COMMENT-RESPONSE SUMMARY REPORT

Peer Review of

Drinking Water Health Advisory for Perchlorate

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Prepared for:

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TABLE OF CONTENTS

I. INTRODUCTION

The United States Environmental Protection Agency (EPA), Office of Water is charged with protecting public health and the environment from adverse exposure to chemicals and microbials in water media, such as ambient and drinking waters, waste water/sewage sludge, and sediments. In support of this mission, the Office of Water/Office of Science and Technology (OST) develops health standards, health criteria, health advisories, and technical guidance documents for water and water-related media. Under this work assignment, documents prepared by OST are to undergo external peer review.

Peer review is an important component of the scientific process. It provides a focused, objective evaluation of a research proposal, publication, risk assessment, health advisory, guidance or other document submitted for review. The criticisms, suggestions and new ideas provided by the peer reviewers ensure objectivity, stimulate creative thought, strengthen the reviewed document and confer scientific credibility on the product. Comprehensive, objective peer review leads to good science and product acceptance within the scientific community.

Under this work assignment the *Drinking Water Health Advisory for Perchlorate* was externally reviewed by a panel of four peer reviewers. The four reviewers were J. DeSesso, D. Hattis, B. Stern, and T. Woodruff.

II. CHARGE TO THE PEER REVIEWERS

1. Does the document convey the necessary scientific information in a manner that can be understood by both the officials from public health organizations and public water systems?

2. Does the Health Advisory describe the perchlorate health effects information that a public health official would need to assess and evaluate options for addressing local perchlorate contamination of drinking water?

3. Is the explanation of the derivation of the Relative Source Contribution clear and easy to understand?

4. Have the sensitive populations been identified appropriately?

5. Is the role of modeling in evaluating the sensitive populations clearly described?

6. Do you have any suggestions on how this draft document could be improved?

III. GENERAL COMMENTS

J. DeSesso

This document is well organized, well conceived, and very well written. The authors did a fine job of explaining some rather difficult material in plain, straightforward English. The reader comes away with the sense that the overall discussion is objective and balanced. The modeling of data was used effectively. The choice of the 90th percentile water intake coupled with iodide uptake inhibition data was conservative, but the authors balance this by using the intakes the resulted in ~1.8% inhibition of iodide uptake as a no effect level and by not assessing extra uncertainty factors.

As is expected of any draft document, there are areas that could be improved. These are mentioned below in the Specific Comments.

Response: The 90th percentile water intake was one of only a very few high end values incorporated into the assessment. It is consistent with EPA policy as outlined in the Exposure Assessment Guidelines (1992) that recommends the use of a plausible upper bound as a surrogate for a distributional analysis.

U.S. EPA. Guidelines for Exposure Assessment. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC, 600Z-92/001, 1992.

D. Hattis

No general comments.

B. Stern

The health advisory needs a concise solid summary of the pharmacokinetics of perchlorate (including its relationship to iodide uptake at the thyroid and its mode of toxic action) and of the physiology of the thyroid system. This context is essential to assist the reader in understanding the biological importance and implications of low levels of iodide uptake inhibition on thyroid hormone synthesis, thyroid system homeostasis, and thyroid hormone requirements for normal metabolism and for fetal, neonatal and child development.

It is not transparent throughout the document that the population at risk is iodine-deficient women during pregnancy and lactation and the fetuses and neonates of iodine-deficient women. Insufficient information is presented on the well-conducted epidemiological studies of pregnant and lactating women, their neonates, and children living in areas with elevated levels of naturally-occurring perchlorate in their drinking water (or food or both), in which iodine intake is sufficient and no adverse effects are observed. In the absence of discussion about iodine deficiency, the potential public health concern of perchlorate in drinking water cannot be well understood and appropriate public health protective actions may not be considered or taken.

Of particular importance are the following:

(1) Perchlorate at pharmacological doses interferes with the uptake of iodine as iodide via inhibition at the sodium-iodide transporter, which is a mechanism that is well documented and well understood. Among biomedical professionals, including toxicologists, it is generally agreed that the only known and likely effect on health of perchlorate is thyrotoxicity (NAS 2005)

(2) No mention is made throughout the document of thyroid system homoestasis – the ability of the system to self-regulate via a feedback loop that involves numerous homeostatic mechanisms specifically design to ensure, within limits, a constant synthesis and availability of thyroid hormone by upregulating production and tissue availability when systemic hormone is low and downregulating these processes when systemic hormone is elevated beyond need. There are numerous mechanisms involved in this homeostatic system, which include increasing the amount of iodine absorbed from the diet, decreasing iodide excretion under conditions of low iodine intake, and increasing the number of iodide transporter proteins at the interface of the blood circulation and thyroid which in turn, increases the efficiency of transferring iodide into the thyroid when there are other substances that compete with iodide uptake at the level of the transporter protein. This is the reason that iodine-deficient women, particularly those with additional iodine requirements due to pregnancy and lactation, are the most sensitive subpopulation. The fetus of the iodine-deficient woman, who depends on maternal supply of thyroid hormone and iodide, is most adversely affected by iodine deficiency because of the essentiality of sufficient thyroid hormone during critical stages of development, differentiation and growth. Similarly, the neonate of the iodine-deficient woman continues to be at high risk at and following parturition – whether nurtured (as in nutrition) via breast milk or infant formula – because she/he continues to be deprived of essential nutrient and hormones during the next critical developmental stage – early infancy.

(3) The thyroid homeostatic system is already under considerable stress from iodine deficiency. Perchlorate is an <u>added</u> environmental stressor that may contribute to perturbing the thyroid regulatory system of already severely stressed individuals and subpopulations. Other anions commonly occurring in the environment, such as thiocyanate, nitrate and bromate, have similar effects in that they inhibit the uptake of iodide from the blood stream into the thyroid gland by the same mechanism. The evolutionary elegance (or in more pragmatic terms, utility) of thyroid homeostasis (and homeostatic systems for other essential elements and hormones) is that it maintains sufficiency under the day-to-day variability in element intake and is capable of rapidly activating internal mechanisms that protect against increases and especially decreases in thyroid hormone production in response to biological need (NAS 2005).

(4) As a result of research on endemic goiter and iodine deficiency in the U.S. by Marine and colleagues, iodinization of table salt was first recommended and implemented in 1920's and 1930's. By 1955, iodine deficiency disorders appeared to have been eliminated via household use of table salt (Salt Institute, 2008). Current trends, however, as monitored by NHANES studies, demonstrate that the percentage of U.S. individuals with iodine deficiency (defined by WHO as < 100 ug/L in urine) increased from 1971-1974 to 1988-1994, and appears to have stabilized at 1988-1994 levels when re-evaluated in NHANES 2001-2002 (Hollowell et al., 1998; Caldwell et al. 2005). All median urinary iodide (UI) concentrations were above the cutoff value noted above, 320 ug/L in 1971-1974 (NHANES I), increased to 145 ug/L in 1988-1994 (NHANES III) and was 168 ug/L in NHANES 2001-2002.

However, these concentrations are single population-based values and do not give any indication of the distribution of values, specifically the percentage of the population that are either significantly above or significantly below the median values. Hollowell et al. (1998) reported that the proportion of the total population with UI concentrations below 50 ug/L (defined by WHO as having "at least" moderate iodine deficiency) was 2.6% (1.6% in males and 3.5% in females) in 1971-1974. These values increased to 11.7% in 1988-1994 (8.1% of males and 15.1% in females). In NHANES 2001-2002, the UI median concentration was 167.8 for the total population, with 11% reporting UI concentrations below 50 ug/L (6.7% in males and 15.3% in females) (Caldwell et al. 2005). Thus, the distribution of UI concentrations in the U.S. population appears to have stabilized; however, a significant percentage of that population, particularly females, is below 50 ug/L. Even a higher percentage is below 100 ug/L (median = 28.4% for total population; males = 19.7%; females = 36.6%) (Caldwell et al. 2005).

(5) The reasons for the prevalence of individuals with iodine deficiency are not clear. In 1955, researchers reported that approximately 75% of U.S. households used iodized salt (Salt Institute 2008) and the population intake of iodine was considered to be adequate. However, in 1999, Lee et al. reported a sharp decline in iodine intake, especially among women of childbearing age.

Although 70% of salt sold for household use is currently fortified with iodine, it is estimated that household table salt accounts for only about 15% of daily salt intake and the salt used in manufacturing of many processed foods may not be iodized (Pearce 2006). A decrease in iodine consumption has been associated with medical recommendations for reducing salt intake for control of blood pressure and other cardiovascular disorders and with increasing use of noniodized salt in manufactured or prepared foods (Lee et al. 1999). Although infant formula iodine fortification is not mandated in the U.S., many of the commonly-used brands contain added iodine (Pearce 2008) although the iodine content, as well as concordance between label notification amounts and actual measured amounts, varies widely (Leung and Pearce, 2008). It should be noted that Canada requires fortification of table salt, table salt substitutes, and infant formula with iodine and also mandates the range of iodine concentrations that must be present in these foods (Leung and Pearce 2008). Utinger (1999), in an editorial in the New England Journal of Medicine, notes that the WHO and the International Council for the Control of Iodine Deficiency Disorders consider the U.S. as a marginally iodine-sufficient nation whereas Canada is classified as optimally iodine-sufficient. It appears that one of the major reasons that the U.S. is reluctant to mandate fortification of table salt is that the mandate would be viewed as contradictory to, or inconsistent with, medical recommendations for reduction in salt consumption (CDC, personal communication). However, as noted for Canada, table salt substitutes are also amenable to iodine supplementation.

Iodine deficiency disorders have a broad spectrum of effects. There is no question that severe iodine deficiency in mothers and fetuses result in pregnancy loss, cretinism, irreversible mental retardation, neurologic dysfunction and growth retardation. Mild iodine deficiency results in learning disability, poor growth and diffuse goiter in school-age children (Utinger 1999). The mode of action, a reduction in thyroid hormone production because of chronic insufficient iodine intake, is well-accepted. Recent epidemiologic studies showing no effects of elevated perchlorate exposures on thyroxine (T4) – the primary thyroid hormone synthesized via iodide-incorporation pathways in the thyroid gland – in iodine-sufficient adults, in iodine-sufficient pregnant women and their neonates during and following pregnancy, and in iodine-sufficient

elementary-school children (e.g., Amitai et al. 2007, Crump et al. 2004, Braverman 2007, Tellez et al. 2006), in conjunction with mechanistic data, strongly suggest that the public health problem is iodine deficiency in pregnant women, neonates and young children, not perchlorate exposure except possibly at very high sustained perchlorate intakes (i.e., in the 100s ug/L in drinking water).

Conceptually, sustained perchlorate intake at low levels may be viewed as having a potentially adverse effect on thyroid function only in borderline moderate iodine-deficient individuals. In severely-iodine deficient persons, the added effect of iodide-uptake inhibition into the thyroid will not be sufficient to increase the already serious and irreversible consequences to the fetus and neonate of a pre-existing biologically significant reduction in thyroid hormone production. In iodine-sufficient individuals no effects have been demonstrated to occur in a range of studies and none are expected. In moderately-sufficient individuals, perchlorate-induced effects are not anticipated to occur as available iodine is likely to be optimally and efficiently utilized, regulated by the myriad of homeostatic mechanisms that conserve iodine availability and direct as much as necessary to adequate thyroid hormone production and to the fetus even at the expense of the mother during pregnancy (the "thrifty phenotype" or "triage" paradigms) (Ames 2006, McArdle et al. 2006). However, in those persons who are borderline marginally iodine-sufficient, the homeostatic regulatory mechanisms may be operating at maximum capacity. Therefore, any added iodide-uptake inhibitory stressor such as perchlorate intake, may be the stimulus that overwhelms compensatory mechanisms, resulting in an exceedence of homeostatic capacity and induction of actual decreases in thyroid hormone synthesis.

(6) This reviewer duly notes that iodine deficiency in the U.S. is a public health mandate that is totally outside the mission and broad scope of regulatory activities required, conducted and implemented by the U.S. EPA to protect public health and the environment. However, perchlorate as a chemical of concern in drinking water and other environmental media is assessed and regulated by U.S. EPA. It is important for public health officials, regulators and others to understand the relationship between perchlorate and iodine deficiency. Further, the intensity and magnitude of current public health concerns about low levels of environmental exposures to perchlorate, including from members of Congress, the media, environmental groups, regulatory agencies not familiar with the biology, toxicology and pharmacology of perchlorate, and the general public (I have read numerous newspaper articles, press releases by government and non-government organizations and on-line blog comments by individuals-at-large) indicate that risk communication is an enormous problem. The amount of misinformation, misleading conclusions and overstatements has led to public perceptions that greatly overestimate the potential dangers of perchlorate to susceptible human populations, except possibly under localized conditions where perchlorate is sustained in drinking water in the order of hundreds or thousands of parts per billion. The elephant in the room is iodine deficiency.

(7) This discussion is perceived by this reviewer to be within the context of charge question #1. Without a clear and concise summary of the potential adverse effects of perchlorate in terms of pharmacokinetics, biology and mode of toxic action that can lead to adverse thyroid effects, presented at the beginning of the Health Advisory, it is difficult to follow and interpret the substance of the document. For example, in the biomonitoring data in the occurrence and exposure section, reference is made to perchlorate short-half life, rapid excretion, urinary clearance as the primary form of elimination, none of which is previously described. The health

effects section is also not transparent, in terms of the range of research and the concordance (or discordance of findings). Many studies are not even cited. I suggest that several paragraphs be devoted to brief summaries of all important human studies. Again as noted above, there is insufficient emphasis of iodine deficiency as circumscribing the sensitive population, with the fetuses and neonates of this population as being the most susceptible and having the most adverse and deleterious health consequences.

I recognize that a major objective of this document is to be concise and relatively short, and to describe both the health and exposure data succinctly, with as few obtusely technical terms as possible, in order to be read and generally understood. However, a description of the biology and physiological context is needed. What also is important to note early in the document is the following:

(A) The oral reference dose (RfD) is not being derived *de novo*;
(B) The oral RfD has already been derived by the National Academy of Sciences, an independent, internationally-recognized and respected organization, and has already been subjected to comments, review and a high level of scrutiny by all major stakeholders;
(C) The RfD is conservative, being based on an effect that is a precursor to an adverse effect (not too much detail – a reference to the appropriate section for further detail would suffice); and
(D) There are two primary objectives to this health advisory: (a) to provide guidance to regional and local public health officials and to regulatory agencies for a level of perchlorate in drinking water that is likely, with a high degree of confidence, to be without adverse health consequences to all exposed populations, including the most susceptible; and (b) to determine a scientifically defensible relative source contribution of drinking water to total exposure from all possible sources, based on a rich data base of exposure information.

This information would explain why relatively little data are presented regarding health effects (relative to exposure and RSC derivation). However, as noted above, what is still needed at the beginning of the document is a brief overview of the toxicokinetics of perchlorate, iodine as an essential element for the synthesis of thyroid hormones, why thyroid hormone sufficiency is important, what homeostasis is – perchlorate affects a self-regulating system which has evolved numerous feedback mechanisms to compensate for deficiency induced by inadequate intake, iodine uptake inhibition, illness) and that within the homeostatic range, which is robust in humans, this system is successful. [The same would be true for excess.] In other words, the biological impacts of perchlorate are very different from those for chemical compounds which have direct target organ toxicity and/or do not directly affect the availability of an essential element for which homeostasis occurs

(8) I think that the relative source contribution section is exceptionally well presented; the authors go to great lengths to describe how they have derived an RSC of 62% and are to be commended for the level of detail given, the amount of high-quality scientific data incorporated into developing the RSC, the scientifically-informed inferential reasoning and the scientific defensibility of their conclusions. I cannot think of a single other chemical in drinking water for which this extensive and comprehensive effort has been conducted. I have a number of minor, specific comments which are presented in response to Charge Question #6.

Response: The issues raised in this comment regarding iodide and thyroid homeostasis, the iodide status of the US population are beyond the scope of a health advisory. However, these issues are being referred to the NAS to obtain advice regarding how to factor them into the Regulatory Determination for perchlorate.

Modifications were made to the Health Advisory to reflect the recommended clarification on source of RfD and its characteristics.

T. Woodruff

In general, this document was well-written and provided a concise and reasonably thorough summary of the information. It was written at the appropriate level for government officials and is also accessible to the knowledgeable public.

However, there are critical gaps in the underlying analyses and review of the science that requires substantial revisions before this document can be made final. This review will focus on two general areas of concern: 1) inadequate consideration of all sensitive subpopulations; and 2) over reliance on an incomplete and un-peer-reviewed EPA PBPK model to justify the HA. In summary, based on the available data on perchlorate, under the currently proposed HA there are expected to be significant portions of sensitive subpopulation that would be exposed to perchlorate at concentrations above the EPA RfD, and thus the draft HA would not be expected to be protective of potential adverse effects for the whole population.

Sensitive subpopulations

The document identifies the primary sensitive subpopulation of concern as fetuses of pregnant women. However, there are two other sensitive and overlapping groups that are not adequately considered in this document - preterm infants and term infants, particularly those term infants who are lower weight than 3.5 kg.

The NRC defined preterm infants along with fetuses as the most sensitive subpopulations (from page 27 of the NRC report "fetuses and preterm newborns constitute the most sensitive populations"). The scientific evidence finds that preterm infants may be more at risk from thyroid perturbations than term infants (Zoeller and Rovet, 2004). However, preterm infants are not discussed in the HA nor are they considered in the analysis to determine the HA. This needs to be modified. There are several approaches that can be used to assess exposures for this sensitive subpopulation which are discussed below.

The other sensitive lifestage that needs to be considered is the neonatal period. Analyses relevant to this lifestage should be more robustly incorporated into the HA. Decrements in thyroid hormone (TH) during early neonatal development have been shown in epidemiologic studies to be linked to future neurological deficits. While this is partially acknowledged in the HA, further evidence can be cited. There are several epidemiologic studies of children diagnosed with congenital hypothyroidism who are treated with T_4, providing good documentation of thyroid hormone levels, amount of thyroid supplement and neurocognitive outcomes, as these children are under continuous medical surveillance. The studies find that even small increments in T_4 dosage (as low as 2 ug/kg-day) can result in significant improvements in later cognitive and school performance (Oerbeck et al., 2003; Selva et al.,

2005; Zoeller and Rovet, 2004). These studies show the sensitivity of the developing brain to adequate THs, and it would be expected that reversing this (i.e. producing decrements in TH) would result in reduction of cognitive performance.

Biological factors make the early infant potentially more at risk from thyroid perturbations than during other lifestages. The infant has diminished storage capacity of T4 compared to an adult (about 1 day in the infant compared to several months in the adult) and the T4 half-life is shorter (about 3 days in the early infant compared to about 7-10 days in adult (Greer et al., 2002; Vulsma et al., 1989). Thus, it is more difficult for the infant to withstand and recover from perturbations to the thyroid system that can result from chemical exposures. The risk from perchlorate exposures would be expected to be greater for an infant compared to an adult at the same exposure level.

The neonatal time period has been identified as a sensitive time period in several reviews of the scientific literature (Ginsberg et al., 2007; Zoeller and Rovet, 2004). The discussion of the sensitivity of the neonatal infant stage to thyroid perturbations should be expanded and the early infant time period identified as a susceptible lifestage in the HA.

In addition, the document needs to consider exposure to these two groups of infants. Currently, the HA relies on two sources of data for the exposure estimates - data from NHANES, which only includes measurements of perchlorate levels in children starting at age 6, and estimates of exposure based on a draft EPA PBPK model. Neither of these addresses exposures to preterm infants and the draft EPA PBPK model does not fully address infant exposures.

Two different exposure scenarios are appropriately considered in the document for infants, exclusive breastfeeding and bottle-feeding. Estimates for both routes of exposure need to incorporate birthweights for infants who weigh less than 3.5 kg, which is the lowest infant weight currently evaluated in the assessment.

In 2005, almost 13 percent of infants were born preterm (<37 weeks of gestation NCHS http://www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_06.pdf), and a significant portion of these infants weight less than 3.5 kg. In addition, about 8% of infants are born less than 2,500 grams even at term. Smaller infants will have a higher dose per body weight exposure to perchlorate from breast milk or formula. EPA needs to incorporate the full range of infant weights observed in the population.

Calculating the perchlorate exposures to breast fed infants is slightly more complicated because the relationship between maternal ingestion and breast milk levels must be calculated. For estimating the exposures to preterm and nonpreterm infants, three sources of information have been or could be used to more fully estimate exposures via breast milk: 1) estimates from the draft EPA PBPK model; 2) measured data in breast milk; and 3) estimates of intake based on ratios of breast to urine perchlorate concentrations measured in the population. Each of these is further discussed below.

1) The draft EPA PBPK model is used in the HA to provide insight into the relationship between ingestion of perchlorate and iodide inhibition (see further comments on this model below). As part of the analysis, EPA provides an estimate of perchlorate exposure

to different populations, including a pregnant woman, fetus, and infants. The EPA PBPK model draft document reports in Table 4 that for drinking water level of 15 ug/L of perchlorate for a healthy 3.5 kg infant at 7 days exclusively breast feeding, the estimated perchlorate intake is 1.36 ug/kg-day, and for the bottle-fed infant ~3.5 ug/kg-day. This is about 2 to 5 times the RfD (0.7 ug/kg-day). While this model has significant limitations (see discussion below), it does provide an estimate of perchlorate exposure to average weight babies of healthy breastfeeding women.

The input portion of this model should be expanded to provide data on all infants of concern, in particular infants under 3.5 kg (the low end of infant weight used in the model) and preterm infants.

2 &3) Estimating perchlorate exposure via breastmilk. Studies of breast milk have found measurable levels of perchlorate in breast milk (see studies cited in the HA). Estimates of perchlorate exposure can be calculated by analyzing breast milk concentrations of perchlorate in combination with breast milk intake and infant weight. An example table is provided in the back (Table 1). A calculation based on measurements in breast milk can provide complimentary information to modeled estimates and should be included in the HA.

Breast milk is an intermediate media between maternal ingestion and neonatal ingestion. Methods are needed to determine corresponding maternal ingestion levels of perchlorate based on concentrations measured in breast milk. One such peer-reviewed method is provided by Ginsberg et al. (Ginsberg et al., 2007). The authors use estimated concentrations of perchlorate in water to estimate concentrations in breast milk using measured relationships between breast milk and urine concentrations of perchlorate. This analysis could be modified to back calculate drinking water concentrations that contribute to perchlorate levels measured in breast milk in the HA. The Ginsberg et al. method can also be used to independently estimate the range of exposures from breast milk feeding via different levels of perchlorate in drinking water.

Relative source contribution and perchlorate in breast milk. The current approach in the HA (as exemplified by Table 5-4) appears to assume that all the perchlorate via breastmilk comes from drinking water ingested by the mother. However, the there is some contribution to perchlorate in breast milk that comes from perchlorate in food, providing an indirect exposure of the infant to food sources. This is identified in the HA text under the discussion of the study by Pearce, *et al.*, (2007) of perchlorate measurements in breast milk from women in the Boston-area. As identified by EPA "the Boston-area public water systems did not detect perchlorate in drinking water samples collected for the US EPA's UCMR from 2001 to 2003, nor did Boston area systems detect perchlorate in samples collected in response to the Massachusetts Department of Environmental Protection (DEP) 2004 emergency regulations for perchlorate." Thus, the perchlorate measured in breast milk must come from primarily or solely food exposure. The concentrations measured in the Boston study via breast milk should be included as a dietary contribution to breast milk exposures (such as in table 5-4) and used in the calculation of the relative source contribution.

While the modeling exercise can give some bounds on the data, it must be compared to measured data, and the measured data gives range of values that may be present in the population. A comparison of these three analyses, appropriately accounting for the range of neonatal and infant weights, should be included in the HA.

A similar set of considerations should be applied to perchlorate exposure via infant formula. The calculation for this source is more straightforward, as the infants are directly exposed to the water via reconstituted dry formula. However, as with the breast milk, weights of preterm and term infants weight less than 3.5 kg must be considered in the exposure calculations and used to determine the HA.

Response: Comments regarding consideration of sensitive subpopulations and life stages will be considered by the NAS during an upcoming review of the scientific underpinnings of the Regulatory Determination for perchlorate. This review will include evaluation of the assumptions about exposure and the expression of the RfD as a biological response rather than a dose.

EPA's modifications to the PBPK model by Clewell and the revised parameters in it have been subjected to external peer review. EPA has made changes to the model in response to the comments received. The peer review comments can be found at the URL attached:
http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=199347

IV. RESPONSE TO CHARGE

1. Does the document convey the necessary scientific information in a manner that can be understood by both the officials from public health organizations and public water systems?

J. DeSesso

The writing style of the Advisory is easy to understand. The authors manage to instruct the reader in regard to requisite information and methodologies without being pedantic. By and large this is a successful document. The reader comes away with a sense of how the problem was approached and how the Agency moved forward. This transparency gives the reader a comfort level with how that reader should address problems that arise when performing his/her job in a manner that is consistent with the intent of the Health Advisory.

Response: No response

D. Hattis

In my view, managers in both categories need much better insights into (1) limitations and uncertainties in the current analysis, and (2) opportunities for better analyses that more fully capture in distributional form the likely implications of interindividual variability in susceptibility--especially the variability in susceptibility related to differences in long term iodide consumption.

Another improvement that I think should be made to help busy risk managers is an executive summary. Such a summary should briefly give the main line of the argument that the water office wishes to make in support of its recommended level—or the summary consequences of alternative levels if my suggestion below of an options analysis is adopted. Decision-makers are more likely to spend the time needed to absorb 41 pages (or more, if the analysis is broadened) if they have some clue at the outset of what sort of analysis they should expect to form the crucial basis of their risk management decision-making.

1.1 Limitations, Uncertainties, and Intellectual Roots of Controversy About the Analysis

A first step toward a revised health advisory that would be more helpful for the target audiences of public health and water system managers is to describe some of the sources of controversy on perchlorate health effects. I think the managers should be helped to understand why perchlorate is special as a neurodevelopmental toxicant, and why the traditional paradigms for arriving at putatively "safe" levels of exposure may be misleading in this case.

The central assumption underlying the methods EPA uses to set RfD's is that there will be some threshold dose for a toxicant below which there will not be an adverse effect. This assumption is derived from a vision of biological systems where there are generally homeostatic controls that

have some finite capacity to offset or accommodate some chemically-induced perturbation as long as the perturbation is not so large as to push some system parameter so far from its normal values that injury results. The thresholds for individual people for specific adverse responses can vary (Hattis et al. 1999), but the usual assumption is that few or no people will have variations in sensitivity that will be large enough that they will not be adequately protected by the use of traditional 10-fold safety factor for human interindividual variability (along with other traditional uncertainty factors).

The concept of homeostatic controls can support the plausibility of a no-adverse-effect level for a particular person (an individual threshold) for a specific mechanism of damage. However the does not necessarily imply the existence of a population threshold (a dose so low as to be at, or below, the lowest threshold dose for any individual in a mixed population with diverse sensitivities). Specifically, there may be a finite expectation for individuals to be affected by even marginal exposures in cases where even without additional exposure some people have no "functional reserve capacity" to act as a buffer between the base health state and a state of at least marginally worse health. Two specific types of cases where this can happen are:

1. Some individuals in the diverse population are already suffering from various kinds of pathological dysfunction in key parameters that may be marginally affected by different toxicants (e.g., a person undergoing a myocardial infarction may have a marginally expanded area of heart muscle death if the oxygen carrying capacity of his or her blood is reduced by a marginal exposure to additional carbon monoxide)

2. Some individuals are presently engaged in a task (e.g., running a 100-yard dash) that taxes some physiological capabilities to their limit, and marginal exposures to a toxicant marginally reduce those physiological capabilities.

The presence of iodide deficiency appears likely to create just such a situation where there is effectively no functional reserve capacity for a significant portion of the population. This is an important concern both during gestation, and in the perinatal period. Moderate and severe iodine deficiency (20-59 µg/day iodine; and <20 µg/day, respectively) is said to lead to a "global loss of 10-15 IQ points at a population level and constitutes the world's greatest single cause of preventable brain damage and mental retardation (Delange 2001)."

Unfortunately there is evidence that population intakes of iodide in the U.S. have declined in recent decades. Hollowell and Haddow report more than a 50% decline in general population urinary iodide concentrations between representative samples of the U.S. population studied in 1988-1994 compared to 1971-1974, although the very most recent data (2000-2002) show no continuing decline. The median urinary iodine from the NHANES 2000 sample is about 161 µg/L and that for 2001-2002 is 168 µg/L. Because urinary excretion is about 1 L/day in adults, these numbers roughly indicate the median iodide intake in µg/day.

The same surveys also provide some information on the changes over time in the distribution of iodide excretion rates in the population, although as Hollowell and Haddow carefully note that because of hour-to-hour and day-to-day fluctuations in iodide urinary concentrations it is not possible to infer the incidence of long term iodide intake deficiency from the distribution of

single spot samples alone. Nevertheless it seems relevant to note that the proportion of low urinary iodide levels in reproductive age and pregnant women has risen appreciably between the 1971-74 and 1988-94 surveys. Out of 208 pregnant women studied in 1971-74, 1% had urinary iodide less than 50 µg/l, whereas 6.9% of 348 pregnant women in 1988-94 had a level as low as this. The corresponding percentages of non-pregnant reproductive age women with iodide levels this low were 4.0% and 15.3% in 1971-74 and 1988-94, respectively. While we cannot directly infer the incidence of chronic iodide deficiency from these data, it is not unreasonable to suspect that the incidence is far from negligible from a public health perspective.

Although gestation is known to be a sensitive period for iodide deficiency and therefore perchlorate inhibition of iodide uptake to the thyroid, there are special reasons to believe that the neonatal period is also a time of special vulnerability. Ginsberg et al. (2007) note:

> "The importance of maternal T_4 has been demonstrated in babies with congenital hypothyroidism who appear normal at birth because of ample maternal hormone during gestation (Vulsma et al. 1989). In contrast to the fetus, the newborn can no longer rely upon maternal hormone as a buffer against inborn biosynthetic deficiencies or external stressors. The only means for hormone transfer from the mother is breast milk; however, breast milk contains very little thyroid hormone (van Wassenaer et al. 2002). Therefore, the neonate must synthesize its own supply of T_4 to maintain normal growth and development. As described below, there are a number of factors that make neonatal thyroid status more vulnerable to perturbation than in adults or the fetus.
>
> First, the serum half life of T_4 is approximately 7-10 days in adults (Chopra and Sabatino 2000), but is approximately 3 days in neonates (Lewander et al. 1989; van den Hove et al. 1999). Thus, the rate of replacement of T_4 (i.e., T_4 secretion from the thyroid gland) must be considerably higher in early life to maintain steady-state levels.
>
> Second, the adult thyroid gland stores a large quantity of thyroid hormone in the form of thyroglobulin; this quantity is estimated to be enough to maintain normal levels of circulating hormone for several months (Greer et al. 2002). In contrast, the neonatal gland stores very little T_4; the amount stored has been estimated at less than that required for a single day (Savin et al. 2003; van den Hove et al. 1999). These differences in thyroid hormone status between adults and neonates indicate that the functional reserve available to adults is virtually absent in neonates. Any reduction in thyroid hormone synthesis in the neonate will result in a reduction in circulating levels, whereas this is clearly not true for the adult. The combined storage deficiency and rapid hormone turnover in neonates necessitates a high rate of T_4 synthesis to keep up with the daily demand for thyroid hormone. This, in turn, is dependent upon an adequate supply of iodide. Given these demands on the neonatal thyroid, it is likely that perchlorate-induced inhibition of iodide uptake has a greater impact in neonates than in utero or at other life stages."

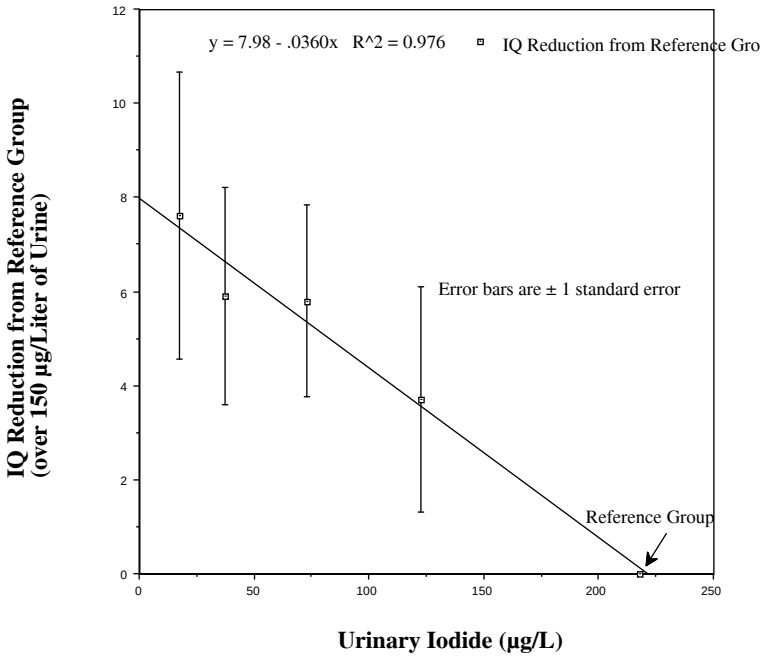
Because of the likely vulnerability of the neonate to even transient fluctuations in iodide and perchlorate intakes, there is reason to question EPA's identification of the late gestational period as the basis for its calculations of the DWEL needed to assure that the most sensitive life stage is below the RfD. This uncertainty should be pointed out to the audience of public health and

water system managers. At the same time it should be pointed out that in the light of the data in Table 5.4, choice of the bottle-fed neonate as the sensitive subgroup would apparently require at least a 5-fold reduction in the DWEL of 15 µg/L, as the 15 µg/L apparently delivers about 3.5 µg/kg-day—about 5 times larger than the adopted RfD of 0.7 µg/kg-day.

There is at present no quantitative analysis of the relative sensitivity of gestational vs early post-natal life stages to developmental impairment from hypothyroidism that is contributed to by iodide deficiency. However there are observational studies that suggest an association between relatively low urinary iodide excretion and diminished IQ levels. Figure 1 shows the results of an analysis I have done based on observations in 9-year old school children in Spain (Santiago et al. 2004). 9-year old children are of course well past the period of rapid brain development in gestation and infancy; and it is probable that the association seen here reflects iodide levels they experienced at an earlier age.

Figure 1

Inferences of the Population Change in Median IQ In Relation to Spot Urinary Iodide Measurements



Data Source: Santiago-Fernandez et al. 2004. Mean urinary iodide concentrations and median IQ in each group were reconstructed from percentile data provided in Santiago-Fernandez et al (2004).

1.2 Opportunities for Better Analysis

1.2.1 Reconsideration of the Main Early Effect Parameter Used to Predict Risks (the Percentage Inhibition of Radioiodide Uptake)

The main measure of perchlorate impact used by EPA (and the NRC analysis before it) is the percentage reduction in radioiodide uptake originally used in the Greer et al. (2002) clinical study. For purposes of initial modeling of dose response observations by Greer et al. (2002) this is a reasonable choice. However it is not the ideal choice for projection of risks in the light of variations among people in iodide intakes. As can be inferred from the quote on the previous page, what is important for the neonate in particular is that there is an adequate absolute rate of production of T4, which depends on the absolute rate of iodide transport, not solely on the percentage of available iodide that is transported.

From basic Michaelis Menten enzyme kinetics, the effect of the competitive inhibitor perchlorate on the fraction of iodide transported into the thyroid is expected to be given by equation 1:

$$\text{Fraction transported} = \frac{V_{max}}{K_m\{1+[\text{Perchlorate}]/K_i\} + [I^-]} \quad (1)$$

Where

$[I^-]$ is the iodide concentration in or around the cell layer immediately outside of the thyroid,

Vmax is the maximum rate of transport at very high iodide concentration,

Km is the iodide concentration at which the transport rate proceeds at half of its maximum velocity,

Ki is a the concentration of perchlorate at which the effective Km is doubled.

It can be seen from this equation that as iodide concentrations approach low levels, the fraction or percentage of available iodide rises to approach a constant value. Thus, if anything, iodide deficient people should tend to have higher, not lower, baseline values of "fraction transported". However, the expression for the absolute amount of iodide transported must include a factor for the iodide concentrations in the numerator as well as the denominator:

$$\text{Absolute iodide transported} = \frac{V_{max}[I^-]}{K_m\{1+[\text{Perchlorate}]/K_i\} + [I^-]} \quad (2)$$

This type of formulation would allow a more natural interpretation of the results of Blount et al. (2007) and integration with data on the relationships between iodide levels, altered thyroid hormone levels, and effects on IQ and other neurodevelopmental parameters. Abstracts of some promising articles from a recent literature search on relationships between IQ, iodide excretion, and iodide supplementation are reproduced below:

Effect of different iodine intake on schoolchildren's thyroid diseases and intelligence in rural areas.

Gao TS, Teng WP, Shan ZY, Jin Y, Guan HX, Teng XC, Yang F, Wang WB, Shi XG, Tong YJ, Li D, Chen W.

Chin Med J (Engl). 2004 Oct;117(10):1518-22.

Department of Endocrinology, First Hospital of China Medical University, Shenyang, China. gaotianshu67@yahoo.com.cn

BACKGROUND: Reports are increasingly appearing on the side effects caused by excessive iodine intake. Our objective was to find out whether iodine excess would impair the thyroid function and intelligence of schoolchildren in rural areas of China. METHODS: A comparative epidemiological study was made on thyroid function and intelligence of the schoolchildren in the areas of low, moderate or excessive intake of iodine. In the area of **low intake of iodine (Panshan**, Liaoning province, median urinary iodine (MUI) was 99 microg/L), of **moderate intake of iodine (Zhangwu,** Liaoning Province, MUI was 338 microg/L) and of **excessive intake of iodine (Huanghua**, Hebei Province, MUI was 631 microg/L). The numbers of schoolchildren from each area selected to take part in a Chinese version of Raven's Test were 190, 236 and 313, respectively, and then 116, 110 and 112 of them were tested for thyroid function, thyroid autoantibody (TAA) and urinary iodine (UI). RESULTS: There were no significant differences in the incidences of overt hyperthyroidism, subclinical hyperthyroidism and overt hypothyroidism in Panshan, Zhangwu and Huanghua. But significant differences were found in the incidences of subclinical hypothyroidism (P = 0.001) in these three areas. The incidences of subclinical hypothyroidism in Huanghua and Zhangwu were 4.76 and 3.37 times higher than that in Panshan. TAA were negative in all the schoolchildren with subclinical hypothyroidism except for one. No significant difference was found among the rates of thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb) in these three areas. Mean serum thyroglobulin (TG) value of Huanghua was markedly higher than those of the other two (P = 0.02). Mean serum TG value of Zhangwu was higher than that of Panshan but the difference was not significant. Mean IQ value of the schoolchildren in Huanghua was markedly higher than that for Zhangwu (P = 0.001). **Mean IQ value of the schoolchildren in Panshan was lower than that of Huanghua** and higher than that of Zhangwu but, **again, the differences were not significant**. CONCLUSIONS: The increase of iodine intake may increase the risk for schoolchildren of subclinical hypothyroidism. In the area of iodine excess, most of the subclinical hypothyroidism cases are not of autoimmune origin. No obvious effect of excess iodine was found on mental development of schoolchildren.

Iodine deficiency and its association with intelligence quotient in schoolchildren from Colima, Mexico.

Pineda-Lucatero A, Avila-Jiménez L, Ramos-Hernández RI, Magos C, Martínez H.

Public Health Nutr. 2008 Jul;11(7):690-8. Epub 2008 Jan 21.

Unidad de Investigación en Epidemiología Clínica, IMSS-Colima, Colima, México.

OBJECTIVE: To determine the prevalence of iodine deficiency, its causes and its association with intelligence quotient (IQ) in Mexican schoolchildren. DESIGN: Cross-sectional analytical study, in which determinations of thyroid gland size, urinary iodine excretion, IQ, iron nutritional status, physical anthropometry, family consumption of goitrogenic foods, type/origin and iodine saturation of salt consumed at home and coliform organisms in drinking water were performed, and the association of each variable with IQ scores was evaluated by multiple regression analyses. SETTING: Municipality of Cuauhtémoc, in Colima, Mexico (altitude: 600-2700 m above sea level). Sea salt is extracted manually nearby and often used for human consumption. Goitre remains present in the region despite over half a century of mandatory salt iodination in the country. SUBJECTS: Three hundred and three children, similar proportions of boys and girls, mean age 9.3 years, randomly selected from 19 public elementary schools. RESULTS: Overall goitre rate was 21.4%; **low urinary iodine excretion was found in 19.5% of the children, high urinary iodine excretion in 32.0%.** IQ scores were transformed into percentile values, with the following categorization: < or = P5 (low IQ), 48.5%; > P5 to < or = P25 (below average), 24.2%; > P25 to < P75 (average), 18.8%; > or = P75 to < P95 (above average), 3.6%; > or = P95 (high IQ), 4.9%. Ninety-two per cent of the population used iodinated salt, but deficient iodine saturation (<50 ppm) was found in 86.8% of salt samples. The main goitrogenic foods consumed were peanuts (by 31.5% of the sample), cabbage (30.1%), broccoli (27.7%) and cauliflower (25.7%). Median counts of coliform organisms (colony-forming units/100 ml of drinking water) were: 207.5 (well water), 151 (cisterns), 52 (private homes), 25 (elementary schools) and 12 (kindergartens). **Moderate iodine deficiency was associated (P < 0.05) with a 4.26 times higher risk of low IQ.** CONCLUSIONS: There is a perturbing negative impact of these findings on human capital acquisition for the region and the country. More attention is needed to ensure effective salt iodination processes, particularly in regions where goitrogens may contribute to the negative effects of iodine deficiency on the intellectual development of children.

Investigation of intelligence quotient and psychomotor development in schoolchildren in areas with different degrees of iodine deficiency.

Tang Z, Liu W, Yin H, Wang P, Dong J, Wang Y, Chen J.

Asia Pac J Clin Nutr. 2007;16(4):731-7.

School of Public Health, China Medical University, 92 North 2nd Road, Shenyang 110001, P R China.

This investigation aims to observe the intelligence and psychomotor development of the schoolchildren in iodine deficiency (ID) areas after the adoption of Universal Salt Iodization (USI), and evaluate the effect of the adoption of USI on their intelligence and psychomotor development. 564 schoolchildren (306 males and 258 females, age range from 8 to 13 yrs) from areas with severe, moderate, and mild ID were investigated. Intelligence quotient (IQ) was measured by Combined Raven's test, second edition. Psychomotor development was examined by Jinyi Psychomotor Test Battery (JPB). We found that **the IQ scores of all subjects in the**

severe and moderate ID areas were 102 +/- 15.6 and 99.5 +/-16.6 respectively, lower than those in the mild ID areas (108 +/- 12.4, p < 0.01). The IQ scores correlated negatively with age (partial r = -0.17; beta = -1.95; p < 0.0001). The total T scores of JPB of all subjects in the severe and moderate ID areas were 316 +/- 42.3 and 330 +/- 47.7 respectively, lower than those in the mild ID areas (342 +/- 48.1, p < 0.05). The total T scores of JPB correlated negatively with age (partial r = -0.15; beta = -4.94; p = 0.0006). We may conclude that after the adoption of USI in the ID areas investigated, USI has probably made a contribution to the partial recovery of intelligence and psychomotor development injured by ID in schoolchildren, and should be strengthened.

The effects of iodine on intelligence in children: a meta-analysis of studies conducted in China.

Qian M, Wang D, Watkins WE, Gebski V, Yan YQ, Li M, Chen ZP.

Asia Pac J Clin Nutr. 2005;14(1):32-42.

The Institute of Endocrinology, Tianjin Medical University, Tianjin 300070, China.
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This study quantifies the effects of iodine on the intellectual development of children using a systematic manual literature search of Chinese publications related to iodine deficiency disorders. The Chinese Medical Reference Database, Medline, and Cochrane library were searched electronically in Chinese and English. Inclusion criteria included: studies conducted in China, comparing children (<16 ys) living in naturally iodine sufficient (IS) with those in severely iodine deficient (ID) areas, or children in ID areas born before and after the introduction of iodine supplementation. Intelligent Quotient (IQ) was measured using Binet or Raven Scales. The iodine sufficient control groups were comparable socially, economically, and educationally with the study groups. Random effects models were used in the meta-analysis. Effect size was the standard deviation IQ point (SIQP), which is equivalent to 15 IQ. Thirty-seven reported studies, total 12,291 children, were analyzed. **The effect size was an increase of 0.83, 0.82, and 0.32 SIQP respectively, for the children living in IS communities compared with those living in ID areas with no iodine supplementation, with inadequate iodine supplementation, or children who had received iodine during their mothers' pregnancy and after birth. These equal to 12.45, 12.3, 4.8 IQ points.** Compared with that of children whose mothers were persistently exposed to ID, the total effect size of the 21 entries was an increase of 0.58 SIQP (8.7 IQ points) in the group receiving iodine supplementation during pregnancy. Furthermore, there was an increase on 1.15 SIQP of Binet or 0.8 SIQP on Raven Scale (17.25 or 12 IQ points) for children born more than 3.5 years after iodine supplementation program was introduced. **The level of iodine nutrition plays a crucial role in the intellectual development of children. The intelligence damage of children exposed to severe ID was profound, demonstrated by 12.45 IQ points loss and they recovered 8.7 IQ points with iodine supplementation or IS before and during pregnancy.** Iodine supplementation before and during pregnancy to women living in severe ID areas could prevent their children from intelligence deficit. This effect becomes evident in children born 3.5 years after the iodine supplementation program was introduced.

1.2.2 Improved Distributional Analysis of Variability in Exposure and Factors Affecting Susceptibility (Especially Iodide Intake)

As is traditional, EPA's analysis of exposure and potential risks by combining selected points from several different distributions to arrive at a result it deems to provide, overall an acceptable risk management position. The fact of the matter is that few if any people are capable of understanding the combined effects of multiple choices from uncertain and variable distributions of different parameters. A far better approach is to choose some meaningful outcome parameter, ideally (a) the population distribution of IQ change or at least (b) the number of people in different susceptibility groups that perchlorate doses and (c) changes in absolute iodide uptake levels, and show the effects of different perchlorate water levels on those outcome parameters. This would effectively communicate to decision-makers the distributional consequences of different policy choices for the people whose health and economic welfare they are charged with protecting. Toward this end, the dietary analysis in the support document for the present work does a very good job at showing the percentile distributions of expected perchlorate intakes. Ginsberg et al. (2007) show how Monte Carlo simulations can be used to combine variability distributions for breast milk/urinary perchlorate concentrations, baseline urinary perchlorate levels, and milk consumption rates to estimate distributions of perchlorate consumption rates for infant with and without water-borne exposures to their mothers. This type of analysis could readily be revised in the light of more recently assembled data from the support documents, and extended to include variability in iodide status for both mothers and (for bottle-fed infants) perchlorate in formula and water used to prepare the formula. This would provide public health and water system decision-makers a much more complete representation of the expected changes in population distributions of exposures and potential neurodevelopmental consequences for choices they might make to alter perchlorate exposure levels from water.

Response: Health Advisories do not have executive summaries in the interest of brevity.

The issues raised in this comment regarding thyroid physiology and homeostasis, dietary iodide interactions, and the iodide status of the US population are beyond the scope of a health advisory. However, these issues are being referred to the NAS to obtain advice regarding how to factor them into the Regulatory Determination for perchlorate.

Recommendations regarding application of distributional analyses and further modeling of response to perchlorate exposures for different age groups will be considered in the context of revision to the assessment upon receiving inputs from the NAS.

B. Stern

The sections on relative source contribution (RSC) are comprehensively and thoroughly described in a manner that is well-written and supported by actual data (and much more detailed than most RSC discussions). However, I do not find the sections on Occurrence and Exposure and on Health Effects, sufficiently detailed, organized or comprehensive in presentation of the "necessary scientific information in a manner that that can be understood by both the officials from public health organizations and public water systems."

Response: Sections on Occurrence and Exposure for the Health Advisory cited those aspects of the data deemed most critical to developing the Health Advisory value. Citations are provided in the document for those readers desiring a more complete discussion.

T. Woodruff

As stated above the document is well-written and clear. However, there are several important pieces of information and other analyses that are missing that make it incomplete. As discussed below, there should be a section added on sensitive subpopulations. In addition, there needs to be analyses completed and included of potential perchlorate exposure via breastmilk and infant formula and a broader, more representative portion of the infant population needs to be included in the analysis.

Response: Comments regarding consideration of sensitive subpopulations and life stages will be considered by the NAS during an upcoming review of the scientific underpinnings of the Regulatory Determination for perchlorate. This review will include evaluation of the assumptions about exposure and the expression of the RfD as a biological response rather than a dose.

2. Does the Health Advisory describe the perchlorate health effects information that a public health official would need to assess and evaluate options for addressing local perchlorate contamination of drinking water?

J. DeSesso

The health effects are clearly stated and balanced in their presentation. Although the Advisory does not explicitly state "dose makes the poison" the presentation of information and the way the information is used to develop the Health Advisory is such that the reader should grasp the content. This reviewer was impressed with the way the Advisory dealt with (and explained the reasoning behind) the use of modeled inhibited iodide uptake for infants and pregnant females when the values were slightly greater than the no effect level. It provided a sense of reasonableness and balance to the document.

Response: Modeled estimates of iodide uptake inhibition for various life stages were used to estimate the biological response anticipated at the various exposure levels. They were compared to the degree of inhibition used by the NRC in establishing a precursor effect level in developing the RfD.

D. Hattis

No. The current draft of the Health Advisory does not give the local manager as much information and relevant insights as he/she needs. There needs to be a much more frank communication of the likelihood that perchlorate is exacerbating current adverse effects on neurological development from sub-optimal iodide intake and related common subclinical hypothyroidism in the general population of women bearing children. Better insights are also needed on the reasons why young infants are likely to have enhanced susceptibility to essentially permanent neurodevelopmental impairment from inadequate iodide intake and the reason this is expected to be incrementally enhanced at nearly all levels of perchlorate water exposure now being considered.

One of the most objectionable parts of the current document is the two-sentence discussion of recent evidence that current levels of perchlorate exposure are associated with measurable differences in thyroid hormone levels in a significant portion of the general U.S. population:

> "Results from studies of the effects of perchlorate exposure on hormone levels have been mixed. One recent study did not identify any effects of perchlorate on blood serum hormones (Amitai et al, 2007), while another study (Blount et al., 2006b) did identify such effects."

The strong implication of this is that the results of the Amitai study contradict the Blount et al. results. Amitai et al. are at pains to dispel this very point in their own discussion of their findings in comparison with those of Blount. The major conclusion of the Amitai paper from their abstract is:

> "This study finds no change in neonatal T_4 levels despite maternal consumption of drinking water that contains perchlorate at levels in excess of the EPA drinking water

> equivalent level (24.5 µg/L) based on the National Research Council reference dose (0.7 µg/kg/day). Therefore the perchlorate reference dose is likely to be protective of thyroid function *in neonates of mothers with adequate iodide intake.* (emphasis added)

The paper's discussion section includes the following:

> "Iodine intake is important for protecting the thyroid from iodide uptake inhibitors such as perchlorate. Blount et al. (21) recently found that perchlorate exposure is associated with decreased thyroid function *in U.S. women with low urinary iodine.* Higher serum iodide levels in the high perchlorate exposure area may modulate any perchlorate-induced inhibition of iodide uptake. A previous study of pregnant women in the coastal areas of Israel indicates iodine sufficiency (urinary iodine median = 143 ug/L, mean = 130 ug/L) (22) based on W.H.O. criteria. Another important difference between the current work and the Blount et al. study is the study population: we examined thyroid function in neonates, while Blount et al. studied adults and adolescents (21). *Based on differences in iodine intake and life stage for the two studies, our findings do not contradict those of Blount et al. (21).*

Therefore the implication that the two studies conflict is misleading. The Blount study is based on much larger numbers of people from the general population and was able to separately analyze associations of urinary perchlorate and thyroid hormone variables in subgroups with different iodide excretion rates.

The extensive analysis in the Blount et al paper of thyroid hormone changes in relation to iodide excretion is discussed much more extensively in the next section (4.1.3) on "Biomonitoring Studies". (Why this category is distinguished from section 4.1.2 titled "Epidemiology Data" escapes me. The two sections should be merged.)

Section 4.1.3 raises the issue of whether the association between thyroid hormone levels and perchlorate seen by Blount et al. reflects a causal association, or instead is

> "mediated by some other correlate of both, although the relationship between urine perchlorate and total TSH and T4 levels persisted after statistical adjustments for some additional covariates known to predict thyroid hormone levels (e.g. total kilocalorie intake, estrogen use, and serum C-reactive protein levels).

The issue of whether perchlorate might be a surrogate for some other causal exposure is further discussed in the next paragraph,

> There are other chemicals, including nitrate and thiocyanate, which can affect the thyroid function. Steinmaus *et al.* (2007) further analyzed the data from NHANES 2001–2002 to assess the impact of smoking, cotinine and thiocyanate on the relationship between urinary perchlorate and blood serum T4 and TSH. Thiocyanate is a metabolite of cyanide found in tobacco smoke and is naturally occurring in some foods, including cabbage, broccoli, and cassava. Increased serum thiocyanate levels are associated with increasing levels of smoking. Thiocyanate affects the thyroid by the same mechanism as perchlorate (competitive inhibition of iodide uptake). Steinmaus et al. analyzed the data to determine whether smoking status (smoker or nonsmoker), serum thiocyanate, or

> serum cotinine were better predictors of T4 and TSH changes than perchlorate, or if the effects reflected the combined effects of perchlorate and thiocyanate.

The result of the Steinmaus et al. (2007) analysis is accurately reported as:

> The authors found no association between perchlorate or T4 and smoking, cotinine or thiocyanate in men or in women with urinary iodine levels greater than 100 µg/l. In addition, they found no association between cotinine and T4 or TSH in women with iodine levels lower than 100 µg/l. However, in women with urinary iodine levels lower than 100 µg/l, an association between urinary perchlorate and decreased serum T4 was stronger in smokers than in non-smokers, and stronger in those with high urinary thiocyanate levels than in those with low urinary thiocyanate levels. Although noting that their findings need to be confirmed with further research, the authors concluded that for these low-iodine women, the results suggest that at commonly-occurring perchlorate exposure levels, thiocyanate in tobacco smoke and perchlorate interact in affecting thyroid function, and agents other than tobacco smoke might cause similar interactions (Steimaus et al. 2007).

So to the extent that the issue has been examined, there is absolutely no evidence that the Blount et al. finding of an association between thyroid hormone levels and low dose perchlorate exposure in women with low iodide levels is mediated by any of the other potentially confounding exposures that have been studied to date. The HA document should explicitly point this out.

The Amitai et al. study is again referred to at the end of section 4.1.3, quoting the T4 results of the three studied groups and the high perchlorate levels without mentioning either the much smaller size of the population examined, or the fact of larger iodide intakes. The impression is therefore again conveyed that those results contradict those of the Blount and Steinmaus papers. This should be corrected.

Response: EPA believes that the Health Advisory clearly indicates that all life stages and population subgroups are adequately protected if the most sensitive subpopulation, the fetus of the hypothyroid woman is protected.

B. Stern

The subchronic health advisory (HA) provides some information for public health officials to assess and evaluate options if local monitoring of drinking water indicates that concentrations exceed the HA over a period of time (i.e., repeated, not single, sampling measurements) or if a plume with elevated concentrations is known to occur from an identified source. The UCMR data given on page 10 could be more clearly presented. The data overall suggest that perchlorate in drinking water systems is not likely to present a problem. Only 160/3865 (4.1%) systems had at least 1 analytical detection of perchlorate ≥ than the LOD, and only 1.9% (637/34,331) of samples had detects, over five years of monitoring, presumably quarterly or possibly monthly. A distribution of the frequency of multiple detects in the same system(s) would be of interest and importance for public health officials because sustained or repeated perchlorate ingestion is the only way that perchlorate might affect the transport of iodide into the thyroid gland in a toxicologically-meaningful manner (because of homeostasis). The presentation of mean and

median concentrations of only detects lacks biological significance with regard to exposure because (1) it does not give means or medians for a given system to which a resident population would be exposed, (2) non-detects, which comprise 98% of the samples are not considered; including the non-detects (whether they are set at 0 or ½ LOD) for a given system would give means and medians significantly lower than those given only for detects; (3) biologically meaningful exposure would be based on means and distributions for a given drinking water supply system to yield an estimate of sustained population exposure. These data suggest that perchlorate exposure via drinking water is very intermittent.

No information is given on groundwater levels of perchlorate which would be of importance for families that obtain their drinking water from wells. Amitai et al. (2007) have reported very high concentrations of perchlorate in wells used for local drinking in the vicinity of a military plant used for decades in Israel. Amitai et al. (2007) also present data showing that high perchlorate concentrations in drinking water do not necessarily translate into high concentrations at the tap. These kinds of information would be important for public health officials to assess and evaluate options for mitigating exposures if perchlorate concentrations exceeding the HA are found in drinking water supplies.

Greater consideration in the document could be given to plumes, for example, from a military facility in which perchlorate had been used, and their rate and expansion of movement. This would assist the public health official in assessing options, DasGupta et al. (2006) have shown that naturally occurring processes form a significant proportion of environmental perchlorate and that non-anthropogenic background levels of perchlorate exist and may explain, at least in part, the ubiquitous presence of perchlorate in biomonitoring samples.

Although an HA is not an action level, HA exceedences are likely to trigger a public health response, given the widespread publicity attending perchlorate in the environment. It is premature to set an action level, at least in part because additional studies are underway including the large CDC study which is measuring multiple indices of thyroid function (such as free T4 which is more biologically relevant to thyroid tissue availability and T3, which is the bioactive form of thyroid hormone in the tissues and which is mainly produced by conversion from T4) as well as other associated variables.

However, information essential for risk communication and public perception of the potentially adverse health effects of perchlorate concentrations at or above the HA is not well presented in the report, either for the local public health official or for the local population, especially for the high-risk populations. This includes pregnant women and their fetuses and nursing infants, as well as infants who are fed powdered formula reconstituted with tap drinking water. I refer here to the relationship between perchlorate and iodine status. Without a more thorough and comprehensive presentation of this relationship, public health officials are not likely to understand that the key event in potential perchlorate thyrotoxicity is insufficient iodine status. Therefore, the option to take action to increase iodine intake among susceptible populations (and the general population) and to educate the public about the essentiality of sufficient iodine intake for fetal, neonatal and child development (and the perchlorate-iodine association) might well not be considered as a priority.

Response: UCMR monitoring includes systems that draw their source water from both surface and ground water. As such, ground water and surface water systems are reflected in the exposure analysis underlying the health advisory. The health advisory value is applicable for all water types, including wells. Available data do not permit analysis of ground water plumes. This question is beyond the scope of the current document.

T. Woodruff

The document provides many of the elements to evaluate potential health effects, but it needs to include a section on sensitive subpopulations, a discussion about the influence of background exposures that modify the risk (see discussion of this below in the EPA PBPK model section), and calculations that are more representative of the sensitive subpopulations. See the discussion of these issues above and in the review of the PBPK model.

Response: The issues will be referred to the NAS for further consideration. The health advisory will be revised based upon the results of their deliberations.

3. Is the explanation of the derivation of the Relative Source Contribution clear and easy to understand?

J. DeSesso

The authors explained the concept of Relative Source Contribution in a common sense fashion before they delved into the data and formulae. This is a strength for the Advisory. This section of the Advisory is the central concept needed to understand what the Agency is trying to do and why. While quantitative risk assessment in general may be somewhat difficult for lay persons to understand, the writing is clear and the information is laid out in an orderly fashion. I think that most motivated readers should be able to understand this section, if they read it carefully. I find no fault with the writing.

The authors wrote good descriptions of the FDA Total Diet Study and various biomonitoring studies that provided a sense of how much perchlorate is found in American diets and in the body burden of various age groups of people. They laid out important concepts like RfD and how it is calculated. They explained the findings of the Greer study in a manner that was easy to follow. (This is a difficult task because the Greer study is a non-traditional study for use in risk assessment.)

Response: The Agency believes that the RSC derivation makes appropriate use of the relatively large data set available for perchlorate in food and water, and the biomonitoring data from CDC.

D. Hattis

In most respects, yes. But there are two problems:

First, Table 5.1 does not include critical age groups for which dietary contributions exceed the RfD—bottle-fed and breast fed infants younger than 6 months.

Second, Table 5.1ists a narrow confidence range (derived from treading LODs as zero or LOD) of the mean intakes from different age groups. The ultimate derivation of the recommended DWEL is based on a 90th percentile estimate—but why limit it to that rather than do a full distributional analysis? The arbitrariness of the choice of the 90th percentile for this purpose needs to be made clear, as well as the consequences of other reasonable options (that is, higher percentiles).

Response: The health advisory was developed as an outgrowth of the NRC (2005) derivation of an RfD for perchlorate that is based upon iodide uptake inhibition, a precursor effect. The modeled estimate of iodide uptake inhibition was used to demonstrate that the health advisory level as developed for the fetuses of hypothyroid women is protective of all other life stages and subpopulations in that no other group is anticipated to exceed the target level of iodide uptake inhibition at water concentrations up to 15 ppb. This determination includes consideration of contribution of perchlorate from food.

The 90th percentile value was used in accord with the recommendations of the Agency's Exposure Characterization Guidelines.

B. Stern

A first reading of the first half of the derivation of the RSC section was somewhat confusing. It was not until p. 30 that I understood suddenly how the RSC was being derived. As noted previously, I think that the derivation is very well done. However, it would be much more comprehensive if the first paragraph in Section 5.2 (Relative Source Contribution) included a summary paragraph about the approach and the following:

1. What is a relative source contribution? How is one calculated? For most lifetime HAs, a default of 20% is used in the absence of data in other environmental source media. This default is likely to be emphasized and proposed by public health groups and individuals because it is the most conservative approach. Thus, it is important to note that the use of the default RSC is not appropriate or relevant or scientifically defensible, given the large amount of solid data of available on perchlorate intake from food, by age and gender. This fact should be mentioned at the beginning of this section, up front, because not addressing this issue may be interpreted as withholding information about the process of determining an RSC (i.e. a lack of transparency).

Second, the HA is for subchronic exposure. Typically, OW standard operating procedures apply an RSC only for lifetime exposure. [NOTE: There is a significant error on page 26, in Step 3. The equation reads "**Lifetime** HA = DWEL x RSC". This should be changed to "Subchronic HA".

The text notes that the "subchronic HA is calculated by factoring in other sources of exposure (such as air, food, soil) in addition to drinking water using the relative source contribution (RSC) for the drinking water." Is this a new procedure? As noted in the previous paragraph, RSCs are generally only applied to lifetime (i.e. chronic) exposure scenarios. A quick search of EPA OW's web site did not find any reference to changing the SOP for deriving a subchronic HA by applying a RSC. I am familiar with work on other chemicals in drinking water that target the reproductive and/or development systems and for which a RSC for short-term and subchronic health advisories are being proposed. This approach is scientifically defensible because the exposure duration for a chemical affecting reproduction or development is significantly less than lifetime. However, an explanation is warranted in both Step 3 and in the first paragraph of Section 5.2.

2. What data are used? The sentence on p. 28 reads: "These exposure data include the analysis by EPA of the UCMR data and CDC's biomonitoring data, as well as FDA's TDS." It would be helpful to "set the stage" for what follows by briefly explaining how these data are utilized in a summary paragraph.

The UCMR data and an allocation of 62% of the RSC to drinking water are at odds with each other. The UCMR data suggests that drinking water exposure to perchlorate is very low. Therefore, a lower RSC based on only UCMR data would be scientifically defensible (Table 3.2). However, the RSC was not calculated by using the UCMR directly. Therefore, to mention it as the first set of data in the above sentence is somewhat misleading. What is utilized is a combination of the NHANES-UCMR data. Section 5.2.2 does not give an adequate description. Some brief discussion of how the UCMR data were used in NHANES is given in Section 3.4, and the RSC section would benefit from restating and perhaps expanding this topic. This is not

clearly stated.

Nevertheless, the RSC derivation uses all available data in a scientifically-supportable manner. The basis for the derivation is that only a relatively small RSC occurs from food. Therefore, a large RSC (i.e. larger than default and based on actual data) can occur from drinking water, even if it may not. It is recommended that this approach be summarized in the first paragraph. Given the UCMR data, subchronic exposure to perchlorate in drinking water is unlikely to meet its allowable RSC. This is an important concept. The data in Table 3.2 show only a small increase in estimated daily perchlorate intakes from drinking water, suggesting a very low RSC from drinking water. It is essential to explain that the RSC is based on the RfD/DWEL, not the actual proportions of perchlorate intake estimated with and without exposure through drinking water.

Response: The Agency believes that the Health Advisory provides sufficient detail on the derivation of the RSC. Citations are provided to permit the interested reader further details as desired. The editorial change on page 26.

T. Woodruff

The explanation is relatively clear. However, the calculation of the RSC for breast milk exposures needs to consider both food sources which are indirectly contributing to breast milk levels and drinking water sources (see comment above). In addition, it should be calculated for preterm and term infants who weight less than 3.5 kg.

In addition, the equations used to determine the HA depend on the calculation of the RfD. There are several significant new scientific publications and reviews that require some revaluation of the appropriate point of departure and uncertainty factors which make up the RfD. The point of departure used in the HA is a NOAEL, which is inconsistent with EPA's preferred approach, which is to use a point of departure based on benchmark dose modeling. NOAEL's and LOAEL's can be highly influenced by study design and the benchmark dose modeling approach alleviates some of this concern. Sufficient data to calculate a BMDL is available both from the Greer study (though this study is not representative of the full range of sensitive lifestages such as discussed in Ginsberg and Rice 2005 (Ginsberg and Rice, 2005)) and could be calculated from the Blount or Steinmaus studies (Blount et al., 2006; Steinmaus et al., 2007).

Some comments to make the tables more clear.

> In table 5-2 and 5-3 the document should spell out RSC. Also, in table 5-2 the label for the last column should explain it is from drinking water, for example it could say "RSC from drinking water as a % of the RfD". I think it might also be helpful to include the equations in the 2nd row under the headers so it is clear how the numbers are calculated. Finally, the RfD should be given in the title or as a footnote. Same comments apply to table 5-3.

Response: EPA intends to raise questions regarding the changing science on perchlorate to the NAS and seek their guidance on how best to apply this new information to the assessment of risk from perchlorate. The recommended modifications to the tables were made.

4. Have the sensitive populations been identified appropriately?

J. DeSesso

The sensitive populations identified in the Health Advisory are the appropriate ones. The most disappointing aspect of this is that the quantity and quality of data for infants and pregnant women is not robust. As noted in my Specific Comments, it would be good to know (at a minimum) the trimester of pregnancy for the women in the biomonitoring studies. While the information for these groups is meager, there is comfort in knowing that the individuals in these sensitive groups are transient. None of them will remain in their respective group for longer than 9-12 months.

Response: As noted previously, there is not sufficient data to support a more robust analysis of pregnant and lactating women in either the Total Diet Study or the NHANES biomonitoring data.

D. Hattis

Almost—the age groups are correct, but the dimension of iodide intake needs to be added and fully explored.

Response: Sufficient data to support the suggested analysis were not available.

B. Stern

No. There is another sensitive subpopulation and that is the neonate (both preterm and full term). Neonates of iodine deficient women who are nursed during the first month or several months of life can be considered to be similar to fetuses in that they receive all their nutrition from their mothers. Breast milk is a filtrate of blood and thus would be anticipated to contain perchlorate if it occurs in maternal blood. Nonetheless, protection of the mother from the adverse effects of elevated levels of perchlorate ingestion, as defined by drinking water concentrations above subchronic HA, will protect the nursing neonate. However, infants who receive formula during this critical postnatal period of development are at risk if they were born to iodine-deficient mothers, especially if the formula is not fortified with iodine. (Iodine fortification of infant formula is voluntary, not mandatory, in the U.S.). Even with fortified infant formula, this population is at risk if fortification is insufficient; it should be noted that there are no mandated standards for iodine content in formula. Further, a proportion of neonates (specific data were not found) are fed powdered infant formula which has been reconstituted with tap water (powdered infant formula being cheaper than the liquid kind). The use of tap water with elevated perchlorate levels may further compromise the iodine status of neonates of iodine-deficient mothers. No data are available which might elucidate this interaction.

The inclusion of this high-risk population is important for risk communication, as well as in response to Charge Question #2.

Response: As suggested in the NRC Report (2005), EPA has identified the fetus of the hypothyroid woman as the most sensitive subpopulation. EPA has investigated the extent to which protecting this subpopulation is protective of others through application of a PBPK model examine the extent of iodide uptake inhibition that would occur at the health advisory

concentration. Based upon the results of the PBPK analysis, EPA concludes that the 15 ppb health advisory level is protective of all life stages and subpopulation.

T. Woodruff

The document should include a specific section titled "Sensitive Subpopulations' which identify the sensitive subpopulations and include a description each one. It is difficult to find the identification of sensitive subpopulations in the document. The group is cursorily mentioned in the first sentence under section 5.2. In addition, the group of sensitive subpopulations needs to be expanded to include preterm and term infants, please refer to comments above.

EPA should also consider relabeling this group (and section) as sensitive lifestages, as "populations" implies that fetuses and infants are a separate group in the population. However, every person must go through this lifestage, so everyone at one time is in this "subpopulation", which makes the subpopulation terminology meaningless. By redefining fetuses and infants as a sensitive lifestage, it appropriately acknowledges the critical period of susceptibility during which exposures can produce permanent biological alterations.

Response: EPA believes that considerations of life stages and sensitive subpopulations are adequately represented in the health advisory. We concur with the recommendation that use of the term "life stage" is more appropriate for fetuses and infants.

5. Is the role of modeling in evaluating the sensitive populations clearly described?

J. DeSesso

The role of PBPK models for evaluating the impact of perchlorate ingestion on the precursor event of iodide uptake in establishing the subchronic Health Advisory for perchlorate was well-presented. The authors explained where the models came from, how they differed, and how they used them in their document. They also gave a balanced presentation about the model uncertainties and were thoughtful in their use of the model results when developing the Health Advisory for sensitive subpopulations.

Response: EPA believes that the model expands the understanding of the impact of perchlorate on the precursor effect of concern across life stages and sensitive subpopulations.

D. Hattis

Somewhat, but the complexity, limitations and uncertainties in the model are not as fully described as is needed. Absent this, I believe the audience is likely to have more confidence in the results of this modeling than is reasonably justified.

The version of the adult model presented by Merrill et al. (2005) has a total of 86 parameters. Of these, 26 are general physiological parameters expressed as single point estimates without any variability except for the % of body weight represented by fat, which differs between men and women. Beyond these there are a total of 60 chemical-specific parameters (31 for iodide and 29 for perchlorate), of which 30 were fit to data from limited available human studies. Of these fitted parameters only two are given with any confidence limits expressing either variability or uncertainty.

With such a complex model with many adjustable parameters fitted to a modest number of human studies.(primarily, in the case of the perchlorate parameters, the radioiodide uptake inhibition data in the limited study of Greer et al.) there is nearly always an opportunity to fit the data in multiple ways. In other words, changes to the values of some parameters can nearly always be changed in one direction if other parameters are adjusted in parallel offset the effects of the first parameter and to maintain the fit to available data. In this process, the behavior of the model outside the realm of the fitted parameters can change appreciably. The presence of 30 parameters would usually make the model very flexible unless the acceptable values of many of the parameters are severely constrained with other information. In my view it is important to communicate to the reader.

The models for pregnant women and their fetuses, lactating women and their babies, and bottle-fed infants as published by Clewell et al. (2007) are similarly complex, but in this case an extra measure of uncertainty is added because of the need to project the parameter values in various ways. In the gestational model, of the 24 perchlorate parameters 13 are projected using a "parallelogram" modeling approach, 7 are simply adopted from rat data.

The modelers themselves are acutely aware of some important limitations of their analysis. They emphasize that

> "There are uncertainties associated with this modeling, as there are for any modeling effort. For example, this analysis does not take into account within-group variability in PK, uncertainty in model parameters and predictions, or population differences in PD. Also, the NRC identified fetuses of pregnant women that are hypothyroid or iodine deficient as the most sensitive subpopulation. Unfortunately, the models were not designed to account for whether the pregnant woman is hypothyroid or iodine deficient. Model predictions of doses in the various subgroups apply to a subgroup average for typical, healthy individuals, and effectively describe the RAIU inhibition relative to that same individual as his/her own control. Some members of a group would be expected to have RAIU inhibition greater than indicated in Table 4 for a particular perchlorate concentration, while others would have lesser inhibition. This would be expected for fetuses as well as for other subgroups. Likewise, the model does not allow for predictions of how RAIU inhibition, or the impact of that inhibition, might change with dietary iodide status (i.e., in an iodide deficient individual, or one with more than sufficient dietary iodide)."

Some, but not all of these caveats are included at the beginning of section 5.2.3 of the document, only to be weakened by the statements that the HA was based on the exposures of late gestation pregnant women and their fetuses. I think the reader should receive the PBPK modelers' qualifications in full where the PBPK modeling results are used—in discussing EPA's evident comfort with the results for breast and bottle-fed infants in Table 5.4. The caveat discussion should also emphasize that there is at present no quantitative estimate of the relative sensitivity of fetuses vs newborn infants to iodide uptake inhibition, particularly at various levels of iodide intake.

Response: The PBPK model used to support development of the health advisory has been peer reviewed. These comments are available on EPA's website. The model in its current iteration is not able to reflect varying levels of iodide intake. However, EPA believes that it provided valuable information concerning the impact of perchlorate on a variety of life stages and subpopulations.

B. Stern

I think that the role of modeling in evaluating the sensitive populations is well described. The advantages to this approach are well presented in the first paragraph in Section 4.1.4. However, I have several points of clarification to make. First, it would be useful to the reader to give examples of other chemicals in which PBPK models were used to predict effects levels and no-effects levels in humans. A sentence or two would suffice. The intent would be to demonstrate that this is not a new approach and that PBPK modeling is increasingly being used for evaluation of chemical effects in humans and to support the use of regulatory toxicology. Given the high public visibility and concern of perchlorate exposure, these examples would support the validity of this approach.

Second, no mention is made in the section that the PBPK modeling involves the use of perchlorate, iodide and/or inhibition data and modeling compartments in rats as well as humans (see Clewell et al. 2007). This indicates a lack of transparency, given that the animal data as reviewed by NAS (2005) minimizes the quantitative importance of animal toxicology data for human dose-response and risk assessment. I completely agree that the animal data cannot be

used to extrapolate quantitatively from rodents to humans for purposes of human health risk assessment. However, given that PBPK modeling involves rodent models, it would be useful to explain the species differences in more detail.

Briefly, recommendations for this discussion would include the following: (1) the utility of hazard characterization (i.e. qualitative characterization of the potential for perchlorate-induced injury to humans) in rodents at extremely high doses which are orders of magnitude greater than environmental exposures; (2) the similarity of the pharmacokinetics of perchlorate in rodents and humans (i.e., absorption, distribution, metabolism, elimination, mode of thyrotoxicity, as well as placental and breast milk transfer from the mother to the fetus and neonate, respectively) and thus, the suitability of PBPK modeling using both rodent and human data, as well as the support of predicted findings from modeling by human data from in well-conducted epidemiology studies; and (3) better supporting data to demonstrate that rats are much more sensitive to agents that disturb thyroid function than are humans, at least in part because homeostatic mechanisms in humans and nonhuman primates are more robust and more refined than in rats which are smaller in size, have shorter life spans, and are much less developed evolutionarily. This is also true for chemicals which disturb the pharmacokinetics of other essential elements (e.g., copper, iron, zinc) required for other requisite physiological functions; humans have a higher homeostatic capacity for regulation of both deficiency and excess for these types of biological systems.

Response: The application of the PBPK model to perchlorate is a new approach. It was possible because of the relative wealth of data available for perchlorate. This application reflects the Agency's efforts to make maximum use of the available data. More information on the modeling activity is available on EPA's website, as indicated in the citations in the health advisory.

T. Woodruff

This part of the document requires revisions. First, the document states on page 37 that the HA does not rely on the PBPK model for determining the HA. However, it is used to provide information about different subpopulations or lifestages. In the discussion of the model (see pages 32-33), EPA acknowledges that the model predicts there are exposures above the RfD, but then uses the results of the model (percent iodide uptake inhibition) to justify these exposures above the RfD. This requires confidence in the EPA PBPK model and, as described below, there are a number of significant limitations to this model which makes predictions of inhibition for a robust estimate of the population unwarranted and very likely underestimated.

Use of the model implies that EPA is free to redefine the RfD for infants. The NRC states that infants and developing children are "also considered sensitive populations". Subsequent further review and analysis of the thyroid hormone and neurodevelopment literature and scientific data brings additional insight into the sensitivity of the infant lifestage (Ginsberg et al., 2007). These enhanced reviews of the literature and the considerations mentioned above do not warrant exposures to infants over the RfD. Finally, there is no consideration in the PBPK model for preterm infants, which has been identified as one of the "most sensitive subpopulations", and based on the analyses of the 3.5 kg infant, it would be expected that exposures for this group would also be over the RfD.

While EPA does not say it is using this model as the basis of the HA, by including the analysis from the model, EPA implicitly is using it to support the HA, despite the limitations. Until these significant limitations are addressed, the model and the results should not be used in its current form to support the HA.

Comments on the PBPK model

Before commenting on some of the limitations of the model, it must be pointed out that the PBPK model is from a draft EPA report "Inhibition Of The Sodium-Iodide Symporter By Perchlorate: An Evaluation Of Lifestage Sensitivity Using Physiologically-Based Pharmacokinetic (PBPK) Modeling" (hereafter referred to as EPA PBPK model), and as such one assumes that it has not gone through peer review and is not final (note this document states "Draft Deliberative – Do Not Cite or Quote"). Thus, it appears that using this in the HA would be inconsistent with EPA policy of only using peer reviewed science for decision making.

The EPA PBPK model does account for some intrinsic characteristics that can influence exposure and kinetics in sensitive subpopulations and EPA should be commended for considering them (these include different excretion rates for infants and factors that influence exposure through breast milk). However, there are a number of other factors that would influence population variability and exposure variability that are not accounted for in the model, some of which are acknowledged explicitly by EPA in the document. These seriously limit the utility of the model to provide robust population estimates. These are described below in further detail.

Population variability and susceptibility characteristics which influence exposure and risks

Infant weight and early gestational ages

EPA estimates exposures for infants based on infant weight of 3.5 kg at 7 days. This does not incorporate two important and relatively large groups of infants, those born preterm and those at the smaller end of the birthweight distribution. In 2005, almost 13 percent of infants were born preterm (<37 weeks of gestation NCHS http://www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_06.pdf). In addition, about 8% of infants were born less than 2,500 grams. Infants who are born preterm were identified by the NRC as one of the most sensitive populations along with fetuses. The smaller infants would have a higher dose per body weight exposure to perchlorate from breast milk. The HA, based on the PBPK draft model, defines the lower end of intake for infants weight 3.6 kg or 3.5 kg for near-term infants (GW 40). It appears that the model cannot account for a significant portion of the infant population, and some of the most sensitive, the preterm infant and fetuses that are earlier in gestation (pre 40 weeks).

Variability in the disease status

The EPA PBPK model, as acknowledged in the draft assessment, does not describe the full population and generally describes average, healthy parts of the population. For example, on page 25, the document states:

> "For example, this analysis does not take into account within-group variability in PK, uncertainty in model parameters and predictions, or population differences in PD. Also, the NRC identified fetuses of pregnant women that are hypothyroid or iodine deficient as the most sensitive subpopulation. Unfortunately, the models were not designed to account for whether the pregnant woman is hypothyroid or iodine deficient. Model predictions of doses in the various subgroups apply to a subgroup average for typical, healthy individuals, and effectively describe the RAIU inhibition relative to that same individual as his/her own control."

This is an important limitation of the model, as hypothyroidism and iodine deficiency affect a significant portion of the population. As the HA draft states "subclinical hypothyroidism and reductions in T4 (i.e., hypothyroxinemia) in pregnant women have been associated with neurodevelopmental delays and IQ deficits in their children (Pop et al., 1999, 2003; Haddow *et al.*, 1999; Kooistra et al., 2006; Morreale de Escobar, 2000, 2004). Animal studies support these observations, and recent findings indicate that neurodevelopmental deficits are evident under conditions of hypothyroxinemia and occur in the absence of growth retardation (Auso *et al.*, 2004; Gilbert and Sui, 2008; Sharlin *et al.*, 2008; Goldey *et al.*, 1995). "

Hypothyroidism is prevalent in the U.S. population. For example, between 1999-2002, an estimated 7.3% of the U.S. population aged 12 years and older reported that they had thyroid disease or were taking thyroid medication (Aoki et al., 2007), and hypothyroidism is frequently undetected. Pregnancy causes an increased demand on the thyroid gland and hypothyroidism has been reported to be slightly more than twice as common among pregnant women than among non-pregnant women ages 12-49 (Aoki et al., 2007). As stated by EPA, the model does not account for this portion of the population.

The model also would not account for iodine deficiency, which is also relatively prevalent in the US with over 1/3 of women having iodine levels below 100 ug/L (WHO guidelines (Caldwell et al., 2005).

This has implications for both the breast feed newborn and fetuses. The fetus is dependent on maternal thyroid levels during the 1st to 2nd trimester (Williams, 2008), further thyroid hormone suppression in women who are already hypothyroid would have consequences for neurodevelopment that would not occur among healthy nonhypothyroid women. The document needs to consider both these lifestages. Nursing mother's who are iodine deficient may pass along less iodine to the breast feeding infant and it is unclear whether this is accounted for in the model

The EPA PBPK model and the HA do not consider fetal exposure. Only the GW 40 fetus is considered (it is not clear that a GW 40 fetus makes very much sense because at 40 weeks, the fetus is a baby and not a fetus anymore as most births occur by 40 weeks).

Finally, the EPA PBPK model and the HA do not account for background exposures from other chemicals and compounds that can interfere with thyroid synthesis. This issue is illustrated in the Stienmaus article and acknowledged in the HA (Steinmaus et al., 2007), where thyroxine levels can influence the effects of perchlorate. There is also ample evidence from other studies that exposure to other chemicals that can interfere with thyroid hormone levels can have an

additive effect on exposures to perchlorate. A recent study tested a mixture of 18 thyroid disrupting compounds (dioxins, dibenzofurans and PCBs), at doses comparable to human exposure levels, for effects on serum T_4 in rats and found that the mixture had a dose-additive effect on T_4 at environmentally-relevant doses and a 2-3 fold greater than dose-additive effect on T_4 at higher doses (Crofton et al., 2005). The NHANES data show that there ubiquitous and simultaneous human exposure to thyroid disrupting compounds multiple TDCs, including dioxins, PCBs, perchlorate, brominated flame retardants, bisphenol A, and several pesticides (Centers for Disease Control and Prevention, 2008). Background exposures to thyroid disrupting chemicals will increase the risk of perchlorate exposure compared exposures to the same level of perchlorate exposure in isolation, and this needs to be accounted for in the model.

The EPA PBPK model provides some information on groups that may be difficult to evaluate on a population level (infants, newborns), but it cannot be used in the HA in its current form as it implies a level of certainty about the effects of perchlorate that are not warranted. It could be used to evaluate the range of exposures that might be expected if the variability and susceptibilities in the population were modeled and this would provide complimentary information to measured data (see comment above).

Response: These questions are encompassed in the charge to NAS that has been developed to evaluate the implications and application of new and developing science on perchlorate to the evaluation of risk.

6. Do you have any suggestions on how this draft document could be improved?

J. DeSesso

Please see the Specific Comments section, which contains minor spelling and grammatical errors as well as suggestions concerning potential expansion or clarification of the text.

It is this reviewer's opinion that the subchronic Health Advisory for perchlorate developed in this document is quite conservative and more than meets the criteria for protecting virtually everyone.

Response: Recommendations in "Specific Comments" have been incorporated.

D. Hattis

Yes. In addition to those outlined above, I would suggest the following modifications to specific parts of the document"

Introduction, 1st paragraph, lines 4-5—I realize that the phrase "concentrations of drinking water contaminants at which adverse health effects are not anticipated to occur" is relatively standard boiler-plate terminology that is closely related to similar descriptions of the intended health protection objectives in choosing RfDs and related recommended values. However in the present context such a vague description, with its implication of a well defined population threshold at which it is expected that no one will be adversely affected, the meaning of this should be more extensively and clearly described. Is it expected that the incidence of x early effect (less than x% inhibition of iodide uptake by the thyroid) will be less than y% in the population of young infants likely to be especially susceptible? That more specific description would be fairer to the reader, even in the absence of other changes to the later analysis that I have suggested in response to other charge questions.

Introduction, 2nd paragraph—This paragraph makes the important claim that the recommended Health Advisory level of 15 µg/L "is based on the recommendations of the National Research Council" and EPA's adopted "Reference Dose (RfD) of 0.7 µg/kg-day." It is important to emphasize here in the introduction that this is true only for a relatively less-exposed subgroup (fetuses of pregnant women), not for other population subgroups (breast and bottle-fed newborns) that may have significantly more sensitivity than the normal adults studied by Greer et al. (2002).

Response: EPA believes that expansion of the paragraph in the Introduction is not warranted. As indicated above, EPA believes that the 15 ppb health advisory level is protective of the most sensitive subpopulation, and is also protective of others.

B. Stern

Many of my suggestions for improvement of the draft document are contained in responses to Charge Questions #1 through #5.

Additional suggestions include the following:

1. Consideration should be given to reordering/reorganizing the sections in the HA document. Although occurrence and exposure typically precedes health effects in the SOP for HA documents, the extensive discussion of biomonitoring data in Section 3.4, necessitates a prior discussion of the toxicokinetics of perchlorate, the pharmacokinetics of iodine and how the two interact. Toxicokinetic terms used in this section have little context to the nontechnical reader. There is a single statement on p. 15 in the second paragraph that mentions urinary excretion as the sole excretion pathways of perchlorate but no reference is given. A very brief paragraph at the beginning of this section on the toxicokinetics of perchlorate and the appropriateness of urinary biomonitoring would be useful. Also, the difference between perchlorate measurement as ug/L and creatinine-corrected averages is not explained. Why is a creatinine correction made? Other limitations of spot urine sampling as an indicator of sustained perchlorate exposure are not well described, nor is how large sample sizes overcome, at least in part on a population basis, these limitations.

p. 12. What do FDA data show regarding iodine intake for the 14 age-gender groups? The mean intake is given but not the tails of the distribution – nor the proportion of the population within group and overall which are below relevant U.S. dietary reference values.

The disconnect between iodine and perchlorate throughout the first part of the document lacks transparency, given that the susceptible populations are iodine-deficient.

Section 4.1.1. More data are needed on iodine and thyroid hormones, on iodine and thyroid hormone homeostasis.

Section 4.1.2. Please qualify the last sentence about Amitai et al. 2007 and Blount et al. 2006b to indicate the differences in the studies and the role of iodine in the findings of each study. Insufficient attention is given to the epidemiology studies, especially the new ones. Amitai et al. (2007) was post NAS (2005) and thus deserves much more extensive discussion; it shows clearly lack of high perchlorate ingestion effects in iodine sufficient women and their neonates. This is a very important study. Blount et al. is given extensive description in Section 4.1.3, but few conclusions are drawn.

Each of the data presentations would benefit from a brief summary and conclusions regarding what the data demonstrate/show.

Response: EPA believes that the organization as presented is appropriate. The expansion of the discussions is beyond the scope of the health advisory.

T. Woodruff

The previous comments, once addressed, will improve the draft document.

Response: No response.

V. SPECIFIC COMMENTS

J. DeSesso
Section 3.2, page 10, paragraph 1, line 1: The acronym "UCMR" should be defined when first used. It is currently defined in section 3.3, page 11 paragraph 1, line 7.

Response: This suggestion has been incorporated.

J. DeSesso
Section 3.4.1, page 15, paragraph 3, lines 1-2: The sentence needs to be modified. Urinary biomonitoring is just that: analysis of what is in the urine. Urinary biomonitoring does *not* analyze "the perchlorate actually ingested in the diets…of individuals." Urinary biomonitoring could be an indirect measure of dietary intake. If so, the manner of deducing/calculating the dietary intake should be specified.

Response: This suggestion has been incorporated.

J. DeSesso
Section 3.4.1, page 16, Table 3-2: The textual description of Table 3-2 needs to be expanded. For 2 of the groups (Females: 15-44; and Pregnant Females) the perchlorate ingestion is higher when the intake is via food only as compared to food plus water. Not only is this is counterintuitive, but also these are the 2 groups that contribute to the sensitive populations. The findings are likely due to the small number of individuals in some subgroups. This is most notable in the Pregnant Females group where the subgroup that experienced perchlorate intake via food only is ~27% higher than intake of the subgroup that ingested perchlorate from food plus drinking water.

It would be very helpful if the authors could provide a sense of how far through pregnancy the females in this group were, as the blood volume, fluid intake and caloric intake increase throughout pregnancy and could distort the reported values if, for instance, one subgroup was predominantly females in month 3 or pregnancy while the other subgroup was predominantly females in month 9. If information about the stage of pregnancy is not available, the Advisory should so state.

Response: EPA believes that the level of detailed provided is sufficient and consistent with information in other health advisories.

J. DeSesso
Section 3.4.2, page 17, paragraph 4: This paragraph describes the Blount et al (2007) study. The authors noted differences between the concentrations of perchlorate in the urinary outputs of pregnant versus lactating women and suggested that breast milk might be an added excretion pathway in lactating women. While this is a reasonable suggestion, the authors report the concentrations in μg/kg/day which sounds like a calculated intake. I would expect the urinary perchlorate values to be expressed in units of μg/L (and if urine was collected over a 24-hour period as μg/day). The Advisory should be clear as to what the reported values mean.

The report ignores the early and continuing work of Nancy Carrasco on the nature of the

symporter and its impact of environmental perchlorate on the constituents in milk and perchlorate's potential for affecting the uptake of iodide by infants (e.g., Carrasco, 1993; Kaminsky et al, 1994; Dohan et al, 2007). Reference to this body of work should be included.

Response: EPA has followed the language in the NRC (2005) report. This language will be retained for consistency with other documents.

J. DeSesso

Section 4.1.1, page 18, paragraph 2, lines 5-7: This sentence appears to be inaccurate. First, during most of the first trimester, the conceptus is an embryo, not a fetus. Second, I am unaware of evidence that the conceptus depends on adequate thyroid hormone for CNS early development. Most evidence points to a major role for thyroid hormone in later development of the CNS (i.e., during the second and third trimester). Thyroid hormone is especially important in the control of neuronal and oligodendroglial differentiation, as well as of apoptosis (see review by Bernal and Nunez [1995]).

Response: EPA has followed the language in the NRC (2005) report. This language will be retained for consistency with other documents.

J. DeSesso

Section 4.1.1, page 19, paragraph 2, lines 5ff: The studies marshaled to support the assertion of this sentence are of non-uniform quality. The Gilbert and Sui paper is particularly weak as their studies of neurobehavior showed no difference between experimental and control groups and their observations regarding decreases in pup thyroid hormones only reached statistical significance after many observations were discarded as outliers. The Goldey et al study reports deficits in auditory function, but the auditory system develops predominantly in the postnatal period in rodents, in contrast to the *in utero* development experienced by humans, which begs the question of relevance.

Response: EPA believes that the characterization of the studies in the health advisory is appropriate.

J. DeSesso

Section 4.1.3, page 21, paragraph 4, last line: Please correct the spelling of *Steinmaus*.

Response: This suggestion has been incorporated.

J. DeSesso

Section 5.0, page 25, last paragraph, line 1: Please correct the sentence to read "…spanning perhaps an order of magnitude…"

Response: This suggestion has been incorporated.

J. DeSesso

Section 5.4.2, page32, paragraph 2, line 2: Gestation in humans lasts 38 weeks (266 days) on average. Clinicians, however, count the weeks of pregnancy from the last missed period (which occurs 2 weeks before fertilization). The most accurate wording would be "gestation week 38

fetus." Alternatively, the less desirable terms "pregnancy week 40" or obstetrical week 40" could be used.

Response: This suggestion has been incorporated.

J. DeSesso

Section 5.2.3 Modeling Uncertainties, page 37: This section appears to be mis-numbered. The correct designation is **Section 5.4.3.**

Response: This suggestion has been incorporated.

J. DeSesso

Section 5.2.4 Summary of Modeling Analysis, page 38: This section appears to be mis-numbered. The correct designation is **Section 5.4.4.**

Response: This suggestion has been incorporated.

J. DeSesso

Section 5.4.4 (corrected), page 38, paragraph 1, line 18: Please re-word sentence to: "…1.1 percent, which is below …"

Response: This suggestion has been incorporated.

J. DeSesso

Section 6.0, page 39, paragraph 1, line 9: Please re-word sentence to: "…drinking water standards that are…"

Response: This suggestion has been incorporated.

J. DeSesso

Section 9.0, page 44, Morreale references: Please note that two references are "Morreale et al (2004).

Response: This suggestion has been incorporated.

J. DeSesso

Section 9.0, page 44, first Morreale reference: Please correct the spellings of *neuropsychological* and *maternal* (.versus material). Please also give complete pagination.

Response: This suggestion has been incorporated.

J. DeSesso

Section 9.0, page 44, Murray reference, line 3: Please correct the spelling of *Epidemiology*.

Response: This suggestion has been incorporated.

D. Hattis

No specific comments.

B. Stern

No specific comments.

T. Woodruff

Section 3.2 Water Occurrence – It is not clear why the document, and subsequent analysis, uses 4 ug/L as essentially the cutoff point for determining which water systems have detectable levels of perchlorate Section 7.0 Analytical Methods states that the MDL can range from a low of 0.005 ug/L to 0.53 ug/L all well below 4 ug/L. This brings into question whether using a cutoff lower than 4 ug/L would identify other water supplies with detectable levels of perchlorate.

Response: This value was used for the assessment because it is the limit of detection and reporting limit for perchlorate in UCMR.

VI. ADDITIONAL REFERENCES

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APPENDIX A

COMMENTS FROM JOHN DeSESSO

Dr. John M. DeSesso is Senior Fellow at Noblis Center for Science and Technology and has more than 30 years experience in., Anatomy and Teratology. He holds a PhD in Anatomy and Teratology from the Medical College of Virginia, Virginia Commonweath University and holds a Level III certification from The American Board of Homeland Security.

General Comments

This document is well organized, well conceived, and very well written. The authors did a fine job of explaining some rather difficult material in plain, straightforward English. The reader comes away with the sense that the overall discussion is objective and balanced. The modeling of data was used effectively. The choice of the 90th percentile water intake coupled with iodide uptake inhibition data was conservative, but the authors balance this by using the intakes the resulted in ~1.8% inhibition of iodide uptake as a no effect level and by not assessing extra uncertainty factors.

As is expected of any draft document, there are areas that could be improved. These are mentioned below in the Specific Comments.

Specific Comments

Section 3.2, page 10, paragraph 1, line 1: The acronym "UCMR" should be defined when first used. It is currently defined in section 3.3, page 11 paragraph 1, line 7.

Section 3.4.1, page 15, paragraph 3, lines 1-2: The sentence needs to be modified. Urinary biomonitoring is just that: analysis of what is in the urine. Urinary biomonitoring does *not* analyze "the perchlorate actually ingested in the diets…of individuals." Urinary biomonitoring could be an indirect measure of dietary intake. If so, the manner of deducing/calculating the dietary intake should be specified.

Section 3.4.1, page 16, Table 3-2: The textual description of Table 3-2 needs to be expanded. For 2 of the groups (Females: 15-44; and Pregnant Females) the perchlorate ingestion is higher when the intake is via food only as compared to food plus water. Not only is this is counterintuitive, but also these are the 2 groups that contribute to the sensitive populations. The findings are likely due to the small number of individuals in some subgroups. This is most notable in the Pregnant Females group where the subgroup that experienced perchlorate intake via food only is ~27% higher than intake of the subgroup that ingested perchlorate from food plus drinking water.

It would be very helpful if the authors could provide a sense of how far through pregnancy the females in this group were, as the blood volume, fluid intake and caloric intake increase throughout pregnancy and could distort the reported values if, for instance, one subgroup was predominantly females in month 3 or pregnancy while the other subgroup was predominantly females in month 9. If information about the stage of pregnancy is not available, the Advisory should so state.

Section 3.4.2, page 17, paragraph 4: This paragraph describes the Blount et al (2007) study. The authors noted differences between the concentrations of perchlorate in the urinary outputs of pregnant versus lactating women and suggested that breast milk might be an added excretion pathway in lactating women. While this is a reasonable suggestion, the authors report the concentrations in μg/kg/day which sounds like a calculated intake. I would expect the urinary perchlorate values to be expressed in units of μg/L (and if urine was collected over a 24-hour period as μg/day). The Advisory should be clear as to what the reported values mean.

The report ignores the early and continuing work of Nancy Carrasco on the nature of the symporter and its impact of environmental perchlorate on the constituents in milk and perchlorate's potential for affecting the uptake of iodide by infants (e.g., Carrasco, 1993; Kaminsky et al, 1994; Dohan et al, 2007). Reference to this body of work should be included.

Section 4.1.1, page 18, paragraph 2, lines 5-7: This sentence appears to be inaccurate. First, during most of the first trimester, the conceptus is an embryo, not a fetus. Second, I am unaware of evidence that the conceptus depends on adequate thyroid hormone for CNS early development. Most evidence points to a major role for thyroid hormone in later development of the CNS (i.e., during the second and third trimester). Thyroid hormone is especially important in the control of neuronal and oligodendroglial differentiation, as well as of apoptosis (see review by Bernal and Nunez [1995]).

Section 4.1.1, page 19, paragraph 2, lines 5ff: The studies marshaled to support the assertion of this sentence are of non-uniform quality. The Gilbert and Sui paper is particularly weak as their studies of neurobehavior showed no difference between experimental and control groups and their observations regarding decreases in pup thyroid hormones only reached statistical significance after many observations were discarded as outliers. The Goldey et al study reports deficits in auditory function, but the auditory system develops predominantly in the postnatal period in rodents, in contrast to the *in utero* development experienced by humans, which begs the question of relevance.

Section 4.1.3, page 21, paragraph 4, last line: Please correct the spelling of *Steinmaus*.

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Section 5.2.4 Summary of Modeling Analysis, page 38: This section appears to be mis-numbered. The correct designation is **Section 5.4.4.**

Section 5.4.4 (corrected), page 38, paragraph 1, line 18: Please re-word sentence to: "…1.1 percent, which is below …"

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Section 9.0, page 44, first Morreale reference: Please correct the spellings of *neuropsychological* and *maternal* (.versus material). Please also give complete pagination.

Section 9.0, page 44, Murray reference, line 3: Please correct the spelling of *Epidemiology*.

Charge Questions

1. **Does the document convey the necessary scientific information in a manner that that can be understood by both the officials from public health organizations and public water systems? (We have assumed that the depth of understanding will differ for the two intended audiences but hope that the message about perchlorate will be clear for both.)**

The writing style of the Advisory is easy to understand. The authors manage to instruct the reader in regard to requisite information and methodologies without being pedantic. By and large this is a successful document. The reader comes away with a sense of how the problem was approached and how the Agency moved forward. This transparency gives the reader a comfort level with how that reader should address problems that arise when performing his/her job in a manner that is consistent with the intent of the Health Advisory.

2. **Does the Health Advisory describe the perchlorate health effects information that a public health official would need to assess and evaluate options for addressing local perchlorate contamination of drinking water?**

The health effects are clearly stated and balanced in their presentation. Although the Advisory does not explicitly state "dose makes the poison" the presentation of information and the way the information is used to develop the Health Advisory is such that the reader should grasp the content. This reviewer was impressed with the way the Advisory dealt with (and explained the reasoning behind) the use of modeled inhibited iodide uptake for infants and pregnant females when the values were slightly greater than the no effect level. It provided a sense of reasonableness and balance to the document.

3. **Is the explanation of the derivation of the Relative Source Contribution clear and easy to understand?**

The authors explained the concept of Relative Source Contribution in a common sense fashion before they delved into the data and formulae. This is a strength for the Advisory. This section of the Advisory is the central concept needed to understand what the Agency is trying to do and why. While quantitative risk assessment in general may be somewhat difficult for lay persons to understand, the writing is clear and the information is laid out in an orderly fashion. I think that most motivated readers should be able to understand this section, if they read it carefully. I find

no fault with the writing.

The authors wrote good descriptions of the FDA Total Diet Study and various biomonitoring studies that provided a sense of how much perchlorate is found in American diets and in the body burden of various age groups of people. They laid out important concepts like RfD and how it is calculated. They explained the findings of the Greer study in a manner that was easy to follow. (This is a difficult task because the Greer study is a non-traditional study for use in risk assessment.)

4. Have we identified the sensitive populations appropriately?

The sensitive populations identified in the Health Advisory are the appropriate ones. The most disappointing aspect of this is that the quantity and quality of data for infants and pregnant women is not robust. As noted in my Specific Comments, it would be good to know (at a minimum) the trimester of pregnancy for the women in the biomonitoring studies. While the information for these groups is meager, there is comfort in knowing that the individuals in these sensitive groups are transient. None of them will remain in their respective group for longer than 9-12 months.

5. Is the role of modeling in evaluating the sensitive populations clearly described?

The role of PBPK models for evaluating the impact of perchlorate ingestion on the precursor event of iodide uptake in establishing the subchronic Health Advisory for perchlorate was well-presented. The authors explained where the models came from, how they differed, and how they used them in their document. They also gave a balanced presentation about the model uncertainties and were thoughtful in their use of the model results when developing the Health Advisory for sensitive subpopulations.

6. Do you have any suggestions on how we could improve this draft document?

Please see the Specific Comments section, which contains minor spelling and grammatical errors as well as suggestions concerning potential expansion or clarification of the text.

It is this reviewer's opinion that the subchronic Health Advisory for perchlorate developed in this document is quite conservative and more than meets the criteria for protecting virtually everyone.

References

Bernal, J. and J. Nunez (1995) "Thyroid Hormones and Brain Development," *Eur J Endocrinol* **133**: 390-398.

Carrasco, N. (1993) "Iodide Transport in the Thyroid Gland," *Biochim Biophys Acta* **1154**: 65-82.

Dohan, O., C. Portulano, C. Basquin, A. Reyna-Neyra, L. M. Amzel, and N. Carrasco (2007) "The Na^+/I^- Symporter (NIS) Mediates Electroneutral Active Transport of the Environmental Pollutant Perchlorate," *Proc Natl Acad Sci* **104**: 20250-20255.

Kaminsky S. M. , O. Levy, C. Salvador , G. Dai, N. Carrasco (1994) "Na^+-I^- Symport Activity Is

Present in Membrane Vesicles from Thyrotropin-deprived non-I^--Transporting Cultured Thyroid Cells," *Proc Natl Acad Sci* **91**: 3789-3793.

APPENDIX B

COMMENTS FROM DALE HATTIS

Dr. Dale Hattis is Research Professor at The Center for Technology, Environment, and Development, George Perkins Marsh Institute, Clark University and has more than 30 years experience in genetics research. He holds a PhD in Genetics from Stanford University and is a member of the Clean Air Scientific Advisory Committee (CASAC) Review Panel on Primary Standards for NOx and Sox, and the Food Quality Protection Act Science Review Board.

1. Does the document convey the necessary scientific information in a manner that that can be understood by both the officials from public health organizations and public water systems? (We have assumed that the depth of understanding will differ for the two intended audiences but hope that the message about perchlorate will be clear for both.)

In my view, managers in both categories need much better insights into (1) limitations and uncertainties in the current analysis, and (2) opportunities for better analyses that more fully capture in distributional form the likely implications of interindividual variability in susceptibility--especially the variability in susceptibility related to differences in long term iodide consumption.

Another improvement that I think should be made to help busy risk managers is an executive summary. Such a summary should briefly give the main line of the argument that the water office wishes to make in support of its recommended level—or the summary consequences of alternative levels if my suggestion below of an options analysis is adopted. Decision-makers are more likely to spend the time needed to absorb 41 pages (or more, if the analysis is broadened) if they have some clue at the outset of what sort of analysis they should expect to form the crucial basis of their risk management decision-making.

1.1 Limitations, Uncertainties, and Intellectual Roots of Controversy About the Analysis

A first step toward a revised health advisory that would be more helpful for the target audiences of public health and water system managers is to describe some of the sources of controversy on perchlorate health effects. I think the managers should be helped to understand why perchlorate is special as a neurodevelopmental toxicant, and why the traditional paradigms for arriving at putatively "safe" levels of exposure may be misleading in this case.

The central assumption underlying the methods EPA uses to set RfD's is that there will be some threshold dose for a toxicant below which there will not be an adverse effect. This assumption is derived from a vision of biological systems where there are generally homeostatic controls that have some finite capacity to offset or accommodate some chemically-induced perturbation as long as the perturbation is not so large as to push some system parameter so far from its normal values that injury results. The thresholds for individual people for specific adverse responses can vary (Hattis et al. 1999), but the usual assumption is that few or no people will have variations in sensitivity that will be large enough that they will not be adequately protected by the use of traditional 10-fold safety factor for human interindividual variability (along with other traditional uncertainty factors).
The concept of homeostatic controls can support the plausibility of a no-adverse-effect level for

a particular person (an individual threshold) for a specific mechanism of damage. However the does not necessarily imply the existence of a population threshold (a dose so low as to be at, or below, the lowest threshold dose for any individual in a mixed population with diverse sensitivities). Specifically, there may be a finite expectation for individuals to be affected by even marginal exposures in cases where even without additional exposure some people have no "functional reserve capacity" to act as a buffer between the base health state and a state of at least marginally worse health. Two specific types of cases where this can happen are:

1. Some individuals in the diverse population are already suffering from various kinds of pathological dysfunction in key parameters that may be marginally affected by different toxicants (e.g., a person undergoing a myocardial infarction may have a marginally expanded area of heart muscle death if the oxygen carrying capacity of his or her blood is reduced by a marginal exposure to additional carbon monoxide)

2. Some individuals are presently engaged in a task (e.g., running a 100-yard dash) that taxes some physiological capabilities to their limit, and marginal exposures to a toxicant marginally reduce those physiological capabilities.

The presence of iodide deficiency appears likely to create just such a situation where there is effectively no functional reserve capacity for a significant portion of the population. This is an important concern both during gestation, and in the perinatal period. Moderate and severe iodine deficiency (20-59 µg/day iodine; and <20 µg/day, respectively) is said to lead to a "global loss of 10-15 IQ points at a population level and constitutes the world's greatest single cause of preventable brain damage and mental retardation." (Delange 2001).

Unfortunately there is evidence that population intakes of iodide in the U.S. have declined in recent decades. Hollowell and Haddow report more than a 50% decline in general population urinary iodide concentrations between representative samples of the U.S. population studied in 1988-1994 compared to 1971-1974, although the very most recent data (2000-2002) show no continuing decline. The median urinary iodine from the NHANES 2000 sample is about 161 µg/L and that for 2001-2002 is 168 µg/L. Because urinary excretion is about 1 L/day in adults, these numbers roughly indicate the median iodide intake in µg/day.

The same surveys also provide some information on the changes over time in the distribution of iodide excretion rates in the population, although as Hollowell and Haddow carefully note that because of hour-to-hour and day-to-day fluctuations in iodide urinary concentrations it is not possible to infer the incidence of long term iodide intake deficiency from the distribution of single spot samples alone. Nevertheless it seems relevant to note that the proportion of low urinary iodide levels in reproductive age and pregnant women has risen appreciably between the 1971-74 and 1988-94 surveys. Out of 208 pregnant women studied in 1971-74, 1% had urinary iodide less than 50 µg/l, whereas 6.9% of 348 pregnant women in 1988-94 had a level as low as this. The corresponding percentages of non-pregnant reproductive age women with iodide levels this low were 4.0% and 15.3% in 1971-74 and 1988-94, respectively. While we cannot directly infer the incidence of chronic iodide deficiency from these data, it is not unreasonable to suspect that the incidence is far from negligible from a public health perspective.

Although gestation is known to be a sensitive period for iodide deficiency and therefore

perchlorate inhibition of iodide uptake to the thyroid, there are special reasons to believe that the neonatal period is also a time of special vulnerability. Ginsberg et al. (2007) note:

> "The importance of maternal T_4 has been demonstrated in babies with congenital hypothyroidism who appear normal at birth because of ample maternal hormone during gestation (Vulsma et al. 1989). In contrast to the fetus, the newborn can no longer rely upon maternal hormone as a buffer against inborn biosynthetic deficiencies or external stressors. The only means for hormone transfer from the mother is breast milk; however, breast milk contains very little thyroid hormone (van Wassenaer et al. 2002). Therefore, the neonate must synthesize its own supply of T_4 to maintain normal growth and development. As described below, there are a number of factors that make neonatal thyroid status more vulnerable to perturbation than in adults or the fetus.
>
> First, the serum half life of T_4 is approximately 7-10 days in adults (Chopra and Sabatino 2000), but is approximately 3 days in neonates (Lewander et al. 1989; van den Hove et al. 1999). Thus, the rate of replacement of T_4 (i.e., T_4 secretion from the thyroid gland) must be considerably higher in early life to maintain steady-state levels.
>
> Second, the adult thyroid gland stores a large quantity of thyroid hormone in the form of thyroglobulin; this quantity is estimated to be enough to maintain normal levels of circulating hormone for several months (Greer et al. 2002). In contrast, the neonatal gland stores very little T_4; the amount stored has been estimated at less than that required for a single day (Savin et al. 2003; van den Hove et al. 1999). These differences in thyroid hormone status between adults and neonates indicate that the functional reserve available to adults is virtually absent in neonates. Any reduction in thyroid hormone synthesis in the neonate will result in a reduction in circulating levels, whereas this is clearly not true for the adult. The combined storage deficiency and rapid hormone turnover in neonates necessitates a high rate of T_4 synthesis to keep up with the daily demand for thyroid hormone. This, in turn, is dependent upon an adequate supply of iodide. Given these demands on the neonatal thyroid, it is likely that perchlorate-induced inhibition of iodide uptake has a greater impact in neonates than in utero or at other life stages."

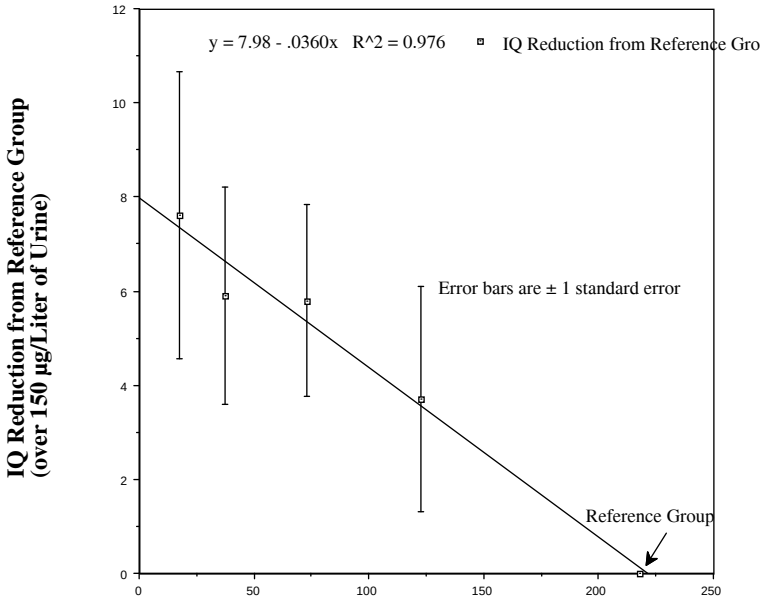
Because of the likely vulnerability of the neonate to even transient fluctuations in iodide and perchlorate intakes, there is reason to question EPA's identification of the late gestational period as the basis for its calculations of the DWEL needed to assure that the most sensitive life stage is below the RfD. This uncertainty should be pointed out to the audience of public health and water system managers. At the same time it should be pointed out that in the light of the data in Table 5.4, choice of the bottle-fed neonate as the sensitive subgroup would apparently require at least a 5-fold reduction in the DWEL of 15 µg/L, as the 15 µg/L apparently delivers about 3.5 µg/kg-day—about 5 times larger than the adopted RfD of 0.7 µg/kg-day.

There is at present no quantitative analysis of the relative sensitivity of gestational vs early post-natal life stages to developmental impairment from hypothyroidism that is contributed to by iodide deficiency. However there are observational studies that suggest an association between relatively low urinary iodide excretion and diminished IQ levels. Figure 1 shows the results of an analysis I have done based on observations in 9-year old school children in Spain (Santiago et al. 2004). 9-year old children are of course well past the period of rapid brain development in

gestation and infancy; and it is probable that the association seen here reflects iodide levels they experienced at an earlier age.

Figure 1

Inferences of the Population Change in Median IQ In Relation to Spot Urinary Iodide Measurements



Data Source: Santiago-Fernandez et al. 2004. Mean urinary iodide concentrations and median IQ in each group were reconstructed from percentile data provided in Santiago-Fernandez et al (2004).

1.2 Opportunities for Better Analysis

1.2.1 Reconsideration of the Main Early Effect Parameter Used to Predict Risks (the Percentage Inhibition of Radioiodide Uptake)

The main measure of perchlorate impact used by EPA (and the NRC analysis before it) is the percentage reduction in radioiodide uptake originally used in the Greer et al. (2002) clinical study. For purposes of initial modeling of dose response observations by Greer et al. (2002) this is a reasonable choice. However it is not the ideal choice for projection of risks in the light of variations among people in iodide intakes. As can be inferred from the quote on the previous page, what is important for the neonate in particular is that there is an adequate absolute rate of production of T4, which depends on the absolute rate of iodide transport, not solely on the percentage of available iodide that is transported.

From basic Michaelis Menten enzyme kinetics, the effect of the competitive inhibitor perchlorate on the fraction of iodide transported into the thyroid is expected to be given by equation 1:

$$\text{Fraction transported} = \frac{V_{max}}{K_m\{1+[\text{Perchlorate}]/K_i\} + [I^-]} \qquad (1)$$

Where

$[I^-]$ is the iodide concentration in or around the cell layer immediately outside of the thyroid,

Vmax is the maximum rate of transport at very high iodide concentration,

Km is the iodide concentration at which the transport rate proceeds at half of its maximum velocity,

Ki is a the concentration of perchlorate at which the effective Km is doubled.

It can be seen from this equation that as iodide concentrations approach low levels, the fraction or percentage of available iodide rises to approach a constant value. Thus, if anything, iodide deficient people should tend to have higher, not lower, baseline values of "fraction transported". However, the expression for the absolute amount of iodide transported must include a factor for the iodide concentrations in the numerator as well as the denominator:

$$\text{Absolute iodide transported} = \frac{V_{max}[I^-]}{K_m\{1+[\text{Perchlorate}]/K_i\} + [I^-]} \quad (2)$$

This type of formulation would allow a more natural interpretation of the results of Blount et al. (2007) and integration with data on the relationships between iodide levels, altered thyroid hormone levels, and effects on IQ and other neurodevelopmental parameters. Abstracts of some promising articles from a recent literature search on relationships between IQ, iodide excretion, and iodide supplementation are reproduced below:
Effect of different iodine intake on schoolchildren's thyroid diseases and intelligence in rural areas.

Gao TS, Teng WP, Shan ZY, Jin Y, Guan HX, Teng XC, Yang F, Wang WB, Shi XG, Tong YJ, Li D, Chen W.

Chin Med J (Engl). 2004 Oct;117(10):1518-22.

Department of Endocrinology, First Hospital of China Medical University, Shenyang, China. gaotianshu67@yahoo.com.cn

BACKGROUND: Reports are increasingly appearing on the side effects caused by excessive iodine intake. Our objective was to find out whether iodine excess would impair the thyroid function and intelligence of schoolchildren in rural areas of China. METHODS: A comparative epidemiological study was made on thyroid function and intelligence of the schoolchildren in the areas of low, moderate or excessive intake of iodine. In the area of **low intake of iodine (Panshan**, Liaoning province, median urinary iodine (MUI) was 99 microg/L), of **moderate intake of iodine (Zhangwu,** Liaoning Province, MUI was 338 microg/L) and of **excessive intake of iodine (Huanghua**, Hebei Province, MUI was 631 microg/L). The numbers of schoolchildren from each area selected to take part in a Chinese version of Raven's Test were

190, 236 and 313, respectively, and then 116, 110 and 112 of them were tested for thyroid function, thyroid autoantibody (TAA) and urinary iodine (UI). RESULTS: There were no significant differences in the incidences of overt hyperthyroidism, subclinical hyperthyroidism and overt hypothyroidism in Panshan, Zhangwu and Huanghua. But significant differences were found in the incidences of subclinical hypothyroidism (P = 0.001) in these three areas. The incidences of subclinical hypothyroidism in Huanghua and Zhangwu were 4.76 and 3.37 times higher than that in Panshan. TAA were negative in all the schoolchildren with subclinical hypothyroidism except for one. No significant difference was found among the rates of thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb) in these three areas. Mean serum thyroglobulin (TG) value of Huanghua was markedly higher than those of the other two (P = 0.02). Mean serum TG value of Zhangwu was higher than that of Panshan but the difference was not significant. Mean IQ value of the schoolchildren in Huanghua was markedly higher than that for Zhangwu (P = 0.001). **Mean IQ value of the schoolchildren in Panshan was lower than that of Huanghua** and higher than that of Zhangwu but, **again, the differences were not significant**. CONCLUSIONS: The increase of iodine intake may increase the risk for schoolchildren of subclinical hypothyroidism. In the area of iodine excess, most of the subclinical hypothyroidism cases are not of autoimmune origin. No obvious effect of excess iodine was found on mental development of schoolchildren.

Iodine deficiency and its association with intelligence quotient in schoolchildren from Colima, Mexico.

Pineda-Lucatero A, Avila-Jiménez L, Ramos-Hernández RI, Magos C, Martínez H.

Public Health Nutr. 2008 Jul;11(7):690-8. Epub 2008 Jan 21.

Unidad de Investigación en Epidemiología Clínica, IMSS-Colima, Colima, México.

OBJECTIVE: To determine the prevalence of iodine deficiency, its causes and its association with intelligence quotient (IQ) in Mexican schoolchildren. DESIGN: Cross-sectional analytical study, in which determinations of thyroid gland size, urinary iodine excretion, IQ, iron nutritional status, physical anthropometry, family consumption of goitrogenic foods, type/origin and iodine saturation of salt consumed at home and coliform organisms in drinking water were performed, and the association of each variable with IQ scores was evaluated by multiple regression analyses. SETTING: Municipality of Cuauhtémoc, in Colima, Mexico (altitude: 600-2700 m above sea level). Sea salt is extracted manually nearby and often used for human consumption. Goitre remains present in the region despite over half a century of mandatory salt iodination in the country. SUBJECTS: Three hundred and three children, similar proportions of boys and girls, mean age 9.3 years, randomly selected from 19 public elementary schools. RESULTS: Overall goitre rate was 21.4%; **low urinary iodine excretion was found in 19.5% of the children, high urinary iodine excretion in 32.0%.** IQ scores were transformed into percentile values, with the following categorisation: < or = P5 (low IQ), 48.5%; > P5 to < or = P25 (below average), 24.2%; > P25 to < P75 (average), 18.8%; > or = P75 to < P95 (above average), 3.6%; > or = P95 (high IQ), 4.9%. Ninety-two per cent of the population used iodinated salt, but deficient iodine saturation (<50 ppm) was found in 86.8% of salt samples. The main goitrogenic foods consumed were peanuts (by 31.5% of the sample), cabbage (30.1%), broccoli (27.7%) and cauliflower (25.7%). Median counts of coliform organisms (colony-

forming units/100 ml of drinking water) were: 207.5 (well water), 151 (cisterns), 52 (private homes), 25 (elementary schools) and 12 (kindergartens). **Moderate iodine deficiency was associated (P < 0.05) with a 4.26 times higher risk of low IQ.** CONCLUSIONS: There is a perturbing negative impact of these findings on human capital acquisition for the region and the country. More attention is needed to ensure effective salt iodination processes, particularly in regions where goitrogens may contribute to the negative effects of iodine deficiency on the intellectual development of children.

Investigation of intelligence quotient and psychomotor development in schoolchildren in areas with different degrees of iodine deficiency.

Tang Z, Liu W, Yin H, Wang P, Dong J, Wang Y, Chen J.

Asia Pac J Clin Nutr. 2007;16(4):731-7.

School of Public Health, China Medical University, 92 North 2nd Road, Shenyang 110001, P R China.

This investigation aims to observe the intelligence and psychomotor development of the schoolchildren in iodine deficiency (ID) areas after the adoption of Universal Salt Iodization (USI), and evaluate the effect of the adoption of USI on their intelligence and psychomotor development. 564 schoolchildren (306 males and 258 females, age range from 8 to 13 yrs) from areas with severe, moderate, and mild ID were investigated. Intelligence quotient (IQ) was measured by Combined Raven's test, second edition. Psychomotor development was examined by Jinyi Psychomotor Test Battery (JPB). We found that **the IQ scores of all subjects in the severe and moderate ID areas were 102 +/- 15.6 and 99.5 +/-16.6 respectively, lower than those in the mild ID areas (108 +/- 12.4, p < 0.01).** The IQ scores correlated negatively with age (partial r = -0.17; beta = -1.95; p < 0.0001). The total T scores of JPB of all subjects in the severe and moderate ID areas were 316 +/- 42.3 and 330 +/- 47.7 respectively, lower than those in the mild ID areas (342 +/- 48.1, p < 0.05). The total T scores of JPB correlated negatively with age (partial r = -0.15; beta = -4.94; p = 0.0006). We may conclude that after the adoption of USI in the ID areas investigated, USI has probably made a contribution to the partial recovery of intelligence and psychomotor development injured by ID in schoolchildren, and should be strengthened.

The effects of iodine on intelligence in children: a meta-analysis of studies conducted in China.

Qian M, Wang D, Watkins WE, Gebski V, Yan YQ, Li M, Chen ZP.

Asia Pac J Clin Nutr. 2005;14(1):32-42.

The Institute of Endocrinology, Tianjin Medical University, Tianjin 300070, China. qianming@eyou.com

This study quantifies the effects of iodine on the intellectual development of children using a systematic manual literature search of Chinese publications related to iodine deficiency disorders. The Chinese Medical Reference Database, Medline, and Cochrane library were

searched electronically in Chinese and English. Inclusion criteria included: studies conducted in China, comparing children (<16 ys) living in naturally iodine sufficient (IS) with those in severely iodine deficient (ID) areas, or children in ID areas born before and after the introduction of iodine supplementation. Intelligent Quotient (IQ) was measured using Binet or Raven Scales. The iodine sufficient control groups were comparable socially, economically, and educationally with the study groups. Random effects models were used in the meta-analysis. Effect size was the standard deviation IQ point (SIQP), which is equivalent to 15 IQ. Thirty-seven reported studies, total 12,291 children, were analysed. **The effect size was an increase of 0.83, 0.82, and 0.32 SIQP respectively, for the children living in IS communities compared with those living in ID areas with no iodine supplementation, with inadequate iodine supplementation, or children who had received iodine during their mothers' pregnancy and after birth. These equal to 12.45, 12.3, 4.8 IQ points.** Compared with that of children whose mothers were persistently exposed to ID, the total effect size of the 21 entries was an increase of 0.58 SIQP (8.7 IQ points) in the group receiving iodine supplementation during pregnancy. Furthermore, there was an increase on 1.15 SIQP of Binet or 0.8 SIQP on Raven Scale (17.25 or 12 IQ points) for children born more than 3.5 years after iodine supplementation program was introduced. **The level of iodine nutrition plays a crucial role in the intellectual development of children. The intelligence damage of children exposed to severe ID was profound, demonstrated by 12.45 IQ points loss and they recovered 8.7 IQ points with iodine supplementation or IS before and during pregnancy.** Iodine supplementation before and during pregnancy to women living in severe ID areas could prevent their children from intelligence deficit. This effect becomes evident in children born 3.5 years after the iodine supplementation program was introduced.

1.2.2 Improved Distributional Analysis of Variability in Exposure and Factors Affecting Susceptibility (Especially Iodide Intake)

As is traditional, EPA's analysis of exposure and potential risks by combining selected points from several different distributions to arrive at a result it deems to provide, overall an acceptable risk management position. The fact of the matter is that few if any people are capable of understanding the combined effects of multiple choices from uncertain and variable distributions of different parameters. A far better approach is to choose some meaningful outcome parameter, ideally (a) the population distribution of IQ change or at least (b) the number of people in different susceptibility groups that perchlorate doses and (c) changes in absolute iodide uptake levels, and show the effects of different perchlorate water levels on those outcome parameters. This would effectively communicate to decision-makers the distributional consequences of different policy choices for the people whose health and economic welfare they are charged with protecting. Toward this end, the dietary analysis in the support document for the present work does a very good job at showing the percentile distributions of expected perchlorate intakes. Ginsberg et al. (2007) show how Monte Carlo simulations can be used to combine variability distributions for breast milk/urinary perchlorate concentrations, baseline urinary perchlorate levels, and milk consumption rates to estimate distributions of perchlorate consumption rates for infant with and without water-borne exposures to their mothers. This type of analysis could readily be revised in the light of more recently assembled data from the support documents, and extended to include variability in iodide status for both mothers and (for bottle-fed infants) perchlorate in formula and water used to prepare the formula. This would provide public health and water system decision-makers a much more complete representation of the expected changes in population distributions of exposures and potential neurodevelopmental consequences for

choices they might make to alter perchlorate exposure levels from water.

2. Does the Health Advisory describe the perchlorate health effects information that a public health official would need to assess and evaluate options for addressing local perchlorate contamination of drinking water?

No. The current draft of the Health Advisory does not give the local manager as much information and relevant insights as he/she needs. There needs to be a much more frank communication of the likelihood that perchlorate is exacerbating current adverse effects on neurological development from sub-optimal iodide intake and related common subclinical hypothyroidism in the general population of women bearing children. Better insights are also needed on the reasons why young infants are likely to have enhanced susceptibility to essentially permanent neurodevelopmental impairment from inadequate iodide intake and the reason this is expected to be incrementally enhanced at nearly all levels of perchlorate water exposure now being considered.

One of the most objectionable parts of the current document is the two-sentence discussion of recent evidence that current levels of perchlorate exposure are associated with measurable differences in thyroid hormone levels in a significant portion of the general U.S. population:

> "Results from studies of the effects of perchlorate exposure on hormone levels have been mixed. One recent study did not identify any effects of perchlorate on blood serum hormones (Amitai et al, 2007), while another study (Blount et al., 2006b) did identify such effects."

The strong implication of this is that the results of the Amitai study contradict the Blount et al. results. Amitai et al. are at pains to dispel this very point in their own discussion of their findings in comparison with those of Blount. The major conclusion of the Amitai paper from their abstract is:

> "This study finds no change in neonatal T_4 levels despite maternal consumption of drinking water that contains perchlorate at levels in excess of the EPA drinking water equivalent level (24.5 μg/L) based on the National Research Council reference dose (0.7 μg/kg/day). Therefore the perchlorate reference dose is likely to be protective of thyroid function *in neonates of mothers with adequate iodide intake.* (emphasis added)

The paper's discussion section includes the following:

> "Iodine intake is important for protecting the thyroid from iodide uptake inhibitors such as perchlorate. Blount et al. (21) recently found that perchlorate exposure is associated with decreased thyroid function *in U.S. women with low urinary iodine.* Higher serum iodide levels in the high perchlorate exposure area may modulate any perchlorate-induced inhibition of iodide uptake. A previous study of pregnant women in the coastal areas of Israel indicates iodine sufficiency (urinary iodine median = 143 ug/L, mean = 130 ug/L) (22) based on W.H.O. criteria. Another important difference between the current work and the Blount et al. study is the study population: we examined thyroid function in neonates, while Blount et al. studied adults and adolescents (21). *Based on differences in iodine intake and life stage for the two studies, our findings do not*

contradict those of Blount et al. (21).

Therefore the implication that the two studies conflict is misleading. The Blount study is based on much larger numbers of people from the general population and was able to separately analyze associations of urinary perchlorate and thyroid hormone variables in subgroups with different iodide excretion rates.

The extensive analysis in the Blount et al paper of thyroid hormone changes in relation to iodide excretion is discussed much more extensively in the next section (4.1.3) on "Biomonitoring Studies". (Why this category is distinguished from section 4.1.2 titled "Epidemiology Data" escapes me. The two sections should be merged.)

Section 4.1.3 raises the issue of whether the association between thyroid hormone levels and perchlorate seen by Blount et al. reflects a causal association, or instead is

> "mediated by some other correlate of both, although the relationship between urine perchlorate and total TSH and T4 levels persisted after statistical adjustments for some additional covariates known to predict thyroid hormone levels (e.g. total kilocalorie intake, estrogen use, and serum C-reactive protein levels).

The issue of whether perchlorate might be a surrogate for some other causal exposure is further discussed in the next paragraph,

> There are other chemicals, including nitrate and thiocyanate, which can affect the thyroid function. Steinmaus *et al.* (2007) further analyzed the data from NHANES 2001–2002 to assess the impact of smoking, cotinine and thiocyanate on the relationship between urinary perchlorate and blood serum T4 and TSH. Thiocyanate is a metabolite of cyanide found in tobacco smoke and is naturally occurring in some foods, including cabbage, broccoli, and cassava. Increased serum thiocyanate levels are associated with increasing levels of smoking. Thiocyanate affects the thyroid by the same mechanism as perchlorate (competitive inhibition of iodide uptake). Steinmaus et al. analyzed the data to determine whether smoking status (smoker or nonsmoker), serum thiocyanate, or serum cotinine were better predictors of T4 and TSH changes than perchlorate, or if the effects reflected the combined effects of perchlorate and thiocyanate.

The result of the Steinmaus et al. (2007) analysis is accurately reported as:

> The authors found no association between perchlorate or T4 and smoking, cotinine or thiocyanate in men or in women with urinary iodine levels greater than 100 µg/l. In addition, they found no association between cotinine and T4 or TSH in women with iodine levels lower than 100 µg/l. However, in women with urinary iodine levels lower than 100 µg/l, an association between urinary perchlorate and decreased serum T4 was stronger in smokers than in non-smokers, and stronger in those with high urinary thiocyanate levels than in those with low urinary thiocyanate levels. Although noting that their findings need to be confirmed with further research, the authors concluded that for these low-iodine women, the results suggest that at commonly-occurring perchlorate exposure levels, thiocyanate in tobacco smoke and perchlorate interact in affecting thyroid function, and agents other than tobacco smoke might cause similar interactions (Steimaus et al. 2007).

So to the extent that the issue has been examined, there is absolutely no evidence that the Blount et al. finding of an association between thyroid hormone levels and low dose perchlorate exposure in women with low iodide levels is mediated by any of the other potentially confounding exposures that have been studied to date. The HA document should explicitly point this out.

The Amitai et al. study is again referred to at the end of section 4.1.3, quoting the T4 results of the three studied groups and the high perchlorate levels without mentioning either the much smaller size of the population examined, or the fact of larger iodide intakes. The impression is therefore again conveyed that those results contradict those of the Blount and Steinmaus papers. This should be corrected.

3. Is the explanation of the derivation of the Relative Source Contribution clear and easy to understand?

In most respects, yes. But there are two problems:

First, Table 5.1 does not include critical age groups for which dietary contributions exceed the RfD—bottle-fed and breast fed infants younger than 6 months.

Second, Table 5.1ists a narrow confidence range (derived from treading LODs as zero or LOD) of the mean intakes from different age groups. The ultimate derivation of the recommended DWEL is based on a 90^{th} percentile estimate—but why limit it to that rather than do a full distributional analysis? The arbitrariness of the choice of the 90^{th} percentile for this purpose needs to be made clear, as well as the consequences of other reasonable options (that is, higher percentiles).

4. Have we identified the sensitive populations appropriately?

Almost—the age groups are correct, but the dimension of iodide intake needs to be added and fully explored.

5. Is the role of modeling in evaluating the sensitive populations clearly described?

Somewhat, but the complexity, limitations and uncertainties in the model are not as fully described as is needed. Absent this, I believe the audience is likely to have more confidence in the results of this modeling than is reasonably justified.

The version of the adult model presented by Merrill et al. (2005) has a total of 86 parameters. Of these, 26 are general physiological parameters expressed as single point estimates without any variability except for the % of body weight represented by fat, which differs between men and women. Beyond these there are a total of 60 chemical-specific parameters (31 for iodide and 29 for perchlorate), of which 30 were fit to data from limited available human studies. Of these fitted parameters only two are given with any confidence limits expressing either variability or uncertainty.

With such a complex model with many adjustable parameters fitted to a modest number of human studies.(primarily, in the case of the perchlorate parameters, the radioiodide uptake inhibition data in the limited study of Greer et al.) there is nearly always an opportunity to fit the data in multiple ways. In other words, changes to the values of some parameters can nearly always be changed in one direction if other parameters are adjusted in parallel offset the effects of the first parameter and to maintain the fit to available data. In this process, the behavior of the model outside the realm of the fitted parameters can change appreciably. The presence of 30 parameters would usually make the model very flexible unless the acceptable values of many of the parameters are severely constrained with other information. In my view it is important to communicate to the reader.

The models for pregnant women and their fetuses, lactating women and their babies, and bottle-fed infants as published by Clewell et al. (2007) are similarly complex, but in this case an extra measure of uncertainty is added because of the need to project the parameter values in various ways. In the gestational model, of the 24 perchlorate parameters 13 are projected using a "parallelogram" modeling approach, 7 are simply adopted from rat data.

The modelers themselves are acutely aware of some important limitations of their analysis. They emphasize that

> "There are uncertainties associated with this modeling, as there are for any modeling effort. For example, this analysis does not take into account within-group variability in PK, uncertainty in model parameters and predictions, or population differences in PD. Also, the NRC identified fetuses of pregnant women that are hypothyroid or iodine deficient as the most sensitive subpopulation. Unfortunately, the models were not designed to account for whether the pregnant woman is hypothyroid or iodine deficient. Model predictions of doses in the various subgroups apply to a subgroup average for typical, healthy individuals, and effectively describe the RAIU inhibition relative to that same individual as his/her own control. Some members of a group would be expected to have RAIU inhibition greater than indicated in Table 4 for a particular perchlorate concentration, while others would have lesser inhibition. This would be expected for fetuses as well as for other subgroups. Likewise, the model does not allow for predictions of how RAIU inhibition, or the impact of that inhibition, might change with dietary iodide status (i.e., in an iodide deficient individual, or one with more than sufficient dietary iodide)."

Some, but not all of these caveats are included at the beginning of section 5.2.3 of the document, only to be weakened by the statements that the HA was based on the exposures of late gestation pregnant women and their fetuses. I think the reader should receive the PBPK modelers' qualifications in full where the PBPK modeling results are used—in discussing EPA's evident comfort with the results for breast and bottle-fed infants in Table 5.4. The caveat discussion should also emphasize that there is at present no quantitative estimate of the relative sensitivity of fetuses vs newborn infants to iodide uptake inhibition, particularly at various levels of iodide intake.

6. Do you have any suggestions on how we could improve this draft document?

Yes. In addition to those outlined above, I would suggest the following modifications to specific

parts of the document"

Introduction, 1st paragraph, lines 4-5—I realize that the phrase "concentrations of drinking water contaminants at which adverse health effects are not anticipated to occur" is relatively standard boiler-plate terminology that is closely related to similar descriptions of the intended health protection objectives in choosing RfDs and related recommended values. However in the present context such a vague description, with its implication of a well defined population threshold at which it is expected that no one will be adversely affected, the meaning of this should be more extensively and clearly described. Is it expected that the incidence of x early effect (less than x% inhibition of iodide uptake by the thyroid) will be less than y% in the population of young infants likely to be especially susceptible? That more specific description would be fairer to the reader, even in the absence of other changes to the later analysis that I have suggested in response to other charge questions.

Introduction, 2nd paragraph—This paragraph makes the important claim that the recommended Health Advisory level of 15 µg/L "is based on the recommendations of the National Research Council" and EPA's adopted "Reference Dose (RfD) of 0.7 µg/kg-day." It is important to emphasize here in the introduction that this is true only for a relatively less-exposed subgroup (fetuses of pregnant women), not for other population subgroups (breast and bottle-fed newborns) that may have significantly more sensitivity than the normal adults studied by Greer et al. (2002).

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APPENDIX C

COMMENTS FROM BONNIE STERN

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1. Does the document convey the necessary scientific information in a manner that that can be understood by both the officials from public health organizations and public water systems? (We have assumed that the depth of understanding will differ for the two intended audiences but hope that the message about perchlorate will be clear for both.)

The sections on relative source contribution (RSC) are comprehensively and thoroughly described in a manner that is well-written and supported by actual data (and much more detailed than most RSC discussions). However, I do not find the sections on Occurrence and Exposure and on Health Effects, sufficiently detailed, organized or comprehensive in presentation of the "necessary scientific information in a manner that that can be understood by both the officials from public health organizations and public water systems".

General Comments:

The health advisory needs a concise solid summary of the pharmacokinetics of perchlorate (including its relationship to iodide uptake at the thyroid and its mode of toxic action) and of the physiology of the thyroid system. This context is essential to assist the reader in understanding the biological importance and implications of low levels of iodide uptake inhibition on thyroid hormone synthesis, thyroid system homeostasis, and thyroid hormone requirements for normal metabolism and for fetal, neonatal and child development.

It is not transparent throughout the document that the population at risk is iodine-deficient women during pregnancy and lactation and the fetuses and neonates of iodine-deficient women. Insufficient information is presented on the well-conducted epidemiological studies of pregnant and lactating women, their neonates, and children living in areas with elevated levels of naturally-occurring perchlorate in their drinking water (or food or both), in which iodine intake is sufficient and no adverse effects are observed. In the absence of discussion about iodine deficiency, the potential public health concern of perchlorate in drinking water cannot be well understood and appropriate public health protective actions may not be considered or taken.

Of particular importance are the following:

(1) Perchlorate at pharmacological doses interferes with the uptake of iodine as iodide via

inhibition at the sodium-iodide transporter, which is a mechanism that is well documented and well understood. Among biomedical professionals, including toxicologists, it is generally agreed that the only known and likely effect on health of perchlorate is thyrotoxicity (NAS 2005)

(2) No mention is made throughout the document of thyroid system homoestasis – the ability of the system to self-regulate via a feedback loop that involves numerous homeostatic mechanisms specifically design to ensure, within limits, a constant synthesis and availability of thyroid hormone by upregulating production and tissue availability when systemic hormone is low and downregulating these processes when systemic hormone is elevated beyond need. There are numerous mechanisms involved in this homeostatic system, which include increasing the amount of iodine absorbed from the diet, decreasing iodide excretion under conditions of low iodine intake, and increasing the number of iodide transporter proteins at the interface of the blood circulation and thyroid which in turn, increases the efficiency of transferring iodide into the thyroid when there are other substances that compete with iodide uptake at the level of the transporter protein. This is the reason that iodine-deficient women, particularly those with additional iodine requirements due to pregnancy and lactation, are the most sensitive subpopulation. The fetus of the iodine-deficient woman, who depends on maternal supply of thyroid hormone and iodide, is most adversely affected by iodine deficiency because of the essentiality of sufficient thyroid hormone during critical stages of development, differentiation and growth. Similarly, the neonate of the iodine-deficient woman continues to be at high risk at and following parturition – whether nurtured (as in nutrition) via breast milk or infant formula – because she/he continues to be deprived of essential nutrient and hormones during the next critical developmental stage – early infancy.

(3) The thyroid homeostatic system is already under considerable stress from iodine deficiency. Perchlorate is an <u>added</u> environmental stressor that may contribute to perturbing the thyroid regulatory system of already severely stressed individuals and subpopulations. Other anions commonly occurring in the environment, such as thiocyanate, nitrate and bromate, have similar effects in that they inhibit the uptake of iodide from the blood stream into the thyroid gland by the same mechanism. The evolutionary elegance (or in more pragmatic terms, utility) of thyroid homeostasis (and homeostatic systems for other essential elements and hormones) is that it maintains sufficiency under the day-to-day variability in element intake and is capable of rapidly activating internal mechanisms that protect against increases and especially decreases in thyroid hormone production in response to biological need (NAS 2005).

(4) As a result of research on endemic goiter and iodine deficiency in the U.S. by Marine and colleagues, iodinization of table salt was first recommended and implemented in 1920's and 1930's. By 1955, iodine deficiency disorders appeared to have been eliminated via household use of table salt (Salt Institute, 2008). Current trends, however, as monitored by NHANES studies, demonstrate that the percentage of U.S. individuals with iodine deficiency (defined by WHO as < 100 ug/L in urine) increased from 1971-1974 to 1988-1994, and appears to have stabilized at 1988-1994 levels when re-evaluated

in NHANES 2001-2002 (Hollowell et al., 1998; Caldwell et al. 2005). All median urinary iodide (UI) concentrations were above the cutoff value noted above, 320 ug/L in 1971-1974 (NHANES I), increased to 145 ug/L in 1988-1994 (NHANES III) and was 168 ug/L in NHANES 2001-2002.

However, these concentrations are single population-based values and do not give any indication of the distribution of values, specifically the percentage of the population that are either significantly above or significantly below the median values. Hollowell et al. (1998) reported that the proportion of the total population with UI concentrations below 50 ug/L (defined by WHO as having "at least" moderate iodine deficiency) was 2.6% (1.6% in males and 3.5% in females) in 1971-1974. These values increased to 11.7% in 1988-1994 (8.1% of males and 15.1% in females). In NHANES 2001-2002, the UI median concentration was 167.8 for the total population, with 11% reporting UI concentrations below 50 ug/L (6.7% in males and 15.3% in females) (Caldwell et al. 2005). Thus, the distribution of UI concentrations in the U.S. population appears to have stabilized; however, a significant percentage of that population, particularly females, is below 50 ug/L. Even a higher percentage is below 100 ug/L (median = 28.4% for total population; males = 19.7%; females = 36.6%) (Caldwell et al. 2005).

(5) The reasons for the prevalence of individuals with iodine deficiency is not clear. In 1955, researchers reported that approximately 75% of U.S. households used iodized salt (Salt Institute 2008) and the population intake of iodine was considered to be adequate. However, in 1999, Lee et al. reported a sharp decline in iodine intake, especially among women of childbearing age.

Although 70% of salt sold for household use is currently fortified with iodine, it is estimated that household table salt accounts for only about 15% of daily salt intake and the salt used in manufacturing of many processed foods may not be iodized (Pearce 2006). A decrease in iodine consumption has been associated with medical recommendations for reducing salt intake for control of blood pressure and other cardiovascular disorders and with increasing use of noniodized salt in manufactured or prepared foods (Lee et al. 1999). Although infant formula iodine fortification is not mandated in the U.S., many of the commonly-used brands contain added iodine (Pearce 2008) although the iodine content, as well as concordance between label notification amounts and actual measured amounts, varies widely (Leung and Pearce, 2008). It should be noted that Canada requires fortification of table salt, table salt substitutes, and infant formula with iodine and also mandates the range of iodine concentrations that must be present in these foods (Leung and Pearce 2008). Utinger (1999), in an editorial in the New England Journal of Medicine, notes that the WHO and the International Council for the Control of Iodine Deficiency Disorders consider the U.S. as a marginally iodine-sufficient nation whereas Canada is classified as optimally iodine-sufficient. It appears that one of the major reasons that the U.S. is reluctant to mandate fortification of table salt is that the mandate would be viewed as contradictory to, or inconsistent with, medical recommendations for reduction in salt consumption (CDC, personal communication). However, as noted for Canada, table salt substitutes are also amenable to iodine supplementation.

Iodine deficiency disorders have a broad spectrum of effects. There is no question that severe iodine deficiency in mothers and fetuses result in pregnancy loss, cretinisim, irreversible mental retardation, neurologic dysfunction and growth retardation. Mild iodine deficiency results in learning disability, poor growth and diffuse goiter in school-age children (Utinger 1999). The mode of action, a reduction in thyroid hormone production because of chronic insufficient iodine intake, is well-accepted. Recent epidemiologic studies showing no effects of elevated perchlorate exposures on thyroxine (T4) – the primary thyroid hormone synthesized via iodide-incorporation pathways in the thyroid gland – in iodine-sufficient adults, in iodine-sufficient pregnant women and their neonates during and following pregnancy, and in iodine-sufficient elementary-school children (e.g., Amitai et al. 2007, Crump et al. 2004, Braverman 2007, Tellez et al. 2006), in conjunction with mechanistic data, strongly suggest that the public health problem is iodine deficiency in pregnant women, neonates and young children, not perchlorate exposure except possibly at very high sustained perchlorate intakes (i.e., in the 100s ug/L in drinking water).

Conceptually, sustained perchlorate intake at low levels may be viewed as having a potentially adverse effect on thyroid function only in borderline moderate iodine-deficient individuals. In severely-iodine deficient persons, the added effect of iodide-uptake inhibition into the thyroid will not be sufficient to increase the already serious and irreversible consequences to the fetus and neonate of a pre-existing biologically significant reduction in thyroid hormone production. In iodine-sufficient individuals no effects have been demonstrated to occur in a range of studies and none are expected. In moderately-sufficient individuals, perchlorate-induced effects are not anticipated to occur as available iodine is likely to be optimally and efficiently utilized, regulated by the myriad of homeostatic mechanisms that conserve iodine availability and direct as much as necessary to adequate thyroid hormone production and to the fetus even at the expense of the mother during pregnancy (the “thrifty phenotype” or “triage” paradigms) (Ames 2006, McArdle et al. 2006). However, in those persons who are borderline marginally iodine-sufficient, the homeostatic regulatory mechanisms may be operating at maximum capacity. Therefore, any added iodide-uptake inhibitory stressor such as perchlorate intake, may be the stimulus that overwhelms compensatory mechanisms, resulting in an exceedence of homeostatic capacity and induction of actual decreases in thyroid hormone synthesis.

(6) This reviewer duly notes that iodine deficiency in the U.S. is a public health mandate that is totally outside the mission and broad scope of regulatory activities required, conducted and implemented by the U.S. EPA to protect public health and the environment. However, perchlorate as a chemical of concern in drinking water and other environmental media is assessed and regulated by U.S. EPA. It is important for public health officials, regulators and others to understand the relationship between perchlorate and iodine deficiency. Further, the intensity and magnitude of current public health concerns about low levels of environmental exposures to perchlorate, including from members of Congress, the media, environmental groups, regulatory agencies not familiar

with the biology, toxicology and pharmacology of perchlorate, and the general public (I have read numerous newspaper articles, press releases by government and non-government organizations and on-line blog comments by individuals-at-large) indicate that risk communication is an enormous problem. The amount of misinformation, misleading conclusions and overstatements has led to public perceptions that greatly overestimate the potential dangers of perchlorate to susceptible human populations, except possibly under localized conditions where perchlorate is sustained in drinking water in the order of hundreds or thousands of parts per billion. The elephant in the room is iodine deficiency.

(7) This discussion is perceived by this reviewer to be within the context of charge question #1. Without a clear and concise summary of the potential adverse effects of perchlorate in terms of pharmacokinetics, biology and mode of toxic action that can lead to adverse thyroid effects, presented at the beginning of the Health Advisory, it is difficult to follow and interpret the substance of the document. For example, in the biomonitoring data in the occurrence and exposure section, reference is made to perchlorate short-half life, rapid excretion, urinary clearance as the primary form of elimination, none of which is previously described. The health effects section is also not transparent, in terms of the range of research and the concordance (or discordance of findings). Many studies are not even cited. I suggest that several paragraphs be devoted to brief summaries of all important human studies. Again as noted above, there is insufficient emphasis of iodine deficiency as circumscribing the sensitive population, with the fetuses and neonates of this population as being the most susceptible and having the most adverse and deleterious health consequences.

I recognize that a major objective of this document is to be concise and relatively short, and to describe both the health and exposure data succinctly, with as few obtusely technical terms as possible, in order to be read and generally understood. However, a description of the biology and physiological context is needed. What also is important to note early in the document is the following:

(A) The oral reference dose (RfD) is not being derived *de novo*;
(B) The oral RfD has already been derived by the National Academy of Sciences, an independent, internationally-recognized and respected organization, and has already been subjected to comments, review and a high level of scrutiny by all major stakeholders;
(C) The RfD is conservative, being based on an effect that is a precursor to an adverse effect (not too much detail – a reference to the appropriate section for further detail would suffice); and
(D) There are two primary objectives to this health advisory: (a) to provide guidance to regional and local public health officials and to regulatory agencies for a level of perchlorate in drinking water that is likely, with a high degree of confidence, to be without adverse health consequences to all exposed populations, including the most susceptible; and (b) to determine a scientifically defensible relative source contribution of drinking water to total exposure from all possible sources, based on a rich data base of exposure information.

This information would explain why relatively little data are presented regarding health effects (relative to exposure and RSC derivation). However, as noted above, what is still needed at the beginning of the document is a brief overview of the toxicokinetics of perchlorate, iodine as an essential element for the synthesis of thyroid hormones, why thyroid hormone sufficiency is important, what homeostasis is – perchlorate affects a self-regulating system which has evolved numerous feedback mechanisms to compensate for deficiency induced by inadequate intake, iodine uptake inhibition, illness) and that within the homeostatic range, which is robust in humans, this system is successful. [The same would be true for excess.] In other words, the biological impacts of perchlorate are very different from those for chemical compounds which have direct target organ toxicity and/or do not directly affect the availability of an essential element for which homeostasis occurs

(8) I think that the relative source contribution section is exceptionally well presented; the authors go to great lengths to describe how they have derived an RSC of 62% and are to be commended for the level of detail given, the amount of high-quality scientific data incorporated into developing the RSC, the scientifically-informed inferential reasoning and the scientific defensibility of their conclusions. I cannot think of a single other chemical in drinking water for which this extensive and comprehensive effort has been conducted. I have a number of minor, specific comments which are presented in response to Charge Question #6.

2. Does the Health Advisory describe the perchlorate health effects information that a public health official would need to assess and evaluate options for addressing local perchlorate contamination of drinking water?

See also answer to charge question #1.

The subchronic health advisory (HA) provides some information for public health officials to assess and evaluate options if local monitoring of drinking water indicates that concentrations exceed the HA over a period of time (i.e., repeated, not single, sampling measurements) or if a plume with elevated concentrations is known to occur from an identified source. The UCMR data given on page 10 could be more clearly presented. The data overall suggest that perchlorate in drinking water systems is not likely to present a problem. Only 160/3865 (4.1%) systems had at least 1 analytical detection of perchlorate ≥ than the LOD, and only 1.9% (637/34,331) of samples had detects, over five years of monitoring, presumably quarterly or possibly monthly. A distribution of the frequency of multiple detects in the same system(s) would be of interest and importance for public health officials because sustained or repeated perchlorate ingestion is the only way that perchlorate might affect the transport of iodide into the thyroid gland in a toxicologically-meaningful manner (because of homeostasis). The presentation of mean and median concentrations of only detects lacks biological significance with regard to exposure because (1) it does not give means or medians for a given system to which a resident population would be exposed, (2) non-detects, which comprise 98% of the samples are not considered; including the non-detects (whether they

are set at 0 or ½ LOD) for a given system would give means and medians significantly lower than those given only for detects; (3) biologically meaningful exposure would be based on means and distributions for a given drinking water supply system to yield an estimate of sustained population exposure. These data suggest that perchlorate exposure via drinking water is very intermittent.

No information is given on groundwater levels of perchlorate which would be of importance for families that obtain their drinking water from wells. Amitai et al. (2007) have reported very high concentrations of perchlorate in wells used for local drinking in the vicinity of a military plant used for decades in Israel. Amitai et al. (2007) also present data showing that high perchlorate concentrations in drinking water do not necessarily translate into high concentrations at the tap. These kinds of information would be important for public health officials to assess and evaluate options for mitigating exposures if perchlorate concentrations exceeding the HA are found in drinking water supplies.

Greater consideration in the document could be given to plumes, for example, from a military facility in which perchlorate had been used, and their rate and expansion of movement. This would assist the public health official in assessing options, DasGupta et al. (2006) have shown that naturally occurring processes form a significant proportion of environmental perchlorate and that non-anthropogenic background levels of perchlorate exist and may explain, at least in part, the ubiquitous presence of perchlorate in biomonitoring samples.

Although an HA is not an action level, HA exceedences are likely to trigger a public health response, given the widespread publicity attending perchlorate in the environment. It is premature to set an action level, at least in part because additional studies are underway including the large CDC study which is measuring multiple indices of thyroid function (such as free T4 which is more biologically relevant to thyroid tissue availability and T3, which is the bioactive form of thyroid hormone in the tissues and which is mainly produced by conversion from T4) as well as other associated variables.

However, information essential for risk communication and public perception of the potentially adverse health effects of perchlorate concentrations at or above the HA is not well presented in the report, either for the local public health official or for the local population, especially for the high-risk populations. This includes pregnant women and their fetuses and nursing infants, as well as infants who are fed powdered formula reconstituted with tap drinking water. I refer here to the relationship between perchlorate and iodine status. Without a more thorough and comprehensive presentation of this relationship, public health officials are not likely to understand that the key event in potential perchlorate thyrotoxicity is insufficient iodine status. Therefore, the option to take action to increase iodine intake among susceptible populations (and the general population) and to educate the public about the essentiality of sufficient iodine intake for fetal, neonatal and child development (and the perchlorate-iodine association) might well not be considered as a priority.

3. Is the explanation of the derivation of the Relative Source Contribution clear and easy to understand?

A first reading of the first half of the derivation of the RSC section was somewhat confusing. It was not until p. 30 that I understood suddenly how the RSC was being derived. As noted previously, I think that the derivation is very well done. However, it would be much more comprehensive if the first paragraph in Section 5.2 (Relative Source Contribution) included a summary paragraph about the approach and the following:

1. What is a relative source contribution? How is one calculated? For most lifetime HAs, a default of 20% is used in the absence of data in other environmental source media. This default is likely to be emphasized and proposed by public health groups and individuals because it is the most conservative approach. Thus, it is important to note that the use of the default RSC is not appropriate or relevant or scientifically defensible, given the large amount of solid data of available on perchlorate intake from food, by age and gender. This fact should be mentioned at the beginning of this section, up front, because not addressing this issue may be interpreted as withholding information about the process of determining an RSC (i.e. a lack of transparency).

Second, the HA is for subchronic exposure. Typically, OW standard operating procedures apply an RSC only for lifetime exposure. [NOTE: There is a significant error on page 26, in Step 3. The equation reads "**Lifetime** HA = DWEL x RSC". This should be changed to "Subchronic HA".

The text notes that the "subchronic HA is calculated by factoring in other sources of exposure (such as air, food, soil) in addition to drinking water using the relative source contribution (RSC) for the drinking water." Is this a new procedure? As noted in the previous paragraph, RSCs are generally only applied to lifetime (i.e. chronic) exposure scenarios. A quick search of EPA OW's web site did not find any reference to changing the SOP for deriving a subchronic HA by applying a RSC. I am familiar with work on other chemicals in drinking water that target the reproductive and/or development systems and for which a RSC for short-term and subchronic health advisories are being proposed. This approach is scientifically defensible because the exposure duration for a chemical affecting reproduction or development is significantly less than lifetime. However, an explanation is warranted in both Step 3 and in the first paragraph of Section 5.2.

2. What data are used? The sentence on p. 28 reads: "These exposure data include the analysis by EPA of the UCMR data and CDC's biomonitoring data, as well as FDA's TDS." It would be helpful to "set the stage" for what follows by briefly explaining how these data are utilized in a summary paragraph.

The UCMR data and an allocation of 62% of the RSC to drinking water are at odds with each other. The UCMR data suggests that drinking water exposure to perchlorate is very low. Therefore, a lower RSC based on only UCMR data would be scientifically

defensible (Table 3.2). However, the RSC was not calculated by using the UCMR directly. Therefore, to mention it as the first set of data in the above sentence is somewhat misleading. What is utilized is a combination of the NHANES-UCMR data. Section 5.2.2 does not give an adequate description. Some brief discussion of how the UCMR data were used in NHANES is given in Section 3.4, and the RSC section would benefit from restating and perhaps expanding this topic. This is not clearly stated.

Nevertheless, the RSC derivation uses all available data in a scientifically-supportable manner. The basis for the derivation is that only a relatively small RSC occurs from food. Therefore, a large RSC (i.e. larger than default and based on actual data) can occur from drinking water, even if it may not. It is recommended that this approach be summarized in the first paragraph. Given the UCMR data, subchronic exposure to perchlorate in drinking water is unlikely to meet its allowable RSC. This is an important concept. The data in Table 3.2 show only a small increase in estimated daily perchlorate intakes from drinking water, suggesting a very low RSC from drinking water. It is essential to explain that the RSC is based on the RfD/DWEL, not the actual proportions of perchlorate intake estimated with and without exposure through drinking water.

4. Have we identified the sensitive populations appropriately?

No. There is another sensitive subpopulation and that is the neonate (both preterm and full term). Neonates of iodine deficient women who are nursed during the first month or several months of life can be considered to be similar to fetuses in that they receive all their nutrition from their mothers. Breast milk is a filtrate of blood and thus would be anticipated to contain perchlorate if it occurs in maternal blood. Nonetheless, protection of the mother from the adverse effects of elevated levels of perchlorate ingestion, as defined by drinking water concentrations above subchronic HA, will protect the nursing neonate. However, infants who receive formula during this critical postnatal period of development are at risk if they were born to iodine-deficient mothers, especially if the formula is not fortified with iodine. (Iodine fortification of infant formula is voluntary, not mandatory, in the U.S.). Even with fortified infant formula, this population is at risk if fortification is insufficient; it should be noted that there are no mandated standards for iodine content in formula. Further, a proportion of neonates (specific data were not found) are fed powdered infant formula which has been reconstituted with tap water (powdered infant formula being cheaper than the liquid kind). The use of tap water with elevated perchlorate levels may further compromise the iodine status of neonates of iodine-deficient mothers. No data are available which might elucidate this interaction.

The inclusion of this high-risk population is important for risk communication, as well as in response to Charge Question #2.

5. Is the role of modeling in evaluating the sensitive populations clearly described?

I think that the role of modeling in evaluating the sensitive populations is well described. The advantages to this approach are well presented in the first paragraph in Section 4.1.4.
However, I have several points of clarification to make. First, it would be useful to the reader to give examples of other chemicals in which PBPK models were used to predict effects levels and no-effects levels in humans. A sentence or two would suffice. The intent would be to demonstrate that this is not a new approach and that PBPK modeling is increasingly being used for evaluation of chemical effects in humans and to support the use of regulatory toxicology. Given the high public visibility and concern of perchlorate exposure, these examples would support the validity of this approach.

Second, no mention is made in the section that the PBPK modeling involves the use of perchlorate, iodide and/or inhibition data and modeling compartments in rats as well as humans (see Clewell et al. 2007). This indicates a lack of transparency, given that the animal data as reviewed by NAS (2005) minimizes the quantitative importance of animal toxicology data for human dose-response and risk assessment. I completely agree that the animal data cannot be used to extrapolate quantitatively from rodents to humans for purposes of human health risk assessment. However, given that PBPK modeling involves rodent models, it would be useful to explain the species differences in more detail.

Briefly, recommendations for this discussion would include the following: (1) the utility of hazard characterization (i.e. qualitative characterization of the potential for perchlorate-induced injury to humans) in rodents at extremely high doses which are orders of magnitude greater than environmental exposures; (2) the similarity of the pharmacokinetics of perchlorate in rodents and humans (i.e., absorption, distribution, metabolism, elimination, mode of thyrotoxicity, as well as placental and breast milk transfer from the mother to the fetus and neonate, respectively) and thus, the suitability of PBPK modeling using both rodent and human data, as well as the support of predicted findings from modeling by human data from in well-conducted epidemiology studies; and (3) better supporting data to demonstrate that rats are much more sensitive to agents that disturb thyroid function than are humans, at least in part because homeostatic mechanisms in humans and nonhuman primates are more robust and more refined than in rats which are smaller in size, have shorter life spans, and are much less developed evolutionarily. This is also true for chemicals which disturb the pharmacokinetics of other essential elements (e.g., copper, iron, zinc) required for other requisite physiological functions; humans have a higher homeostatic capacity for regulation of both deficiency and excess for these types of biological systems.

6. Do you have any suggestions on how we could improve this draft document?

Many of my suggestions for improvement of the draft document are contained in responses to Charge Questions #1 through #5.

Additional suggestions include the following:

1. Consideration should be given to reordering/reorganizing the sections in the HA document. Although occurrence and exposure typically precedes health effects in the SOP for HA documents, the extensive discussion of biomonitoring data in Section 3.4, necessitates a prior discussion of the toxicokinetics of perchlorate, the pharmacokinetics of iodine and how the two interact. Toxicokinetic terms used in this section have little context to the nontechnical reader. There is a single statement on p. 15 in the second paragraph that mentions urinary excretion as the sole excretion pathways of perchlorate but no reference is given. A very brief paragraph at the beginning of this section on the toxicokinetics of perchlorate and the appropriateness of urinary biomonitoring would be useful. Also, the difference between perchlorate measurement as ug/L and creatinine-corrected averages is not explained. Why is a creatinine correction made? Other limitations of spot urine sampling as an indicator of sustained perchlorate exposure are not well described, nor is how large sample sizes overcome, at least in part on a population basis, these limitations.

p. 12. What do FDA data show regarding iodine intake for the 14 age-gender groups? The mean intake is given but not the tails of the distribution – nor the proportion of the population within group and overall which are below relevant U.S. dietary reference values.

The disconnect between iodine and perchlorate throughout the first part of the document lacks transparency, given that the susceptible populations are iodine-deficient.

Section 4.1.1. More data are needed on iodine and thyroid hormones, on iodine and thyroid hormone homeostasis.

Section 4.1.2. Please qualify the last sentence about Amitai et al. 2007 and Blount et al. 2006b to indicate the differences in the studies and the role of iodine in the findings of each study. Insufficient attention is given to the epidemiology studies, especially the new ones. Amitai et al. (2007) was post NAS (2005) and thus deserves much more extensive discussion; it shows clearly lack of high perchlorate ingestion effects in iodine sufficient women and their neonates. This is a very important study. Blount et al. is given extensive description in Section 4.1.3, but few conclusions are drawn.

Each of the data presentations would benefit from a brief summary and conclusions regarding what the data demonstrate/show.

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APPENDIX D

COMMENTS FROM TRACEY WOODRUFF

Dr. Tracey J. Woodruff is Associate Professor and Director of the Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco and has 15 years experience in environmental health. She received her PhD in Bioengineering from The University of California, Berkeley and San Francisco and holds a Pew Foundation Postdoctoral Fellow in Health Policy from the University of California, San Francisco.

Peer Review of Drinking Water Health Advisory for Perchlorate

In general, this document was well-written and provided a concise and reasonably thorough summary of the information. It was written at the appropriate level for government officials and is also accessible to the knowledgeable public.

However, there are critical gaps in the underlying analyses and review of the science that requires substantial revisions before this document can be made final. This review will focus on two general areas of concern: 1) inadequate consideration of all sensitive subpopulations; and 2) over reliance on an incomplete and un-peer-reviewed EPA PBPK model to justify the HA. In summary, based on the available data on perchlorate, under the currently proposed HA there are expected to be significant portions of sensitive subpopulation that would be exposed to perchlorate at concentrations above the EPA RfD, and thus the draft HA would not be expected to be protective of potential adverse effects for the whole population.

Sensitive subpopulations

The document identifies the primary sensitive subpopulation of concern as fetuses of pregnant women. However, there are two other sensitive and overlapping groups that are not adequately considered in this document - preterm infants and term infants, particularly those term infants who are lower weight than 3.5 kg.

The NRC defined preterm infants along with fetuses as the most sensitive subpopulations (from page 27 of the NRC report “fetuses and preterm newborns constitute the most sensitive populations”). The scientific evidence finds that preterm infants may be more at risk from thyroid perturbations than term infants (Zoeller and Rovet, 2004). However, preterm infants are not discussed in the HA nor are they considered in the analysis to determine the HA. This needs to be modified. There are several approaches that can be used to assess exposures for this sensitive subpopulation which are discussed below.

The other sensitive lifestage that needs to be considered is the neonatal period. Analyses relevant to this lifestage should be more robustly incorporated into the HA. Decrements in thyroid hormone (TH) during early neonatal development have been shown in epidemiologic studies to be linked to future neurological deficits. While this is

partially acknowledged in the HA, further evidence can be cited. There are several epidemiologic studies of children diagnosed with congenital hypothyroidism who are treated with T_4, providing good documentation of thyroid hormone levels, amount of thyroid supplement and neurocognitive outcomes, as these children are under continuous medical surveillance. The studies find that even small increments in T_4 dosage (as low as 2 ug/kg-day) can result in significant improvements in later cognitive and school performance (Oerbeck et al., 2003; Selva et al., 2005; Zoeller and Rovet, 2004). These studies show the sensitivity of the developing brain to adequate THs, and it would be expected that reversing this (i.e. producing decrements in TH) would result in reduction of cognitive performance.

Biological factors make the early infant potentially more at risk from thyroid perturbations than during other lifestages. The infant has diminished storage capacity of T4 compared to an adult (about 1 day in the infant compared to several months in the adult) and the T4 half-life is shorter (about 3 days in the early infant compared to about 7-10 days in adult (Greer et al., 2002; Vulsma et al., 1989)). Thus, it is more difficult for the infant to withstand and recover from perturbations to the thyroid system that can result from chemical exposures. The risk from perchlorate exposures would be expected to be greater for an infant compared to an adult at the same exposure level.

The neonatal time period has been identified as a sensitive time period in several reviews of the scientific literature (Ginsberg et al., 2007; Zoeller and Rovet, 2004). The discussion of the sensitivity of the neonatal infant stage to thyroid perturbations should be expanded and the early infant time period identified as a susceptible lifestage in the HA.

In addition, the document needs to consider exposure to these two groups of infants. Currently, the HA relies on two sources of data for the exposure estimates - data from NHANES, which only includes measurements of perchlorate levels in children starting at age 6, and estimates of exposure based on a draft EPA PBPK model. Neither of these addresses exposures to preterm infants and the draft EPA PBPK model does not fully address infant exposures.

Two different exposure scenarios are appropriately considered in the document for infants, exclusive breastfeeding and bottle-feeding. Estimates for both routes of exposure need to incorporate birthweights for infants who weigh less than 3.5 kg, which is the lowest infant weight currently evaluated in the assessment.

In 2005, almost 13 percent of infants were born preterm (<37 weeks of gestation NCHS http://www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_06.pdf), and a significant portion of these infants weight less than 3.5 kg. In addition, about 8% of infants are born less than 2,500 grams even at term. Smaller infants will have a higher dose per body weight exposure to perchlorate from breast milk or formula. EPA needs to incorporate the full range of infant weights observed in the population.

Calculating the perchlorate exposures to breast fed infants is slightly more complicated

because the relationship between maternal ingestion and breast milk levels must be calculated. For estimating the exposures to preterm and nonpreterm infants, three sources of information have been or could be used to more fully estimate exposures via breast milk: 1) estimates from the draft EPA PBPK model; 2) measured data in breast milk; and 3) estimates of intake based on ratios of breast to urine perchlorate concentrations measured in the population. Each of these are further discussed below.

1) The draft EPA PBPK model is used in the HA to provide insight into the relationship between ingestion of perchlorate and iodide inhibition (see further comments on this model below). As part of the analysis, EPA provides an estimate of perchlorate exposure to different populations, including a pregnant woman, fetus, and infants. The EPA PBPK model draft document reports in Table 4 that for drinking water level of 15 ug/L of perchlorate for a healthy 3.5 kg infant at 7 days exclusively breast feeding, the estimated perchlorate intake is 1.36 ug/kg-day, and for the bottle-fed infant ~3.5 ug/kg-day. This is about 2 to 5 times the RfD (0.7 ug/kg-day). While this model has significant limitations (see discussion below), it does provide an estimate of perchlorate exposure to average weight babies of healthy breastfeeding women.

The input portion of this model should be expanded to provide data on all infants of concern, in particular infants under 3.5 kg (the low end of infant weight used in the model) and preterm infants.

2 &3) Estimating perchlorate exposure via breastmilk. Studies of breast milk have found measurable levels of perchlorate in breast milk (see studies cited in the HA). Estimates of perchlorate exposure can be calculated by analyzing breast milk concentrations of perchlorate in combination with breast milk intake and infant weight. An example table is provided in the back (Table 1). A calculation based on measurements in breast milk can provide complimentary information to modeled estimates and should be included in the HA.

Breast milk is an intermediate media between maternal ingestion and neonatal ingestion. Methods are needed to determine corresponding maternal ingestion levels of perchlorate based on concentrations measured in breast milk. One such peer-reviewed method is provided by Ginsberg et al. (Ginsberg et al., 2007). The authors use estimated concentrations of perchlorate in water to estimate concentrations in breast milk using measured relationships between breast milk and urine concentrations of perchlorate. This analysis could be modified to back calculate drinking water concentrations that contribute to perchlorate levels measured in breast milk in the HA. The Ginsberg et al. method can also be used to independently estimate the range of exposures from breast milk feeding via different levels of perchlorate in drinking water.

Relative source contribution and perchlorate in breast milk. The current approach in the HA (as exemplified by Table 5-4) appears to assume that all the perchlorate via breastmilk comes from drinking water ingested by the mother. However, the

there is some contribution to perchlorate in breast milk that comes from perchlorate in food, providing an indirect exposure of the infant to food sources. This is identified in the HA text under the discussion of the study by Pearce, *et al.*, (2007) of perchlorate measurements in breast milk from women in the Boston-area. As identified by EPA "the Boston-area public water systems did not detect perchlorate in drinking water samples collected for the US EPA's UCMR from 2001 to 2003, nor did Boston area systems detect perchlorate in samples collected in response to the Massachusetts Department of Environmental Protection (DEP) 2004 emergency regulations for perchlorate." Thus, the perchlorate measured in breast milk must come from primarily or solely food exposure. The concentrations measured in the Boston study via breast milk should be included as a dietary contribution to breast milk exposures (such as in table 5-4) and used in the calculation of the relative source contribution.

While the modeling exercise can give some bounds on the data, it must be compared to measured data, and the measured data gives range of values that may be present in the population. A comparison of these three analyses, appropriately accounting for the range of neonatal and infant weights, should be included in the HA.

A similar set of considerations should be applied to perchlorate exposure via infant formula. The calculation for this source is more straightforward, as the infants are directly exposed to the water via reconstituted dry formula. However, as with the breast milk, weights of preterm and term infants weight less than 3.5 kg must be considered in the exposure calculations and used to determine the HA.

Other Comments

Section 3.2 Water Occurrence – It is not clear why the document, and subsequent analysis, uses 4 ug/L as essentially the cutoff point for determining which water systems have detectable levels of perchlorate Section 7.0 Analytical Methods states that the MDL can range from a low of 0.005 ug/L to 0.53 ug/L all well below 4 ug/L. This brings into question whether using a cutoff lower than 4 ug/L would identify other water supplies with detectable levels of perchlorate.

Response to Charge Questions

1. Does the document convey the necessary scientific information in a manner that that can be understood by both the officials from public health organizations and public water systems? (We have assumed that the depth of understanding will differ for the two intended audiences but hope that the message about perchlorate will be clear for both.)

As stated above the document is well-written and clear. However, there are several important pieces of information and other analyses that are missing that make it incomplete. As discussed below, there should be a section added on sensitive subpopulations. In addition, there needs to be analyses completed and included of potential perchlorate exposure via breastmilk and infant formula and a broader, more

representative portion of the infant population needs to be included in the analysis.

2. Does the Health Advisory describe the perchlorate health effects information that a public health official would need to assess and evaluate options for addressing local perchlorate contamination of drinking water?

The document provides many of the elements to evaluate potential health effects, but it needs to include a section on sensitive subpopulations, a discussion about the influence of background exposures that modify the risk (see discussion of this below in the EPA PBPK model section), and calculations that are more representative of the sensitive subpopulations. See the discussion of these issues above and in the review of the PBPK model.

3. Is the explanation of the derivation of the Relative Source Contribution clear and easy to understand?

The explanation is relatively clear. However, the calculation of the RSC for breast milk exposures needs to consider both food sources which are indirectly contributing to breast milk levels and drinking water sources (see comment above). In addition, it should be calculated for preterm and term infants who weight less than 3.5 kg.

In addition, the equations used to determine the HA depend on the calculation of the RfD. There are several significant new scientific publications and reviews that require some revaluation of the appropriate point of departure and uncertainty factors which make up the RfD. The point of departure used in the HA is a NOAEL, which is inconsistent with EPA's preferred approach, which is to use a point of departure based on benchmark dose modeling. NOAEL's and LOAEL's can be highly influenced by study design and the benchmark dose modeling approach alleviates some of this concern. Sufficient data to calculate a BMDL is available both from the Greer study (though this study is not representative of the full range of sensitive lifestages such as discussed in Ginsberg and Rice 2005 (Ginsberg and Rice, 2005)) and could be calculated from the Blount or Steinmaus studies (Blount et al., 2006; Steinmaus et al., 2007).

Some comments to make the tables more clear.

In table 5-2 and 5-3 the document should spell out RSC. Also, in table 5-2 the label for the last column should explain it is from drinking water, for example it could say "RSC from drinking water as a % of the RfD". I think it might also be helpful to include the equations in the 2nd row under the headers so it is clear how the numbers are calculated. Finally, the RfD should be given in the title or as a footnote. Same comments apply to table 5-3.

4. Have we identified the sensitive populations appropriately?

The document should include a specific section titled "Sensitive Subpopulations' which identify the sensitive subpopulations and include a description each one. It is difficult to find the identification of sensitive subpopulations in the document. The group is

cursorily mentioned in the first sentence under section 5.2. In addition, the group of sensitive subpopulations needs to be expanded to include preterm and term infants, please refer to comments above.

EPA should also consider relabeling this group (and section) as sensitive lifestages, as "populations" implies that fetuses and infants are a separate group in the population. However, every person must go through this lifestage, so everyone at one time is in this "subpopulation", which makes the subpopulation terminology meaningless. By redefining fetuses and infants as a sensitive lifestage, it appropriately acknowledges the critical period of susceptibility during which exposures can produce permanent biological alterations.

5. Is the role of modeling in evaluating the sensitive populations clearly described?

This part of the document requires revisions. First, the document states on page 37 that the HA does not rely on the PBPK model for determining the HA. However, it is used to provide information about different subpopulations or lifestages. In the discussion of the model (see pages 32-33), EPA acknowledges that the model predicts there are exposures above the RfD, but then uses the results of the model (percent iodide uptake inhibition) to justify these exposures above the RfD. This requires confidence in the EPA PBPK model and, as described below, there are a number of significant limitations to this model which makes predictions of inhibition for a robust estimate of the population unwarranted and very likely underestimated.

Use of the model implies that EPA is free to redefine the RfD for infants. The NRC states that infants and developing children are "also considered sensitive populations". Subsequent further review and analysis of the thyroid hormone and neurodevelopment literature and scientific data brings additional insight into the sensitivity of the infant lifestage (Ginsberg et al., 2007). These enhanced reviews of the literature and the considerations mentioned above do not warrant exposures to infants over the RfD. Finally, there is no consideration in the PBPK model for preterm infants, which has been identified as one of the "most sensitive subpopulations", and based on the analyses of the 3.5 kg infant, it would be expected that exposures for this group would also be over the RfD.

While EPA does not say it is using this model as the basis of the HA, by including the analysis from the model, EPA implicitly is using it to support the HA, despite the limitations. Until these significant limitations are addressed, the model and the results should not be used in its current form to support the HA.

Comments on the PBPK model

Before commenting on some of the limitations of the model, it must be pointed out that the PBPK model is from a draft EPA report "Inhibition Of The Sodium-Iodide Symporter By Perchlorate: An Evaluation Of Lifestage Sensitivity Using Physiologically-Based Pharmacokinetic (PBPK) Modeling" (hereafter referred to as EPA PBPK model), and as such one assumes that it has not gone through peer review and is not final (note this

document states "Draft Deliberative – Do Not Cite or Quote"). Thus, it appears that using this in the HA would be inconsistent with EPA policy of only using peer reviewed science for decision making.

The EPA PBPK model does account for some intrinsic characteristics that can influence exposure and kinetics in sensitive subpopulations and EPA should be commended for considering them (these include different excretion rates for infants and factors that influence exposure through breast milk). However, there are a number of other factors that would influence population variability and exposure variability that are not accounted for in the model, some of which are acknowledged explicitly by EPA in the document. These seriously limit the utility of the model to provide robust population estimates. These are described below in further detail.

Population variability and susceptibility characteristics which influence exposure and risks

Infant weight and early gestational ages

EPA estimates exposures for infants based on infant weight of 3.5 kg at 7 days. This does not incorporate two important and relatively large groups of infants, those born preterm and those at the smaller end of the birthweight distribution. In 2005, almost 13 percent of infants were born preterm (<37 weeks of gestation NCHS http://www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_06.pdf). In addition, about 8% of infants were born less than 2,500 grams. Infants who are born preterm were identified by the NRC as one of the most sensitive populations along with fetuses. The smaller infants would have a higher dose per body weight exposure to perchlorate from breast milk. The HA, based on the PBPK draft model, defines the lower end of intake for infants weight 3.6 kg or 3.5 kg for near-term infants (GW 40). It appears that the model cannot account for a significant portion of the infant population, and some of the most sensitive, the preterm infant and fetuses that are earlier in gestation (pre 40 weeks).

Variability in the disease status

The EPA PBPK model, as acknowledged in the draft assessment, does not describe the full population and generally describes average, healthy parts of the population. For example, on page 25, the document states:

> "For example, this analysis does not take into account within-group variability in PK, uncertainty in model parameters and predictions, or population differences in PD. Also, the NRC identified fetuses of pregnant women that are hypothyroid or iodine deficient as the most sensitive subpopulation. Unfortunately, the models were not designed to account for whether the pregnant woman is hypothyroid or iodine deficient. Model predictions of doses in the various subgroups apply to a subgroup average for typical, healthy individuals, and effectively describe the RAIU inhibition relative to that same individual as his/her own control."

This is an important limitation of the model, as hypothyroidism and iodine deficiency affect a significant portion of the population. As the HA draft states "subclinical

hypothyroidism and reductions in T4 (i.e., hypothyroxinemia) in pregnant women have been associated with neurodevelopmental delays and IQ deficits in their children (Pop et al., 1999, 2003; Haddow *et al.*, 1999; Kooistra et al., 2006; Morreale de Escobar, 2000, 2004). Animal studies support these observations, and recent findings indicate that neurodevelopmental deficits are evident under conditions of hypothyroxinemia and occur in the absence of growth retardation (Auso *et al.*, 2004; Gilbert and Sui, 2008; Sharlin *et al.*, 2008; Goldey *et al.*, 1995). "

Hypothyroidism is prevalent in the U.S. population. For example, between 1999-2002, an estimated 7.3% of the U.S. population aged 12 years and older reported that they had thyroid disease or were taking thyroid medication (Aoki et al., 2007), and hypothyroidism is frequently undetected. Pregnancy causes an increased demand on the thyroid gland and hypothyroidism has been reported to be slightly more than twice as common among pregnant women than among non-pregnant women ages 12-49 (Aoki et al., 2007). As stated by EPA, the model does not account for this portion of the population.

The model also would not account for iodine deficiency, which is also relatively prevalent in the US with over 1/3 of women having iodine levels below 100 ug/L (WHO guidelines (Caldwell et al., 2005)).

This has implications for both the breast feed newborn and fetuses. The fetus is dependent on maternal thyroid levels during the 1st to 2nd trimester (Williams, 2008), further thyroid hormone suppression in women who are already hypothyroid would have consequences for neurodevelopment that would not occur among healthy nonhypothyroid women. The document needs to consider both these lifestages. Nursing mother's who are iodine deficient may pass along less iodine to the breast feeding infant and it is unclear whether this is accounted for in the model

The EPA PBPK model and the HA do not consider fetal exposure. Only the GW 40 fetus is considered (it is not clear that a GW 40 fetus makes very much sense because at 40 weeks, the fetus is a baby and not a fetus anymore as most births occur by 40 weeks).

Finally, the EPA PBPK model and the HA do not account for background exposures from other chemicals and compounds that can interfere with thyroid synthesis. This issue is illustrated in the Stienmaus article and acknowledged in the HA (Steinmaus et al., 2007), where thyroxine levels can influence the effects of perchlorate. There is also ample evidence from other studies that exposure to other chemicals that can interfere with thyroid hormone levels can have an additive effect on exposures to perchlorate. A recent study tested a mixture of 18 thyroid disrupting compounds (dioxins, dibenzofurans and PCBs), at doses comparable to human exposure levels, for effects on serum T_4 in rats and found that the mixture had a dose-additive effect on T_4 at environmentally-relevant doses and a 2-3 fold greater than dose-additive effect on T_4 at higher doses (Crofton et al., 2005). The NHANES data show that there ubiquitous and simultaneous human exposure to thyroid disrupting compounds multiple TDCs, including dioxins, PCBs, perchlorate, brominated flame retardants, bisphenol A, and several pesticides (Centers for

Disease Control and Prevention, 2008). Background exposures to thyroid disrupting chemicals will increase the risk of perchlorate exposure compared exposures to the same level of perchlorate exposure in isolation, and this needs to be accounted for in the model.

The EPA PBPK model provides some information on groups that may be difficult to evaluate on a population level (infants, newborns), but it cannot be used in the HA in its current form as it implies a level of certainty about the effects of perchlorate that are not warranted. It could be used to evaluate the range of exposures that might be expected if the variability and susceptibilities in the population were modeled and this would provide complimentary information to measured data (see comment above).

6. Do you have any suggestions on how we could improve this draft document?

The previous comments, once addressed, will improve the draft document.

Table 1. Estimated perchlorate intake in breast milk based on measured concentrations of breast milk in perchlorate, breast milk consumption per day and infant body weight

RFD = 0.7 ug/kg/day

Perchlorate in Breast Milk Studies	Concentration of Perchlorate in Breast Milk(ug/L)				
	min	max	median	mean	
Pearce 2007 (n=49)	1.3	411	9.1	33	Discussion of this study states there is no perchlorate in the drinking water supply, so breast milk exposure must be from food
Kirk 2005 (n=36)	1.4	92.2		10.5	
Dasgupta 2008 (n=13)	0	48	7.3	9.3	

Assumed breastmilk ingestion (L/day) 0.52*

Perchlorate ingestion (ug/kg-day) = Perchlorate in Breast milk (ug/L)*Breastmilk Ingest (L/day)/BW (kg)

	Neonatal BW (kg)	3.5	2.5	1.5
Concentration of perchlorate in breast milk	For a median/mean of 10.2 ug/L	**1.6**	**2.2**	**3.6**
	For a higher end of 33 ug/L	**4.9**	**6.9**	**11.4**

*Note this is an approximate average, there is expected to be variability in this number

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