Perchlorate (ClO_4^-) and Perchlorate Salts

CASRN 7790-98-9 Ammonium perchlorate
CASRN 7791-03-9 Lithium perchlorate
CASRN 7778-74-7 Potassium perchlorate
CASRN 7601-89-0 Sodium perchlorate

This U.S. EPA IRIS Summary is based on the U.S. Government-sponsored technical review of the "Health Implications of Perchlorate Ingestion EXIT Disclaimer" by the National Research Council of the National Academies (NRC, 2005). The NRC perchlorate committee took into consideration presentations at the committee's public meetings, submitted public comments, and the comments made by technical experts on the draft NRC perchlorate report. The conclusions, recommendations and final content of the NRC (2005) report rest entirely with the committee and the National Research Council. The NRC review follows two external draft toxicological reviews of perchlorate prepared by EPA (1998, 2002) that were also subject to public comment and independent external peer review. The IRIS Summary has undergone review by EPA health scientists from several program offices, regional offices, and the Office of Research and Development. Sections I (Chronic Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the positions that were reached during the review process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website at http://www.epa.gov/iris/backgrd.html.

STATUS OF DATA FOR Perchlorate and Perchlorate Salts

File First On-Line 02/18/2005

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	02/18/2005
Inhalation RfC (I.B.)	qualitative discussion	02/18/2005
Carcinogenicity Assessment (II.)	yes	02/18/2005

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Perchlorate and Perchlorate Salts
CASRN 7790-98-9 Ammonium perchlorate
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Section I.A. Last Revised —02/18/2005

In general, the oral RfD is an 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. The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis and is expressed in units of mg/kg-day. Please refer to the background document for an elaboration of these concepts. Since RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	RfD
Radioactive iodide uptake inhibition (RAIU) in the thyroid **Adult human volunteers** **Greer et al. (2002)**	NOEL: 0.007 mg/kg/day LOEL: 0.02 mg/kg/day	10	0.0007 mg/kg/day

* Conversion Factors and Assumptions - Iodide uptake inhibition is a key biochemical event that precedes all potential thyroid-mediated effects of perchlorate exposure. Because iodide uptake inhibition is not an adverse effect but a biochemical change, this is a No Observed Effect Level

(NOEL). The use of a NOEL differs from the traditional approach to deriving an RfD, which bases the critical effect on an adverse outcome. Using a nonadverse effect that is upstream of the adverse effect is a more conservative and health-protective approach to perchlorate hazard assessment. The point of departure is based on a non-statistically significant mean 1.8% (standard error of the mean 8.3%) decline in RAIU in healthy adults following two weeks exposure to a daily perchlorate dose of 0.007 mg/kg/day. An intraspecies uncertainty factor of 10 is applied to protect the most sensitive population, the fetuses of pregnant women who might have hypothyroidism or iodide deficiency. Dose is given as perchlorate anion.

I.A.2. Principal and Supporting Studies (Oral RfD)

Greer, M.A., Goodman, G., Pleus, R.C., Greer, S.E. 2002. Health effect assessment for environmental perchlorate contamination: The dose response for inhibition of thyroidal radioiodide uptake in humans. Environ. Health Perspect. 110:927-937.

Greer et al. (2002) studied 21 healthy women and 16 healthy men (mean age 38 years, range 18-57 years) who were given potassium perchlorate in doses of 0.007, 0.02, 0.1 and 0.5 mg perchlorate/kg body weight per day for 14 days. The dose was administered in 400 ml of water with instructions that 100 ml be consumed four times each day. Thyroid uptake of radioiodide was measured at 8 and 24 hours after radioiodide administration: at baseline, on days 2 and 14 of perchlorate administration, and 15 days after cessation of dosing. The human subjects research ethics of the study were approved by the Oregon Health & Science University Institutional Review Board (IRB). On day 14 of administration, the mean 24-hour radioiodide uptake was 98.2% of the baseline value in the seven subjects given 0.007 mg/kg/day, a non-statistically significant decrease of 1.8% (standard error of the mean 8.3%). The day-14 24-hour radioiodide uptake value was 83.6% of the baseline value (16.4% decrease; n=10) in the subjects given 0.02 mg/kg/day, 55.3% of the baseline value (44.7% decrease; n=10) in those given 0.1 mg/kg/day, and 32.9% of the baseline value (67.1% decrease; n=10) in those given 0.5 mg/kg/day.

The effects of perchlorate in these healthy adult humans did not change over time, as indicated by very similar results for thyroid radioiodide uptake measurements on day 2 of perchlorate administration compared to day 14 in the three higher dose groups (uptake was not measured on day 2 in the lowest dose group). The 8-hour thyroid radioiodide uptake values 15 days after exposure were very similar to the baseline values, indicating rapid disappearance of inhibition on cessation of dosing. The results were similar in the women and men. The statistical no observed effect level (NOEL) for perchlorate-induced inhibition of thyroid iodide uptake was 0.007 mg/kg/day.

There were no changes in serum thyroxine (T4), triiodothyronine (T3) and thyroid stimulating hormone (TSH, thyrotropin) concentrations in the Greer et al. (2002) study, except for a very

small decrease in serum TSH concentrations in the subjects given 0.5 mg/kg/day (not an increase, as would be expected if thyroid secretion decreased, and probably explicable on the basis of multiple measurements of TSH concentrations over the course of each day). One woman had a slightly high serum TSH concentration at baseline (18 mU/L), and it was slightly lower (15 mU/L) on day 14 of perchlorate administration at 0.007 mg/kg/day.

The NRC (2005) reviewed a number of benchmark dose models for the radioiodide uptake inhibition point of departure, as developed by the U.S. EPA (2003), California Environmental Protection Agency (CalEPA 2004) and Crump and Goodman (2003). The NRC (2005) concluded that these analyses used different models, approaches, parameters, response levels, and input data, making the comparison of results difficult. Although the NRC Committee recognized that BMD modeling can be an improvement over the use of the NOAEL or LOAEL as a point of departure, there appeared to be no consensus on the criteria for choosing one BMD approach over another. Because no clear justifications were provided with the individual analyses of the Greer et al. (2002) data that allowed selection of one set of results over another, the NRC Committee concluded that using the NOEL (0.007 mg/kg/day) for iodide inhibition from Greer et al. (2002) as the point of departure provided a reasonable and transparent approach to perchlorate risk assessment.

Four additional intentional dosing human studies were cited by the NRC (2005) Committee in their review of perchlorate health effects. Brabant et al. (1992) administered 200 micrograms of iodide daily to five healthy men for 4 weeks, and then 900 mg of potassium perchlorate daily (~9 mg/kg/day, assuming a 70 kg person) for 4 weeks. There were no differences in serum T4, T3 or thyroid volume at the end of each four week period. The mean 24-hour serum TSH, serum free T4, and total thyroid iodide content were slightly lower at the end of the perchlorate period than at the end of the iodide period. Lawrence et al. (2000) administered 10 mg potassium perchlorate (~0.1 mg/kg/day) in water to nine healthy men, ages 22 - 30 years old. There were no changes in serum T4, T3 or TSH concentrations during the 14 day ingestion period. 24-hour radioiodide uptake was decreased 41% at day 14 of perchlorate administration. Lawrence et al. (2001) administered 3 mg potassium perchlorate (~0.03 mg/kg/day) to eight healthy men for 14 days, leading to small, non-statistically significant reductions in mean 24-hour RAIU level (10.3%), and no changes in T4, T3 or TSH. Braverman et al. (2004; abstract) conducted a study of potassium perchlorate administration to 13 healthy subjects over 6 months: four were given placebo, five were given 0.5 mg daily (~0.007 mg/kg/day), and four were given 3 mg daily (~0.04 mg/kg/day). There were no changes in thyroid RAIU or T3, T4 or TSH, compared to baseline, at any time in either placebo or perchlorate groups.

The data from epidemiological studies of the general population provide some information on possible effects of perchlorate exposure, although these studies are inherently limited with respect to establishing causality and cannot serve as the basis for quantitative risk assessment.

Acknowledging that ecologic epidemiological data alone are not sufficient to demonstrate whether or not an association is causal, the NRC (2005) committee found that these studies can provide evidence bearing on possible associations. Noting the limitations of specific studies, the NRC (2005; chapter 3) committee concluded that the available epidemiological evidence is not consistent with a causal association between perchlorate and congenital hypothyroidism, changes in thyroid function in normal-birthweight, full-term newborns, or hypothyroidism or other thyroid disorders in adults. The committee considered the evidence to be inadequate to determine whether or not there is a causal association between perchlorate exposure and adverse neurodevelopmental outcomes in children. The committee noted that no studies have investigated the relationship between perchlorate exposure and adverse outcomes among especially vulnerable groups, such as the offspring of mothers who had low dietary iodide intake, or low-birthweight or preterm infants.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF = 10

Intraspecies Factor = 10. The intraspecies uncertainty factor accounts for variability in responses among humans, and is intended to protect populations that are more sensitive than the population tested. Because the critical study (Greer et al., 2002) for perchlorate was based on healthy adult men and women, an uncertainty factor of 10 is applied to protect the most sensitive population, the fetuses of pregnant women who might have hypothyroidism or iodide deficiency. In pregnant women who have undiagnosed hypothyroidism, perchlorate exposure could exacerbate the hypothyroidism by inhibiting iodide uptake by the thyroid. In the NHANES III cohort, daily iodide intake was less than 50 microgram in 15% of women of childbearing age, and 7% of pregnant women. However, serum thyroid hormone and TSH concentrations were similar for those who had a daily iodide intake of less than 50 micrograms compared to people with higher daily intakes. Thus, the NRC (2005) concluded that the data indicate that iodide deficiency in the U.S. population is mild, if it exists. An uncertainty factor of 10 was viewed by the NRC (2005) committee as conservative and health-protective, especially given that the point of departure is based on a non-adverse effect that precedes the adverse effect in the continuum of possible effects of perchlorate exposure. They note that inhibition of thyroid iodide uptake is the only effect that has been consistently documented in humans exposed to perchlorate.

Interspecies Factor - Not applicable, as the NOEL is based on human data.

LOAEL - NOAEL Extrapolation - Not applicable, as the point of departure is based on a statistical no observed effect level. Because this NOEL is for a nonadverse effect, this is considered to be a more conservative and health-protective approach than traditional hazard assessments.

Subchronic to Chronic Extrapolation UF = 1: The point of departure is based on the lack of inhibition of radioiodide uptake in the thyroid gland following a 14-day exposure to perchlorate. Chronic exposure will have no greater effect than that resulting from short term exposure, because if the precursor event of inhibition of iodide uptake does not occur, then there will be no changes in thyroid function in the short or long term. Prolonged exposure may actually have less effect because of the capacity of the pituitary-thyroid system to compensate for iodide deficiency by increasing iodide uptake. If some inhibition of iodide uptake by the thyroid did occur at the minimal dose at the point of departure, data from humans indicate that longer exposures are not likely to result in a greater or more severe response. Perchlorate also does not accumulate in the body but is rapidly cleared via excretion in the urine, even during chronic exposure.

Database Adequacy UF =1: The adequacy of the database is typically described in terms of a specific set of animal toxicological studies. For example, chronic toxicity, reproductive toxicity, developmental toxicity, and carcinogenicity studies are typically required to have the highest confidence in a database of studies. However, mode-of-action studies and relevant human studies can eliminate the need for various animal studies. For perchlorate, the selection of the point of departure is designed to prevent the first step in the mode of action continuum, and studies on downstream events are not necessary. Therefore, an uncertainty factor for database adequacy is not considered necessary for perchlorate because of the consistency of the human data across multiple studies and the reliance on a precursor, non-adverse, biochemical event as the point of departure. In addition to the five intentional dosing human clinical studies in healthy adults noted above, the studies of long-term treatment of hyperthyroidism with perchlorate and the studies of occupational and environmental exposure add confidence to the overall database. The absence of a long-term study is covered under the subchronic-chronic discussion.

I.A.4. Additional Studies/Comments (Oral RfD)

The fundamental mechanisms involved in the function and regulation of the pituitary-hypothalamus-thyroid system in rats are qualitatively similar to those in humans. However, differences in binding proteins, binding affinities of the proteins for the hormones, turnover rates of hormones, and thyroid stimulation by placental hormones lead to important quantitative differences between the two species. The biochemical and physiologic differences between rats and humans related to the thyroid affect their responses to goitrogens, such as perchlorate. Therefore, although studies in rats provide useful qualitative information on potential adverse effects of perchlorate exposure, they are limited in their utility for quantitatively assessing human health risk associated with perchlorate exposure. For instance, regarding the initial step of radioiodide uptake inhibition, Yu et al. (2002) evaluated thyroid impacts in rats exposed to perchlorate in drinking water at 0, 1.0, 3.0, and 10.0 mg/kg/day for 1, 5, and 14 days. After one day of perchlorate, inhibition of iodide uptake was about 15%, 55% and 65% for the respective doses. By 14 days, the inhibition of iodide uptake was observed only in the high dose group. The

data show that the initial inhibition of radioiodide uptake by perchlorate in rats is similar to that in humans. However, rats compensate for the inhibition within 5 days of perchlorate administration. A similar response was not observed in the 14-day Greer et al. (2002) study, suggesting that compensation occurs more quickly in rats because rats have a smaller reserve capacity of thyroid hormones than humans.

Among a number of rodent studies conducted on perchlorate toxicity, the Argus (2001) report provides a comprehensive evaluation of perchlorate impacts on rat development. In this study, female rats (dams) were exposed to perchlorate through gestation and lactation. Ammonium perchlorate was administered in drinking water at concentrations that provided doses of 0, 0.01, 0.1, 1.0 and 30 mg/kg/day. Administration began 2 weeks before mating and extended through postnatal day 22. The offspring were exposed to perchlorate in utero, through their mother's milk, and through any consumption of the perchlorate contaminated water provided to their mothers. There were dose-related increases in serum TSH and dose-related decreases in serum total T4 and T3 in the dams, fetuses, and pups. Serum T4 was decreased significantly in dams at all doses during gestation. A downward trend was observed in serum T3 in the dams, albeit not statistically significant during gestation until the highest dose group. Serum TSH was substantially increased in the pregnant dams at all doses. Statistically significant changes in thyroid hormones and TSH were noted in the fetuses and pups, although the changes tended to be more modest than those in the dams.

Argus (2001) also conducted histological evaluations of the thyroid gland at the same time as the thyroid hormone and TSH measures. In dams, histological examination revealed colloid depletion, follicular-cell hypertrophy, and follicular-cell hyperplasia. These effects were mainly restricted to the highest dose group (30 mg/kg/day), although colloid depletion and follicular-cell hyperplasia were increased at 1.0 mg/kg/day on postnatal days 10 and 22, respectively. In rat fetuses and pups, colloid depletion of the thyroid was the most consistent histological finding, observed consistently in the highest-dose animals and, to a smaller extent, in the 1.0 mg/kg/day group. The thyroid morphology of the two lower-dose groups of animals (0.01 and 0.1 mg/kg/day) was similar to that of controls.

The effects of maternal perchlorate exposure on offspring brain development in Sprague-Dawley rats were also examined by Argus Laboratories (Argus, 1998, 2001). Dams were exposed to the above noted perchlorate doses (Argus, 2001). Pups were sacrificed at several post-natal ages and their brains fixed and sectioned for histological evaluation. The thickness of various brain regions was measured (morphometry). Statistical analyses revealed a number of significant effects, most notably an increase in the thickness of the posterior corpus callosum. However, questions and concerns about the studies have been raised, including apparent systematic differences in the plane of section among treatment groups, lack of clear and consistent dose-response relationships, doubts about the biologic plausibility of the changes observed, and

concerns that the measures used were relatively insensitive and would be unlikely to pick up subtle differences in neurodevelopment. On the basis of its review of the data, the NRC (2005) committee concluded that the evidence in Argus (1998, 2001) was inadequate to determine whether or not a causal relationship exists between maternal perchlorate exposure and pup neurodevelopmental abnormalities.

The NRC (2005) committee also noted that perchlorate could theoretically produce several types of adverse immunological reactions, possibly mediated by a direct effect on the cells involved or by modulation of thyroid hormone-immune system homeostasis. The potential for perchlorate to cause any of these adverse immunological reactions has been studied in animals, the results of which are summarized in the NRC (2005) report. Based on their evaluation, the NRC committee concluded that the evidence favors rejection of a causal relationship between ingestion of perchlorate and an immunotoxic effect in animals.

I.A.5. Confidence in the Oral RfD

Study — Medium-High: The study was well conducted and provides a clear dose-response curve for radioiodide uptake inhibition in adult humans, although it is limited by small numbers of subjects (n=7) in the lowest dose group. The principal study is supported by four other human clinical studies of similar methodology that provide consistent results.

Database — Medium: The database consists of a number of human clinical studies of precursor events (radioiodide uptake inhibition), supported by other clinical studies, occupational and environmental epidemiologic studies, and studies of long-term perchlorate administration to patients with hyperthyroidism. The available epidemiological studies do not assess the possibility of adverse outcomes among vulnerable groups, such as the offspring of mothers who were exposed to perchlorate and had a low dietary iodide intake. The animal data consist of a number of studies to assess perchlorate impacts, albeit limited in certain situations by concerns about the veracity of some endpoints and the applicability of rodent studies of thyroid function to humans. Concerns have also been expressed about the absence of a long-term study, although the majority of the NRC (2005) committee concluded that, by preventing the precursor, non-adverse, event of iodide uptake inhibition, chronic exposure will have no greater effect than that resulting from short-term exposure.

RfD — High: The overall confidence in this RfD assessment is high because it is based on a no-effect level for a well-characterized biochemical precursor effect (iodide uptake inhibition), accompanied by a 10 fold uncertainty factor for susceptible populations. The RfD should protect the health of even the most sensitive populations, because a dose that does not inhibit thyroid iodide uptake will not affect thyroid function, even in subjects with an abnormal thyroid gland or a very low iodide intake.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — National Research Council. 2005. Health Implications of Perchlorate Ingestion. The National Academies Press. Washington, D.C.

This source document was prepared by the National Research Council of the National Academies on behalf of the United States Government InterAgency Working Group on Perchlorate. The NRC report followed draft Perchlorate Toxicological Reviews prepared by the U.S. EPA, which had also been subject to public comment and peer review.

Other EPA Documentation — Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization. External Review Draft, NCEA-1-0503, January 16, 2002.

Agency Completion Date -- 02/18/2005

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Perchlorate and Perchlorate Salts
CASRN 7790-98-9 Ammonium perchlorate
CASRN 7791-03-9 Lithium perchlorate
CASRN 7778-74-7 Potassium perchlorate
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Section I.B. Last Revised — 02/18/2005

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m3) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Since RfCs can also be derived for the noncarcinogenic

health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

An inhalation reference concentration has not been derived because the available inhalation data are insufficient to characterize dose-response relationships or portal-of-entry modulation of internal dose. Perchlorate is not likely to come out of solution given its low vapor pressure. Droplet size during showering would likely preclude significant inhalation of perchlorate-contaminated water as an aerosol. Particulate inhalation exposures to perchlorate dust have been investigated in two published studies of ammonium perchlorate production workers (Gibbs et al., 1998; Lamm et al., 1999). Exposures were estimated through personal breathing zone and area sampling, adjusted by dose estimation assumptions (Gibbs et al., 1998) or particle size measures accompanied by urinary perchlorate excretion (Lamm et al., 1999). Both studies had small numbers of exposed workers. The cross-sectional epidemiological design means the studies were subject to possible selection bias of affected workers who left employment before the study. Neither study reports any significant relation of estimated perchlorate exposure to changes in thyroid hormone or TSH measures, except for an increase in TSH with duration of shift (Gibbs et al., 1998): the postshift mean serum TSH concentration was higher than the preshift concentration and exceeded it by more after a 12-hour shift than after an 8-hr shift, a difference expected because there is a circadian increase in serum TSH concentrations (NRC, 2005).

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Not applicable.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

Not applicable.

I.B.4. Additional Studies/Comments (Inhalation RfC)

Not applicable.

I.B.5. Confidence in the Inhalation RfC

Not applicable.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Not applicable.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Perchlorate and Perchlorate Salts
CASRN 7790-98-9 Ammonium perchlorate
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Section II Last Revised — 02/18/2005

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Draft Revised Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is an upper bound on the estimate of risk per mg/kg-

day of oral exposure. Similarly, a "unit risk" is an upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water (see Section II.B.1.) or per $\mu g/m^3$ air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Under U.S. EPA's 1999 Draft Revised Guidelines for Carcinogen Risk Assessment, perchlorate is not likely to pose a risk of thyroid cancer in humans, at least at doses below those necessary to alter thyroid hormone homeostasis, based on the hormonally-mediated mode of action in rodent studies and species differences in thyroid function. The epidemiological evidence is insufficient to determine whether or not there is a causal association between exposure to perchlorate and thyroid cancer. Sufficient evidence is available from rodent studies to indicate that goitrogenic doses of perchlorate cause follicular cell tumors of the thyroid, both following prolonged ingestion and from a two-generation study where a low incidence of early onset adenomas was reported. Perchlorate is non-mutagenic under standard tests. Extensive data indicate that thyroid-pituitary disruption is the sole mode of action for the observed thyroid tumors caused by perchlorate in rodents.

II.A.2. Human Carcinogenicity Data

Two ecological epidemiological studies have been conducted to determine whether there is an association between perchlorate exposure and thyroid cancer. Li et al. (2001) analyzed Nevada Medicaid data for a two year period (1997, 1998) to compare the prevalence of specific thyroid diseases, including malignant thyroid cancer, by county of residence as characterized by the presence or absence of perchlorate in the drinking water (only one county had perchlorate detected in the drinking water in this time period). The prevalence ratio (exposed/non-exposed county) was 0.75 (95% confidence interval 0.35 - 1.59), although the number of thyroid cancer cases was too small to a have reasonable chance of detecting an association if one existed. Morgan and Cassady (2002) compared the observed and expected incident cases of cancer among residents of 13 contiguous census tracts in Redlands, California, whose drinking water wells had been tested over various years for both trichloroethylene and perchlorate contamination. No excess of thyroid cancer was observed in the residents (SIR 1.0, 99% confidence interval 0.63-1.47). Limitations of this study include the mixed exposure to trichloroethylene and perchlorate and derivation of expected numbers from a region that includes the exposed community. In both studies it was impossible to adjust for potential confounding

variables. As a result, the epidemiological evidence is considered insufficient to determine whether or not there is an association between perchlorate exposure and thyroid cancer.

II.A.3. Animal Carcinogenicity Data

Few long term cancer bioassays of perchlorate exposure have been conducted. The existing studies have reported that high doses of perchlorate in rodents cause statistically significant increases in follicular cell nodules (Fernandez Rodriguez et al. 1991), adenomas (Kessler and Kruskemper 1966), and carcinomas (Pajer and Kalisnik 1991). Other studies have demonstrated the ability of perchlorate to promote thyroid tumors initiated by other chemical or irradiation means (Hiasa et al. 1987, Fernandez-Santos et al. 2004; Pajer and Kalisnik 1991). Fernandez Rodriguez et al. (1991) administered 1% potassium perchlorate in drinking water to female Wistar rats for 1 - 12 months, reporting that after 6 months of treatment multiple (often bilateral) follicular cell nodules of complex morphology appeared in the diffusely enlarged thyroid glands. Kessler and Kruskemper (1966) administered potassium perchlorate to male Wistar rats in drinking water at 0 or 1% (~1,339 mg/kg/day). Four of the 11 treated rats developed benign tumors of the thyroid gland. Pajer and Kalisnik (1991) administered 0 or 1.2% (~2,147 mg/kg/day) sodium perchlorate in drinking water to female BALB/c mice for up to 46 weeks. There were three groups of controls and three groups of mice treated with perchlorate, some of which were also administered varying levels of whole body irradiation. Thyroid follicular cell carcinomas were observed in five of the six non-irradiated perchlorate treated mice, and in all 14 irradiated perchlorate treated mice.

In a two-generation study (Argus 1999), there were follicular cell adenomas in one control male rat in the initial parent (P1) generation and two high-dose (30 mg/kg/day) males in the first offspring (F1) generation at 19 weeks of age. Bayesian analysis of the early onset thyroid adenomas concluded that they were statistically increased relative to the entirety of the National Toxicology Program database (Dunson, 2001). The NRC (2005) concluded that the thyroid tumors in the offspring were most likely treatment related, but that they would be expected in high dose male rats in the presence of a markedly goitrogenic dosing regimen, as existed under the conditions of the study.

II.A.4. Supporting Data for Carcinogenicity

Perchlorate has been evaluated in standard *in vitro* and *in vivo* assays to assess genotoxicity. The results of these assays are negative. Ammonium perchlorate was not mutagenic in the Ames assay (with or without S9 activation)(ManTech Environmental Technology, Inc., 1998; Zeiger, 1999a). Negative results were also found in the mouse lymphoma gene mutation assay with and without S9 activation (ManTech Environmental Technology, Inc., 1998; BioReliance, 1999). Ammonium perchlorate did not induce chromosomal anomalies when evaluated for micronuclei

induction in the bone marrow of mice when administered via drinking water gavage or ip injection (ManTech Environmental Technology, Inc., 1998; Zeiger et al., 1999b). No increases in micronuclei were found in Sprague-Dawley rats when evaluated from the 90-day study at the highest dose, which produced both thyroid hormone perturbations and follicular cell hyperplasia (Springborn Laboratories, Inc., 1998). Because perchlorate does not have the potential to be mutagenic or clastogenic, mutagenicity is not considered a possible mode of carcinogenic action for this chemical.

Mode of Action

Perchlorate is a negatively charged ion (ClO_4^-) that can affect thyroid function through competitive inhibition of the transport of iodine into the thyroid. Iodine is an important component of thyroid hormones T4 and T3, and the transfer of iodine from the circulation into the thyroid is an essential step in the synthesis of these two hormones. Iodine transport into the thyroid is mediated by a protein molecule known as the sodium(Na+)-iodide(I-) symporter (NIS). NIS molecules bind iodide with very high affinity, but they also bind other ions that have a similar shape and electric charge, such as perchlorate. The binding of these other ions to the NIS inhibits iodide transport into the thyroid, which can result in intrathyroidal iodide deficiency and consequently decreased synthesis of T4 and T3. There is remarkable compensation for iodide deficiency, however, where the body maintains the serum concentrations of thyroid hormones within narrow limits through feedback control mechanisms. This feedback includes increased secretion of thyroid stimulating hormone (TSH) from the pituitary gland, which has among its effects the increased production of T4 and T3. Sustained changes in thyroid hormone and TSH secretion can result in thyroid hypertrophy and hyperplasia, possibly followed by hypothyroidism in people unable to compensate with an increase in thyroid iodide uptake.

The pituitary-thyroid system of rats is similar to that of humans, i.e., decreases in thyroid hormone production result in increased secretion of TSH, which then increases thyroid production and release of T4 and T3. However, there are differences in binding proteins, binding affinities of the proteins for the hormones, turnover rates of the hormones, and thyroid stimulation by placental hormones that lead to important differences between the two species. These differences mean that rats are sensitive to the development of thyroid tumors because their thyroid function is easily disrupted. The NRC (2005) concluded that humans are much less susceptible than rats to disruption of thyroid function and, therefore, are not likely to develop thyroid tumors as a result of perchlorate exposure.

As noted by the International Agency for Research on Cancer (IARC, 2001), "Agents that lead to the development of thyroid neoplasia through an adaptive physiological mechanism belong to a different category from those that lead to neoplasia through genotoxic mechanisms or through mechanisms involving pathological responses with necrosis and repair. Agents that induce

thyroid follicular cell tumors in rodents by interfering with thyroid hormone homeostasis, can with some exceptions, notably the sulfonamides, also interfere with thyroid hormone homeostasis in humans if given at a sufficient dose for a sufficient time. These agents can be assumed not to be carcinogenic in humans at concentrations that do not lead to alterations in thyroid hormone homeostasis."

EPA (1998) reached similar findings regarding the relevance of rodent thyroid follicular cell tumors to humans. In this document, EPA provides a cancer mode-of-action framework for determining whether a chemical is acting via disruption of the thyroid-pituitary axis. Perchlorate satisfies these areas of inquiry regarding data demonstrating 1) increases in thyroid growth, 2) changes in thyroid and pituitary hormones, 3) site of antithyroid action, 4) dose correlations, 5) reversibility of effects during the early stages, 6) lesion progression, 7) structure-activity analysis, and 8) multiple other studies supporting this mode of action, particularly data regarding perchlorate's inhibition of the sodium-iodide symporter and the lack of evidence for mutagenicity. EPA thus concludes that perchlorate is not likely to be carcinogenic to humans, at least at doses below those necessary to alter thyroid hormone homeostasis. In this situation where thyroid-pituitary disruptive effects have not been used as the critical effect in deriving the RfD, it is inappropriate to calculate a margin-of-exposure based on the RfD or the biochemical precursor event of iodide uptake inhibition. This conclusion is strengthened by the determination of the NRC (2005) that it is unlikely that perchlorate poses a risk of thyroid cancer in humans.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not applicable.

II.B.1. Summary of Risk Estimates

II.B.1.1.

Not applicable (see text)

II.B.1.2.

Not applicable (see text)

II.B.1.3.

Not applicable (see text)

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Dose-response data to derive the RfD for perchlorate are presented in Section 1.A.2.

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

The overall confidence is high that perchlorate is not likely to be carcinogenic to humans, at least at doses below those necessary to alter thyroid hormone homeostasis. This is based on extensive mechanistic data on the mode-of-action of perchlorate, commencing with the inhibition of iodide uptake at the sodium-iodide symporter, and the conclusion that thyroid-pituitary disruption is the sole mode of action for the observed thyroid tumors caused by perchlorate in rodents.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not applicable.

II.C.1. Summary of Risk Estimates

Not applicable.

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Not applicable.

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

Not applicable.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure

Not applicable.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — National Research Council. 2005. Health Implications of Perchlorate Ingestion. The National Academies Press. Washington, D.C.

This source document was prepared by the National Research Council of the National Academies on behalf of the United States Government InterAgency Working Group on Perchlorate. The NRC report followed draft Perchlorate Toxicological Reviews prepared by the U.S. EPA, which had also been subject to public comment and peer review.

Other EPA Documentation — Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization. External Review Draft, NCEA-1-0503, January 16, 2002.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date - 02/18/2005

II.D.3. EPA Contacts (Carcinogenicity Assessment

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Perchlorate and Perchlorate Salts
CASRN 7790-98-9 Ammonium perchlorate
CASRN 7791-03-9 Lithium perchlorate
CASRN 7778-74-7 Potassium perchlorate
CASRN 7601-89-0 Sodium perchlorate

VI.A. Oral RfD References

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VII. Revision History

Substance Name — Perchlorate and Perchlorate Salts
CASRN 7790-98-9 Ammonium perchlorate
CASRN 7791-03-9 Lithium perchlorate
CASRN 7778-74-7 Potassium perchlorate
CASRN 7601-89-0 Sodium perchlorate

File First On-Line 02/18/2005

Date	Section	Description
02/18/2005	All	IRIS Summary first posted

VIII. Synonyms

Substance Name — Perchlorate and Perchlorate Salts
CASRN — 7790-98-9
CASRN — 7791-03-9
CASRN — 7778-74-7
CASRN — 7601-89-0
Last Revised — 02/18/2005

- 7790-98-9
- 7791-03-9
- 7778-74-7
- 7601-89-0
- Sodium perchlorate
- Lithium perchlorate
- Potassium perchlorate
- Sodium perchlorate