Clinical and epidemiological studies of perchlorate exposure show that a considerable amount of perchlorate exposure is sustained without hormone changes. Humans clearly possess a significant capability to adapt to low iodine intake without adverse effects on thyroid hormone balance.

2.1.4 *The level of perchlorate exposure needed to cause 70% inhibition of iodide uptake is approximately 17,000 ppb in drinking water, and there is evidence that 70% inhibition is insufficient to cause measurable changes in thyroid hormone levels.*

The clinical trial by Greer *et al.* (2002) was designed to estimate the dose-response function for inhibition of iodide uptake, and in particular, estimate the threshold below which no inhibition would occur. Inhibition of iodide uptake is not adverse but merely the initial biochemical phenomenon in perchlorate's mode of action. Identifying the threshold yields a credible value for a no-effect level that would be inherently highly protective.

The highest dose administered by Greer and colleagues was 0.5 mg/kg-d, which is equivalent to about 17,000 ppb in drinking water. At this dose, 70% inhibition of iodide uptake was observed. No changes in thyroid hormone levels, TSH, blood chemistry, or complete blood count (including differential) were observed after 14 days. Although the study was not long enough to exclude the possibility that such changes could occur if the duration of exposure were substantially extended, evidence from occupational studies supports the conclusion that this possibility is highly unlikely.

Lamm *et al.* (1999) performed an occupational study of perchlorate workers, and the highest exposed group received doses equivalent to 0.5 mg/kg-d. No changes in thyroid hormone levels, TSH or blood chemistry were observed despite what appears to have been 70% inhibition of iodide uptake, based on Greer *et al.* (2002). Therefore, there is credible evidence that 70% inhibition of iodide uptake is insufficient to cause thyroid hormone changes, at least in healthy male workers. Opportunities to test for similar effects in women are limited, but in Greer *et al.* (2002), there was no difference in dose response for inhibition of iodide uptake by the NIS between men and women. Attempting to estimate effects in pregnant women is probably infeasible as well as ethically dubious given heightened public concern about the alleged risks from levels thousands of times lower.

2.1.5 *Long-term epidemiological studies demonstrate that exposures exceeding 100 ppb in drinking water do not affect thyroid hormone levels in children receiving adequate iodine nutrition—100 times higher than the drinking water equivalent of the U.S. EPA Draft RfD.*

Perchlorate is found naturally in some parts of the world, including Chile. A study by Crump *et al.* (2000) was designed to determine if perchlorate in drinking water affects thyroid function in newborns and school-age children (ages 6-8). Children were studied in three cities in northern Chile that have relatively "high" (100 to 120 ppb), "low" (5 to 7 ppb), or non-detectable (< 4 ppb) concentrations of perchlorate in drinking water. School-age children were examined for goiters and blood was taken for analysis of TSH, T_4, and T_3. Blood from newborns was obtained and analyzed for the presence of congenital hypothyroidism and TSH levels.

Among these schoolchildren, there were no adverse thyroid hormonal changes or goiter prevalence among lifelong residents of the cities with high and low perchlorate contamination compared to the city with no perchlorate contamination. TSH levels in newborns were significantly lower in the high perchlorate city compared with the city with no perchlorate in the drinking water; this is opposite to the known pharmacological effect of perchlorate, and the magnitude of difference was not clinically significant.

This is the first epidemiological investigation of the potential effects of lifelong, and presumably daily, perchlorate exposure in school-age children. Most importantly, these children were known to have been exposed to perchlorate. Perchlorate in drinking water at concentrations as high as 100 to 120 ppb had no effect on suppressing thyroid function in newborns or school-age children.

2.1.6 *The level of perchlorate exposure that is without any detectable effect in humans is approximately 245 ppb perchlorate in drinking water—10 to 40 times greater than environmentally relevant exposure levels.*

Perchlorate exposure that is too low to cause *any* effect is clearly too low to cause an *adverse* effect. It is for that reason that the clinical study by Greer and colleagues is so important. In healthy adult volunteers, no measurable inhibition of iodide uptake was found at a perchlorate dose of 0.007 mg/kg-d, or about 245 ppb in drinking water.

For ethical reasons, a similar study cannot be performed in pregnant women. Thus, we must draw inferences about populations of concern from other scientific information. However, there is no reason to believe that the kinetics of substrate uptake by the NIS would differ for pregnant women.

2.1.7 *Neurobehavioral decrements in offspring have only been associated with significantly hypothyroid women, not those with transient hormone changes within the normal range—these effects are irrelevant to environmental perchlorate exposures that cause no hormone changes.*

In the 2002 perchlorate risk assessment, U.S. EPA cites studies by Haddow *et al.* (1999), Pop *et al.* (1995 and 1999), and other investigators to demonstrate "concerns for deficits in neuropsychological development related to maternal thyroid deficiency." By citing these studies, U.S. EPA implies a direct relationship between perchlorate exposure and adverse neurodevelopmental effects. However, a review of these studies shows that impaired neurodevelopment is associated only with the most hypothyroid individuals, not individuals with thyroid hormone levels within normal ranges and confounding variables such as depression, socioeconomic status, and presence of positive TPO-Ab titers may have significantly impacted results. Further, the relevance of these studies to perchlorate exposure is not evident since studies of children exposed to perchlorate in drinking water at concentrations as high as 120 ppb showed that thyroid hormone and TSH levels were within normal reference ranges and did not differ from levels in children not exposed to perchlorate, and adults exposed to levels as high as a 17,000 ppb drinking water equivalent concentration showed no effects on thyroid hormones. Environmental concentrations of perchlorate are well below levels that could cause changes in thyroid hormones. Thus while these studies of maternal hypothyroxinemia or hypothyroidism have scientific merit for their intended purpose, observations taken from these studies cannot be used to draw inferences about the effects of low dose environmental perchlorate exposure (Bruce *et al.* 2003).

3.0 RESPONSE TO CHARGE QUESTION III

3.1 Evaluation of key animal studies used to assess human health effects from ingestion of perchlorate.

3.1.1 Based on the studies conducted, no reliable evidence exists of any adverse effect not mediated by inhibition of thyroidal iodide transport.

Animal studies do not provide reliable evidence of adverse effects on brain or behavior (Bruce *et al.* 2002a; Bruce and Pleus 2002b; Goodman 2003a; Schwartz 2002; TERA 2001; Wahlsten 2002a, 2002b, 2002c, 2002d, 2002e, 2003; Wolff 1998).

In many cases, U.S. EPA's interpretations of the findings of the animal studies contradict those of the investigators. For example, in the Argus (2000) developmental toxicity study in rats, ossification sites per litter for sternal centers and forelimb phalanges were significantly reduced at 30 mg/kg-d. The authors called these findings "reversible developmental delays." U.S. EPA disagreed and contends that developmental delays, be they permanent or reversible, are not to be discounted as potential indicators of developmental toxicity. In this same study, three dams in the 30 mg/kg-d dose group showed an increase in localized alopecia that was statistically significant. The authors commented that such incidence is within the range observed historically at their testing facility. U.S. EPA disagrees and considers these findings biologically significant and exposure related (Bruce *et al.* 2002b; Goodman 2002).

3.1.2 The animal studies on which U.S. EPA relies are subject to considerable methodological disputes and errors of interpretation.

3.1.2.1 Rat brain morphometry data are unreliable.

Due to methodological problems and inconsistencies with other studies, several experts (with expertise in rat and human neurodevelopment, neurobehavior, and thyroidology, and in statistical analyses) have concluded that the data on rat pups compiled in the Effects Study (Primedica 2001) are subject to considerable methodological disputes and errors of interpretation. These studies are the foundation of ERD even though they cannot be relied upon to assess whether perchlorate significantly alters brain morphometry in rats. The following aspects of the study design and methods used were identified as problematic and, in some cases, unacceptable (Bruce *et al.* 2002b; Bruce and Pleus 2002b; Schwartz 2002; TERA 2001; Wahlsten 2002a, 2002b, 2002c, 2003):

- Use of coronal sections for brain measurements when sagittal sections are preferred;
- Use of single-width distances as a measure of effect when multiple width measures, at a minimum, or area or volume measures are preferred;
- Taking symmetrical measures from the right and left sides of the brain but treating these data as independent;
- Lack of blinding to the gender and treatment status of all animals during tissue analyses;
- Lack of evaluation of post-puberty animals;
- Fixation and (freehand) sectioning methods that may have differentially affected dose groups;

- Use of inadequate statistical methodologies;
- Lack of demonstrated association between changes in linear dimensions of brain structures and the presumed mechanism of action of perchlorate (*i.e.*, hypothyroidism);
- Lack of a positive control;
- Lack of a biologically plausible, *inverse* U-shaped dose-response relationship for effects on the posterior corpus callosum, which turn out to be artifacts of group differences in the plane of (freehand) sectioning;
- Hypothyroidism was not induced, even at the highest dose (Bruce *et al.* 2002b; Goodman 2003b);
- Data cannot be compared with literature values because of the unorthodox study methods;
- The most sensitive response to maternal hypothyroidism is a delay in the migration of cerebellar external granular layer; however, upon independent examination, this cell layer was found to have migrated normally at all doses;
- Results of this study are inconsistent with the results of the earlier Argus Research Laboratories, Inc. (1998) study; and
- The rat brain morphometry changes alleged by U.S. EPA to have been detectable in Argus Research Laboratories, Inc. (2001) do not have any known behavioral/functional correlate.

3.1.2.2 U.S. EPA's assertions of neurobehavioral effects in rats are in error.

A number of concerns with U.S. EPA's interpretation of the motor activity data have been noted (Bruce *et al.* 2002a, 2002b; Wahlsten 2002c, 2002d). For example, delays were not seen in Argus (1998) for acoustic startle, an endpoint that the literature says is a more sensitive neurobehavioral endpoint for hypothyroidism-inducing agents than motor activity.

Both of the neurobehavioral studies (Argus 1998 and Bekkedal *et al.* 2000) report no significant effects in any of the 24 neurobehavioral indices. Despite these findings, after obtaining the data U.S. EPA performed post hoc statistical tests of the motor activity data to isolate statistically significant effects.

3.1.3 Iodine physiology of humans and rats differs.

Rats and humans share the same basic thyroidal mechanisms and regulatory systems (Greer *et al.* 2002). However, Goodman (2002) notes that the homeostatic responses of the two species are quite different. Greer *et al.* (2002) report, "...although the physiology of the pituitary-thyroid axis is very similar in the rat and the human, the rat thyroid is much more rapidly responsive to any perturbation of iodine metabolism leading to decreased thyroid hormone formation." These species differences may affect the ability to extrapolate from observations in rats to humans (Bruce and Pleus 2002b; Goodman 2002, 2003b; Greer 2002; Schwartz 2002).

Further, Greer (2002) has explained why extrapolating from the rat to the human must be done not mechanically but with great care:

The basic qualitative changes that occur in hypothalamic-pituitary-thyroid adaptation to iodine deficiency or to drugs which interfere with thyroid hormone synthesis are similar in the two species. However, there are major species differences in the dose-response relationships of a number of drugs which act on the thyroid.

In short, with regard to the thyroid, studies in the rat must be carefully interpreted when extrapolating to humans (Bruce *et al.* 2002a, 2002b; Greer 2002; Schwartz 2002; Wahlsten 2002b, 2002c, 2002d).

3.1.4 Exogenous factors can significantly affect measured thyroid hormone levels in rats.

A number of factors including circadian rhythms, sampling and analytical methods, timing of rat handling activities just prior to sacrifice, environmental variables such as changes in room temperatures, and stress can significantly affect measured thyroid hormone levels in rats. These factors have the greatest impact on TSH concentrations, but T_3 levels can also be significantly affected (Bruce *et al.* 2002b; Goodman 2003b).

3.1.5 Reanalysis of rat thyroid hormones in regulatory studies shows no indication of hypothyroidism in pups and fetuses

Goodman (2003b) reviewed and analyzed the perchlorate pharmacokinetics and toxicity rat studies that were cited in the ERD. She reports that the T_4/T_3 ratio for offspring of dams treated with various doses of perchlorate, which is the most stable measure of thyroid hormone during development in the rat, showed no indication that either the fetuses or the pups were hypothyroxinemic, hypothyroid, or experiencing TSH stimulation as a result of perchlorate inhibition of thyroidal iodide uptake. U.S. EPA considers only T_4 and T_3 changes, which occur rapidly in the early postnatal period; however, their ratio remains constant. The data obtained in the developmental regulatory studies do not support any effect on hormone levels in fetal rats or rat pups resulting from reduced intrathyroidal iodine.

3.1.6 Results of Pathology Working Group on rat thyroid show improper statistical analysis.

U.S. EPA presented a Bayesian analysis from which they concluded the presence of adenomas in two offspring from mothers in the highest dose group of a 2-generation rat study was a statistically significant finding. The U.S. EPA analysis included the frequency of "C" cell tumors from one study with the frequency of thyroid cell tumors in the second. "C" cells are the base cell for the parathyroid gland and are responsible for the production of the hormone calcitonin, which has nothing to do with iodine metabolism or NIS. Thyrocytes are the base cell for the thyroid gland and are responsible for the production of the hormone thyroxine, which directly has to do with iodine metabolism and the NIS (Lamm 2003a).

3.1.7 Soybean products in rodent chow may have confounded study results.

U.S. EPA failed to consider the effects that soybean products in rodent chow may have had on confounding study results. Isoflavones (*e.g.*, genistein and daidzein) in soy have known goitrogenic effects, and have been cited as a cause of hypothyroidism in humans given soy-based formula. Furthermore, there is evidence of synergism in antithyroid properties of soy combined with iodine deficiency in rats (Doerge and Sheehan 2002). Lacking additional detailed study of the potential synergistic interaction between perchlorate and the diet, it is not possible to adjust, correct, or extrapolate those observations to humans (see Appendix G). What can be said is that any measurable effect supposedly due to perchlorate is likely to be substantially attributable to soy.

4.0 RESPONSE TO CHARGE QUESTION IV

4.1 Based on evaluation of the available animal and human studies, what insights can inform the selection of uncertainty factors used in the approximation of a safe lifetime exposure for humans, especially sensitive subpopulations?

Perchlorate has a nearly ideal database for risk assessment and minimal uncertainty, which must be considered in the selection of uncertainty factors used in the approximation of a safe lifetime exposure for humans. The large composite uncertainty factor in U.S. EPA's draft 2002 RfD overstates the level of uncertainty and variability supported by the scientific literature.

4.1.1 The perchlorate database is robust, not uncertain.

We know a lot about perchlorate. It has been used medicinally for decades in the treatment of hyperthyroidism (including Graves' disease), to lessen the effect of administered sodium pertechnetate, and as a diagnostic agent for various thyroid disorders. In the 1990s, interest in perchlorate as an environmental contaminant increased at the same time that the ability to detect it in environmental media improved. This compelled dozens of DoD- and industry-sponsored human and animal studies designed to determine the health effects from low-level exposure. The database for perchlorate is robust, not uncertain. The adequacy of the database compels that no uncertainty factor is required.

4.1.2 Information is available that can be used to dismiss uncertainty factors related to extrapolation from acute to chronic exposures.

Perchlorate does not accumulate in the body due to its rapid clearance, so the accumulations that usually distinguish short-term from long-term exposure are not expected in exposed populations. Further, a study of workers at a perchlorate manufacturing plant showed no changes in blood chemistry or thyroid hormone levels after years of exposure to levels of perchlorate equivalent to approximately 17,000 ppb in drinking water (Lamm *et al.* 1999). These levels are similar to the highest dose administered in the Greer *et al.* (2002) clinical study, which also demonstrated normal thyroid hormone levels.

4.1.3 *Adequate human data obviates the use of rat data making an interspecies uncertainty factor unnecessary.*

Human data are more useful for assessing the human health effects from perchlorate exposure than animal data. U.S. EPA's own guidance specifies a preference for human data over animal data of equal quality. A wealth of high-quality human data exists for perchlorate, ranging from its historical use as a pharmaceutical agent to more recent clinical, and ecological and occupational epidemiology studies. An interspecies uncertainty factor is not necessary if human data are used in the estimation of a safe lifetime exposure for humans.

Even if U.S. EPA chooses to use animal data, which primarily comprises rat studies, the need for an interspecies uncertainty factor is tempered by the fact that rats are more sensitive to the effects of perchlorate than humans. Even though rats and humans share the same basic thyroidal mechanisms and regulatory systems, there are critical differences, such as the lack of thyroid binding globulin (TBG) and an iodine reserve in the rat. Because rats are more sensitive to the effects of perchlorate than humans, we concur with U.S. EPA's ERD that an interspecies uncertainty factor is not necessary.

4.1.4 *Very good data in humans support reduced uncertainty factors, and they show that the use of a large composite uncertainty factor results in a redundant accounting for scientific uncertainty.*

The effect of multiple uncertainty factors must be examined to ensure that their composite effect is reasonable. In the case of perchlorate, a composite uncertainty of factor of 300 might be reasonable provided that the point of departure was a genuine adverse effect. Inhibition of iodide uptake is merely a third-order precursor to an adverse effect, and one that is orders of magnitude below a genuine adverse effect. Applying *any* uncertainty factor while using inhibition of iodide uptake as the point of departure results in a redundant accounting for scientific uncertainty.

4.1.4.1 There are orders of magnitude of difference in dose between that which causes inhibition of iodide uptake and that which causes changes in thyroid hormones.

Two well designed and controlled 14-day clinical studies of perchlorate (Greer *et al.* 2002; Lawrence *et al.* 2000, 2001) have defined the dose-response relationship for the perchlorate mechanism of action, inhibition of iodide uptake, and identified a no effect level for perchlorate for thyroid hormone and blood chemistry changes at doses ranging from 0.007 to 0.5 mg/kg-d (or about 245 to 17,000 ppb in drinking water).

Two occupational studies in humans (Gibbs *et al.* 1998; Lamm *et al.* 1999) provide data demonstrating that years of exposure cause no adverse effects. While this evidence does not provide conclusive support for the notion that 17,000 ppb is without appreciable risk, it is highly supportive of the conclusion that the threshold for inhibition of iodide uptake is a no observed effect level. Doses averaging about 0.4 mg/kg-d (or about 14,000 ppb in drinking water) have yielded no adverse effects on blood chemistry or thyroid hormones.

Several ecological epidemiological studies (Li *et al.* 2000a, 2000b) of people in the U.S. suspected to be exposed to low concentrations of perchlorate in drinking water have found no adverse effects on blood chemistry or thyroid hormone or TSH levels. One study in Chile of children known to be exposed to levels high than 100 ppb indicated that children naturally exposed to perchlorate presumably *in utero* and through childhood had no adverse effects on blood chemistry or thyroid hormones.

No reliable evidence exists of any adverse effect not mediated by inhibition of thyroidal iodide transport. Further, a clear understanding exists of the potential effects because of the vast literature on iodine deficiency disorders, but these effects have not been seen.

4.1.4.2 Variability and small numbers of subjects in the clinical studies is an uncertainty that can be addressed.

In the Greer *et al.* (2002) study, a total of 37 subjects are in the 4 dose groups. A highly consistent dose-response curve was found over a 70-fold dose range and a range of inhibition of iodide uptake from 0 to 70% above a substantial baseline level attributable to normal phenomena such as diet. Thus, there is significant confidence in the NOEL estimate. In addition, adequate numbers of subjects for each dose group are available to conduct valid and reliable statistical analyses. No difference was seen between males and females in this study. A NOEL is, by definition, fully protective of every member of the population with a built-in margin of safety. An exposure level too low to cause any biochemical effect is clearly too low to cause an adverse effect.

Greer *et al.* (2002) accounts for intra-individual variability in that it included extreme cases of subjects whose urinary iodine excretion values (which reflects iodine status) changed from 50 to 300 µg/L and from 450 to 125 µg/L between the baseline and last exposure day. Both intrinsic (reflecting physiological differences) and extrinsic factors (including exposure to the environmental goitrogens nitrate and thiocyanate) are expected to account for the effects on both intra- and inter-subject variability in the RAIU. The results of this study were very consistent with the Lawrence *et al.* (2000, 2001) studies.

In addition, modeling results of the data from Greer *et al.* (2002) suggest that those with the lowest iodine intake at baseline were less sensitive to perchlorate inhibition of thyroidal iodide uptake. "Therefore, exposure to perchlorate at the NEL measured by Greer *et al.* is also safe for men and women with dietary iodine intakes that generally would be considered moderately low" (Goodman 2003a).

The variability in the RAIU measurement and the calculated inhibition is due mainly to method or intra-individual variability, and does not indicate high individual variability in thyroid function or iodide uptake in the population or in sensitivity to inhibition by perchlorate. Similar variability in the baseline and treatment measurements indicates that the variability is not due to differences between individuals in their response to perchlorate.

5.0 RESPONSE TO CHARGE QUESTION V

5.1 Would adverse effects other than those associated with iodide update inhibition be expected as a result of ingesting low levels of perchlorate on a daily basis?

5.1.1 No reliable evidence exists of any adverse effect not mediated by inhibition of thyroidal iodide transport.

The pharmacokinetics and pharmacodynamics of perchlorate are well characterized in humans and lab animals. Perchlorate has nearly five decades of clinical use and pharmacological research history. Its mechanism of action is well researched and understood. Perchlorate is not metabolized and is excreted by the kidneys with a half-life of 8-12 hours. It does not bioaccumulate in tissues.

Toxicological studies of perchlorate conducted in animals, including over 13 new studies since 1997, show that perchlorate is not a mutagen, a teratogen, a reproductive toxicant, or an immunotoxicant, nor is it carcinogenic. In addition, occupational studies have shown no effect of perchlorate on a number of biochemical parameters.

Upon conclusion of his review of U.S. EPA's 1998 Draft Risk Assessment, the Chairman of the 1999 Peer Review Workshop, Dr. Curtis Klaassen, reiterated these facts stating:

> *[T]he toxic effects of perchlorates appear to be limited to the consequence of its inhibition of iodide transport into the thyroid gland.... The data presented indicate that all of the adverse effects produced by perchlorate are associated with its initial inhibition of iodide uptake to the thyroid gland.* (see Appendix C)

6.0 RESPONSE TO CHARGE QUESTION VI

6.1 U.S. EPA failed to consistently consider and evaluate human studies.

The Agency considered only two human studies (Brechner *et al.* 2000; Schwartz 2001) in the development of their risk assessment, and excluded several other well-conducted studies in human populations that were not suggestive of adverse effects (Crump *et al.* 2000; Li *et al.* 2000a, 2000b, 2001; Gibbs *et al.* 1998; Lamm *et al.* 1999; Greer *et al.* 2002), including two studies (Lamm *et al.* 1999; Greer *et al.* 2002) that were quantitative and did not indicate adverse effects due to perchlorate exposures up to 0.5 mg/kg-d.

Rather than incorporate the full and robust data set of Greer *et al.* 2002 in its 2002 draft risk assessment U.S. EPA used only a 1999 abstract for a professional meeting. However, all raw data, summarized data, and a draft manuscript were provided to U.S. EPA in June 2001.

Although U.S. EPA's document states that scientific limitations are the basis for rejecting the Greer study, no substantive issues are raised. On page 4-31 of their draft risk assessment, they cite uncertainty with the small sample size, especially in the lowest dose group; but the dose-response curve shows an effect that is clearly consistent across all dose groups and all subjects. U.S. EPA states that the use of euthyroid subjects was a deficiency of the study. Use of euthyroid subjects is not a limitation of a study of perchlorate effects on inhibition of iodide uptake in normal adults; furthermore, use of pregnant, lactating, elderly, or hypothyroid adults would be unethical as well as introduce many other confounding variables. U.S. EPA notes that the duration of the study was too short to observe hormone effects. This is not a valid criticism because the study was designed to study the effect of perchlorate on inhibition of iodide uptake and the authors make no claim that the thyroid hormone measurements were expected to change. Indeed, given that thyroid hormone reserves in the human are sufficient to adequately supply the body for several months, it would be illogical to expect any hormone changes in this protocol. U.S. EPA also points out that the study was intended to collect data on perchlorate kinetics. This seems to represent a bias on their part about the reason for doing the study.

Most of their bases are not true criticisms of the study, but rather, valid statements about areas of uncertainty associated with the use of the data in risk assessment. The extrapolation of these results to iodine-deficient, hypothyroid, or pregnant populations is a critical area of intraspecies uncertainty that should be considered, but does not undermine the reliability of the study results. It is not credible to conclude that these uncertainties make the use of animal data preferable to or more reliable than human data.

In contrast, U.S. EPA reviewed uncritically the ecological studies by Brechner *et al.* (2000) and Schwartz (2001) yet found them "most compelling." Brechner *et al.* observed statistically significant differences in neonatal TSH levels in Flagstaff and Yuma, Arizona, and concluded that perchlorate exposure in Yuma explained this difference. This result has been recently refuted by Lamm (2003b) who compared subpopulations of exposed and unexposed babies born at the same hospital in Yuma and found no significant differences in TSH.

The ecological epidemiological study by Schwartz (2001) is a non-peer reviewed Master's thesis, and the underlying data have not been disclosed. Lamm and Soldin (2002) and Lamm *et al.* (2002) report that they lack sufficient information to validate its exposure assignments and raise other methodological questions. A recent paper by Kelsh *et al.* (2003) revisits the identical issue addressed by Schwartz, contradicts those results in the case of TSH, and finds no support for the concern that low-level perchlorate exposure is associated with primary congenital hypothyroidism.

Two occupational studies in humans (Gibbs *et al.* 1998; Lamm *et al.* 1999) demonstrate that exposure over several years at levels hundreds of times greater than the identified threshold cause no adverse effects or thyroid hormone and blood chemistry changes.

The ERD expressed several criticisms of the occupational studies of inhalation exposures leading to U.S. EPA's conclusion that these studies could not be used. The primary criticisms were that the exposures were not adequately characterized in terms of particle size and that exposure through the respiratory route was not relevant to exposure through drinking water. However, Lamm *et al.* (1999) reported urinary perchlorate measurements, a valid measure of internal dose that corroborated the exposure estimates based on job categories and atmospheric measurements. The pharmacokinetics of perchlorate are well understood, so the urine measurement is a better description of dose than the inhaled concentration.

6.2 U.S. EPA failed to consider other key studies relevant to assessing the risk due to exposure to perchlorate.

In assessing the risks associated with perchlorate, U.S. EPA appears to have ignored over 50 years of peer reviewed scientific publications documenting that other substances share the same mode of action. The relative potencies by which these different anions inhibit iodide uptake by the thyroid are the following: $ReO_4^- > ClO_4^- > BF_4^- > SCN^- > ClO_3^- > NO_3^-$ (Wolff 1966). Of these, nitrate, perchlorate, and thiocyanate are of clinical and/or environmental importance.

The relative potencies perchlorate, nitrate and thiocyanate are reasonably well established on a serum concentration basis. The serum half-life of each is also relatively well established. Perchlorate is an order of magnitude more potent than thiocyanate (Wyngaarden *et al.* 1952; Wyngaarden *et al.* 1953; Wolff 1966; Greer *et al.* 1966); however, the half-life of thiocyanate is an order of magnitude longer than that of perchlorate (Schulz *et al.* 1979; Lamm *et al.* 1999). Nitrate is the least potent and has the shortest serum half-life (Tannenbaum 1979; Green *et al.* 1981; Schultz *et al.* 1985; Wagner *et al.* 1984), but is present in the diet and environment at the highest concentrations. Population norms for thiocyanate and nitrate concentrations in serum and urine are known. A PBPK model is available to correlate perchlorate doses to serum concentrations.

The literature documenting the inhibition of iodide uptake by various substances is extensive. In particular, there are studies of thiocyanate in presumed sensitive human subpopulations that can be useful in answering key questions regarding the effect of inhibition of iodide uptake at critical stages of life, both in the presence of iodine deficiency and in iodine sufficiency (Chanoine *et al.* 1991; Vanderpas *et al.* 1984; Biassoni *et al.* 1998). These studies are relevant to assessing risks among the same subpopulations from the inhibition of iodide uptake of perchlorate.

7.0 Additional Considerations for the Committee to Develop an Informed Response to the Charge

7.1 Scientific studies must be judged on their merits and not on the basis of who sponsored them.

Almost all of the underlying science relevant to human health risk assessment was funded by PSG, the Department of Defense, or other parties that will be regulated by standards based on the Committee's report. These regulated parties voluntarily funded these studies in the belief that credible public policy decisions required credible science, and in no instances has PSG interfered with scientists' freedom of inquiry. Nevertheless, there are some who will dismiss this rich scientific literature just because it was "industry funded."

PSG asks the Committee to publicly disregard these complaints and judge the scientific evidence on its merits.

7.2 The purpose of risk assessment is to objectively and realistically assess risk by using credible science—not to make implied, undisclosed and non-transparent risk management decisions.

The PSG has fully embraced the philosophy that the best science be used to establish the RfD. PSG has provided irrefutable tangible evidence of its support by expending millions of dollars for scientific research intended to enable an objective, realistic and scientifically balanced characterization of perchlorate risks. Most of this research was performed in accordance with protocols selected by U.S. EPA and performed by U.S. EPA-selected contractors. At U.S. EPA's request, PSG even relinquished its legitimate right to see the data that the Agency obtained at PSG's expense until such time as U.S. EPA staff completed their review and published their revised health assessment in 1998 and 2002.

In our response to Charge Question III, we summarize the fact that many of the studies that U.S. EPA relied on were poorly designed, badly implemented, or so grossly misinterpreted to the point that they offer little or no value for estimating human health risks. Despite glaring errors and weaknesses, U.S. EPA seeks to use them as the basis for their human health risk assessment. More worrisome still, the Agency persists in commingling matters of risk assessment and risk management such that the public cannot discern where science ends and the Agency's policy preferences begin.

Risk assessment must be clearly distinguished from the management of risk. The National Academy's Red Book (NRC 1983) established this principle and PSG fully embraces it.

7.3 There must be clear distinctions between science and science policy.

The Committee's charge is to review the underlying science of perchlorate and answer a relatively short set of critical scientific questions. Although the Committee has been asked to refrain from providing policy guidance to the U.S. EPA, PSG recognizes that it would be difficult, and indeed undesirable, for the Committee to completely divorce its deliberations from the larger policy context. Nevertheless, it is essential for reasoned public discussion that the Committee clearly distinguishes its views of the underlying science from any policy views that members of the Committee might hold dear. This is especially important with respect to matters of science policy—chiefly, the appropriate degree of precaution to take into account in the characterization of risk. A strong preference for precaution in determining how much perchlorate exposure is "safe" necessarily implies a high degree of risk-taking in other areas, most notably the ability of the Departments of Defense and Energy and the National Aeronautics and Space Administration to fulfill their statutory missions.

The RfD is the single most important scientifically derived health safety value for perchlorate. The RfD will be the dominant input into the development of site remediation standards and drinking water standards, along with technological feasibility, cost, and other factors.

Even though the Committee is not charged with deriving the RfD, it needs to be aware that U.S. EPA regional offices and several states are considering, and in some cases have already adopted as a regulatory benchmark, the "provisional" RfDs U.S. EPA issued in 1992 and 1995 or the RfD the Agency proposed in the ERD. They have done so with little or no adjustment for the other factors normally considered in setting enforceable regulatory standards. Indeed, the normal policy space between the derivation of an RfD and the elucidation of regulatory standards has nearly vanished ever since U.S. EPA issued its first guidance letter on the assessment and management of perchlorate in 1992. At that time, U.S. EPA's Superfund Technical Support Center sent a guidance letter to U.S. EPA Region IX setting a "provisional" RfD of 0.0001 mg/kg-d, equivalent to 4 ppb in drinking water. This figure was based on the study of 12 Graves' disease patients by Stanbury and Wyngaarden (1952) combined with a composite uncertainty factor of 1,000 (Dollarhide 1992). In 1995 the Agency expanded the "provisional" RfD to a range of 0.0001 to 0.0005 mg/kg-d, equivalent to 4-18 ppb in drinking water, but retained Stanbury and Wyngaarden (1952) as its basis (Dollarhide 1995). Nine years and millions of dollars worth of health effects research later, U.S. EPA's risk management guidance has not changed. There is considerable concern that no amount of scientific information showing no risk will be sufficient to motivate the Agency to admit a need for correction.

7.4 The Reference Dose proposed should actually satisfy the definition of a Reference Dose– that is, it should be the highest level of exposure that is "without appreciable risk over a lifetime of exposure."

RfDs are provided and interpreted as point values. However, U.S. EPA defines the RfD as "[a]n estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." This definition is ambiguous in several respects.

- The definition does not specify whether the 10-fold uncertainty lies above, below, or on both sides of the value chosen, and risk assessors often interpret RfDs differently than do risk managers (Felter and Dourson, 1995)
- Actual uncertainty may exceed the factor of 10 despite the definition.
- The definition does not require that the value selected be the maximum value that satisfies the definition.

PSG agrees that the value U.S. EPA proposes to establish as the RfD clearly meets the definition of being "without appreciable risk." However, PSG also believes that perchlorate exposures hundreds, and perhaps thousands, of times greater also meet this definition. It is critical that the Committee frame any discussion of RfDs to ascertain the *highest* level of exposure that is without appreciable risk. As indicated above, regulatory agencies are poised to use directly whatever value the Committee derives, without significant adjustment for other factors normally considered in standard setting.

7.5 The population of greatest concern is the developing fetus, and any level of perchlorate that is "without appreciable risk" to that subpopulation is inherently safe for all other subpopulations of concern.

There appears to be near universal agreement that the developing fetus is the subpopulation of greatest concern. Moreover, there also appears to be a consensus that protecting the developing fetus from harm ensures that all other subpopulations of concern are also protected. Finally, because the fetus requires material thyroid hormones, protecting the pregnant woman also protects her developing child.

7.6 The population of greatest susceptibility is women who are hypothyroid because of iodine deficiency and become pregnant.

Iodide is essential in the production of thyroid hormones. In cases of severe maternal iodine deficiency, adverse and irreversible neurodevelopmental injury can occur in offspring.

Iodine deficiency is either rare or non-existent in the United States, primarily due to our rich and varied diet and the iodinization of salt and processed foods. Moreover, proper iodine nutrition ensures an adequate supply of T_4 to the mother and, therefore, her fetus. Environmentally relevant perchlorate exposures are well below the threshold for inhibition of iodide uptake, so adverse thyroidal effects are simply infeasible in pregnant women who are euthyroid.

For pregnant women who are hypothyroid because of Hashimoto's thyroiditis, immediate medical intervention is necessary to ensure that their children do not experience developmental impairment. In these cases, neither increasing the amount of iodine in the diets nor eliminating environmentally relevant exposures to perchlorate will have a beneficial effect.

Women who are hypothyroid because of iodine deficiency could be at risk from *high* levels of perchlorate exposure, and if they become pregnant their children also could be at risk. Of course, these children already face substantial developmental risks from their mothers' iodine deficiency. These risks will not vanish if perchlorate exposure is eliminated. A public health protective strategy requires eliminating iodine deficiency. Fortunately, the iodinization of table salt combined with varied and nutritionally balanced diets has succeeded in ensuring that the U.S. is free of iodine deficiency disease.

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