

of perchlorate are well known and have been extensively reviewed (Wolff 1998; Goodman 2003). Traditionally toxicologists test chemicals by looking for clear indications of adverse effects in laboratory animals. Such indications might include tumors, hyperplasia, microscopic lesions, and structural abnormalities. Once adverse effects have been characterized, toxicological testing evolves by lowering the exposure dose in order to define a no-observable-adverse-effect level (NOAEL) or failing that, a lowest-observable-adverse-effect level (LOAEL). When these doses are established, uncertainty factors are applied to establish safe values for human exposure. However, when the pharmacology of an agent is known, this knowledge can be used to establish with virtual certainty a lower bound other than zero for a safe exposure level. Identifying the threshold of a precursor to a precursor to a possible adverse effect in humans logically increases both precision and *certainty*, and thus overcomes the limitations of the traditional uncertainty factor approach. For perchlorate, iodide uptake is the initial step (precursor) of the biochemical pathway that could lead to a clinically significant reduction in circulating thyroid hormones (TH). Such a change in TH could lead to developmental deficits in the fetus, the accepted population of concern. Greer et al. (2002) measured a no-observed-effect level (NOEL) of 0.007 mg/kg-day and estimated a true no-effect level (NEL) of 0.005 to 0.006 mg/kg-day for inhibition of radioiodine uptake (RAIU) by perchlorate in men and women. Apart from being an inherently safe dose, the estimated NEL provides a plausible lower bound for a reference dose derived from traditional animal toxicology studies. Further, the NEL has inherently greater precision than a NOAEL or LOAEL and this precision should be reflected when choosing values for uncertainty factors.

1754 EXPOSURE ASSESSMENT FOR PERCHLORATE IN DRINKING WATER.

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Perchlorate is a public health issue of recent interest because it has been found at low levels in the drinking water used by millions of Americans. High level exposure to perchlorate inhibits thyroidal iodide uptake, and disruption of thyroid function can result in neurological effects. Monitoring conducted in California indicates that perchlorate has been measured in approximately 8% of the drinking water supplies, and 60% of those sources contain less than 10 ppb. Preliminary data has suggested that perchlorate can accumulate in leafy vegetables. Further, it has been found in cows milk and human breast milk. Assuming 10 ppb of perchlorate in drinking and irrigation water supplies, we evaluated the potential perchlorate exposure from a variety of scenarios: 1) ingestion of water and water based drinks (e.g., coffee) for the total US population, children age 1-6 years, and women of childbearing age, 2) mothers milk ingestion for a nursing neonate, 3) lettuce ingestion among child-bearing age women, which considered recent data regarding perchlorate accumulation in lettuce, and 4) total water intake from all food and drink sources (e.g., moisture in produce, soda, dairy, etc). For the neonate evaluation, we used a simple pharmacokinetic model to estimate steady-state perchlorate levels in the milk of lactating mothers. For all other scenarios, consumption data from the USDA was used to estimate ingestion at the 50th and 90th percentiles. Nutrient recipes were used to translate the foods as consumed into various nutrients, including moisture (water). The bodyweight-adjusted doses at the 50th percentile ranged from 0.00003 mg/kg-day (nursing neonate and lettuce ingestion) to 0.001 mg/kg-day for the total water intake (direct, indirect and foodbased) for women age 18 to 40 years. Exposures at the 90th percentile were approximately 2.5-times higher. These estimates are preliminary and based on conservative simplistic exposure assumptions. The estimated doses are all lower than those that have been shown to affect thyroidal iodine uptake among humans, a precursor to know adverse effects.

1755 DERIVATION OF A RFD FOR PERCHLORATE: IDENTIFYING A CRITICAL HEALTH ENDPOINT AND THE MOST SENSITIVE SUBPOPULATION.

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Perchlorate (ClO₄⁻) is a drinking water contaminant and is known to inhibit of thyroidal iodide uptake. While environmental agencies have proposed a RfD for ClO₄⁻, their approaches and reliance on human versus animal experimental data differ. A critical evaluation of the human scientific literature was conducted to identify a critical endpoint for the derivation of a RfD for ClO₄⁻ and clearly define possible sensitive subgroups for exposure and uncertainty assessments. Numerous studies have evaluated the effects of ClO₄⁻ in humans in medical, community, occupational and experimental settings. Based on our assessment, it was concluded that a decrease in thyroidal iodide uptake is the most sensitive effect of ClO₄⁻ and the Greer et al. (2002) study is the most appropriate for deriving a RfD. There are clear differences in thyroid function between the human fetus, neonate and adult. It was concluded from our evaluation that the developing neonate would be most

susceptible to the effects of ClO₄⁻. The basis for this conclusion is that during gestation, fetal development is dependent on and protected by transfer of maternal thyroid hormones and as long as maternal thyroid iodide uptake and hormone levels are maintained, normal fetal development would be expected. Following birth, the neonate is dependent on its own production of thyroid hormone with iodide supply originating from maternal breast milk. Iodide uptake in the neonatal thyroid and iodide levels in breast milk should be maintained at normal levels for normal neurodevelopment to occur in the infant. Dietary iodide intake in the US was concluded to be sufficient to prevent thyroid changes, precluding pregnant women as a sensitive subgroup. Thus, it appears that derivation of a RfD ClO₄⁻ based on protection against inhibition of thyroidal iodide uptake, the first step in the production of thyroid hormones, would prevent adverse effects during fetal and neonatal development. Exposure and uncertainty assessments will focus on the developing neonate as the most sensitive subgroup.

1756 SCIENTIFIC RATIONALE FOR THE DERIVATION OF A REFERENCE DOSE (RFD) FOR PERCHLORATE.

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Perchlorate (ClO₄⁻), a contaminant in drinking water, inhibits thyroidal iodide (I⁻) uptake and may disrupt the production of thyroid hormones (TH) leading to thyroid dysfunctions and other neurological deficits. Pregnant women, fetuses, neonates and people with I⁻ deficiency or compromised TH status may be especially at risk. Governmental agencies have used various methods to draft risk assessments for ClO₄⁻, producing disparate results. We have critically reviewed the rationale for the most appropriate approach to derive a RfD for ClO₄⁻. The major conclusions are: (1) I⁻ uptake inhibition is a precursor to TH level perturbation, which in turn is a precursor to thyroid dysfunction. A health risk assessment for ClO₄⁻ must recognize that I⁻ uptake inhibition is not a genuine adverse effect; (2) Human dose-effect data are available, and are preferable to animal data in order to avoid the uncertainties of interspecies extrapolation; (3) Controlled human volunteer studies offer more reliable exposure information and are preferable to other epidemiological and community studies. (4) The benchmark dose methodology is recommended for dose-response assessment and the benchmark dose effect level (BMDL) corresponding to one standard deviation from the mean of the control population should be used; (5) As the half-life of perchlorate in humans is moderate (8 h), allowing steady state level to be readily attained, no adjustment factor is needed for extrapolating I⁻ uptake inhibition data from less than chronic exposure; (6) Many surveys have shown that the dietary I⁻ intake is sufficient in the US population and very few women are I⁻ deficient; (7) There is evidence that person-to-person variation, including those individuals at sensitive developmental life stages, is less than 3 fold. On the basis of these considerations, we have derived a BMDL of 0.0126 mg/kg-d based on the thyroidal I⁻ uptake inhibition data in the Greer et al. (2002) study (Environment Health Perspect. 110:927). We applied an overall uncertainty factor of 3 to arrive at a tentative RfD of 0.0042 mg/kg-d.

1757 USE OF HUMAN AND ANIMAL PBPK MODELS IN RISK ASSESSMENT FOR PERCHLORATE.

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Perchlorate has been used as a solid rocket propellant and ignitable source in munitions for many years. Recently, it has been found in surface and ground waters of multiple environmental sites, especially in the western United States. The primary effect of this chemical is inhibition of iodide uptake by the thyroid. Sufficient inhibition over time results in a depression of thyroid hormone formation and subsequent compensatory increase of thyroid stimulating hormone (TSH). The most sensitive measure of thyroid function disruption is iodide uptake inhibition and the most sensitive population in humans is likely to be the fetus. However there are no quantitative dose-response toxicity data available for the fetus in either animals or humans. To assist in addressing this issue, perchlorate physiologically based pharmacokinetic (PBPK) models were developed for rats at different life stages including the normal adult, pregnant female and fetus, and lactating female and neonate. In addition, a PBPK model for adult humans was also developed. These PBPK models were verified using iodide uptake inhibition studies in rats and humans. Effective doses for iodide inhibition in rats and humans at different life stages were estimated. Results indicated that the fetus is the most sensitive life stage for iodide uptake inhibition. By applying the ratio of predicted effective doses between adult rats and humans to those predicted for rats of different life stages, an effective dose of 0.006 mg/kg/day can be estimated for 5% iodide uptake inhibition in the human fetus. By using this effective dose in human fetus as the point-of-departure, a risk estimate for perchlorate of 0.002 mg/kg/day can be developed by applying an uncertainty factor of 3 fold to account for intraspecies variation. This new risk level confirms the previously proposed value of 0.002 mg/kg/day determined by other methods.