relationship is that as perchlorate dose increases in food, so does intake of nitrate, thiocyanate, and iodine. Figure 2 presents the cumulative intake of the four agents based on NHANES data using perchlorate equivalence of the urinary concentration of nitrate and thiocyanate. Two things become clear. First, as iodine level increases, so does total cumulative dose. Second, perchlorate contributes, by far, the smallest amount to total cumulative dose. The chart shows that as the goitrogen load increases, people tend to have increased intake of iodine, probably due to greater ingestion of total food.

C. Use of Data on Perchlorate Occurrence in Drinking Water

To estimate how many people potentially could be exposed to perchlorate in drinking water, EPA used data from its first cycle of the UCMR1 (http://www.epa.gov/safewater/ucmr/ucmr1/index.html). The Notice presents the resulting population estimates in Table 3. The Agency estimated the size of the population exposed to perchlorate at different threshold levels (4 µg/L or higher, 5 µg/L or higher, *etc.*) by assuming that the entire population served by a public water system (PWS) is exposed to perchlorate at concentrations above a threshold level if at least one sample collected in the PWS contained perchlorate at or above the threshold level (even if all other samples are lower, or nondetect). Based on this assumption, the Notice reports an estimate of 16.6 million (M) people exposed to perchlorate at concentrations above the method reporting limit (MRL) of 4 µg/L. In addition, the Agency developed an alternative assessment by assuming that populations served by PWSs are equally distributed among entry points to the PWS and that only those portions of the population served by entry points with reported concentrations above the threshold are

exposed. Based on this assumption, the Notice reports an estimate of 5.1M people exposed to perchlorate at concentrations above the MRL of 4 µg/L.

The Notice asks for comment on three general questions regarding the use of occurrence data to estimate exposure to perchlorate. Responses to these questions, based on the best available scientific information, follow.

1.EPA requests comment on the potential use of a Bayesian model to estimate the number of public water systems, and the population served by such systems, with at least one estimated sample detection greater than 1, 2, 3, 4, 5, 7, 10, 12, 15, 17, 20, and 25 µg/L.

With regard to perchlorate's regulatory determination, extrapolating the frequency of occurrence of perchlorate in U.S. drinking water at concentrations less than the MRL of 4 µg/L is unnecessary because scientific data provide no evidence that adverse health effects can occur at these levels. Data for average adults (*e.g.*, Greer *et al.*, 2002) suggest that IUI at water concentrations less than 245 ppb (the drinking water equivalent of the POD) would be statistically insignificant, and the Notice suggests, based on EPA's PBPK model for several life stages, that IUI at water concentrations corresponding to the RfD (*i.e.*, 24.5 ppb) would be less than 2%.

Further, UCMR1 data are insufficient for estimating population sizes exposed to concentrations greater than the MRL of 4 µg/L, and therefore may not be used to reliably estimate exposures below the MRL. As elaborated below, examination of EPA's occurrence analysis is made difficult by the fact that the Notice lacks the required transparency concerning the assumptions it used to calculate sizes of populations potentially exposed to different threshold concentrations (Table 3, U.S. EPA, 2009b). The Notice's summary of the UCMR1 data likely overestimates current exposure concentrations and the number of people exposed to perchlorate above various threshold levels.

Scientific and statistical concerns with the Notice's use of the UCMR1 data set include the following:

- **UCMR1 covers the years 2001 to 2005; some of these data are nearly a decade old**. Data collected during this time overestimate current concentrations of perchlorate in drinking water. Guidelines EPA has established since 1992, including interim guidance for remediation and water exposure levels, and remediation of contaminated sites by responsible parties, have resulted in reductions in perchlorate levels in ground and surface water. For example, public information shows that annual average concentrations of perchlorate at the Las Vegas drinking water intake in Lake Mead declined almost 60% between 2000 and 2004 (from 13.1 ppb to 5.6 ppb), and the annual average concentrations in the Metropolitan Water District Colorado River Aqueduct intake at Lake Havasu on the Lower Colorado River declined about 50% between 2000 and 2004 (from 6.4 ppb to less than 4 ppb), and in 2004 nine of the twelve monthly samples were at levels too low to detect (*i.e.*, below 4 ppb) (http://www.epa.gov/region/toxic/perchlorate/per_nv.html). The Colorado River supplies water for agriculture in Arizona and California as well as drinking water for Southern California.
- **Environmental exposure levels of perchlorate are declining.** Although not an occurrence study, a recent study reports that urinary concentration of perchlorate is lower

in NHANES 2003-2004 participants compared to NHANES 2001-2002[15] suggesting population exposure was lower during 2003-2004 (Mendez *et al.*, 2009).

- **Examination of the UCMR1 data set demonstrates that several major U.S. cities did not detect perchlorate in their drinking water**. These cities are large metropolitan areas with corresponding large populations and include Washington DC, New York City, Newark, Baltimore, Philadelphia, Pittsburgh, Minneapolis/ St. Paul, Chicago, Milwaukee, Detroit, Cleveland, Indianapolis, Memphis, Nashville, Atlanta, St. Louis, San Francisco, Seattle, and Portland. Perchlorate is not ubiquitous in drinking water, but areas of detection appear to be regionalized. This does not diminish the importance of perchlorate where it has been detected at levels above the MRL (4 µg/L). States where significant perchlorate is present, *e.g.*, California, have either promulgated drinking water standards or adopted EPA interim guidance. As a result, the trend of occurrence is toward lower water concentrations.
- **The population estimates presented in Table 3 of the Notice could not be validated**. The Notice does not present all of the assumptions used to calculate population sizes. When extremely conservative assumptions are made, calculated population sizes are still much lower than EPA's estimates. For example, if it is assumed that the entire population served by a PWS is exposed to perchlorate at levels above the MRL when at least one sample collected in the PWS contained perchlorate at or above the MRL (even if all other samples did not detect perchlorate) and that the size of the population is the maximum associated with the category assigned to a given PWS (*i.e.*, very small, small, medium, large, very large), the computed maximum exposed population size is approximately 10.5M—this is approximately 60% of EPA's maximum estimate of 16.6M. This lower estimate is still extremely conservative and unlikely to accurately represent the size of the exposed population. The entire population served by the PWS is not likely to be served water from the entry point that had the highest reported concentration, and actual population sizes for each PWS are likely to be distributed across the range of population sizes associated with a given population category. Alternatively, if it is assumed that the population served by a PWS is equally distributed among entry points to the PWS and the total exposed population is computed based only on those entry points where perchlorate was detected above the MRL (*i.e.,* in a manner consistent with the last column of EPA's Table 3), the estimated population size is about half of EPA's 5.1M estimate.
- **It appears that EPA included monitoring data for untreated source water in its exposure estimates**. Based on the data retrieved from EPA's UCMR1 website, the UCMR1 data includes a total of 34,728 analyses for perchlorate (EPA reports 34,221 analyses), with 647 detections of perchlorate at or above the MRL (EPA reports 637 detects). These detections include 288 detections in source water (out of 10,684 samples, or a frequency of detection of 2.7%) and 348 detections in entry point water (out of 23,319 samples, or 1.5%) (perchlorate was not detected in any samples from the midpoint of distribution systems (n = 16), the point of maximum retention (n = 19), or the location in distribution systems where disinfectant residual is lowest (n = 6); perchlorate was detected in 11 of 684 samples from "unknown" locations). Thus, it is questionable as to whether the number of people presented in the Notice is likely to drink untreated source

[15] NHANES 2001-2002 is the basis for the study by Blount *et al.* (2006). See following section for the full discussion on Blount *et al.* (2006).

water from PWSs, and data from drinking water entry points indicates that concentrations at the entry points are generally lower.

These observations indicate that using the UCMR1 database to extrapolate exposures to concentrations below the MRL would be inappropriate, as it would produce highly inaccurate estimates.

2. EPA requests comment on using U.S. Census data to estimate the portions of the population that are in the sensitive life stage at any one time.

U.S. Census data might be useful if PWS data are paired with U.S. Census data for the same locations. As discussed above, the relevance of the UCMR1 data to current exposure is unclear since the UCMR1 data, which were collected from 2001 to 2005, likely overestimate current concentrations, and approximately half of the perchlorate water samples in the UCMR1 database are from untreated source waters. Evaluating perchlorate in drinking water at low concentrations (*e.g.*, less than the concentration corresponding to the RfD of 24.5 ppb) is unnecessary as no adverse health effects are expected at these levels.

*3. EPA requests comment on how the Agency should account for the variation of perchlorate levels over time in public water systems. EPA believes that estimating the number of systems, entry points and populations with at least one detection above the HRL is appropriate for the perchlorate regulatory determination because a single quarterly or semi-annual sample more closely reflects the short term exposure during life stages of concern (*i.e.*, fetuses, preterm newborns, infants and young children). However, EPA requests comment on whether the Agency should consider other approaches such as estimating the number of systems, entry points and populations with two or more detections above HRL or some other approach.*

As discussed above, there are fundamental scientific and statistical issues with the UCMR1 database for estimating current exposures to perchlorate in drinking water, so any application of the data therein would be unreliable. First, UCMR1 data are likely to overestimate current exposure concentrations because data were collected from 2001-2005 and subsequent remediation and treatment has reduced these concentrations, and approximately half of the perchlorate water samples in the UCMR1 database are from untreated source waters. Second, data in the UCMR1 database are insufficient for estimating population sizes because, for PWSs with multiple entry points to the distribution system, the database does not specify the size of subpopulations distributed water from specific entry points where perchlorate was detected.

III. OTHER COMMENTS

In Section IV of the Notice, EPA discusses its consideration of studies published since EPA adopted the NRC RfD for perchlorate. The Notice states:

> EPA's preliminary regulatory determination is based on NRC's (NRC, 2005) recommendation to use data from the Greer *et al.* (2002) study as the basis for the perchlorate RfD/risk assessment. Since the publication of the NRC report, researchers have investigated perchlorate occurrence in humans by analyzing for perchlorate in urine and breast milk—such biomonitoring data has the potential to better inform EPA's analysis of exposure to perchlorate through food and water and to provide insight into the possible interactions of other physiologic conditions (*e.g.*, iodine deficiency) with perchlorate ingestion. EPA's preliminary regulatory determination described the consideration of these studies, many of which were

> published after the NRC report (including, but not limited to, Blount *et al.* (2006 and 2007), Steinmaus *et al.* (2007), and Amitai *et al.* (2007)).

EPA's conclusion to this section is:

> EPA agrees that additional important data have become available since the RfD was derived in 2005. However, EPA has evaluated the new data and has decided to make the regulatory determination based upon the current RfD.

The weight-of-scientific evidence supports this EPA conclusion.

As a reminder, Intertox provided comments to these studies in a 2008 submission; these comments are located in the EPA docket (Intertox, 2008). Intertox also provided comments to the Draft OIG report (Intertox, 2009). Nonetheless, these studies are summarized below. EPA has also posted several additional documents to the docket that require additional context.

A. The 2009 FR Notice Docket

The EPA Docket for this Notice (Docket ID No. EPA–HQ–OW–2009–0297) includes a number of documents including a commentary that provides criticism of the NRC expert panel's conclusions on perchlorate, but does not provide new scientific data from which to base a regulatory determination (Ginsberg and Rice, 2005). To provide a transparent compendium of available information, if the Agency provides or uses any commentaries, it should consider all commentaries. For example, a response to Ginsberg and Rice (2005) was published in the same journal. This response was co-authored by the NRC perchlorate panel chair and three other members from the 18-member panel and provides point-by-point science based rebuttals to why the Ginsberg and Rice (2005) assertions are incorrect. The response authors conclude by stating that the NRC-recommended RfD "provides a wide margin of safety for all subjects of all ages" (Johnston, *et al*., 2005). **We request that EPA add this response to the docket.**

B. Recent Studies Listed in the 2009 *FR* Notice

The Notice states that EPA has evaluated additional data made available since the 2005 RfD determination. In response to comments suggesting that other studies, particularly Blount *et al.* (2006), be used for defining a regulatory standard, EPA noted that new studies have provided important information to the scientific literature, but that it has "decided to make the regulatory determination based upon the current RfD." The papers EPA listed are summarized below. Based on these data, Greer *et al.* (2002) continues to provide the best scientific information to be used as the basis for EPA's perchlorate RfD risk assessment.

Most of these comments have been presented by Intertox in the past. Where appropriate, however, these summaries are updated with new information.

Blount *et al.* (2006)

Using the NHANES 2001-2002 data set and a cross-sectional study design, Blount *et al*. (2006) report measurement of urinary perchlorate, urinary iodide, serum TSH, and serum total T4 levels in men and women over the age of 12. The 2001-2002 NHANES data provide the largest group of subjects to date from which sampling data can be derived. The authors report that perchlorate levels were not associated with total T4 or TSH levels in men, but were a negative predictor of total T4 and a positive predictor of TSH in women with urinary

iodine less than 100 μg/L. They report that in women with urinary iodine greater than 100 μg/L, urinary perchlorate was a positive predictor of TSH, but not associated with T4. The significance of evaluating women with urinary iodide less than 100 μg/L is based on the World Health Organization (WHO) statement that a median urinary iodine concentration for the entire population, based on spot samples of less than 100 μg/L, is indicative of overall iodine deficiency for that population (WHO, 2004).

This study has drawn a great deal of attention as it may be misinterpreted to demonstrate an "effect" of perchlorate, albeit at exposures below those that cause measurable IUI. A number of considerations, however, should be noted to better understand the significance of the data reported.

First, as stated above, ATSDR (2008) reviewed this study in their assessment and did not feel it merited any special consideration over other studies in the well developed perchlorate literature database. It states that its decision "…was made after a careful evaluation of the NRC report and of studies that have been published after the NRC (2005) report. The results from newer studies do not change the bottom-line recommendation" (ATSDR, 2008).

Second, it is important to interpret the results of scientific research based on what is known about the biological system. For example, there is a difference between "statistical significance and "clinical significance." A "statistically significant" difference simply means it is unlikely that a difference between two variables (***e.g.***, measurements) is due to chance. With a well designed experiment, statistical significance can be extremely important. Because statistical significance is also a function of sample size, variability in the variables measured, *etc.*, the finding of statistical significance does not necessarily mean the difference is large, important, or biologically significant. For biological data, it is important to understand whether something that is statistically significant is also clinically significant; that is, whether a change in a variable or parameter is large enough to affect a clinical or medical condition (***e.g.***, development of hypothyroidism). Blount *et al.* (2006) report statistically significant relationships for some variables, but do not report any variables with clinical significance, such as free T4.

The type of study conducted by Blount and colleagues (***i.e.***, a cross-sectional study) cannot determine causation, only *association* between the variables studied (Wartenberg and Buckler, 2001). If important variables are missing, then spurious conclusions can be made. Thus, without a full set of thyroid-specific variables measured, including repeated 24-hour urinary iodide measurement, any association should be examined carefully for reliability.

Furthermore, perchlorate did not actually lower (nor was it associated with) thyroid hormone levels outside the normal range of values. Assuming that it had, the NRC committee does *not* think that "…transient changes in serum thyroid hormones or TSH concentrations are adverse health effects; they are simply biochemical changes that might precede adverse effects" (NRC, 2005). For each individual in the NHANES study, a single spot urine sample and a single plasma sample for analysis of thyroid hormones and other parameters were collected. These data do not provide more than a "snapshot" or transient assessment of these individuals.

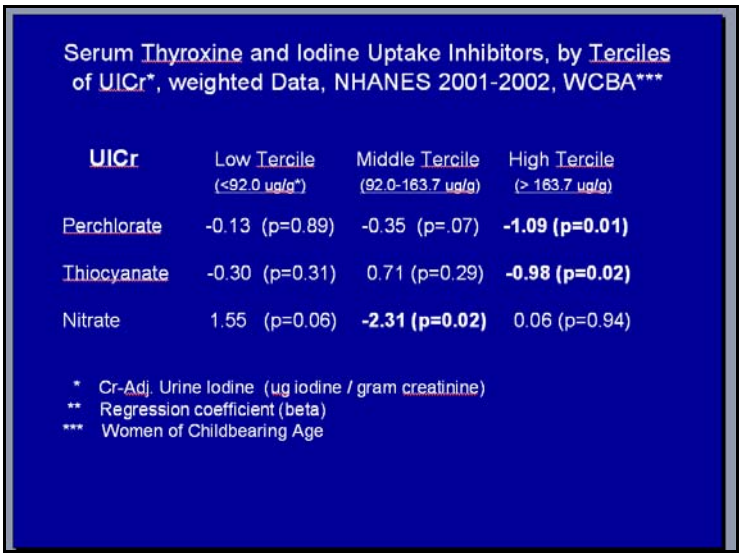
Regarding Blount *et al*. (2006), ATSDR states, "limitations of the study acknowledged by the investigators include those common to cross-sectional analyses, the assumption that urinary perchlorate correlate with levels in the thyroid stroma and tissue, and the measurement of total T4 rather than free T4" (ATSDR, 2008).

Third, any study must have careful consideration for the parameters and variables that are measured or available and how these variables relate to the outcome of interest. NHANES is designed to collect a broad range of data about the health and diet of people in the United States. NHANES collected data on some parameters relevant to thyroid function, but these parameters fall short of providing sufficient information needed to clearly understand thyroid health. Only two clinical measures of thyroid function were taken (total serum T4 and TSH). Missing where free T4, thyroid binding globulin (TBG), and T3 among others. Iodine status was reported on the basis of spot urine samples, which are neither the preferred, nor most reliable, measure of urinary iodide (Barr *et al.,* 2005). Further, NHANES did not collect data on the incidence of autoimmune thyroiditis, the most common thyroid disorder in the U.S., which causes changes in serum T4, T3, and TSH concentrations due to errant immune mechanisms attacking the thyroid gland, called Hashimoto's thyroiditis (NRC, 2005). Intertox (2008) provides a more thorough discussion regarding the use of spot urine testing, confounders, and use of the available NHANES variables to draw conclusions.

This study did not present urinary measures normalized to creatinine, although creatinine was included as a variable in the regression analysis. The concentration of dissolved substances in urine, such as iodide, may vary between individuals or between samples from the same individual based on water intake. Normalization with creatinine is meant to normalize for dilution, not variability due to differences in exposure. It is not a perfect method, but is commonly used to account for this dilution (Furnee *et al.,* 1994). Normalization may have been particularly useful in dividing the women up in to those with urinary iodide less than and greater than 100 μg/L.

At a recent symposium on perchlorate held in conjunction with the annual Society of Toxicology (SOT) meeting in Seattle, Lamm *et al.* (2008) presented their initial reanalysis of the NHANES dataset used by Blount *et al.* (2006) with an adjustment for urinary creatinine. Lamm *et al.* considered a subset of women from the Blount *et al.* (2006) study who were of childbearing age (15-44 years old; the Blount *et al.* (2006) study group included all women over the age of 12) as well as the interaction of thiocyanate and nitrate, both in urine. They found there was no significant association between perchlorate and total T4, including women with urinary iodide less than 92 μg/g (Figure 3).

Figure 3. Urinary reanalysis results of the NHANES data



Lamm *et al.*, 2008

In a peer-reviewed letter to the editor of *Thyroid*, Gibbs and Van Landingham (2008) reviewed data from their previously published study (Téllez *et al.*, 2005), and showed that in a cohort of pregnant women in Chile, the data do not support the association between environmental perchlorate exposure and changes in thyroid hormones and are consistent with the recent negative findings by both Pearce *et al.* (2007a) and Lamm *et al.* (2008), both presented at the Seattle SOT meeting.

More recently, Mendez *et al.* (2009) used probabilistic modeling to estimate the total dose of perchlorate from food and drinking water using three drinking water scenarios based on UCMR1 data. The highest estimated dose through water and food was 0.15 µg/kg-d at the 95th percentile, well below the RfD of 0.7 µg/kg-d. When compared to the NHANES 2001-2002 estimates based on urinary output (used by Blount *et al.*), they found that intraday variability contributed to the overestimation of dose based on the NHANES data. Interestingly, they also found that the urinary excretion of perchlorate in NHANES 2003-2004 was significantly lower than in 2001-2002. Two data points do not represent a trend, but this lower urinary excretion may represent lower doses through food and water in subsequent NHANES studies.

Fourth, not only were the thyroid hormone values within normal clinical ranges, but urinary perchlorate levels as a surrogate for dose demonstrate that these perchlorate exposures are well below the threshold for zero inhibition of iodide uptake, a nonadverse effect. Exposures that are below the threshold for iodine uptake inhibition are below the NOEL for perchlorate and are not adverse (NRC, 2005; Greer *et al.*, 2002).

Finally, based on the premise that science is incremental and knowledge builds collectively over time, concerns raised by scientists related to the Blount *et al.* (2006) study should be considered an opportunity for further study. Furthermore, recognizing that urinary spot iodine or single point iodine measures are not a good indicator of iodine status, a different approach is being considered by Dr. Blount. More research should be conducted to better understand the results of this study.

Steinmaus *et al.* (2007)

Steinmaus *et al.* (2007) used the same dataset as Blount *et al.* (2006) to assess the correlation between smoking, thiocyanate and urinary perchlorate, and thyroid hormone levels. The same methodological issues reported for Blount *et al.* (2006) apply to this study. As in Blount *et al.* (2006), the authors did not find any interaction between perchlorate and smoking and TSH or total T4 in women with urinary iodine levels greater than or equal to 100 μg/L or in men. They did conclude that in women with urinary iodine less than 100 μg/L, perchlorate increased the risk of lower total T4 and higher TSH, just as was reported in the Blount *et al.* study. This association was stronger when the woman was also a smoker or had high urinary thiocyanate levels.

Amitai *et al.* (2007)

This ecological study aimed to "…assess the effect of gestational perchlorate exposure through drinking water on neonatal thyroxine (T4)" by comparing T4 levels among newborns whose mothers lived in areas with drinking water perchlorate levels associated with "very high exposure" (10 to 100-fold greater compared to levels in the U.S.; ≥340 μg/L), "high exposure" (42-94 μg/L), or "low exposure" (<3 μg/L). T4 levels were measured within 36 to 48 hours after birth but there was no comment on whether the infants were breast fed or formula fed during the postnatal period. The authors found that there were no differences between neonatal T4 levels among the groups. This study provides evidence that the current RfD and values greater are conservative and health protective to the most sensitive individuals in the population.

Pearce *et al.* (2007)

The objective of the Pearce *et al.* study was "to determine whether breast milk iodine concentrations in Boston-area women are adequate for infant nutrition, and whether breast milk iodine concentrations may be associated with environmental perchlorate or cigarette smoke exposure." Pearce *et al.* measured breast milk iodine and perchlorate concentrations as well as iodine, perchlorate, and cotinine in urine. They then compared the levels found in breast milk to 17 commercial infant formulae. Neither breast milk nor urinary perchlorate levels were significantly correlated with breast milk iodine concentrations. Although perchlorate was detectable in infant formulae, the levels were lower than in breast milk. A significant number of women in this study had iodine levels that were insufficient to meet the infant's needs, but the authors did not suggest this was due to perchlorate exposure or that it represents a chronic iodine deficiency.

Kirk *et al.* (2005)

With the aim to determine what amount of perchlorate children are exposed to, Kirk *et al.* measured perchlorate and iodide levels in cow and human breast milk and compared these values to corresponding levels of perchlorate in drinking water in the area. Perchlorate was measurable in 81 of the 82 samples. The average perchlorate levels in cow milk and human milk were 2 and 10.5 μg/L, respectively. The maximum levels in cow and human milk were 11 and 92 μg/L, respectively. There was no correlation between levels of perchlorate in breast milk and perchlorate in drinking water. The authors speculated that there was a correlation between higher levels of perchlorate and lower levels of iodine in breast milk; however, they note that this relationship only existed for the breast milk samples with the highest perchlorate levels (6 subjects out of 82). The authors recognize that this relationship

may be coincidental due to the small number of samples with perchlorate levels greater than10 μg/L, stating that "If we take all the available data, there is no meaningful correlation between the perchlorate and iodide levels in breast milk." As with previous studies, due to the design, this study was not able to evaluate a causal relationship.

Kirk *et al.* (2007)

To determine the variability in the excretion of perchlorate, thiocyanate, and iodide in human milk, Kirk *et al.* had lactating women collect six samples of milk on each of three days or as many samples as possible over three days. They found that a significant variation over time for all the anions tested. The average iodide, perchlorate and thiocyanate levels were 87.9 μg/L, 5.8 μg/L, and 35.6 μg/L, respectively. The study was not designed to determine whether perchlorate or thiocyanate contributed to IUI in mammary tissue. This study was a biomonitoring study and did not measure any adverse effects or exposures.

Dasgupta *et al.* (2008)

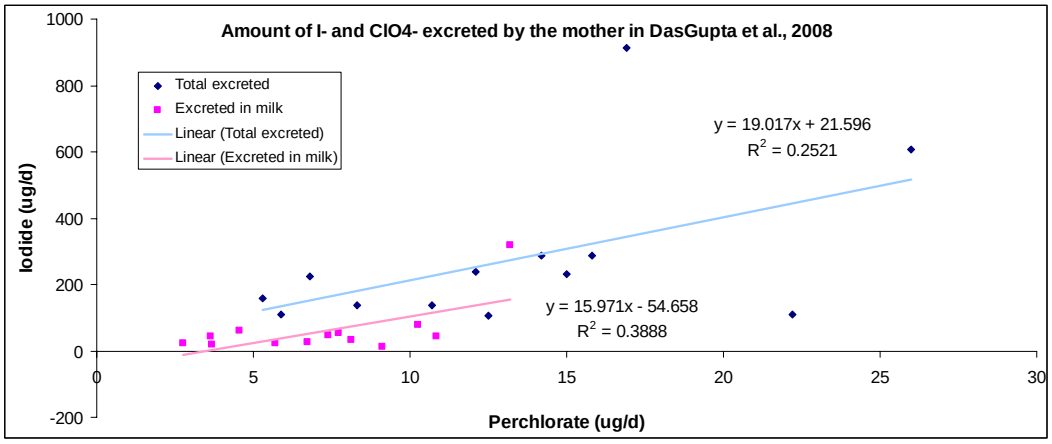
"The objective of this present study was to study the excretion of perchlorate, thiocyanate, and iodine in milk and urine and relate the observed pattern within the broad framework of parallel/competitive transport by the NIS." Using breast milk and urine samples from 13 lactating women and using EPA default values for infant body weights and milk intakes, the authors mathematically modeled infant intakes and doses of iodide, perchlorate, and thiocyanate. They calculated the fraction of iodide, perchlorate, and thiocyanate in breast milk compared to the total that is excreted in both breast milk and urine. They used a ratio of these fractions in milk to determine the selectivity of either perchlorate or thiocyanate over iodide. They report "that 12 of 13 infants did not have an adequate intake of iodine…and 9 out of 13 infants were likely ingesting perchlorate at a level exceeding the reference dose…" They also concluded that the selectivity of perchlorate over iodide was 3.14 ± 1.2.

There are a number of unresolved issues related to the experimental design of this paper. The population is small and there is no information on the selection process of the participants (*i.e.*, they are not a random sample). Only three biological variables were measured in the women. The rest of the variables, including the variables used to derive the conclusions, are calculated from these three or are default values for infant intake and infant weights. The three measurements were the concentrations of perchlorate, iodine, and thiocyanate in urine and breast milk. Where other research has measured more biologically relevant information, such as serum concentrations of analytes that would be most reflective of relative concentrations at the NIS (Tonacchera *et al.*, 2004; Pearce *et al.*, 2007), this work is based on very few measured observations. The estimated doses, the key variable for understanding possible effects, are based on average body weight and intakes for an infant. For such a simple and critical variable and in such a small study population, it is surprising that actual body weights were not measured.

In addition to study design, the data presented in this paper appear to contradict the interpretation by the authors of the paper. Based on estimated weights, the authors say that nine out of 13 infants are consuming daily doses in excess of the RfD, yet Table 1 of Dasgupta *et al.* suggests there are 8 infants who exceed the RfD of 0.7 μg/kg-d (subjects 1, 2, 8, 11, 13, 15, 16, 20). Furthermore, if one reviews these estimates to measured variables, the infants with estimated perchlorate doses greater than the RfD are also estimated to have the greatest iodine intake. By plotting the values for total iodide excretion (column 4), total perchlorate excretion (column 7), estimated maternal breast milk iodide excretion (equivalent

to estimated infant iodide intake; column 5), and estimated maternal breast milk perchlorate excretion (product of total perchlorate excreted and percent of perchlorate in milk; column 7 x column 9) found in Table 1 of the paper, the results demonstrate that perchlorate and iodide are positively correlated (See Figure 4). If perchlorate was inhibiting the transport of iodide into milk, the association would be negative.

Figure 4. Plotting of data reported by Dasgupta *et al.*, 2008 to illustrate the association between concentrations of iodine and perchlorate in urine and milk in lactating women.



In addition to the questions regarding interpretation of the data presented in this paper, there are concerns about the interpretation of their previous work (Kirk *et al.*, 2005) and how that study impacts this recent study. For example, Dasgupta *et al.* (2008) remark that "in real mothers perchlorate does inhibit the transport of iodine into milk and because of competitive inhibition both analytes cannot be high at the same time." This statement, however, is based on a previous study in which the researchers defined their cut off values[16] above which milk iodide or perchlorate was considered "high." They report that no milk samples had both high perchlorate and high iodide (Kirk *et al.*, 2005). In the present study, they report the same trend although they do not define a cut off value. Yet if the previous cut off values are applied to the current study, there are many samples that had simultaneously high perchlorate and iodide (Figure 4). Based on the previous conclusions about competitive inhibition of analytes (Kirk *et al.*, 2005), this study does not demonstrate that perchlorate competitively inhibits iodide transport into milk at the concentrations experienced by these women.

Schier *et al.* (2009)

The authors measure the concentration of perchlorate in reconstituted powdered infant formula and used this information to estimate a mean and upper-bound dose of perchlorate in infants solely fed formula. They also estimated the perchlorate concentration in water that would cause an infant in the 10th, 50th or 90th percentile of body weight to receive a dose equal to the RfD every day. The authors concluded that some infants could be at risk for exceeding the RfD even with minimal amounts of perchlorate in water used for reconstitution, but "the clinical relevance of exceeding the perchlorate RfD in both an iodide-sufficient and iodide-deficient state are unclear."

[16] The cut off values from Kirk *et al.* (2005) were defined as follows: High iodide in breast milk was greater than 60 µg/L and high perchlorate in breast milk was greater than 20 µg/L.

This study provides information to the literature on potential exposures given that all the assumptions made about exposure hold true. This study is focused on the exclusively formula fed infant. The most sensitive subpopulation for perchlorate health effects and the group that the RfD is based, is fetuses of hypothyroid mothers. This paper compares the RfD to estimated doses in a population that is not the considered the most sensitive. The RfD is 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.

This report does not demonstrate that this population is receiving doses of perchlorate at or above the RfD. This study suggests that some individuals have the potential to exceed the RfD, if all the assumptions implied hold true. Exceeding the RfD is not or meant to be a bright line threshold of effects. As noted above, the perchlorate RfD is based on a NOEL in addition to an UF adjustment.

McLanahan *et al.* (2009)

In an attempt to evaluate the mode of action of perchlorate, McLanahan *et al.* coupled a biologically-based dose response model of the hypothalamic-pituitary-thyroid axis with a PBPK model for perchlorate. The model was based on rats and evaluated changes in serum thyroid hormones with exposure to doses of perchlorate up to 10 mg/kg-d (a DWEL of 350,000 ppb). With this high dose, the authors found that the model outputs were inconsistent with observed data from experimental studies (Yu *et al*., 2002). The authors must add a numerical adjustment factor to their model so that output from the model agrees with experimental data. They conclude that:

> ClO_4^- administered in drinking water (or by other routes of administration) interacts with the rat thyroid gland itself, potentially altering thyroid hormone synthesis or secretion. This interaction is in addition to blocking thyroidal uptake of iodide. Current presumptions of a single MOA for ClO_4^- on the HPT axis do not appear tenable based on these results.

Modeling can be very valuable in research. This model, however, is based exclusively on rats. As many have noted, rat and human thyroid endocrinology must be evaluated carefully as the differences between the two species are important. Rats have smaller stores of thyroid hormones and are more sensitive to IUI than humans (NRC, 2005). This model is not able to predict output that is consistent with observed experimental data. Thus, without the addition of a numerical adjustment factor (called the "proportional inhibition term") this model does not produce comparable results to experimental data. The need for this numerical adjustment factor suggests unaccounted data needs or terms in the model, a species difference, or the effects of pendrin given the higher dose levels. The authors say no more than what is quoted above and provide no additional information as an explanation.

Greer *et al.* (2002)

As noted above and briefly reiterated here, the mechanism of action (MOA) of perchlorate in humans is the inhibition of iodide uptake (IUI). The MOA has been reviewed by numerous authoritative bodies (NRC, EPA, ATSDR, *etc.*) who have concluded that it is not adverse. Iodide uptake is mediated by the NIS in the thyroid follicular cell. Greer *et al.* found a level where there was no statistical change in IUI and therefore, no downstream effects were possible.

That IUI is not adverse has been well-documented by NRC, EPA, New Jersey, California, and ATSDR. Much is documented about exposures to perchlorate at environmentally relevant doses up to therapeutic doses, the amount of IUI these doses cause, and the lack of downstream effects with environmentally relevant doses. For example, many studies demonstrate a statistically significant IUI, but no change in thyroid hormones for weeks or months (Greer *et al.*, 2002; Braverman *et al.*, 2005; Lawrence *et al.*, 2000 and 2001; *etc.*). Moreover, the literature regarding perchlorate at therapeutic doses demonstrates the effect of IUI and changes in hormones. The NRC committee members unanimously stated that transient changes in thyroid hormones are not adverse and prolonged changes in thyroid hormones must occur for a person to become hypothyroid.

Some have argued that the study population of the Greer Study was too small to exhibit statistical significance of small changes in IUI, particularly with the variability reported. It is important to note that decisions regarding statistical power and sample size were conducted ***a priori,*** in accordance with standard experimental design. These were stated and agreed upon by the researchers and EPA. The questions by some about variability have been raised ***a posteriori,*** after the results are known. Based on all the information available when the experiment was designed, the sample sizes in the Greer Study were sufficient. Notably, with a dose of 0.02 mg/kg-d, a 16% IUI (24-hr value) was statistically significant.

Regarding the variability of the low dose group, IUI from "background" (as noted above in Figure 3) perchlorate, nitrate, thiocyanate, and other agents found in the diet and drinking water were not controlled. This likely explains a significant proportion of daily interpersonal RAIU changes. Furthermore, 1) variability in RAIU for the low dose group was not different from RAIU for other dose groups, 2) all volunteers had normal baseline RAIU values when compared to the literature, and 3) when baseline RAIU is low, small absolute changes will appear large as relative RAIU, which is a mathematical, not physiologic, phenomenon.

In a dose-response study, one dose group should not be taken in isolation. The best way to evaluate the low-dose variability in RAIU is to examine all data generated by the study. Simple inspection of the data show a decrease in RAIU change with increasing dose—IUI occurred in a classic and unequivocal dose-response manner. Additionally, the No Effect Level (NEL) using linear regression of all relevant RAIU clinical data was 6 µg/kg-d for 24 hours, which was similar the NOEL of 7 µg/kg-d. Considering the data from Lawrence *et al.* (2001) which demonstrated a higher dose of perchlorate (approximately 40 µg/kg-d assuming 3 mg/d for a 70 kg person) with a non-statistically significant decrease in RAIU (as well as no corresponding change in thyroid hormones) strengthens this understanding.

IV. CONCLUSIONS

1. The use of scientifically derived PBPK models represents the best scientific approach for evaluating the relative sensitivity of different life stages and to compare to occurrence data. As constructed, however, the perchlorate PBPK model likely overestimates IUI from perchlorate exposures for various life stages. Only when the best available science is shared in a transparent process can the public be empowered to assist the Agency in achieving the best public health decisions. Nonetheless, the predicted levels of IUI in the Notice are very low and would be indistinguishable from fluctuations resulting from differences in diet and feeding styles. No adverse health concern at any life stage would be expected based on exposure to perchlorate at the POD dose (7 µg/kg-d).

2. The proposed use of alternative HRLs based upon body weight and water consumption of other life stages is not a scientifically-based process. If there were a lack of data for a particular chemical, then perhaps this approach would be defensible. For perchlorate, however, where the effort of scientists to reduce uncertainty has been long standing and focused, the use of body weight and water consumption would increase uncertainty. The PBPK modeling provides greater and more biologically significant information.
3. EPA's proposed analysis of occurrence data is concerning in that the estimated population sizes in the Notice could not be reproduced, the data from UCMR1 are not current and likely overestimate current exposures, and the highest concentration detected anywhere in a PWS was used to estimate exposures for all people served by the PWS, even if the sample was collected from untreated source water or all other samples were nondetects. Altogether, these assumptions produce an inaccurate and overly conservative estimate of potential human perchlorate exposures from drinking water.

In summary, EPA's existing, scientifically based RfD remains a conservative, health-protective toxicity guideline value. Perchlorate concentrations in drinking water at or below the 15 ppb HRL set by EPA, along with its existing, preliminary determination, pose no significant health risk, even to the most sensitive individuals consuming water on a daily basis over a lifetime. Finally, the best available science establishes that none of the three requirements of the SDWA are met; therefore, there is no scientific justification to regulate perchlorate under this statute.

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APPENDIX A

SUPPLEMENTAL TABLES

Table 1. Comparison of body weights from Kahn and Stralka (2008) and NHANES 1996-2000 in lbs.

Age Range		Kahn and Stralka (2008)	NHANES 1996-2000
< 1 month	Mean	8.8	10.6
1 month to 3 months		11	12.3
3 months to 6 months		15.4	16.3
< 1 month	90th %ile	8.8	12.8
1 month to 3 months		13.2	15.6
3 months to 6 months		19.8	19.1
< 1 month	95th %ile	11	13.6
1 month to 3 months		15.4	16
3 months to 6 months		22	20

Table 2. Alternative HRLs based on corrected water intake rates.

	Life Stage (mo)	RfD (µg/kg-d)	RSC	Mean Ingestion rate (mL/kg-d)	Alt HRL (µg/L)
Consumers only	0-1	0.7	0.59	137	3
All individuals	0-1	0.7	0.59	52	8
Consumers only	1-3	0.7	0.59	119	3
All individuals	1-3	0.7	0.59	48	9
Consumers only	3-6	0.7	0.59	80	5
All individuals	3-6	0.7	0.59	52	8
Consumers only	0-6	0.7	0.59	95	4
All individuals	0-6	0.7	0.59	50	8

Table 3. Comparison of daily water ingestion to blood volume.

Life Stage	Blood Volume (mL/kg) [c]	Water Ingestion (mL/kg-d)		Water intake as a percent of blood volume	
		Mean	95th %ile	Mean	95th %ile
Adult	75	19.9 [a]	40 [a]	27%	53%
< 1 month	85	137 [b]	238 [b]	161%	280%
1 month – 3 month	85	119 [b]	285 [b]	140%	335%
3 months – 6 months	85	80 [b]	173 [b]	94%	204%

[a] U.S. EPA, 1997
[b] U.S. EPA, 2009b
[c] Dallman *et al.*, 2003

APPENDIX B

INITIAL REVIEW OF HOPONICK *ET AL.*, 2009

Initial Review of: Hoponick JR, Melillo PR, Visser NT and Henshel DS. 2009. "Examining the Correlation between Perchlorate Concentrations in California Drinking Water and Low Birth Weight Percentage Using Population-Scale Regression Analysis," obtained from C. Matthews, Contractor, US EPA, Office of Environmental Information, EPA Docket Center, EPA Docket OW-2009-0297-0492, received via email on September 30, 2009.[1]

This document (Hoponick *et al*., 2009) appears to be a manuscript that has been submitted for publication. The study is an ecological epidemiological study, and is short in length. The authors evaluate the association between the mean perchlorate concentration measured in groundwater wells in 13 counties in California (measured between 1997 and 2004), and the percent of neonatal births with low birth weight (LBW), coded by zip code from 1993 to 2002. Zip code data sets for percent of births with LBW for each year were "averaged to the county level by averaging all data within each county." Based on this evaluation, the authors conclude that "log perchlorate data are significantly correlated with LBW for all years" and that "the increase is relatively linear from the lowest detectable perchlorate levels (3.3 ppb) to about 10 ppb, where the response appears to saturate." They further conclude, "Log perchlorate data also significantly positively correlates with TSH level for 1998, the only year for which TSH data was available."

An initial analysis of the manuscript was conducted using information derived from the manuscript. The source of data and an analysis of the methods and conclusions is provided below. Comments are divided into the following categories: data related to perchlorate concentrations in drinking water, data related to LBW, data related to neonatal TSH, and discussion of confounding factors.

EPA should review the scientific basis of this manuscript to assure itself that the data are reliable. Upon request, additional information can be provided. What might be useful is to review a recently published paper which reports no effect on birth weight, head circumference, and body length associated with perchlorate exposure (Blount *et al*., 2009).

Briefly, the following is noted regarding the manuscript.

Perchlorate Concentrations in Drinking Water

Hoponick *et al.* (2009) conducted statistical analyses using the mean concentrations of perchlorate in drinking water,[2] collected between 1997 and September 9, 2004, and averaged across each of 13 counties. The authors present mean concentrations for any California county that "contained two or more perchlorate detections from at least one drinking water source since 1997." Data were obtained from the California Department of Health Services website: http://www.cdph.ca.gov/certlic/drinkingwater/Pages/Perchloratehistory.aspx. A downloadable MS Excel file of the data is here: http://www.cdph.ca.gov/certlic/drinkingwater/Documents/Perchlorate/Perchlorateforweb-earlyfindings.XLS.

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[1] http://www.regulations.gov/search/Regs/contentStreamer?objectId=0900006480a27182&disposition=attachment&contentType=xml

[2] The paper alternatively calls the water source either "groundwater wells" or "drinking water wells."

Some observations about these data are as follows:

- The CDHS website only provides downloadable data for detects of perchlorate in water only. It is not clear from the manuscript whether the analysis considered nondetects in the calculation of mean perchlorate concentrations.
- Neither the CDHS website nor the manuscript indicate the analytical method that was used to measure perchlorate during this time. For example, a change in analytical method could impact the concentration data.
- The manuscript does not indicate the range of concentrations detected in the wells, the number and percentage of wells or water systems in which perchlorate was detected in each county, or how frequently perchlorate was detected in specific wells.
- The data obtained from CDHS shows that many wells were sampled repeatedly. However, the manuscript does not indicate how multiple detections at the same location were considered in the calculation of the county average.
- The manuscript does not indicate the extent to which sampled wells contribute to drinking water for the public in a given county, or whether water from wells was treated prior to distribution (but after sampling).
- Some of sample dates in the CDHS database cannot be discerned because they appear to be miscoded.
- The manuscript does not indicate how the timing of sample collection was assumed to relate to the association with LBW data.
- It appears that some average concentrations reported in the manuscript include data from wells designated in the CDHS database as "inactive" or "destroyed," and therefore would not contribute to drinking water that is distributed to the public. It is not clear how inclusion of these data is assumed to provide reliable measures of exposure.

Percent of Neonatal Births with Low Birth Weight (LBW)

Hoponick *et al*. (2009) report that data on neonatal birth weights were obtained from the California Department of Public Health (CDPH) for the years 1993 to 2002. The authors define "low birth weight" as a birth weight less than 2,500 grams (5.5 lbs.). The link provided in the paper redirects to here: http://ww2.cdph.ca.gov/programs/deodc/Pages/default.aspx . Annual data by zip code for the years 1993 to 2002 are available.[3]

Some initial observations of these data are as follows:

[3]
- 1993: http://ww2.cdph.ca.gov/data/statistics/Documents/birthzip1993.xls
- 1994: http://ww2.cdph.ca.gov/data/statistics/Documents/birthzip1994.xls
- 1995: http://ww2.cdph.ca.gov/data/statistics/Documents/birthzip1995.xls
- 1996: http://ww2.cdph.ca.gov/data/statistics/Documents/birthzip1996.xls
- 1997: http://ww2.cdph.ca.gov/data/statistics/Documents/birthzip1997.xls
- 1998: http://ww2.cdph.ca.gov/data/statistics/Documents/birthzip1998.xls
- 1999: http://ww2.cdph.ca.gov/data/statistics/Documents/birthzip1999.xls
- 2000: http://ww2.cdph.ca.gov/data/statistics/Documents/birthzip2000.xls
- 2001: http://ww2.cdph.ca.gov/data/statistics/Documents/birthzip2001.xls
- 2002: http://ww2.cdph.ca.gov/data/statistics/Documents/birthzip2002.xls

- %LBW is lowest in 1996 for six of 13 counties and highest in 2002 for eight of 13 counties. The manuscript does not discuss these differences, or how they might relate to perchlorate exposure. For example, might there have been a change in the measurement or reporting method for birth weight?
- Sacramento County has 135 zip codes, but in 2002 (for example) the CDPH data only includes birth weight data for 49 zip codes. Further, the CDHS data includes only 34 water samples for perchlorate (from a total of 14 locations in five systems), after exclusion of data from inactive or destroyed wells. It is not clear how from the manuscript how data from these wells was extrapolated to assumed exposure across the county, or to specific zip codes, and how birth weight data for missing zip codes was considered. It appears that all individuals in the county were assumed to be exposed to the average perchlorate concentration computed from the available samples, and that the county average %LBW was based on the 49 zip codes for which data were available.

Neonatal TSH Data

The manuscript remarks "TSH data was obtained by contacting the CDHS directly, and 1998 was the only year CDHS provided." We were not able to find the data in the manuscript to support this statement.

Confounding Factors

The manuscript states, "The confounding factors data from 2003 was obtained from the California Interview Survey (CHIS) Database, which is operated by the University of California Los Angeles Center for Health Policy Research, in cooperation with CDHS and the Public Health Institute." The CHIS database is available (http://www.chis.ucla.edu/get-data.html). The only confounding variables reportedly considered by the authors were race and percentage of uninsured individuals. However, the literature on low birth weight is extensive and many other factors are known to influence birth weight including maternal health status, maternal age, smoking, alcohol/ drug use, prenatal care, maternal education level, and other socio-economic factors (Bailey and Byrom, 2007; Nobile *et al*., 2007). It appears that these factors were not evaluated.

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Nobile CG, Raffaele G, Altomare C, Pavia M. 2007. Influence of maternal and social factors as predictors of low birth weight in Italy. *MC Public Health* 7:192.