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. The solid propellant on U.S. Space Shuttle booster rockets is approximately 70% ammonium perchlorate. It has been estimated that over 90% of perchlorates produced are used for defense and aerospace activities. 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.

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.

In January 1997, the California Department of Health Services began to test for perchlorates at the Aerojet aerospace facility outside of Sacramento as regulators became aware of groundwater contamination at the site. To perform a complete assessment at the site, new methods to detect the perchlorate anion were developed that improved the detection limits by 2 orders of magnitude from 400 to 4 µg/L. Monitoring studies with this more sensitive method detected perchlorate contamination far from known sources of its production and use. Within a short time, it was detected in surface water, groundwater, and drinking water samples in California, Nevada, and Utah.

The detection of the perchlorate anion far from its source of production and use seemed to be at odds with the explosive reactivity of the solid perchlorate salts. This is because perchlorates have a large energetic barrier that must be overcome before they begin reacting and, therefore, they are relatively stable at

moderate temperatures. Moreover, dilute aqueous solutions of the perchlorate salts, typical of those found in the environment, have almost no oxidizing power.

Although experimental studies detailing the environmental fate of perchlorates are limited, the current consensus indicates that they are persistent. 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. The available data set is not yet sufficient to predict which plants are capable of accumulating and/or reducing perchlorate.

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. It will not volatilize to the atmosphere, although perchlorates may be present in wind-borne dusts, especially near hazardous waste sites. Few studies were located that discuss bioaccumulation of perchlorates. Based on existing data, bioconcentration of perchlorate appears to be low, although it has been detected in plants, mammals, amphibians, fish, and insects near a site of known contamination.

Human exposure to perchlorates is expected to occur primarily through the ingestion of contaminated water, as it has been found in drinking water supplies, tap water samples, and groundwater. Levels of potential exposure by this route are difficult to assess, as a comprehensive survey of monitoring data has not been published in the peer reviewed literature. Perchlorates have also been found in food, cow’s milk, and human breast milk. Members of the general population may also be exposed to low levels of perchlorates as a result of their presence in tobacco products. Discovery of trace quantities of perchlorates in areas where they have not been known to be manufactured or used indicates that humans may be exposed in these areas as well. However, the nature of this contamination and exposure is unclear and must be studied further. Occupational exposure to perchlorates may occur through the inhalation of and dermal contact with the dusts formed during its manufacture and use. Deposition of perchlorate dust into the mouth is also possible. Children’s exposure to perchlorate is also expected to occur primarily through the ingestion of contaminated drinking water, food, and milk. They may also ingest perchlorates if they put small fireworks or contaminated soil in their mouths. Children may undergo dermal exposure if they crawl over perchlorate-contaminated soil. Children may also be exposed if they touch contaminated soil with their hands and then place their hands in their mouth.

2.2 SUMMARY OF HEALTH EFFECTS

The primary 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 toxic 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, but 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 for those living near waste sites is through drinking 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$0.04 mg/kg/day for 14 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. 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 ($\geq$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. Two 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. Also being debated is whether morphological changes observed in some areas of the brain from pups exposed to perchlorate *in utero* represent true alterations caused by treatment with the test material or are just normal variation. 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 in humans exposed to perchlorate have not detected clinically significant alterations in thyroid function. 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. 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. Similar findings were reported in a study of neonates in California. However, as indicated earlier, the methods used in the latter two studies have been criticized in the literature. In another study, school-age children were examined and no association was found 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 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, and particle size of the perchlorate aerosol was not factored in the estimation of absorbed dose. 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, 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. It was reported that a maximum inhibition of approximately 70% relative to baseline occurred in subjects who received the highest dose of perchlorate, 0.5 mg/kg/day. No toxicologically significant inhibition was observed at a dose of 0.02 mg/kg/day. One limitation of these studies is their low power due to the small sample sizes, 37 subjects in one study and 9 in another.

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 20% decrease in serum T3 was reported 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). As discussed in detail in Section 3.5.3, Animal-to-Human Extrapolations, there are studies in humans and rats that provide comparative information that strongly suggests that rats are more sensitive than humans to perchlorate-induced disruption of thyroid hormone levels. Doses of perchlorate that depressed serum levels of T3 and T4 and increased levels of TSH in rats had minimal effects on thyroid iodide uptake. By contrast, similar doses administered to humans caused no significant changes in serum hormone, but inhibited thyroid iodide uptake by as much as 70%. These observations suggest that considerably greater inhibition of thyroid iodide uptake is required to produce a decrease in serum thyroid hormone levels in humans compared to rats. This is 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.

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 also suggest that maternal thyroid hormones may be sufficient to maintain normal levels of hormone in the fetus as long as 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.

2.3 MINIMAL RISK LEVELS

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.

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.

Oral MRLs

At this time, ATSDR is not deriving acute or intermediate oral MRLs. Through our normal process, ATSDR invites public comment on the derivation of these values.

ATSDR adopts the National Academy of Sciences (NAS 2005) chronic reference dose (RfD) of 0.0007 mg/kg/day for the chronic oral MRL. 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/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 radioactive iodine (RAIU) was measured 8 and 24 hours after administration of radioactive iodine on exposure days 2 and 14 and also 15 days after exposure. 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 antiglobulin 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).

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 studies were used as the basis for adopting the RfD for the chronic MRL. This is supported by long-term studies of workers (Braverman et al. 2005; Gibbs et al. 1998; Lamm et al. 1999) and of the general population (Li et al. 2001) exposed to perchlorate that found no significant alterations in thyroid function in the populations examined.

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 et al. 1999; Vulsma et al. 1989). This suggests that, in the complete absence of fetal thyroid function, the maternal thyroid is able

to maintain adequate 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. 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).