

## Health Implications of Perchlorate Ingestion

Compounds containing the perchlorate ion have been used in solid rocket fuels and propellants since the early 1900s. These compounds are also used in explosives, pyrotechnics, and blasting formulations, and perchlorate has been detected in certain fertilizers, particularly those derived from Chilean ores. High doses of perchlorate were used in the 1950s and 1960s to treat people with an overactive thyroid gland, but perchlorate is rarely used medicinally today.

Environmental perchlorate contamination was first discovered in wells at California Superfund sites in 1985, and as of September 2004, has been reported in 35 states. It is estimated that more than 11 million people have perchlorate in their public drinking water supplies at levels of at least 4 parts per billion, based on sampling data collected by the U.S. Environmental Protection Agency (EPA) as of May 2004. Perchlorate has also been detected in some foods, such as lettuce, cow's milk, and human breast milk. Ingestion of sufficient amounts of perchlorate from contaminated food or water may interfere with the production of thyroid hormones because perchlorate can compete with the uptake of iodide into the thyroid gland, and iodide is a necessary component of thyroid hormones.

As the agency tasked with protecting public drinking water, EPA has issued draft risk assessments that proposed a safe reference dose (RfD) on which to base a federal drinking water standard, but no standard has yet been set. Critics claim the EPA risk assessments are based on flawed scientific studies and do



not appropriately consider all relevant data. *Health Implications of Perchlorate Ingestion*, a National Research Council report, provides an independent assessment of the potential adverse health effects of perchlorate ingestion and reviews the findings presented in EPA's 2002 draft risk assessment.

EPA based its proposed reference dose on studies of observed adverse health effects in rats exposed to perchlorate, and it applied an uncertainty factor of 300 to add a margin of safety. In contrast, the National Research Council report recommends basing the reference dose on available studies in humans using a nonadverse effect—the inhibition of iodide uptake by the thyroid. This approach is health-protective because no adverse health effects will occur if iodide uptake remains unaffected. As an additional margin of safety, the report recommends applying an uncertainty factor of 10 to protect sensitive groups, such as the developing fetus, newborns, and infants.

The National Research Council report finds that a reference dose of 0.0007 milligrams per kilogram body weight per day would protect the health of even the most sensitive groups of people over a lifetime of exposure. Although this report recommends a reference dose for perchlorate, it did not recommend a drinking water standard because that was outside the study committee's charge. Converting a reference dose to a drinking water standard, which is a maximum allowable concentration in tap water, involves numerous additional steps, assumptions, and policy choices beyond a reference dose. For information on how drinking water standards are developed, see <http://www.epa.gov/safewater/standard/setting.html>.

### **Potential Effects of Perchlorate Exposure on Thyroid Function**

Thyroid hormones regulate metabolic activity, affect the function of virtually every organ system, and are required for normal central nervous system development and skeletal growth in fetuses and infants. Perchlorate can reduce the uptake of iodide by the thyroid gland, thereby decreasing thyroid hormone synthesis. The resulting iodide deficiency, if severe, could lead to hypothyroidism (deficiency of thyroid hormone production), which can result in clinical disorders, such as goiter and developmental defects in fetuses.

However, the body can compensate for changes in iodide availability because it has an efficient mechanism that acts to keep thyroid hormone production and secretion within normal or nearly normal limits, protecting against both hypothyroidism and hyperthyroidism (overproduction of thyroid hormones). The National Research Council report finds that iodide uptake would probably have to be reduced by at least 75% for months or longer for adverse health effects to occur in healthy people. A decrease is potentially more likely to affect sensitive groups of people, but there are no data to determine the magnitude of a decrease that would cause adverse effects in these groups.

### **EPA's Risk Assessment**

A primary purpose of EPA's perchlorate risk assessment was to calculate an oral reference dose.

EPA defines a reference dose as an estimate (with uncertainty of perhaps tenfold) of a daily oral exposure to the human population (including sensitive groups) that is likely to be without risk of deleterious effects during a lifetime. EPA uses a reference dose to calculate federal drinking water standards and hazardous waste cleanup guidelines. Several issues have been debated concerning EPA's assessment of potential adverse health effects of perchlorate exposure, including the following:

- The adequacy and relevance of human data for assessing health risks posed by perchlorate exposure.
- The quality and validity of some animal data.
- Identification of a critical effect and a critical study to serve as the starting point or "point of departure" for the risk assessment.
- Application of uncertainty factors to the point of departure.

### **Available Human Data**

Epidemiologic studies and clinical studies provide human data. Epidemiologic studies examine the health effects on human populations—typically workers or the general public—who have been exposed to a contaminant. Clinical studies investigate the health effects resulting from experimental administration of a substance to human volunteers.

The available epidemiologic studies are not consistent with the hypothesis that perchlorate exposure at the doses investigated causes any of the following health effects: congenital hypothyroidism, significant changes in thyroid function in newborns, or hypothyroidism and other thyroid disorders in adults. There are not enough epidemiologic data to determine whether there is an association between perchlorate exposure and adverse developmental effects on the nervous systems of children or between perchlorate exposure and thyroid cancer. The study committee believes thyroid cancer to be an unlikely outcome of perchlorate exposure in humans.

Clinical studies in humans provide more useful data. In a study by Greer et al. (2002), groups of healthy men and women were given perchlorate in doses of 0.007 to 0.5 mg/kg of body weight per day for 14 days.<sup>1</sup> The study identified a no-observed-effect

<sup>1</sup> Greer, M.A., G. Goodman, R.C. Pleus, and S.E. Greer. 2002. Health effects assessment for environmental perchlorate contamination: The dose-response inhibition of thyroïdal radioiodide uptake in humans. *Environ. Health Perspect.* 110:927-937.

level for inhibition of iodide uptake by the thyroid at 0.007 mg/kg per day. Furthermore, there were no significant changes in thyroid hormone concentrations at any dose. These findings are supported by the results of other similar studies, one of which was of 6-months duration. In addition, a 1984 study of long-term treatment of patients with hyperthyroidism found that moderately high doses of perchlorate did not cause hypothyroidism, even when administered after the patients' blood levels of thyroid hormones had returned to normal.

### **Animal Studies**

Rats have been used to study health effects of perchlorate because their pituitary-thyroid systems are similar to those of humans. However, there are sufficient differences in the biology of rats and humans that studies in rats provide only qualitative information on potential adverse effects of perchlorate exposure.

### **Determining a Point of Departure**

In any risk assessment, a critical effect and a critical study are identified to serve as a point of departure (starting point) from which to derive a reference dose. For perchlorate, EPA based its point of departure on changes in brain structure, thyroid structure, and blood levels of thyroid hormones reported in rats exposed to perchlorate.

As in most risk assessments, EPA used *adverse* effects as the point of departure. However, the National Research Council report recommends using a *non-adverse effect*—specifically, the inhibition of iodide uptake by the thyroid gland—as the basis of the risk assessment. Inhibition of iodide uptake is a reliable and valid measure, has been unequivocally demonstrated in humans exposed to perchlorate, and is the key biochemical event that precedes all other thyroid-mediated effects of perchlorate. Using a non-adverse effect that is “upstream” of any adverse effects is an especially health-protective approach to the perchlorate risk assessment.

The report recommends using a study by Greer et al. (2002) as the critical study on which to base the risk assessment because human data provide a more reliable point of departure than the animal data and

because the study measures the recommended critical effect (inhibition of iodide uptake).

### **Uncertainty Factors**

Uncertainty factors are intended to provide a safety margin for the reference dose. Five kinds of uncertainty factors are typically considered in calculating a reference dose. Those factors are intended to account for differences between humans and laboratory animal species, human variability, failure to establish a dose at which no adverse effect is observed, lack of data from long-term exposures, and other database gaps.

In its draft risk assessment, EPA proposed a total uncertainty factor of 300 to apply to its point of departure of 0.01 mg/kg per day based on adverse health effects observed in rats. Accordingly, EPA proposed a reference dose of 0.00003 mg/kg per day.

In contrast, the National Research Council study committee recommends applying a total uncertainty factor of 10 to its point of departure—the no-observed-effect level of 0.007 mg/kg per day in humans from the Greer et al. (2002) study. The total uncertainty factor used by EPA and that recommended by the committee cannot be directly compared because EPA and the committee used different studies and end points on which to base the risk assessment.

Those differences affect the selection of the uncertainty factors. The committee's recommended uncertainty factor reflects a full factor of 10 for human variability and is intended to protect the most sensitive population—the fetuses of pregnant women who might have hypothyroidism or iodide deficiency and other potentially sensitive populations, such as newborns and infants. No other uncertainty factors were considered necessary given the recommended point of departure—a no-observed-effect level for inhibition of iodide uptake by the thyroid gland based on human data.<sup>2</sup>

With its recommended point of departure and total uncertainty factor, the committee calculated a reference dose of 0.0007 mg/kg per day. The committee did not provide a corresponding recommendation for a drinking water standard. The derivation of a drinking water standard as noted above requires numerous policy assumptions and decisions that the committee was not charged to address in its report.

<sup>2</sup> One committee member felt that an additional uncertainty factor of 3 should be used for database adequacy. However, the other 14 committee members concluded that the database, which includes five human clinical studies, occupational and environmental epidemiologic studies, studies of long-term perchlorate administration to patients with hyperthyroidism, and animal toxicology studies, is sufficient.

## Looking to the Future

New research could provide a more complete understanding about the effects of perchlorate, especially regarding the effects of chronic exposure and the effects on sensitive populations. The report suggests the following research:

- A clinical study designed to determine the potential effects of long-term, low-dose perchlorate exposure on thyroid function, with a special focus on the mechanisms of thyroid compensation.
- A series of studies using human tissues grown in the laboratory and animal studies to understand better iodide transport between a mother and her fetus through the placenta and to determine whether perchlorate affects development independently of its effect on iodide uptake by the thyroid.
- New epidemiologic research to assess the possible health effects of perchlorate exposure in populations of pregnant women and their fetuses and newborn infants.
- Studies to measure more precisely the extent of, and risk factors for, iodide deficiency, particularly in pregnant women and their offspring.

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**This brief was prepared by the National Research Council based on the committee's report. For more information,** contact the Board on Environmental Studies and Toxicology at 202-334-3060. *Health Implications of Perchlorate Ingestion* is available from the National Academies Press, 500 Fifth Street, NW, Washington, DC 20001; 800-624-6242 or 202-334-3313 (in the Washington area); [www.nap.edu](http://www.nap.edu).

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