2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PERCHLORATES IN THE UNITED STATES

Perchlorates are high melting point inorganic salts that are soluble in water. There are five perchlorate salts that are manufactured in substantial amounts: magnesium, potassium, ammonium, sodium, and lithium perchlorate. Perchlorates are powerful oxidizing agents and at elevated temperatures, they can react explosively. The production volume of ammonium perchlorate far outpaces the other salts and it is used primarily as the oxidant for solid rocket boosters as well as some other industrial applications. The solid propellant on U.S. Space Shuttle booster rockets is approximately 70% ammonium perchlorate. The rockets that use perchlorates in defense and aerospace activities are engineered to utilize all of the perchlorate during a successful launch. Perchlorates are also used extensively in electroplating, fireworks, munitions, and other pyrotechnic devices. Perchlorates are also present in fertilizers that were made with Chilean saltpeter.

Perchlorates are released to the environment from a combination of anthropogenic and natural sources. Perchlorate releases from accidents at manufacturing facilities and unsuccessful rocket launches, as well as activities related to the manufacture, disposal, or research of propellants, explosives, or pyrotechnics, are well documented. Perchlorate releases from fireworks, road safety flares, the use of certain fertilizers, and natural sources of perchlorate in the environment have also been documented. Perchlorate may be released to the environment when certain consumer products that contain perchlorate are used or disposed of. These potential releases are discussed in greater detail in Chapter 6.

In water, perchlorates will rapidly dissolve and completely dissociate into the perchlorate anion and the corresponding cation. The cations of the solid perchlorate salts listed in Table 4-1 are naturally occurring and ubiquitous in the environment. It is the perchlorate anion that is responsible for the potential adverse health effects. In the remainder of this document, perchlorates will be used to refer to the solid salts and perchlorate anion (or simply perchlorate) will be used to refer to the anionic species that is monitored in the environment.

The perchlorate anion is highly mobile in wet soil and it is expected to ultimately partition to surface water and groundwater. On dry soil, it is immobile. Perchlorate is an ionic compound and therefore, does not volatilize from soil or water surfaces. Few studies were located that discuss bioaccumulation of perchlorates. Based on existing data, bioconcentration of perchlorate appears to be low for aquatic and

terrestrial species, although it has been detected in mammals, amphibians, fish, and insects near a site of known contamination. Perchlorates have been shown to accumulate in the leaves of some food crops, tobacco plants, and more generally in broad leaf plants. As water transpires from the leaves, perchlorate remains behind in the leaf due to it involatility under most environmental conditions. Although experimental studies detailing the environmental fate of perchlorates are limited, the current consensus indicates that they are persistent under most environmental conditions. The *in situ* degradation of the perchlorate anion in the environment has not yet been demonstrated, although laboratory studies indicate that it undergoes biodegradation by a wide variety of microorganisms under anaerobic conditions. There is also a growing body of evidence that the perchlorate anion may be reduced to chloride by plants.

Human exposure to perchlorates is expected to occur primarily through the ingestion of food and water containing perchlorate. Efforts are being made to determine the relative contribution of perchlorate from food and water. Data from the recently completed FDA Total Diet Study indicate that 74% of the foods analyzed had at least one sample in which perchlorate was detected. The perchlorate dietary intake was estimated for 14 different age/gender groups in the United States. The lowest intake range was estimated as 0.08–0.11 μg/kg/day for males aged 25–30 years, and the highest estimated intake was 0.35–0.39 μg/kg/day for children 2 years old. Children had the highest estimated intake on a body weight basis as compared to the other age groups because they consume more food per body weight and have different food consumption patterns when compared to the other age groups. Perchlorate has also been detected in breast milk and in certain consumer products such as dietary (vitamin and mineral) supplements, bottled water, and tobacco products.

The detection of perchlorate in drinking water supplies and in tap water samples indicates that members of the general population may be exposed by ingestion of water. Perchlorate has been identified at least once in approximately 4% of community water systems from 26 different states and 2 territories, with detectable levels averaging 9.8 μg/L and ranging from the method detection limit of 4 μg/L to a maximum at 420 μg/L.

Occupational exposure to perchlorates may occur through the inhalation of the dusts formed during their manufacture and use. Deposition of perchlorate dust into the mouth is also possible. Section 6.5 discusses exposures to the general population and occupational exposures in greater detail.

2.2 SUMMARY OF HEALTH EFFECTS

The primary and most sensitive target of the perchlorate anion (perchlorate) is the thyroid gland. Perchlorate inhibits the transport of iodide (I^-) from the blood into the thyroid follicle cells. The inhibition is thought to be accomplished by perchlorate competitively blocking iodide binding to a carrier, or sodium/iodide symporter (NIS), which catalyzes the simultaneous transfer of Na^+ and I^- across the basolateral membrane of thyroid follicle cells. Perchlorate inhibition of the NIS can limit the availability of iodide needed for the production of the thyroid hormones thyroxine (T4) and triiodothyronine (T3), which in turn, may affect the circulating levels of T4 and T3. All known effects of perchlorate on the thyroid hormone system derive directly or secondarily from the inhibition of the NIS.

T3 is essential for normal development of the nervous system and for the regulation of metabolism of cells in nearly all tissues of the body. Disruption in the availability of T3 in target tissues can result in adverse effects on a wide variety of organs and systems. Although some production of T3 occurs in the thyroid, most of the T3 that is available to extrathyroidal target tissues derives from deiodination of T4 outside the thyroid. This reaction is catalyzed by selenium-requiring microsomal enzymes known as iodothyronine deiodinases.

Because of its ability to inhibit thyroid iodide uptake, perchlorate (potassium perchlorate) was used in the past to treat subjects with hyperactive thyroids, including people with Graves' disease, an autoimmune disorder. Perchlorate currently is used to treat amiodarone-induced thyrotoxicosis and for diagnosing impairments in the synthesis of thyroid hormones in the thyroid (perchlorate iodide discharge test). Doses for clinical uses of perchlorate have ranged from 5 to 20 mg/kg/day. Considerable information exists on the effects of perchlorate in patients with Graves' disease and in subjects with hyperthyroidism of other etiology, and some of this information is also presented in Chapter 3 of this document. However, the main purpose of this review is to describe the effects of perchlorate on subjects otherwise without thyroid disorders.

The main route of exposure to perchlorate for the general population and those exposed to contaminated media is through ingestion of food and/or water. As noted previously, efforts are being made to determine the relative contribution of perchlorate from food and water. Information on the effects of perchlorate in humans comes from occupational studies, studies of the general population (adults, children, and neonates), and studies of controlled exposure in volunteers. Occupational studies and studies in volunteers who ingested daily doses of perchlorate $\leq$0.05 mg/kg/day for 14 days or

≤0.04 mg/kg/day for 6 months days showed no evidence of adverse hematological, hepatic, renal effects, or clinically significant thyroid effects. A study of the general population exposed to perchlorate via the drinking water found no significant increase in the incidence of thyroid diseases relative to a comparison group whose drinking water did not have perchlorate. Most studies of children and neonates in areas where perchlorate has been detected in the drinking water have reported no significant alterations in indices of thyroid function among the subjects studied. Two studies of Arizona and California residents found that increased levels of perchlorate in drinking water were associated with increased serum concentration of thyroid stimulating hormone (TSH) in neonates, but the methods used in these two studies have been criticized in the literature. There are no reports of exposure to perchlorate being associated with adverse reproductive effects or cancer in humans, or with adverse immunologic effects in healthy humans.

The thyroid is also the main target of perchlorate toxicity in animals. Most experimental studies in animals designed to characterize the effects of perchlorate exposure have been done in rats. Rats have been shown to be more sensitive to agents that disturb thyroid function than are humans. Significant changes in serum levels of thyroid hormones at perchlorate doses as low as 0.009 mg/kg/day were observed in 14- and 90-day studies in adult rats. Studies in mice have reported similar findings. In general, morphological alterations in the thyroid become noticeable at doses higher than those that induced changes in serum hormone levels. There is no conclusive evidence that perchlorate is an immunotoxicant in animals. Perchlorate did increase the response to a known contact sensitizer in mice, but it is not known whether perchlorate itself is a contact sensitizer. Perchlorate has shown no evidence of being a neurotoxicant when administered to adult animals, although no comprehensive testing has been done in adult animals. A 2-generation reproductive study in rats did not observe any significant alterations in standard reproductive indices. Several developmental studies have shown that administration of low doses of perchlorate (≥0.009 mg/kg/day) to pregnant animals results in alterations in thyroid parameters (serum T4, T3, and TSH, and changes in morphology of the thyroid) in newborn and young animals. Some studies that conducted neurobehavioral testing in offspring of rats exposed to perchlorate during pregnancy reported no significant treatment-related effects, but the interpretation of the results has generated some debate among scientists. Perchlorate has produced thyroid cell hyperplasia and papillary and/or follicular adenomas and/or carcinomas in rats and mice exposed to relatively high doses. Perchlorate itself does not appear to be genotoxic.

An expanded discussion of thyroid effects of perchlorate in healthy adults and the young exposed perinatally is presented below. Neurodevelopmental effects are included under the same heading of

Endocrine (Thyroid) Effects since neurodevelopmental alterations are assumed to occur due to perchlorate-induced perturbation of maternal and/or fetal thyroid function.

Endocrine (Thyroid) Effects. As mentioned above, adverse effects on a wide variety of organ systems can result from disruption in the availability of T3 to target tissues. Organ systems affected by disturbances in T3 levels include the skin, cardiovascular system, pulmonary system, kidneys, gastrointestinal tract, liver, blood, neuromuscular system, central nervous system, skeleton, male and female reproductive systems, and numerous endocrine organs, including the pituitary and adrenal glands. Such an array of secondary potential targets underscores the need to maintain an adequate level of circulating thyroid hormones. Furthermore, because thyroid hormones play a critical role in the neurological development of the fetus, there is concern that altered thyroid levels (maternal and/or fetal) during pregnancy could result in neurodevelopmental effects.

For the most part, recent studies do not indicate that perchlorate exposure produces large changes in thyroid function in males or in women with adequate iodine intake. In an occupational study in which the investigators estimated a maximum ingested dose of 34 mg perchlorate/day, or approximately 0.5 mg/kg/day assuming a body weight of 70 kg, no significant alterations of thyroid parameters were observed. Another study of adults from the general population found no significant increase in the prevalence of thyroid diseases in a population exposed to perchlorate in the drinking water (4–24 μg/L) (0.0001–0.0007 mg/kg/day) relative to a comparison population not exposed to perchlorate. With two exceptions, studies of neonates in areas with perchlorate contamination in the drinking water have also found no evidence of altered thyroid parameters among the newborns. One study found that increased levels of perchlorate in drinking water (6 μg/L) (0.0002 mg/kg/day) were associated with increased serum concentration of TSH in a study of neonates in Arizona. Another study reported similar findings of neonates in California. However, as indicated earlier, the methods used in the latter two studies have been criticized in the literature. A study also examined school-age children in Chile, and found no association between the concentration of perchlorate in water and altered thyroid function. In that study, residents from one location were exposed to perchlorate in water at a concentration of approximately 100 μg/L. Assuming a daily intake of 1–2 L of water for the school-age children and a body weight of about 25 kg (measured in the study), the daily intake of perchlorate via drinking water could have been 0.004–0.008 mg/kg/day. As often occurs with human studies, the studies mentioned above have various design limitations that must be considered in applying findings to health risk assessment. For example, in some of the occupational studies, there could have been exposure misclassification. In addition, occupational studies had a cross-sectional design and, thus, were unable to account for any effects of

exposure to perchlorate that might have occurred in workers who left employment for any reason. In the studies that measured TSH in neonates, TSH was measured on a low T4 percentile subset without consideration of age at screen; since T4 distribution depends on age, births with screen ages that have higher T4 are less likely to be selected for TSH analysis. Explicit measures of perchlorate exposure were not obtained in these studies. For example, in a study, exposures were estimated from place of birth; thus, individual levels of exposure could not be linked to T4 levels. Regardless of these and other limitations, these studies collectively appear to rule out a large perchlorate-related effect on thyroid function.

The 14-day studies of controlled exposure in volunteers showed that iodide uptake by the thyroid (assessed as radioiodine uptake) can be inhibited to a considerable extent in humans without a significant change in circulating levels of thyroid hormone and TSH. This is not unexpected given the relatively large storage capacity of the thyroid gland of humans. A study reported a maximum inhibition of approximately 70% relative to baseline in subjects who received the highest dose of perchlorate, 0.5 mg/kg/day. No significant inhibition was observed at a dose of 0.02 mg/kg/day. Another study in volunteers administered up to approximately 0.04 mg perchlorate/kg/day for 6 months found no significant alterations in thyroid function tests, including radioiodine uptake.

Studies in animals have shown that exposure to perchlorate can induce a wide range of effects on the thyroid depending on the dose and duration of exposure. Studies conducted in the past 10 years have used much lower doses than earlier studies and have described changes in thyroid parameters in rats administered doses as low as 0.009 mg perchlorate/kg/day. The effects have been observed in adults and also in young rats exposed *in utero* and via dams' milk. A study reported a 20% decrease in serum T3 in male rats following 14 days of dosing with 0.009 mg perchlorate/kg/day, and a 14% decrease in T4 and 12% decrease in T3 in males given the same dose level for 90 days. The magnitude of the effects was dose-related and the effects were also observed in females, although the latter appeared somewhat less sensitive. At higher doses (≥0.17 mg/kg/day), serum levels of TSH increased and histological alterations were evident in the thyroid gland (8.5 mg/kg/day).

Administration of perchlorate to pregnant animals can result in alterations in thyroid parameters in the offspring. The lowest maternal dose at which this has been reported is 0.009 mg perchlorate/kg/day. This dose level (and higher) significantly increased TSH and decreased T4 in the dams on gestation day 21, and decreased T3 in newborn pups. Whether alterations in fetal thyroid parameters are due solely to an altered maternal thyroid, to altered fetal thyroid, or to a combined effect is not totally clear. However, there is sufficient information that supports the view that maternal thyroid hormones are crucial for

normal development. Rat fetal tissues have been shown to contain both T4 and T3 prior to the onset of hormone production by the fetal thyroid on approximately day 17 of gestation. Furthermore, thyroid hormone-responsive genes that are important in early development of the brain are expressed in the rat fetus prior to fetal thyroid hormone production, and expression of these genes is sensitive to the maternal thyroid hormone status. Disruption of the maternal thyroid hormone system of rats by removal of the maternal thyroid or maternal iodide deficiency results in decreased levels of thyroid hormones in the fetus and congenital hypothyroidism. In studies with perchlorate, there is only one published report of thyroid effects in the offspring in the absence of apparent maternal thyroid effects. This was reported in a study in guinea pigs administered doses as high as 531 mg/kg/day of perchlorate during pregnancy. Overall, the available information in animals suggests that as long as serum maternal levels of thyroid hormones are maintained within normal levels during pregnancy, there is no apparent developmental risk. Observations in humans show that placental transfer of maternal thyroid hormones results in cord blood levels that are just below the lower range of normal in newborn infants, suggesting that transfer during fetal life is at least partially protective in cases where the fetus cannot produce adequate amounts of T4, providing that the maternal thyroid hormone production is not compromised. If this is the case, then inhibition of fetal thyroid iodide uptake by perchlorate would not be expected to be sufficient, in itself, to produce hypothyroidism *in utero*, and any effects of perchlorate on fetal hormone status are likely to be caused by the combined effects of limiting iodide uptake in the maternal and fetal thyroids. PBPK models predict that pregnant women and the fetus will have higher blood concentrations of perchlorate and greater iodide uptake inhibition at a given concentration of perchlorate in drinking water than either nonpregnant adults or older children.

As discussed in detail in Section 3.5.3, Animal-to-Human Extrapolations, the response of human adults to short-term oral dosages (mg/kg/day) of perchlorate is quantitatively different from the response observed in rats given comparable dosages. Similar doses of perchlorate result in a more pronounced hypothalamic-pituitary-thyroid (HPT) response in rats, which serves to regulate thyroid iodide transport and hormone production in response to a decrease in serum thyroid hormones and iodide levels. Differences in the perchlorate dose-response relationships between human and rats are thought to be related to a smaller and more rapid turnover of the hormone pool in the rat thyroid and to a more rapid clearance of secreted hormone in the rat (serum half-life for T4 is shorter in rats than in humans). The NAS recommended that animal studies did not adequately serve as a surrogate for human studies due to specific species differences with humans, as demonstrated in the studies discussed above.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for perchlorates. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure. In addition, no dermal exposure risk from perchlorate has been documented in the literature.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

No MRLs were derived for inhalation exposure to perchlorate since adequate experimental data were not available by this route of exposure. No inhalation studies in animals were located. The inhalation database in human is limited to three studies of workers at ammonium perchlorate production facilities exposed during an unusual schedule of three 12-hour shifts followed by 3 days without exposure (long-time, intermittent exposure) (Braverman et al. 2005; Gibbs et al. 1998; Lamm et al. 1999).

Oral MRLs

ATSDR adopts the National Academy of Sciences (NAS 2005, *Health Implications of Perchlorate Ingestion*) recommended chronic reference dose (RfD) of 0.0007 mg/kg/day for the chronic oral MRL for the perchlorate anion (rather than for individual salts). EPA has also adopted this value and the perchlorate Integrated Risk Information System (IRIS) (*Perchlorate and Perchlorate Salts Summary*)

summary was first posted on 02/18/2005. ATSDR's decision was made after a careful evaluation of the NAS report and of studies that have been published after the NAS (2005) report. The results from newer studies do not change the bottom-line recommendation.

NAS based its derivation of the RfD on the findings of a study by Greer et al. (2002). The RfD was based on a no-observed-effect level (NOEL) of 0.007 mg perchlorate/kg/day for thyroidal uptake of radioactive iodine (RAIU) in 37 healthy (euthyroid) volunteers (16 males, 21 females) who consumed potassium perchlorate in drinking water in doses of 0.007, 0.02, 0.1, or 0.5 mg perchlorate/kg/day for 14 days. In 24 subjects, thyroidal uptake of RAIU was measured 8 and 24 hours after administration of radioactive iodine on exposure days 2 and 14 and also 15 days after exposure. To estimate daily iodine intake, 24-hour urine samples were collected. Free and total T4, T3, and TSH were sampled 16 times throughout the study. Serum antibodies to thyroglobulin and thyroid peroxidase were also measured. Hematological and clinical chemistry tests were also conducted throughout the study. Baseline thyroid iodide uptake varied greatly among the subjects: 5.6–25.4% for the 8-hour uptake and 9.8–33.7% for the 24-hour uptake. Perchlorate inhibited RAIU in a dose-related manner. As a percentage of baseline RAIU, inhibition in the 0.007, 0.02, 0.1, and 0.5 mg/kg/day dose groups was 1.8, 16.4, 44.7, and 67.1%, respectively. The small decrease in RAIU at 0.007 mg/kg/day was not statistically significant and is well within the variation of repeated measurements in normal subjects. The dose is considered the NOEL. No significant differences were seen between the 8- and 24-hour measurements or between the 2- and 14-day measurements. On post exposure day 15, RAIU rebounded to values slightly over but not significantly >100%. Consumption of perchlorate did not significantly alter serum TSH, free T4, or total T4 and T3 levels. Serum anti-thyroglobulin levels were below detection levels in all samples tested. Serum anti-thyroid peroxidase levels were elevated in two subjects at the screening visit and thus, were not related to treatment with perchlorate. Hematology and clinical chemistry tests to assess liver and kidney function revealed no significant deviations from normal ranges. No difference was observed between the response of male and female subjects. The RfD was calculated by dividing the NOEL of 0.007 mg/kg/day for inhibition of radioiodide uptake and serum hormone levels by an uncertainty factor of 10 (see below). As indicated by the NAS (2005), iodide uptake inhibition is a key biochemical event that precedes all potential thyroid-mediated effects of perchlorate exposure. Using a nonadverse effect that is upstream of adverse effects is a conservative approach to perchlorate hazard assessment.

Based on the known mechanism of action of perchlorate as a competitive inhibitor of NIS and on the elimination half-time of perchlorate of approximately 8 hours (perchlorate is not expected to accumulate in the body), the NAS concluded that a dose that produced minimal inhibition of thyroid iodide uptake

after 14 days of continuous exposure would also have no appreciable effects on thyroid iodide uptake with more prolonged (i.e., intermediate or chronic) exposure. On this basis, the 14-day study was used as the basis for adopting the RfD for the chronic MRL. This is supported by another 14-day study (Lawrence et al. 2000), long-term studies of workers (Braverman et al. 2005; Gibbs et al. 1998; Lamm et al. 1999), and studies of the general population (Li et al. 2001; Téllez et al. 2005) exposed to perchlorate that found no significant alterations in thyroid function in the populations examined. A study by Braverman et al. (2006) in which 13 volunteers dosed with perchlorate in capsules for 6 months at doses of 0, 0.5, and 3 mg/day exhibited no changes in iodine uptake or thyroid hormone level was considered for derivation of the MRL. However, this study was limited by a small number of subjects per group (4–5), dosing by capsule rather than intermittent exposure in drinking water, and lack of information on RAIU during the first 3 months of the study.

An uncertainty factor of 10 was applied to the NOEL of 0.007 mg/kg/day. The uncertainty factor of 10 is intended to protect the most sensitive population—the fetuses of pregnant women who might have hypothyroidism or iodide deficiency. Other sensitive populations include preterm infants and nursing infants. As discussed by NAS (2005), preterm infants are more sensitive than term infants. The fetus is dependent on maternal thyroid hormones at least until the fetal thyroid begins to produce T4 and T3 (Zoeller and Crofton 2000). In humans, this occurs at approximately 16–20 weeks of gestation. Thyroid hormones are present in human amniotic fluid at 8 weeks of gestation prior to the onset of fetal thyroid hormone production (Contempre et al. 1993; Thorpe-Beeston et al. 1991). Thyroid hormone receptors are present and occupied by hormone at this time as well, suggesting that the fetus is capable of responding to maternal thyroid hormones (Bernal and Pekonen 1984; Ferreiro et al. 1988). The contribution of maternal thyroid hormones to the fetal thyroid hormone status is also evident from infants who have an inherited disorder that abolishes T4 production but are born, nevertheless, with normal serum thyroid hormone levels (i.e., euthyroid) and become hypothyroid after birth if not administered thyroid hormones within the first 2 weeks after birth (Larsen 1989; van Vliet 1999; Vulsma et al. 1989). This suggests that in the complete absence of fetal thyroid function, the maternal thyroid is able to maintain at least partially protective levels of thyroid hormone in the fetus at late term. Uncorrected maternal hypothyroidism, on the other hand, may result in impaired neurodevelopment of the fetus (Haddow et al. 1999; Pop et al. 1999). By inhibiting NIS in breast tissue (Levy et al. 1997; Smanik et al. 1997; Spitzweg et al. 1998), perchlorate may also limit the availability of iodide to nursing infants, who depend entirely on breast milk for the iodide needed to produce thyroid hormone (Agency for Toxic Substances and Disease Registry 2004). No information is available on the doses in humans that might decrease iodide uptake into breast milk. A recent study of 57 women in the Boston area found that 47%

of the women sampled may have been providing breast milk with insufficient iodine to meet the infants' requirements (Pearce et al. 2007); however, the breast milk iodine concentrations were not correlated with perchlorate exposure. Radioiodine uptake into mammary milk was decreased in rats exposed to 1 or 10 mg/kg/day perchlorate in drinking water (Yu et al. 2002). Studies conducted in cows and goats have also shown that perchlorate can decrease radioiodine uptake into mammary milk (Howard et al. 1996). As discussed by Ginsberg et al. (2007), additional factors that make neonates a sensitive group include their shorter serum half-life for T4 of approximately 3 days compared to approximately 7–10 days in adults, a lower storage capacity of the thyroid for T4, and possibly slower urinary clearance of perchlorate due to immature renal function. Another potential susceptible population is women with urinary iodine levels <100 µg/L, as regression analysis of a population study by Blount et al. (2006) indicated that perchlorate exposure was correlated with decreased T4 and increased TSH. Limitations of the study acknowledged by the investigators include those common to cross-sectional analyses, the assumption that urinary perchlorate correlate with levels in the thyroid stroma and tissue, and the measurement of total T4 rather than free T4. According to the World Health Organization (WHO 2004), median urinary iodine levels ≥100 µg/L indicate sufficient iodine intake for the non-pregnant population, whereas pregnant women should maintain urinary levels of iodine >150 µg/L. The American Thyroid Association (2006) recommends that women generally consume iodine from dairy products, bread, seafood, meat, and some iodized salt, but pregnant and lactating women may require additional supplements and vitamins.

Recently, Blount et al. (2007) assessed perchlorate exposure in a representative sample of the U.S. population and compared the results with the NAS-recommended RfD (NAS 2005). The study comprised 2,820 participants of National Health and Nutrition Survey (NHANES) (2001–2002), 6 years and older. The investigators assessed perchlorate exposure based on urinary perchlorate, urinary creatinine concentration, and physiological parameters predictive of creatinine excretion rate. By measuring perchlorate in urine, the investigators assessed combined exposure to perchlorate from all sources. In adults, the estimated median dose of perchlorate was 0.066 µg/kg/day and the 95th percentile of the distribution of estimated daily dose was 0.234 µg/kg/day (CI, 0.202–0.268 µg/kg/day), both values lower than the MRL of 0.0007 mg/kg/day (0.7 µg/kg/day) that ATSDR adopted from the NAS. Only 11 out of 1,532 adults aged 20 years and older had estimated perchlorate exposure that exceeded the NAS-recommended RfD. Since the study included participants 6-year-old and older, the investigators did not have exposure information for infants. In women of reproductive age, which Blount et al. (2007) suggested can be used as surrogate population for assessment of fetal exposure, the median estimated perchlorate dose was 0.057 µg/kg/day and the 95th percentile 0.214 µg/kg/day. For a subset of 110 pregnant women, the estimated median perchlorate dose was 0.066 µg/kg/day. The median dose of

0.066 µg/kg/day for adults estimated by Blount et al. (2007) is in the same range of the lower-bound range of average perchlorate food intakes for men and women over 20 years of age of 0.08–0.11 µg/kg/day recently estimated by the FDA in the Total Diet Study (Murray et al. 2008).

The MRL has been reviewed by experts in the field of perchlorate toxicology in 2007 after publication of the NAS (2005) report and the publication of the results of the Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) data (Blount et al. 2007). The expert peer reviewers concluded that the MRL should still be based on the RfD as recommended by the NAS Panel Report (2005) given the research data available at the time of the 2007 peer review.