EXECUTIVE SUMMARY

The purposes of this document is to present an assessment that updates previous provisional values issued by the U.S. Environmental Protection Agency (EPA) for an oral reference dose (RfD) for perchlorate and revises the assessment previously released as a draft external review document (U.S. Environmental Protection Agency, 1998d). The objective of this assessment is to derive a human health risk estimate, based on an evaluation of its potential to cause toxicity or cancer, and to provide a screening-level ecological risk assessment for perchlorate based on all toxicity data that recently have become available to the Agency as of fall 2001. Another important objective was to evaluate the evidence for indirect exposures, i.e., those exposures not by direct ingestion of contaminated water. This revised assessment incorporates data from new studies and analyses in response-level to recommendations made at a previous peer review of the 1998 draft (Research Triangle Institute, 1999). Most of these data were obtained as results of a testing strategy that was designed with knowledge of the mode of action for perchlorate toxicity that identified major data gaps in the data available prior to 1997. This executive summary concisely presents key findings from the present assessment.

SUMMARY FINDINGS

Sources of Perchlorate Contamination and Occurrence

- Perchlorate is an oxidizing anion that originates as a contaminant in ground and surface waters from the dissolution of ammonium, potassium, magnesium, or sodium salts. Perchlorate is exceedingly mobile in aqueous systems and can persist for many decades under typical ground and surface water conditions.
- Ammonium perchlorate is manufactured for use as the oxidizer component and primary ingredient in solid propellant for rockets, missiles, and fireworks. Because it is a reducing agent, it can undergo a variety of intramolecular redox reactions that lead to the release of gaseous products. Through such reactions, it acts as a thrust booster.
- Perchlorate salts are also used on a large scale as a component of air bag inflators. Perchlorate salts are also used in nuclear reactors and electronic tubes, as additives in lubricating oils, in

tanning and finishing leather, as a mordant for fabrics and dyes, in electroplating, in aluminum refining, and in rubber manufacture, as a mordant for fabrics and dyes, and in the production of paints and enamels. Chemical fertilizer had been reported to be a potential source of perchlorate contamination, but new investigations by the Agency have determined that this is not an issue for agricultural applications.

- Large-scale production of perchlorate-containing chemicals in the United States began in the mid-1940s. Because of its shelf life, perchlorate must be washed out of the United States' missile and rocket inventory to be replaced with a fresh supply. Thus, large volumes have been disposed of in various states since the 1950s.
- Perchlorate began to be discovered at various manufacturing sites and in well water and drinking water supplies within the months following the April 1997 development of an ion chromatography analytical method that achieved a method detection limit (MDL) of approximately 1 ppb and a minimum reporting limit (MRL) of 4 ppb. There are 20 states with confirmed releases in ground or surface water. There are 40 states that have confirmed perchlorate manufacturers or users based on EPA Information Request responses.

  In California, most of the locations where perchlorate has been detected are associated with facilities that have manufactured or tested solid rocket fuels for the Department of Defense or the National Aeronautics and Space Administration.
- To date, there has not been a systematic national survey of perchlorate occurrence and a National Primary Drinking Water Regulation for perchlorate does not currently exist. Perchlorate was placed on the Contaminant Candidate List (CCL) in March 1998. The CCL lists priority contaminants (defined as either known or anticipated to occur in public water systems) in need of research, guidance development, regulatory determinations, or monitoring by the states. Perchlorate was listed as a contaminant that required additional research and occurrence information before regulatory determinations could be considered.
- Perchlorate was placed on the Unregulated Contaminants Monitoring Rule (UCMR) in March 1999 (Federal Register, 1999) to gather needed exposure information. Under the UCMR, all large public water systems and a representative sample of small public water systems were required to monitor for perchlorate beginning in January 2001. This effort does not extend to investigating potential sources in ground and surface water that have not migrated into public water supplies. Identification of the magnitude and extent of perchlorate occurrence in the

environment is important in assessing the routes of exposure to humans and for determining the different types of organisms and ecosystems that may be affected.

- In early 2000, an analytical method to detect perchlorate in drinking water (EPA Method 314.0) using ion chromatography was published as a direct final rule (Federal Register, 2000). The EPA Method 314.0 was also approved as a monitoring method for the UCMR (Federal Resister, 2000). The MDL for the method is 0.53 ppb and the MRL is 4 ppb. Improvements developed commercially in the analytical capabilities may lower the MRL to the sub-part per billion level in the near future.
- Adequate exposure characteristics of transport and transformation in the environment are also absent. Preliminary biotransport studies at six contaminated sites indicate a potential for uptake into plant and animal tissues in ecosystems. Extension of analytical methods to detect perchlorate in plant and animal tissues awaits validation before a conclusive determination can be made.

An Integrated Approach to Comprehensive Risk Characterization

- Perchlorate is of concern for several reasons. First, there were uncertainties in the toxicological database available that could be used to evaluate the potential for perchlorate to produce human health effects when present at low levels in drinking water. The purpose of the targeted toxicity testing strategy was to develop a database to address key data gaps. Secondly, the actual extent of the occurrence of perchlorate in ground and surface waters is not known at this time. Additionally, the efficacy of different treatment technologies for various water uses (such as drinking water or agricultural applications) and different scales (i.e., large or small volumes) is still being determined. Finally, the extent and nature of ecological impact or transport and transformation phenomena in various environmental media have only, as yet, been studied superficially.
- To adequately and comprehensively characterize the risks posed by perchlorate contamination and to develop scientifically-based management strategies that effectively mitigate the potential risks posed by perchlorate contamination, several advances are essential. The analytical methods used to characterize various exposures must be accurate and precise. The exposure estimates cannot be gauged with respect to their risk unless robust health and ecological risk estimates are available. Treatment technologies should be targeted to levels of concern and

tailored to the intended water use. Technology transfer is necessary so that all affected parties and concerned citizens are apprised of accurate and reliable information that is up to date with the evolving state of the science.

- The toxicity testing strategy was expedited through a unique partnership between the Department of Defense and EPA, together with members of an Interagency Perchlorate Steering Committee (IPSC), which includes other governmental representatives from the National Institute for Environmental Health Sciences (NIEHS) and affected state, tribal, and local governments.
- The charge of the IPSC is to facilitate and coordinate accurate accounts of related technological issues (occurrence surveys, health assessment, ecotoxicology assessment, treatability, waste stream handling, and analytical detection). This assessment is intended to address the need for evaluation of perchlorate's potential to cause human health effects or impact on ecological systems, based on currently available data.

Physicochemical Characteristics

- As an oxidant, perchlorate is kinetically nonlabile. This means the reduction of the central chlorine atom from an oxidation state of +7 (perchlorate) to −1 (chloride ion) occurs extremely slowly. Sorption is not expected to attenuate perchlorate because it absorbs weakly to most soil minerals. Natural chemical reduction in the environment is not expected to be significant. These two factors account for perchlorate being both very mobile in aqueous systems and persistent for many decades under typical ground and surface water conditions.
- The activation energy to perchlorate reduction is so high that it cannot be expected to act as an oxidant under human physiological conditions (i.e., dilute solution, unelevated temperatures, neutral pH). This is supported by absorption, distribution, metabolism, and elimination studies that show perchlorate is excreted virtually unchanged in the urine after absorption.

Hazard Identification and Mode of Action Testing Strategy

- The health effects and toxicity database available in the spring of 1997 was determined to be inadequate for quantitative risk assessment by an independent (non-EPA) peer review. A testing strategy was developed based on a hazard identification using the available data and the suspected mode of action for perchlorate to target testing on potential effects of perchlorate.

Data from this effort was used to support the previous EPA draft assessment and this revised assessment in 2002.

- To design a testing strategy based on the mode of action for a chemical, it is necessary to understand its toxicokinetics and toxicodynamics. Perchlorate is readily absorbed from the intestinal tract, and oral uptake is considered to be the major route of exposure. Because of its high charge, perchlorate does not pass readily through the skin. Exposure via inhalation is expected to be negligible because the vapor pressure of perchlorate salts and acids is expected to be low at room temperatures. Droplet size during showering likely would preclude inhalation of perchlorate-contaminated water as an aerosol. Perchlorate is known to inhibit the uptake of iodide in the thyroid at the sodium (Na+)–iodide (I-) symporter, or NIS, thereby causing a reduction in the hormones thyroxine (T4) and triiodothyronine (T3). When these hormones enter the blood circulation, they are bound to plasma proteins. There may be other locations of inhibition of iodide transport in the gland. Perchlorate itself is not metabolized in the thyroid or peripheral tissues.
- Control of circulating concentrations of these hormones is regulated primarily by a negative feedback known as the hypothalamic-pituitary-thyroid axis or feedback system involving three organs: (1) the thyroid, which produces T4 and T3; (2) the pituitary gland which produces TSH; and (3) the hypothalamus, which also responds to and helps to maintain optimal T4 and T3 levels. The hypothalamus stimulates the pituitary gland through thyrotrophic-releasing hormone (TRH) to produce thyroid stimulating hormone (TSH), which then prompts the thyroid to produce T4 and T3. Cells in the hypothalamus and pituitary gland respond to the levels of circulating T4 and T3, such that when thyroid production levels are low, there is a signal to increase the output of TRH and TSH. Circulating hormone levels (T4, T3, and TSH) can be monitored readily to serve as biomarkers of exposure and effect of agents that disrupt the status of this negative feedback system.
- The hypothalamic-pituitary-thyroid feedback system for regulation of thyroid hormones is conserved across species. Differences in plasma protein binding between rats and humans account for differences in the circulating half-life of the hormones and in thyroid response to TSH between the species. New studies since 1999 have confirmed that the inhibition of iodide uptake by perchlorate at the NIS is essentially the same sensitivity across species. This is

important when considering decrements in T4 as important to neurodevelopmental effects versus neoplasia that results in the gland due to stimulation by TSH.

- Given its mode of action as an inhibitor of iodide uptake that results in disturbances of the hypothalamic-pituitary-thyroid axis, concerns arose about the potential for perchlorate to cause carcinogenic, neurodevelopmental, developmental, reproductive, and immunotoxic effects. Further, there is concern for ecotoxicology effects on various aquatic and terrestrial plants and animals.
- The human health testing strategy for perchlorate developed in 1997 originally included eight different recommended studies to address data gaps and enhance the mechanistic information on the mode of action. The goal of these studies was to provide a comprehensive database on which to arrive at a revised human health risk assessment with greater confidence than previous recommended provisional values. These studies are described briefly below.
  (1) A 90-day oral bioassay to identify other target tissues in young adult rats; to provide data on the effects of repeated exposures to perchlorate on T3, T4, and TSH levels; to evaluate recovery of effects after 30 days; and to screen for some reproductive parameters. A genotoxicity assay also was performed on rats from the terminal sacrifice.
  (2) A neurodevelopmental study in rats to evaluate the potential for functional and morphological effects in offspring from the mother exposed during pregnancy and lactation.
  (3) A Segment II developmental study in rabbits to evaluate the potential for perchlorate to cause birth defects and to provide data on thyroid hormone effects in a second species other than the rat.
  (4) A two-generation reproductive toxicity study to evaluate the potential for perchlorate to cause deficits in reproductive performance in adult rats and for toxicity in the young offspring.
  (5) Absorption, distribution, metabolism, and elimination (ADME) studies to characterize the pharmacokinetics of perchlorate in laboratory animals and humans and to provide data necessary to allow construction of models for quantitative description of different internal dose metrics and interspecies extrapolation.

(6) Mechanistic studies that characterize the effects of perchlorate on the iodide uptake mechanism across species as a link with the ADME studies to aid in the quantitative extrapolation of dose across species.

(7) A battery of genotoxicity assays to evaluate the potential for carcinogenicity by evaluating the potential for direct effects on deoxyribonucleic acid (DNA).

(8) Immunotoxicity studies to evaluate the potential for perchlorate to disrupt immune function, including cell-mediated and humoral toxicity.

- After the External Peer Review in 1999, additional studies were performed to replicate the neurodevelopmental study (i.e., changes in brain morphometry and motor activity); determine the developmental toxicity potential in rats versus rabbits; investigate additional aspects of immunotoxicity; and develop a consistent nomenclature and scoring system for the histopathological lesions in the thyroid gland. Additional pharmacokinetic data was also developed into physiologically-based pharmacokinetic (PBPK) models of perchlorate and iodide distribution.
- A battery of ecological screening tests as part of the 1997 testing strategy was conducted as part of the 1997 testing strategy in laboratory organisms representative of ecological receptors across soil, sediment, and water to evaluate dose-response relationships. These were considered to be a tier of tests to give an idea of gross toxicity that would determine the need and types of tests to be performed in the next tier. The tests did not measure the amount of perchlorate in the tissues of the species being tested. Based on stakeholder input and the need for a more focused battery of tests, lettuce was substituted for duckweed because of Tribal concerns regarding the sizable lettuce crop along the Colorado river. The following species were selected for the first round of testing:

  (1) *Daphnia magna* (water flea) to represent an aquatic invertebrate

  (2) *Ceriodaphnia magna* (water flea) to represent an aquatic invertebrate

  (3) *Lactuca sativa* (lettuce) to represent a vascular plant

  (4) *Pimephales promelas* (fathead minnow) to represent an aquatic invertebrate

  (5) *Eisenia foetida* (earthworm) to represent a soil invertebrate

  (6) *Microtus pennsylvanicus* (meadow vole) to represent an herbivore

- Other studies in the set of tests included the Frog Embryo Teratogenesis Assay: *Xenopus* (FETAX) and a phytoremediation study to examine uptake, distribution, and degradation in

experimental systems with rooted cuttings of woody plants, including willow, Eastern Cottonwood, and eucalyptus.

- Additional studies, some of chronic duration, on effect levels in aquatic animals, an aquatic plant, a terrestrial plant, and a soil invertebrate have been performed since 1999. A study of perchlorate occurrence in six selected sites with known or suspected contamination also examined perchlorate concentrations in site media and in various ecological receptors.

Human Health Assessment

- The testing strategy confirmed that the target tissue for perchlorate toxicity was the thyroid gland. Anti-thyroid effects included iodide uptake inhibition, perturbations of T3, T4, and TSH hormones, and thyroid histopathology in adult, fetal, and postnatal rats across studies with a range of experimental design. Thyroid weight in these studies was also effected. Other than effects in the thyroid, no effects were observed in rabbits of the developmental study, but the developmental study in rats identified 30 mg/kg-day as the lowest observed adverse effect level (LOAEL).
- Competitive inhibition of iodide uptake at the NIS by perchlorate is the key event leading to both potential neurodevelopmental and neoplastic sequelae. The decrement in iodide uptake leads to subsequent drops in T4 and T3 that can lead to permanent neurodevelopmental deficits. Because of strong correlations between changes in iodide uptake inhibition with decrements in T3 and T4; between T3 and T4 with changes in TSH; and between changes in T3, T4, or TSH with thyroid histopathology, an assessment model was proposed that used the changes in T3, T4, and TSH as the precursor lesions to subsequent effects that potentially could lead to thyroid tumors or to altered neurodevelopment. This assessment approach essentially harmonizes noncancer and cancer approaches because it is presumed that the no-observed-adverse-effect-level (NOAEL) for the precursor lesions will preclude any subsequent sequelae at higher doses.
- Thyroid tumors were observed in previous studies in rats exposed in long-term bioassays at high doses. Thyroid tumors were more recently also diagnosed in the first-generation (F1) adults (second parental generation [P2]) at 19 weeks in a two-generation reproductive study. Both the latency and incidence of these tumors were significant relative to the entirety of the National Toxicology Program data base for this type of tumor and in this strain of rat. These

effects and the demostration of a progression with duration of effects on hormones and thyroid histopathology in the 90-day study raised the concern that extended exposures to perchlorate may change the hypothalamic-pituitary-feedback system or the cellular sensitivity and demand for thyroid hormones.

- The rat model is considered relevant yet conservative for human health risk assessment of potential thyroid neoplasia because of the differences in thyroid structure and hormone half-lives. Perchlorate was demonstrated to be nongenotoxic in the testing battery employed, suggesting the antithyroid effects are an indirect mode of action for thyroid tumor formation.
- Due to the age- and time-dependent nature of the key event of perchlorate toxicity and its anti-thyroid effects, the revised RfD was based on weight-of-the-evidence approach to the entire data base. The RfD is proposed to be protective of both neurodevelopmental and neoplastic sequelae. An administered dose of 0.01 mg/kg-day was supported as a lowest-observed-adverse-effect level (LOAEL) based on effects on brain morphometry in pups from a PND21 sacrifice in a neurodevelopmental study that repeated similar observations made in a similar 1998 study, hormonal effects indicative of hypothyroidism (decreased T4 and increased TSH) in the dams of those same pups on GD21, thyroid histopathology and hormone changes in these same pups at various developmental stages (GD21, PND4, PND9, and PND21), thyroid histopathology and hormone changes at the 14- and 90-day sacrifice dates in a subchronic study, and indications of immunotoxicity (dermal contact hypersensitivity).
- A human equivalent exposure (HEE) was calculated using physiologically-based pharmacokinetic (PBPK) models for interspecies adjustment based on the area under the curve (AUC) of perchlorate in the serum as the dose metric. The HEE for the maternal dams was chosen for operational derivation because brain morphometry effects may have been programmed *in utero* and because the dams of effected pups were hypothyroid.
- A composite uncertainty factor of 300 was used to address uncertainties in the extrapolations required for the RfD derivation. A three-fold factor for intraspecies variability was retained due to the variability observed in the data and PBPK modeling for the adult humans and because the subjects used to develop the models did not provide kinetic data for the potentially susceptible population. There was also uncertainty in the parallelogram approach to extending the adult structures to predict doses for different life stages in the human. A full factor of ten was applied to extrapolate the LOAEL for the adverse effects (brain morphometry, colloid

depletion and hormone changes) observed in various studies at the 0.01 mg/kg-day dosage level. A three-fold factor for duration was applied due to the concern for the biological importance of the statistically significant increase in tumors observed in the F1-generation pups (second parental, P2 generation) at 19 weeks and the evidence for progression of effects with extended exposure in the 90-day study. The finding of tumors at 19 weeks raised concern for *in utero* programming, i.e., that disruption of thyroid hormones in the developing fetus may predispose the developing neonate and adult to future insults to the thyroid gland. This factor can also be viewed as part of a data base deficiency since there are no adequate long-term bioassays of perchlorate. Finally, a three-fold factor was applied for inaccurate characterization of immunotoxicity since recent studies reinforced concern for this potential endpoint. Because the test article was ammonium perchlorate, an adjustment factor of 0.85 was made for the percent of molecular weight of the salt from ammonium (15.35%), so that the RfD is expressed for perchlorate as the anion alone. This was done to be compatible with the analytical methods that measure the anion in environmental samples and because most perchlorate salts readily dissolve in water. The resultant revised RfD value for perchlorate is 0.00003 mg/kg-day. Confidence in the principal study, the data base and the RfD were all designated as medium.

Screening Ecological Risk Assessment

- A secondary acute value of 5 mg/L (as perchlorate) was derived to be protective of 95% of aquatic organisms during short-term exposures with 80% confidence. The secondary chronic value of 0.6 (as perchlorate) likewise was derived to be protective of 95% of aquatic organisms during short-term exposures with 80% confidence. These values were derived based on sodium perchlorate and are probably protective even if ammonium perchlorate is the contaminant released. Calculated ammonia-nitrogen concentrations corresponding to those values are below the acute and chronic ambient water quality criteria for ammonia, regardless of pH.
- For terrestrial plants, the quartile inhibitory concentrations for growth in soil and sand were 78 mg/kg (293 mg/L) and 41 mg/kg (160 mg/L), respectively. A factor of 10 was applied to account for interspecies variance to obtain a screening benchmark of 4 mg/kg.

- Because of limited data on effects for soil invertebrates, a conservative estimate of a threshold for soil community effects was derived at 1 mg/kg. The equivalent aqueous phase benchmark is 2.8 mg/L.
- A factor of 10 for interspecies variance and LOAEL to NOAEL extrapolation was applied to the human health risk LOAEL estimate based on rat data (0.01 mg/kg-day) to obtain a screening benchmark of 0.001 mg/kg-day for the representative herbivore (meadow vole) because it also is a rodent. The population-level implications of this effect are unknown, but it seems likely that such effects on the thyroid could diminish survivorship and fecundity, which would diminish population production.
- Data are available showing that perchlorate accumulates in the tissues of exposed fish, amphibians, and invertebrates. However, data are insufficient to determine whether perchlorate is concentrated in those tissues to levels exceeding the levels of exposure. By contrast, several studies have shown that perchlorate is taken up and concentrated in aerial plant parts, especially leaves, although studies designed for the purpose of quantifying plant concentration factors have not yet been conducted.

Uncertainties and Assessment Research Needs

- Accurate exposure information is a requisite for risk characterization for both human and ecological assessments. These data should include transport and transformation processes, notably the fate of perchlorate in irrigated soils because of the potential for evaporative concentration.
- Research concerning the human health risks of perchlorate needs to better characterize the dose-response for perchlorate inhibition of iodide uptake in adults, fetuses, and neonates. More definitive studies linking iodide uptake inhibition and the degree of perturbation of the hypothalamic-pituitary-thyroid axis (i.e., changes in T3, T4, and TSH levels) and association with neurobehavioral problems, thyroid changes, and neoplastic sequelae may continue to improve the confidence in the assessment. Understanding the relative sensitivity of laboratory animal assays of neurodevelopmental effects versus epidemiological studies of neuropsychological development also needs to be advanced. Research on potential factors influencing sensitivity is critically requisite. Animal models of thyroid impairment such as iodide deficiency and "womb to tomb" exposure designs should be explored.

- Because only a screening tier of tests has been performed, the major uncertainty derives from data gaps. Data on bioaccumulation in aquatic biota would allow evaluation of exposure of organisms that feed on fish and other aquatic organisms. Effects of perchlorate on algae and aquatic macrophytes are required to estimate risks to aquatic primary producers. Data on bioaccummulation in aquatic plants are necessary to assess direct impact to primary consumers (i.e., planktonic and benthic invertebrate communities). Data on accumulation in terrestrial vascular plants also should be investigated further. The factor applied for the use of subchronic data in fish could be addressed by chronic effect testing. Effects also should be determined in nondaphnid invertebrates and of dietary exposure in birds and herbivorous or litter-feeding invertebrates.

Risk Characterization

- As noted above, the lack of exposure information precludes comparison with the human health and ecological toxicity assessment for accurate characterization of risk. Indirect human exposure pathways can be addressed best by a new EPA document, Methodology for Assessing Health Risks Associated with Multiple Pathway of Exposure to Combustor Emissions, which is scheduled for final release in January 2002.
- Noncancer neurobehavioral effects have been shown at lower doses. The estimate for perchlorate has been based on precursor effects considered protective for both the thyroid neoplasia and neurodevelopmental effects. It is appropriate for comparison against direct oral exposures. The frequency and magnitude of exposure are key attributes for characterization compared with those assumptions of continuous lifetime exposure assumed in the derivation. The degree to which the particular suspected population at risk fits with the assumptions used in the RfD derivation should be kept in mind when performing any risk characterization. Further, RfD estimates are not intended to serve as a "bright line" because, by definition, there is an order-of-magnitude uncertainty around the estimate. This typically translates into a range of threefold below to threefold above the RfD.
- Ecological risk could not be precluded nor accurately characterized because of the significant data gaps described above.