PSG

PERCHLORATE STUDY GROUP

A coalition of aerospace, defense, chemical and allied industries

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

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Re: Comments in Response to EPA Notice *Drinking Water: Preliminary Regulatory Determination on Perchlorate* [EPA-HQ-OW-2008-0692; FRL-8727-6].

The Perchlorate Study Group (PSG) is pleased to submit comments to the Environmental Protection Agency (EPA) on Docket ID No. EPA-HQ-OW-2008-0692, entitled *Drinking Water: Preliminary Regulatory Determination on Perchlorate*. As manufacturers and users of perchlorate, the PSG is committed to ensuring that the best available science is provided in public debate and applied in the subsequent setting of regulatory standards. The member companies of the PSG include Aerojet, American Pacific Corporation (AMPAC), Alliant Techsystems (ATK), and Tronox.

For over ten years, the PSG has worked cooperatively and effectively with the US Environmental Protection Agency (EPA) and other federal agencies, state governments, and water purveyors to:

- increase scientific and medical understanding of perchlorate's possible effects on human health; and,
- assess the level of perchlorate in drinking water that is expected to pose no adverse effects to human health.

We therefore appreciate this opportunity to submit these comments relating to EPA's preliminary determination.

I. The EPA's Proposed Determination is Backed by the Best Science and the Statute

The PSG agrees with EPA's preliminary determination that a Federal drinking water regulation would not meet the SDWA criteria and that EPA has ample justification for this determination. EPA has an extraordinary wealth of comprehensive, authoritative scientific information relating to perchlorate's health effects, supplemented by extensive occurrence and exposure data. The Agency is therefore exceptionally well-positioned to issue a well-considered regulatory determination. The best available scientific data supports a determination under the Safe Drinking Water Act (SDWA) that public water systems do not present a meaningful opportunity for risk reduction.

Public water systems do not offer a meaningful risk reduction opportunity since EPA's data show that only a few percent of systems have had detectable levels of perchlorate and virtually all of them are routinely below EPA's unusually protective reference dose (RfD). EPA also has extensive data that show the US population's total exposure to perchlorate - from food and water - is below the RfD for 99.996 percent of the population. EPA should spend its limited resources on significant potential threats to human health in order to most effectively protect the public health.

The comments below present a detailed analysis of the issues relating to EPA's determination. The attachment from Intertox describes in more detail the state of the scientific literature. The overwhelming weight of scientific evidence indicates that EPA is acting correctly in its determination not to establish a Federal drinking water standard.

II. The EPA Should Publish its Final Determination as Soon as Possible

In the *Federal Register* notice, EPA has set a timeline for public comment, a final decision, and the possible decision to set a Health Advisory (HA). EPA's timeline for a final determination is wise for two principal reasons.

First, the 45-day period provides ample time for the public to review EPA documents and submit comments as EPA has offered substantial opportunities for public comment on this matter. EPA previously provided a 60-day public comment period on the Contaminant Candidate List 2 (CCL) preliminary regulatory determinations for 11 chemicals issued May 1, 2007 via publication in the *Federal Register* as well as on its website.[1] In that publication, EPA also extended the opportunity to the public to comment on perchlorate. The PSG and other organizations commented extensively on that notice. EPA, indicating it was not issuing a determination at that time, discussed the various scientific and technical data being reviewed and considered by the agency, including the National Academy of Sciences (NAS) report, the Unregulated Contaminant Monitoring Rule 1 (UCMR) occurrence data, and options to use data to establish the relative source contribution (RSC). The agency also identified options for potential methodologies that could be employed to make a determination, including the option of using the NHANES and UCMR 1 data. EPA has selected that approach as its basis for its preliminary determination. Thus EPA has offered the public multiple opportunities for public comment, more than most substances on the CCL for which EPA has made a determination.

Second, EPA has ample scientific and technical data to make a final determination on or before the planned date of December 2008. As noted in the attached scientific summary, perchlorate

[1] 72 Fed. Reg. 24016 (2007) (published May 1, 2007).

is one of the most well-studied chemicals with detailed information on the mechanism of action, dose-response, and health effects. This issue also is not new. EPA released its first draft risk assessment on perchlorate in 1998, followed by a second in 2002. The 2005 NAS report was a comprehensive review of the science. The animal and human studies that have been published since the NAS report reduce the uncertainty and reinforce the NAS panel's finding that there will not be any adverse health effects from perchlorate at environmentally-relevant concentrations.

New studies published since the NAS report increase the weight of evidence that the current RfD protects human health including the most sensitive members of our population. In addition, testimony by Congressional members and witnesses alike have discussed the lengthy amount of time that EPA has spent studying the health effects, urging the agency to issue a determination as soon as practicable. We join them in urging EPA to issue the final determination promptly.

III. The Current Scientific Literature Provides Overwhelming Support for EPA's Findings under the Safe Drinking Water Act's Criteria for this Determination

In the SDWA, EPA is directed by Congress to make a determination whether to set a National Primary Drinking Water Regulation (NPDWR) based on the following criteria:

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 (73 FR 60264).

EPA has provided sufficient support for its findings under the SDWA. To take the statutory criteria in turn:

May perchlorate have an adverse effect on the health of persons?

Everything - including water itself - may cause an adverse effect if the dose is sufficiently high. The plain meaning of the first criterion relates to the dose of the contaminant at levels which people are likely to be exposed to through drinking water.

The scientific literature is clear that perchlorate will not cause adverse effects at the concentrations under review here. The NAS report declares,

> *An important point is that inhibition of thyroid iodide uptake is the only effect that has been consistently documented in humans exposed to perchlorate. The continuum of possible effects of iodide-uptake inhibition caused by perchlorate exposure is only proposed and has not been demonstrated in humans (with the exception that in patients with hyperthyroidism doses of 200 mg daily or higher may reduce thyroid secretion). More importantly, the outcomes at the end of the continuum are not inevitable consequences of thyroid exposure.*

In other words, except for its deliberate medical use, perchlorate has never been shown to have caused adverse effects in humans. Moreover, the NAS also concluded that perchlorate is not likely to be a carcinogen.

In addition to the NAS conclusions, subsequent studies indicate perchlorate has not been demonstrated to have an adverse effect on the health of persons at environmentally relevant levels (*Blount et al*., 2006). The weight-of-evidence suggests that adverse effects do not occur following chronic exposures to perchlorate at doses much greater than the RfD (*Téllez et al*., 2005; *Amitai et al*., 2006; *Braverman et al*., 2006).

EPA's preliminary determination includes imprecise language that bears clarification:

> *Perchlorate interacts with the sodium iodide symporter, reducing iodine uptake into the thyroid gland and,* ***at sufficiently high doses****, the amount of T4 produced and available for release into circulation.* ***Sustained changes*** *in thyroid hormone secretion can result in hypothyroidism.* (p. 60275; emphasis added)

The NAS concluded that perchlorate will not cause adverse effects under consideration in this determination. The NAS findings are consistent, as well as the overwhelming majority of the large body of available peer-reviewed science on perchlorate.

The "sufficiently high doses" that EPA refers to are orders of magnitude higher, approximately 0.4 mg/kg-d (approximately 19,000 ppb)[2]. These levels have never been reported in public drinking water systems. According to the NAS report, even these levels do not inevitably lead to adverse effects.

The NAS independently evaluated the science and its conclusions and recommendations are published in the report *Health Implications of Perchlorate Ingestion* (2005). The NAS report recommended an RfD of 0.7 µg/kg-d based on a No Observed Effect Level (NOEL), or the dose

[2] See, NAS, at 171-172 (pdf version) ("…a sustained exposure at more than 0.4 mg/kg per day would most likely be required to cause a sufficience decline in iodide uptake and thyroid hormone production to result in adverse health effects in normal adults. That estimate is based on clinical studies and studies of long-term treatment of patients who had hyperthyroidism.

at which no effects occur, adverse or otherwise (*NAS*, 2005). One of the critical studies that served as the basis for this RfD was the study by *Greer et al*. (2002) which demonstrated that there was no inhibition of iodide uptake by the thyroid at a dose of 7 µg/kg-d. Some have argued that the low dose group contained only seven subjects; however the NAS correctly dismissed this assertion, pointing out that there were four doses provided across 37 subjects. Importantly, the NAS also noted that it did not examine Greer in isolation. According to the NAS report, the findings in Greer are supported by other clinical studies, occupational and environmental epidemiologic studies, and studies of long-term perchlorate administration to patients with hyperthyroidism.

Further, the NAS 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." The committee views its recommendation to use [IUI] by the thyroid as the basis of the perchlorate risk assessment to be the most health-protective and scientifically valid approach (NAS, 2005).*

In using a NOEL, the NAS committee adopted a notably conservative, health-protective approach. This dose is already lower than any dose in which adverse effects occur; an *additional* safety factor of 10 is applied to the already conservative NOEL. The NAS was acting to ensure protection for the most sensitive individuals in a population, in this case, hypothyroid or iodine-deficient pregnant women and their developing fetuses. **Importantly, the NAS panel did consider other sensitive populations besides pregnant women and their fetuses. They also considered the potential effect on infants, developing children, people who have compromised thyroid function, and people who are iodide-deficient.** *The NAS panel stated that using a NOEL as the point of departure is a more conservative and health-protective approach than EPA's customary approach of using the adverse effect* (*NAS*, 2005).

The NAS panel also took time to distinguish between a No Observable Adverse Effect Level (NOAEL) from a NOEL. The experts observed that there was confusion between the two and clarified that the NOAEL is based upon an adverse effect, whereas the NOEL is based upon a dose at which no effect occurs, adverse or otherwise. (*NAS*, 2005).

EPA adopted the RfD recommended by the NAS and confirmed that it was conservatively based on the NOEL, not the NOAEL. EPA should clarify its finding as to the potential adverse effects of perchlorate to bring the final determination into alignment with its own NAS-based reference dose.

In sum: perchlorate will not cause adverse effects at levels under consideration in this determination. This conclusion reflects the best available scientific findings, including the NAS

report and the overwhelming majority of the large body of available peer-reviewed science on perchlorate.

Is perchlorate known to occur or is there a substantial likelihood that perchlorate occurs at a frequency and at a level of public health concern in public water systems?

Perchlorate is not known or likely to occur in public water systems with high enough frequency nor does it occur at levels of public health concern. The NHANES studies and breast milk biomonitoring studies, notwithstanding their limitations, reveal that the US population is not exposed to levels of perchlorate that could cause an adverse effect, even when all exposure sources - in food and water - are considered.

In the NHANES results, Americans 6 years and older had a 50th percentile dose of perchlorate at the time of sampling equivalent to 2.2 ppb in drinking water. (*Blount*, 2006) This dose is less than 10 percent of the conservative NOEL level that is the basis of EPA's RfD and 7,000 times lower than the NOAEL. Less than 0.004% of the population has the potential for exposure to perchlorate above the RfD. (*Blount*, 2006) By all standard regulatory benchmarks EPA uses to determine acceptable incremental potential population risk from drinking water exposure, total perchlorate exposure has not required regulation. If total exposure does not present a meaningful risk for regulatory purposes, it follows that the risk from exposure to perchlorate in drinking water only is even smaller.

The sole effect of setting a drinking water standard would be to reduce this already insignificant fraction. Rarely does EPA have both toxicology and exposure measures of such high quality. This evidence shows that drinking water is not a significant source of perchlorate for the population.

The nationally-representative Unregulated Contaminant Monitoring Rule 1 results show that perchlorate does not occur frequently or at levels of public health concern in public water systems. The process for collecting data on unregulated contaminants in large and small water systems has been well established and relied upon by EPA for past Contaminant Candidate List (CCL) regulatory determinations. The UCMR is the most complete source of information on contaminant occurrence in the nation's drinking water sources. The use of UCMR sampling data for regulatory determinations has been well established.

Additionally, as evidenced by sampling results from Lake Mead, the Las Vegas Wash, and the Metropolitan Water District of Southern California, perchlorate levels continue to decline since the time of the UCMR 1 sampling. The preliminary determination assumes that the concentrations measured in the UCMR 1 survey are still occurring. In fact, levels in many of the highest reported drinking water systems have significantly declined due to source control.

EPA's UCMR monitoring found a mean concentration of less than 10 ppb in systems with perchlorate - over 100 times lower than the NAS adverse effect level. Only a few systems have found any samples with concentrations greater than 100 ppb. Even the maximum level detected in the US is approximately 50 times lower than the dose at which the NAS panel determined adverse effects could begin. Specifically, the NAS panel noted that "…a sustained exposure of more than 0.4 mg/kg per day would most likely be required to cause a sufficient decline in iodide uptake and thyroid hormone production to result in adverse health effects in normal adults." (NAS 2005) For these reasons, perchlorate is not known or likely to occur in public water systems with a frequency and at levels of public health concern.

IV. The Scientific Literature Supports EPA's Findings that There is Not a Meaningful Opportunity for Risk Reduction from a National Drinking Water Standard

The evaluation of data on the health effects of perchlorate, national occurrence, and exposure using the SDWA "meaningful risk reduction" criteria support EPA's determination that an NPDWR for perchlorate is unnecessary.

Following the release of the NAS report, EPA set an RfD for perchlorate at 0.7 µg/kg-d. The RfD is defined as "…an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime (*EPA*, 2005). The RfD does not distinguish between perchlorate in drinking water and in food. In establishing the amount of perchlorate that would be expected to pose no risk to health in drinking water alone, the RSC is factored in resulting in the HRL or "the benchmark against which EPA compared the concentration of a contaminant found in public water systems to determine if it is at a level of public health concern (73 FR 60275)." EPA has established that it would not be meaningful to set an NPDWR, but is now considering issuing a Health Advisory (HA), in the form of an MCLG.

If EPA decides a Health Advisory is necessary, the RfD is sufficiently conservative to serve as the HA. As presented in the PSG's comments on the May 1, 2007 notice, the best available scientific analysis demonstrates that all of EPA's approaches lead to an RSC of essentially one. Drinking water is not a meaningful contributor to total perchlorate exposure - and not even a minor source of total inhibition of iodine uptake, the non-adverse effect that is the basis of the RfD.

Alternatively, the HRL identified in its preliminary determination could also serve as an even more conservative, but no more protective, HA. What is striking is that either approach would be highly conservative. In fact, the high level of conservatism, and health protection, is far greater than EPA indicated by the agency's longstanding policies, themselves properly weighted toward greater protection.

The HRL relies on the NAS-recommended RfD that has several levels of conservatism (that is, exceptional health protection) built into calculation of dose. As EPA has noted, its RfD was based upon the recommendations of the NAS which, as noted, used a much more conservative and health-protective approach to derive its recommended safe dose than EPA has previously used.[3] EPA embeds an additional level of conservatism in calculating the final HRL by verifying their calculations using PBPK modeling of pregnant women as opposed to relying on the standard of assuming an adult as the focus of its calculations.

To determine the RSC, the EPA uses the NHANES-UCMR data to estimate doses to people who were exposed through food only (73 FR 60273). The UCMR 1 shows the median concentration of perchlorate in drinking water to be 6.4 µg/L (73 FR 60269). The 90th percentile estimated dose to the women exposed only through food was 0.263 µg/kg/d which corresponds to 38% of the RfD. This leaves 62% of the RfD left for exposure through water. Using this data, a HRL was calculated as such:

$$HRL = \left(\frac{RfD \times BW}{DWI} \right) \times RSC$$

Where,
RfD = 0.7 mg/kg-d
BW = 70 kg
DWI = drinking water intake = 2 L/d
RSC = 62%

This results in a HRL of 15 ppb. The derivation of the HRL was based on the body weight and water intake of an adult[4], not the pregnant woman and her fetus. The EPA modeled the amount of IUI in a pregnant woman and her fetus using PBPK modeling and found that the amount of IUI expected was equivalent to the NOEL from *Greer et al*. (2002). EPA then compares this HRL to perchlorate occurrence data in drinking water to evaluate the percent of the population exposed to perchlorate above the HRL.

For the perchlorate determination, EPA may also use the evaluation criteria under the CCL 1 regulatory determinations to determine whether a meaningful opportunity to regulate health risk exists. EPA's regulatory evaluation process follows the recommendations on a protocol from EPA's stakeholder advisory panel, the National Drinking Water Advisory Council (NDWAC). To assist EPA in evaluating the third statutory criteria, the NDWAC protocol recommended

[3] NAS, at 170-71.

[4] The standard EPA default procedure for converting dose into drinking water equivalent levels assumes 2 liters (67.6 oz) of water consumed per day and a body weight of 70 kg (154 lbs). These default values are not symmetrically representative of the population. This water consumption (WC) default is approximately equal to the 88th percentile water intake for adults aged 20 through 64 (calculated from Table 3-11 of U.S. EPA's Exposure Factors Handbook; EPA, 1999). However, 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 (from EPA, 1999; Tables 7-3 and 7-4).

"that EPA consider estimating the national population exposed above half the health reference level (or benchmark) and the national population exposed above the health reference level (or benchmark)."

EPA used this approach for evaluating substances in its CCL 1 regulatory determinations. This approach allows EPA's decision-making process to be replicated and therefore provides greater transparency and objectivity into the agency's final decisions rendered on the third statutory criterion. It also has the support of major stakeholders and has been subject to public comment. The PSG points out that EPA could, in addition to its valid reasoning in the preliminary determination, relay a similar evaluation process for its perchlorate determination.

A comparison of occurrence data for perchlorate and relevant compounds from EPA's CCL 1 regulatory determinations and the CCL 2 determinations reveals that perchlorate ranks as a lower opportunity for risk reduction than the sodium, manganese, sulfate, and boron, all of four of which EPA has made determinations not to regulate.

If the HRL is 15 ppb, EPA estimates that between 0.29 percent and 0.8 percent of PWSs have at least one detection greater than 15 µg/L, affecting 0.9 million to 2 million people served. Between 1.14 percent and 2.12 percent of PWSs had at least one detect with concentrations at ½ of the HRL (7 µg/L), affecting between 0.8 percent and 2.5 percent of the population served or between 2.2 million and 7.2 million people served, respectively.

Table 1: Comparison of Risk Opportunity between Perchlorate and Other Compounds

	Percent of PWS with Detects	Population Percentile Above 1/2 HRL	Population Served Above 1/2 HRL (millions)
Sodium	100	18.5	15.9
Perchlorate	3.6	0.0043	2.2-7.2
Manganese	68	4.6	3.9
Sulfate	88.1	10.2	21.8
Boron	82	2.9	2.5

The percentage of PWSs with perchlorate detections was very low (3.6 percent) compared to the next lowest unregulated compound, manganese at 68 percent. Sodium, for example, was detected in all PWSs. Perchlorate also has one of the lowest populations served by PWSs with detections above half the HRL with 2.2 million people. Perchlorate is well within the range of values for the evaluation criterion EPA uses. Like these other constituents, perchlorate is widely found in the diet and has minimal adverse health effects at the RfD. Although EPA's approach of using actual food data has more scientific justification, even if EPA adopts its customary approach for the proposed regulatory determination, it should find that perchlorate does not pose a meaningful opportunity to reduce risk.

V. EPA's Methodology to Support the HRL Could be Explained More Completely

In the preliminary determination, EPA puts forth a methodology to measure the contribution of food to total exposure by combining two nationally-representative data sets. The best available scientific understanding supports EPA's use of actual data as opposed to default parameters to derive the RSC. As EPA set out in its 2007 notice, EPA has multiple options to estimate the contribution of food to total exposure. At that time, the PSG presented analysis of the scientific merits of these options. The conclusions in those comments remain valid: no matter which scientifically-valid approach EPA takes, EPA can and should conclude that a national drinking water standard would not yield a meaningful reduction in human health risk.

The approach outlined in the proposed determination and background document appears to have several limitations. These limitations may be omissions in the description and not in the

methodology. While adequate to meet EPA's statutory obligation, we suggest that EPA's description could benefit from additional explanation. These suggestions are listed below.

- Sample Description. Both UCMR and NHANES are nationally representative samples. The sample frame and the sample weights are published and have undergone peer review. EPA takes a subsample from these data sets and compares them for its analysis. EPA's analysis could benefit from a more complete description of the characteristics of these subsamples. Further description would assist the public especially since EPA is comparing absolute levels of perchlorate measured in drinking water and in total exposure. Many factors could influence absolute amounts of food and drinking water consumption in a person at a given time such as climate, weight, age, and income. It is unclear from the analysis how the sample populations in Bins I, II, and III compare on these characteristics. For example, if the Bin III (and more importantly, its subgroups) population has a larger Body Mass Index (BMI) than the average US population, the sample population may consume more food than average. In this scenario, Bin III's absolute amount of perchlorate may be larger than the typical person in the US.

- Sample Population Size. The importance of describing the sample in more detail is magnified by the small number of individuals in the sample results EPA uses. EPA uses the 90^{th} percentile result from the 98 pregnant women in Bin III. EPA has not described the statistical relation of this sample to the US population. In addition, based on the shape of the distribution described in *Blount* (2006), the upper percentile results must be driven by relatively few observations. In other words, the analysis relies on the results from just a few women of unknown relationship to the whole US population or the subpopulation of pregnant women.

  Viewed in this way, EPA's analysis is a convenience, non-statistically representative sample that is comparable to other study populations in *Greer et al*. (2002), *Pearce et al*. (2007), *Téllez et al*. (2005), and *Amati et al*. (2007). These studies all show that for total doses in excess of the RfD, there are no measurable adverse health effects on the study populations, including sensitive populations. Therefore, while EPA constructs this study population to estimate an RSC, it primarily reinforces the PSG's position that no effects occur below the RfD even for sensitive subpopulations. Until EPA provides more description of its study population, its advantages over the other published, peer-reviewed studies is unclear.

- Temporal Comparison. In its background document, EPA describes how it linked the two study populations in the dimension of space - EPA assigned individuals to the bins based on whether a drinking water system in the county reported any single detection of perchlorate. EPA notes, but does not fully describe, how EPA handled temporal associations. The UCMR data was gathered from 2000 to 2005 according to EPA. The

NHANES survey was conducted during 2001 and 2002. It is not clear whether EPA only used the UCMR counties that reported detections in 2001 and 2002 or all years in the UCMR dataset. This consideration is important since many systems that detected perchlorate did not do so routinely. If EPA used the UCMR data from all years, EPA should describe how many individuals in the Bin III subgroups lived in counties with an actual detection during the 2001-2002 time period.

Additionally, on the NHANES sample, it is unclear how EPA adjusted the food consumption data to reflect seasonality. People eat different foods at different times of the year. While NHANES adjusts for this fact in its study design, it is unclear how and if EPA did so in its subsample. For example, if 50 percent of the pregnant women in Bin III were surveyed by NHANES in the summer, the food consumption patterns (and the distribution of absolute levels of perchlorate) would be different than if only 25 percent were sampled during that time.

- Concentrations below Detection Limits Assumed to be Zero. EPA notes that one limitation is that the analysis assumes that all detections below 4 ppb are assumed to zero. EPA states:

> *It is uncertain how the 4 µg/l detection limit in the UCMR might affect the assignment of NHANES to Bin III. However, EPA believes that the classification is reasonable and that it is unlikely that any false negatives would significantly change the findings because there is a low frequency of occurrence above the method reporting limit (less than two percent of all samples had detects), it is reasonable to assume that there would be a corresponding low frequency of occurrence below it* ***if at all****. (EPA envisions a scenario with a high frequency of occurrence at very low concentrations unlikely).* (pg 13)

First, while the misclassification problem among bins is interesting, it is clear how the detection limit will bias the results within Bin III. Bin III is supposed to represent individuals that only receive perchlorate through food. EPA uses the Bin III results to calculate the dose received from food. If some of this dose actually derives from drinking water, EPA is overestimating the dose from food, underestimating allowance available from drinking water, and underestimating the HRL.

Consider this scenario. In the pregnant women subgroup of Bin III, the 98 pregnant women have an average estimated perchlorate intake of 0.123 µg/kg/day. In the analysis, EPA assumes the water contribution is zero. Suppose the true water concentration for the 98 women is ½ the detection limit (or 2 µg/l), a common EPA assumption in risk assessments and other

drinking water exposure scenarios. The women then receive a dose of 0.057 µg/kg/day from drinking water. This amount is 46 percent of their total dose. Their estimated food dose is correspondingly lower, the relative source contribution would be lower, and the HCL should be greater than 15 ppb. While the ½ the detection limit is merely an assumption, it illustrates the main point - the censoring of the data due to the detection limit can have a large effect on the Bin III results.

This effect will only be large if a significant proportion of the Bin III population has concentrations of perchlorate in drinking water below the levels of detection. EPA finds "high frequency of occurrence at very low concentrations unlikely." If "high" means 90 percent of the population, this scenario is unlikely.

Table 2 in the proposed determination shows the estimated population served with at least one sample above the detection limit has an exponential shape to it (each time the concentration is cut in half, the estimated population exposed at that level doubles.) It is reasonable to assume that this relationship continues below the detection limit. By assuming all people in Bin III receive no perchlorate from drinking water, EPA overestimates the concentration from food and creates an overly conservative HRL.

In summary, EPA's approach is scientifically appropriate in using actual observed data to estimate the RSC and the HCL. All approaches have limitations; however, any limitations in EPA's analysis have to be viewed in context of the extensive body of literature on perchlorate's mode of action and measured effects in humans. When EPA's analysis is viewed in the context of the NAS findings and other published studies, EPA's analysis is one more way to demonstrate that total exposure to perchlorate in the US is common and without adverse effect. EPA's analysis is more than adequate to demonstrate that perchlorate does not occur at a frequency and level of health concern to warrant an NPDWR.

VI. Sensitive Subpopulations Could Be Exposed to Drinking Water with Greater than 15 ppb Perchlorate without Adverse Health Effects

As stated in these comments, in the Intertox summary, and in our comments to EPA's May 1st, 2007 notice, EPA should use an HRL equal to the RfD to reflect the conservative approach of the RfD and the ample evidence that exposure at the RfD have no effect on individuals, including sensitive subpopulations.

However, even if EPA uses its methodology in the final determination, EPA should use a larger Bin III subgroup to mitigate the potential limitations discussed previously. Using the sample group of females of childbearing age increases the sample size significantly. Switching the subpopulation of concern to women of childbearing age increases the sample size by five-fold, lowering the reliance on just a few observations. More importantly, it captures the

subpopulation the NAS panel identified as the most sensitive - fetuses of women with low iodine consumption. The most critical period for the fetus in a woman with sustained iodine deficiency may even occur before she knows she is pregnant. As EPA notes, assigning one value for consumption, body weight, and other parameters to represent all of pregnancy is difficult. For these reasons, if EPA continues its approach, we recommend EPA use the HRL derived from the Bin III estimate of food consumption for all women of childbearing age.

VII. The Published, Peer-Reviewed PBPK Model is Part of the Best Available Science EPA Can Use for the Determination

One uncertainty in the derivation of the HRL as well as in the literature database is the lack of studies that measure radioactive iodine uptake (RAIU) in the sensitive population, pregnant women and the developing fetus. Obviously, it would be unethical to conduct such as study. However, Physiologically Based Pharmacokinetic (PBPK) modeling has been found to be useful in reducing uncertainty and in filling scientific gaps in human health data on a substance. EPA policy has been to use PBPK modeling for determining human equivalent exposures (HEEs) and adjusting default uncertainty factors.[5] The NAS perchlorate panel agreed with EPA in finding PBPK modeling is "the best available approach" in determining HEEs (NAS, 2005).[6] EPA personnel have co-authored studies involving PBPK modeling and perchlorate (*Merrill et al*., 2005) and present for this preliminary determination, a model from *Clewell et al*. (2007) that was modified by making coding changes which served to improve the predictability of the model and therefore its overall usefulness. With this modified model, EPA is able to predict doses and changes in RAIU in pregnant women, fetuses, infants, and young children.

The utility of PBPK modeling has been previously recognized by EPA and has been endorsed by the NAS for use in reducing scientific uncertainty.

Using a 90th percentile water intake and based on data specifically for a pregnant woman, the model predicted that,

> *…the pregnant woman's dose of perchlorate would not exceed the reference dose if she consumed drinking water with a concentration of 15 µg/L or less, which is consistent with the derivation of the HRL from the reference dose, but*

[5] U.S. EPA Risk Assessment Forum, *A Review of the Reference Dose and Reference Concentration Process*, December 2002.

[6] The NAS panel also concluded the following: "By applying factors for life-stage differences (such as pregnant or lactating female rat vx adult male rat) and for species differences (such as adult rat vs adult human or pregnant or lactating rat vs pregnant or lactating human), one can constrain PBPK simulations by using known physiologic measures and biochemical constants to estimate HEEs in potentially sensitive populations that may not be suitable for experimental validation."

> *based on average body weight, 90th percentile water consumption, and 90th percentile food exposure for pregnant women.* (73 FR 60280)

The model verified that exposures to 15 ppb of perchlorate in drinking water will not reduce RAIU significantly, even assuming concurrent exposure through food and water intake in the 90th percentile. This combination of high-end exposure assumption is highly unlikely, probably at the extreme end of the population distribution. For this hypothetical pregnant woman, the percent RAIU inhibition was 1.1%. The greatest inhibition was seen in 7 day old infants at 2.2%. These percent inhibitions are consistent with the 1.8% inhibition of iodine uptake from the *Greer et al*. (2002) No Observed Effect Level (NOEL). In fact, although 2.2% is greater than 1.8% found in Greer et al., (2002), it is well within the standard error from Greer et al. (2002) of 8.3% and would still constitute a NOEL. The NAS report noted that "the very small 1.8% decrease in thyroid radioiodide uptake identified in *Greer* was *well within* the normal variation, and therefore 1.8% IUI does not define the limit beyond which adverse effects occurs has has been incorrectly argued. The PBPK modeling is in accord with results from other corroborative studies, such as *Téllez et al*. (2005), which show no adverse effect on sensitive populations.

In summary, EPA's PBPK modeling supports the point that the HRL derived by the agency is even more health protective than the already conservative NAS-based RfD that has been adopted by EPA. The modeling provides scientific support that incorporating an additional level of conservatism in deriving an HRL is unnecessary as the RfD is already very conservative; based on this support, a National Primary Drinking Water Regulation would not provide a meaningful reduction in risk.

VIII. EPA Should Publish a More Accurate Estimate of the Population Exposed above the HRL in the Final Determination

In the proposed determination, EPA estimates that 16,000 pregnant women may consume drinking water with concentrations above the HRL of 15 ppb. It was appropriate to estimate pregnant women, because although we all begin life as a fetus, the fetal exposure period is finite and an individual becomes less susceptible to the effects of possible reduced thyroid function as he ages. The actual number is likely to be much lower than the estimate in the proposed determination. EPA assumes that if the drinking water testing at the entry point reports at least one sample above the detection limit during the 2000-2005 UCMR sampling period, the entire population that draws drinking water from that intake is exposed. EPA then multiplies this estimate of the exposed population by an estimate of the proportion of the national population that is pregnant during any given year.

The major overestimate in EPA's calculation concerns the population exposed above the HRL. Under the UCMR regulation, public water systems were required to take multiple samples throughout the year at each sampling point. Large public water systems were required to

monitor throughout a three-year period. Many of the sampling points only reported a single detection during the sampling period. Few systems reported perchlorate detections in every sample. Therefore, assuming the total population is exposed at any given time is a gross over-estimate. A more likely estimate is the ratio of positive defects to total samples multiplied by the service population.

There are many reasons why a system may have intermittent or a single detection. At the beginning of the UCMR sampling period, laboratory experience with detecting perchlorate was evolving. There have been many anecdotal reports of false detections. Even where perchlorate was found in the drinking water, its occurrence may have been intermittent. Since perchlorate can be naturally formed and then fall to the earth in precipitation, it is likely that watershed concentrations ebb and flow with the natural water cycle.

EPA's estimate in the proposed determination also overestimates the likely number of individuals with drinking water concentrations above the HRL for several other reasons. First, EPA failed to remove individuals who primarily consume bottled water or have in-house treatment systems. EPA did exclude these individuals in its analysis of the UCMR/NHANES data sets.

Second, EPA did not account for system changes in response to the UCMR monitoring. Some states have enacted state-specific drinking water standards. Others have issued advisory levels. Public water systems have responded and have made changes to reduce perchlorate concentrations. These changes are exactly the responses the Safe Drinking Water Act encourages. By prompting local actions, drinking water issues are separated into the local and national concerns. EPA should properly account for these local actions in its population estimate so as to reinforce its finding that exposure does not occur with sufficient frequency to warrant national regulation.

More importantly, EPA should provide the public context for this exposure estimate. Even though there may be potentially exposed individuals above the HRL, the overwhelming scientific evidence from clinical studies, environmental studies, and from PBPK modeling demonstrates that no one faces an appreciable risk of adverse effect from exposures at EPA's reference dose.

IX. EPA Should Make Conforming Changes to its Regulation and Policies Consistent with this Determination

At the same time of its final determination, EPA should maintain its March 2006 guidance for use by EPA regions and states, but update it with the new Health Advisory, if the decision is made to set one. The RfD is a conservative safe dose as has been noted throughout our comments. The current guidance allows state and local officials to factor in site-specific

considerations and populations as opposed to making local decisions guidance data based upon nationally representative exposure data.

Issuing a health advisory and revised guidance at the same time as the agency issues a final determination provides a strong clear message from EPA headquarters to EPA regions as well as state and local public health officials on the final federal policy related to perchlorate. It brings to close any uncertainty at the federal level on the issue, thereby providing state and local officials with regulatory certainty and allowing them to move forward in addressing site-specific contamination.

Finally, should a final determination be made not to establish a NPDWR for perchlorate, EPA should also make clear that its final determination also removes perchlorate from the CCL3 list. Based on EPA's careful consideration of the scientific evidence, it has fully evaluated perchlorate and met its requirements under the law. Continued consideration of perchlorate would siphon resources away from the long list of other substances and microbes on the CCL3.

X. References

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