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## Special Report

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# Scientific Review: Perchlorate Research

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### Summary Authors:

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This report was prepared for the Alliance for Food and Farming to provide agriculture with a better understanding of the science surrounding this issue. The intent is to provide an overview of the documentation available, the review articles that have been published, a comprehensive reference list of the articles that have been published on the subject of perchlorate and copies of the most relevant articles. This report is specifically focused on the health related aspects of the perchlorate issue and possible impacts on consumers as understood today.

### Introduction:

Perchlorate ( $\text{ClO}_4$ ) is the most oxygenated member of a series of four anions made up of chlorine and oxygen. The anion has a charge of negative one and can form an acid or a salt in combination with  $\text{H}^+$  or another cation such as sodium, potassium or ammonium ion. Perchlorate salts are ionic and dissociate completely when dissolved in water. The dissociated ions are very stable and may persist for years in solution. Perchlorate belongs to the Hofmeister series of ions and as such, effects on metabolism have been hypothesized and studied. Because of the similarity in ionic size to iodide, perchlorate is a competitive inhibitor of iodine absorption. This factor resulted in the pharmacological use of perchlorate to treat Graves disease in the 1950's- 1960's (Morgans & Trotter, 1960)

Until March of 1997, the detection limit for perchlorate in drinking water was 400  $\mu\text{g/L}$  (ppb). At this time the California Department of Health Services (DHS) developed a more sensitive analytical procedure using ion chromatography and achieved a detection limit in the range of 4-5 ppb.(DHS 2000). EPA method 314.0 (Federal Register, 2000) currently exists for the analysis of perchlorate in water and achieves this low level of detection.

Many authors have reviewed the literature on the effects of perchlorate on humans as well as on animal models (Cal EPA, 2002; U.S. EPA , 2002; Soldin et al. 2001; Zoeller, 2003). These authors have concluded that the primary mechanism of action for perchlorate is as an inhibitor of iodine uptake thereby interfering with thyroid hormones.

Since most Americans have an iodine rich diet and thus a surplus of iodide in the thyroid (Hollowell et al. 1998). The primary concern is for special subgroups - iodine deficient individuals, pregnant women and newborn infants. Most of the current literature involves developing an understanding of whether any observed effects are meaningful.

The research that has been conducted on perchlorate can be categorized in a number of ways. There have been chemical detection studies, environmental surveys, human epidemiological studies, human exposure studies, animal model studies for acute toxicity and chronic effects, testing to determine modes of action and pharmacological effects. This document will not cover the chemical detection and environmental distribution works except as they directly influence the health impact studies.

### ***National Academy of Sciences Committee Findings:***

The National Academy of Sciences - Division on Earth and Life Studies - Board On Environmental Studies and Toxicology and the Institute Of Medicine - Division Of Health Sciences Policy was asked for a "Toxicological Assessment of Perchlorate Ingestion" by the U.S. Environmental Protection Agency in conjunction with the Department of Defense, Department of Energy and National Aeronautics and Space Administration. The NAS committee has evaluated the current state of the science regarding potential adverse effects resulting from disruption of thyroid function in humans and laboratory animals at various stages of life. The committee evaluated the animal studies to determine their relevance to human toxicology and to determine whether EPA's findings in its 2002 Draft Toxicological Review and Risk Characterization for Perchlorate are consistent with the scientific evidence. The committee also identified research that could reduce the uncertainty in the current understanding of human health effects associated with low-level perchlorate ingestion.

Key elements from this document which relate to our summary are as follows:

Perchlorate can affect thyroid function because it inhibits the transport of iodide into the thyroid. This "inhibition of thyroid iodide uptake is the only effect that has been consistently documented in humans." There is no evidence that perchlorate causes new thyroid disorders, thyroid nodules, thyroid tumors, or carcinomas.

Animal studies to date have primarily used rats. There are significant biochemical and physiologic differences between rats and humans which result in significant differences in their responses to iodide transport inhibitors such as perchlorate. While these studies provide some qualitative information regarding potential adverse effects of perchlorate, the results cannot be used to predict human health risks.

The committee notes that "a sustained exposure at more than 0.4 mg/kg per day would most likely be required to cause a sufficient decline in iodide uptake and thyroid hormone production to result in adverse health effects in normal adults." Using the convention of a 70 kg person drinking 2 L of water per day, an equivalent concentration in water would be about 14,000 ppb. That being said, any potential harmful effect from perchlorate can only happen if iodide uptake by the thyroid is inhibited. In order to prevent the possibility of any adverse effects from perchlorate, the committee recommends using a non-adverse biochemical effect (inhibition of iodide uptake) rather than an adverse effect (hypothyroidism) as a point of departure for the perchlorate risk assessment. To this end they recommend using the Greer et al. (2002) study where

0.007 mg/kg per day (250 ppb) caused no observed inhibition of iodide uptake. The results were consistent with other studies.

The NAS committee discusses the establishment of a reference dose (RfD) for daily oral exposure to perchlorate. Using the Greer et al (2002) starting value of 0.007mg/kg per day, it recommends an uncertainty factor of 10 be applied. This further measure of safety would ensure that the most sensitive populations, the fetuses of pregnant women who might have hypothyroidism or iodide deficiency, be protected. This would lead to an RfD of 0.0007 mg/kg per day (24.5 ppb). The EPA has used this recommendation to revise its draft RfD of 0.00003 mg/kg per day (1ppb) to 0.0007 mg/kg per day.

### ***Modes of Action of Perchlorate***

There is a large body of literature surrounding the possible modes of action of perchlorate and reviews of this literature have been conducted by numerous authors (US EPA 1998a, b; Cal EPA 2002; Soldin et al. 2001; Zoeller, 2003, Juberg, 2002). These reviews cover many different potential modes of action for perchlorate and conclude that the observed adverse effects caused by perchlorate are related to the disruption of thyroid hormone regulation. It is generally agreed that the effects of perchlorate are related to the inhibition of iodine uptake. Due to this effect, perchlorate was used in the treatment of Graves disease (hyperthyroidism) in the 1950's-1960's (Crooks & Wayne, 1960) The principal hormones secreted by the thyroid are thyroxine (T4) and triiodothyronine (T3) which both contain iodine. These hormones influence the growth and maturation of tissues, cell respiration and total energy expenditure and the turnover of essentially all substrates (including proteins, carbohydrates and cholesterol), vitamins, and hormones. The major substrates for synthesis of thyroid hormone are tyrosine and iodine with tyrosine generally not rate limiting (Cal EPA. PHG 2002). As a trace element, iodine can be rate limiting. Iodine is absorbed through the gastrointestinal tract as iodide and absorbed through passive diffusion or active transport.

Thyroid tissue concentrates iodide by the sodium-iodide symporter (NIS) molecule. Control of T4 and T3 is mainly regulated by negative feedback and involves thyroid releasing hormone (TRH) and thyroid stimulating hormone (TSH). Circulating levels of T4, T3 and TSH can be used to serve as biomarkers of exposure and effects of agents that disrupt thyroid/pituitary status. (US EPA 1998 a,b from Cal Public Health Goal). As reported in Soldin et al., 2001, Perchlorate inhibits uptake of iodide at the cellular level. Unlike other antithyroid agents, such as methimazole and propylthiouracil, perchlorate does not block the synthesis of thyroid hormones. The half-life of perchlorate in laboratory animals is 2-20 hours and in humans approximately 8 hours and it does not accumulate.

The thyroid can usually maintain normal thyroid hormone levels unless the iodide supply is less than approximately 50 µg/day or iodine uptake is decreased for a prolonged period of time resulting in hypertrophy and hyperplasia of the thyroid. Perchlorate could inhibit iodide accumulation enough to cause goiter and hypothyroidism when ambient iodine intake is low or uptake is sufficiently inhibited. Animal models have failed to show that perchlorate may cause inhibition of organic binding of iodine within the thyroid by affecting thyroid peroxidase which had also been proposed (Soldin et al. 2001)

### ***Health Effects***

Health effects of perchlorate have been studied for many years and showed that perchlorate is not metabolized in humans. In early human studies, Eichler (1929) as cited in Stansbury and Wyngaarden, (1952) reported recovery of 70% of a 1-2 g dose of perchlorate in the urine within 12 hours and 85-90 % within 24 hours. In another study (Durand, 1938) showed 95% recovery in 48 hours. These data support the concept that perchlorate does not accumulate in human tissue.

In the proposal to the NAS panel the US EPA reported that toxicity testing conducted in the late 1990s confirmed that the principal target organ of perchlorate's toxicity is the thyroid gland. The toxicity studies have shown that perchlorate exposure inhibits iodide uptake, alters levels of thyroid hormones (thyroxine [T4] and triiodothyronine [T3]) and thyroid stimulating hormone (TSH), and causes changes in thyroid histopathology in rats at various stages of life. Because perchlorate has been shown to disrupt the pituitary-hypothalamic-thyroid axis by inhibiting iodide uptake, EPA believed that perchlorate exposure may cause serious adverse effects, including carcinogenic, neurodevelopmental, developmental, reproductive, and immunotoxic effects. However, questions were raised by some regarding the animal model developed and used by EPA to predict human health effects, the levels at which adverse effects result from chronic iodide inhibition or changes in thyroid hormones, the relevance of effects observed in the animal studies to human health (e.g., changes in brain morphometry), and EPA's use of uncertainty factors in the derivation of its RfD. These questions resulted in the NAS Committee Review referenced above.

It is important to recognize that there are adverse effects associated with both too much and too little iodine in the diet. As with most dietary factors there is a range where they function properly and either too much or too little can lead to disease. The National Health and Nutrition Examination Survey III (NHANES III) data as reported in Hollowell et al. 1998 uses urinary iodine concentrations as an indicator of dietary iodine sufficiency. This study found that the median of the population was 14.5 µg/dL and 11.7 % of the population was found to have low urinary iodine concentrations (<5 µg/dL). The median urinary iodine concentrations in iodine-sufficient populations should be > 10 µg/dL and no more than 20% of the population should have concentrations less than 5 µg/dL. Using this definition there is no iodine deficiency in the general population, but it does not preclude the possibility that some women of childbearing age are not getting the optimal daily amount of iodine. There has been a downward trend since the high levels identified in the 1971-1974 NHANES I when more concerns were raised about iodine-induced conditions than iodine deficiency.

Congenital hypothyroidism occurs in 1 in 3,000 to 1 in 4,000 live births. While this condition results in severe intellectual deficits in these children, it is also difficult to diagnose based upon clinical symptoms alone. Therefore universal screening of newborns for circulating T4 and/or TSH has been implemented in a number of countries. (Zoeller, 2003 from Delange 1997, Klein and Mitchell 1996). It has been suggested that fetal damage may be the most important potential effect of perchlorate exposure due to the sensitivity of the fetus to thyroid hormone deficiency. Zoeller (2003) reviews the literature focused on thyroid hormone and brain development as it relates to evaluating potential thyroid toxins. In this review he concludes that recent information on the clinical effects of TH insufficiency clearly indicates that very small but persistent changes can produce adverse effects in adults and can produce permanent changes in brain development. He cautioned that risk analysis in the absence of specific neurodevelopmental endpoints is challenging for childhood exposure of these chemicals.

Ammonium perchlorate was tested in a battery of genotoxicity tests, and found to be negative in all tests (U.S. EPA, 1998a, 2002). This is consistent with the fact that perchlorate is relatively inert at physiological conditions and does not appear to be metabolized to mutagenic or clastogenic metabolites in humans as well as in test animals. In an occupational study, Lamm, et al. (1999) showed absorption of airborne perchlorate at levels from 0.004-167 mg total perchlorate per day was not accompanied by clinical evidence of thyroid abnormality. Workers were grouped into four exposure categories with mean absorbed perchlorate doses of 1, 4, 11 and 34 mg perchlorate per day. Thyroid function was assessed through a number of thyroid function parameters as well as physical examination and no differences were found among the four groups. They demonstrated a no-observed adverse-effect-level (NOAEL) based upon this work of 34 mg/day of perchlorate absorption. No occupational thyroid disease was found among these workers.

### ***Animal Research***

The California EPA evaluated a number of animal studies that sought to determine carcinogenicity of perchlorate. Interpretation of the results was hampered by a number of factors such as small study groups, short exposure and observation duration, lack of multiple dose groups and co-exposure to other cancer causing agents. Gauss (1972) treated female NMRI mice with one percent potassium perchlorate in the diet or a control diet for 160 days. While some thyroid changes were observed no progression to malignancy was observed for the study. The California EPA found no carcinogenicity studies on humans exposed to perchlorate. In a two generation reproductive toxicity study in rats, York et al, 2001 concluded that perchlorate is not a reproductive toxicant in rats when exposed in drinking water from conception to 19 weeks of age to levels as high as 30 mg/kg-day. Animal studies documented the LD<sub>50</sub> for mice varied from 76 to 2000 mg/kg depending upon the cation and whether it was administered orally or intraperitoneally (Von Burg, 1995; Schilt, 1979, U.S. EPA, 1971; Shigan, 1963; Joesten & Hill, 1966). They also concluded that genotoxicity is not a potential mode of carcinogenic action for perchlorate (U.S. EPA, 1998a, 2002, Zeiger, 1998). Subchronic toxicity was evaluated in several studies. US EPA (2002) concluded that there was dose- and time - dependent effect of perchlorate on thyroid hormones and TSH and that the LOAEL based upon decreases in T3 and T4 at 90 days is 0.01 mg/kg-day. The NOAEL for TSH is 0.05mg/kg-day. They also reported some data showing that some of the effects were reversible since 30 days after cessation of treatment, serum T3 levels were not significantly different from the control for all but the highest dose level group.

### ***Population Studies and Research Using Human Subjects***

Greer et al. (2002) conducted a study on human subjects to study the effects of perchlorate in drinking water. In this study they administered 0.007, 0.02, 0.1 or 0.5 mg/kg-day (body weight adjusted doses) to 37 male and female volunteers for 14 days. They evaluated iodine uptake using <sup>123</sup>I. The no-observed-effect level (NOEL) for this study was more narrowly defined to indicate the highest exposure level tested at which inhibition of thyroidal iodide uptake is not statistically or biologically significant. Test methodology for both exposure and blood draw took into account circadian variation. The results demonstrated that perchlorate at the doses given, suppresses only iodide transport. The results also showed 0.007mg/kg/day was the NOEL for inhibition of thyroidal radioactive iodine uptake (RAIU). They estimated a true NEL of 5.2-6.4 µg/kg-

day for 8 hour and 24 hour evaluations. Based upon the variability observed in this test there is a 95% probability that thyroidal iodide uptake will be inhibited by no more than 8.3-9.5% at a dose of 5.2-6.4  $\mu\text{g}/\text{kg}\cdot\text{day}$ . It is expected that an inhibition of 9.5% would be physiologically insignificant to individuals with sufficient iodine intake. Further conclusions based upon average body weight of 70 kg and drinking water intake of 2L/day, this dose would result if the water contained 180-220  $\mu\text{g}/\text{l}$  (ppb). This study also found that even with inhibited thyroidal radioiodine uptake, there was no effect on serum levels of thyroid hormones except in the 0.5 mg/kg-day dose group which showed a slight downward trend in morning blood draws during perchlorate exposure which was recovered by 15 days postexposure evaluation. Lamm and Doemland (1999) reported that while perchlorate has been detected in the water supplies of seven counties in Nevada and California the incidence of congenital hypothyroidism did not show an increase over projected levels. On the other hand Brechner et al. (2000) found that there were slightly elevated levels of TSH in newborns in an area with perchlorate in the drinking water when compared to a similar area without perchlorate. The effect of these differences on long-term health has not been established. In Crump et al.(2000) they studied three cities in Chile with varying levels of natural perchlorate in their drinking water. Their results did not support the hypothesis that perchlorate in drinking water at levels up 100 -120  $\mu\text{g}/\text{L}$  suppresses thyroid function in newborns or school age children. In 2000, Li et al. reported on a study to determine neonatal thyroid stimulating hormone as a function of perchlorate in drinking water. In this study they concluded that there were no effects from environmental exposure to perchlorate  $\leq 15 \mu\text{g}/\text{L}$ .

### ***Neonates and Pregnant Women***

Prior to 1960, perchlorate was commonly used to treat women with hyperthyroidism during pregnancy. Crooks and Wayne (1960) reported treating 12 pregnant thyrotoxic patients with potassium perchlorate (600 mg/day or 1000mg/day) to control the disease. One infant had slight thyroid enlargement that disappeared in 6 weeks while the others showed no abnormality of any kind. The fact that the women were suffering from thyrotoxicosis may have an impact on the effect on the fetus. Connell (1981) reported a case of a female Graves disease patient who was treated with 200 mg/day perchlorate for 22 years with good control of the disease and no apparent adverse effects.

There have been epidemiological studies of newborns in populations exposed to varying quantities of perchlorate in their drinking water. These studies encompass cities in Chile with natural perchlorate in their drinking water (Crump et al. 2000) as well as cities in the U.S. that have perchlorate contamination of their drinking water (Brechner, et al. 2000; Z Li et al. 2000; FX Li et al. 2000). In studies based upon Las Vegas and Reno NV, Li et al. 2000 did not find a significant difference in mean blood T4 between the two cities studied. Las Vegas is a city with perchlorate observed in the drinking water periodically throughout the year, while there is no perchlorate observed in the Reno drinking water supply. The study was sensitive enough to determine differences in mean T4 levels based on day of life sampled as well as birth weight and gender. During the 15 months of the study, there were eight months with no detectable perchlorate in the Las Vegas drinking water. This was the perchlorate positive location. This study also only included normal birth weight children in both cities.

One published study of perchlorate effects on neonatal T4 levels is from Nevada (Z Li et al., 2000). It found that there was no significant exposure-related difference in mean neonatal T4 levels between Las Vegas (with perchlorate exposure) and Reno (without

perchlorate exposure). The variables that did affect the difference were birth weight, gender, and sampling prior to the fourth day of life. The mean age at time of sampling in Las Vegas was six hours sooner than in Reno.

The California EPA Draft Public Health Goal issued in December of 2002 has a detailed evaluation of the data available to that date. In a master's dissertation, using similar data to the Li study, Schwartz (2001) evaluated the serum T4 and TSH levels of all newborns in California during 1996. They identified pregnant women with marginal or frank iodide deficiency and their fetuses as potentially sensitive sub-populations for perchlorate exposure. The Cal EPA seems to use the dissertation by Schwartz (2001) as a cornerstone of their recommendations, while rejecting the findings of a number of other researchers with contrary findings. Other authors have identified some factors within this work that may affect the conclusions. California is currently reviewing its Public Health Goal based upon the NAS Committee recent findings.

### **Conclusions:**

Perchlorate is a relatively well-studied chemical due to its pharmacological uses. The relatively low levels found in some wells and public water systems are unlikely to cause adverse effects in humans. According to the research reviewed, perchlorate is not a carcinogen, does not accumulate in the body and is excreted within hours. The effects on the thyroid appear to be not significant in an iodine sufficient population.

### **Addendum: November 2004**

Three new studies were presented in October 2004 at the 76th annual meeting of the American Thyroid Association in Vancouver, British Columbia, Canada. These studies are not published as of yet, but have been summarized by the 2004 Science Letter via NewsRx.com and on the American Thyroid Association website: [www.thyroid.org](http://www.thyroid.org). As presented, these findings corroborate studies reviewed in our summary document.

In one study Lewis Braverman, MD, and colleagues recruited 13 volunteers to explore the effects of long-term ingestion of perchlorate on thyroid function. While the sample size was too small to be statistically significant, findings suggest that daily ingestion of 0.5 mg or 3.0 mg (equivalent to 250 ppb or 1500 ppb in the water supply) of perchlorate do not affect thyroid function in adults with normal thyroid levels. These results are similar to those of Greer et al. (2002) where doses of 0.007, 0.02, 0.1 or 0.5 mg/kg-day (body weight adjusted doses) administered to 37 male and female volunteers for 14 days affected iodine transport but not thyroidal iodine uptake. Given their assumptions for a default body weight of 70 kg and an exposure assumption of 2L water per day, these doses correspond to levels in water of 250 ppb, 700 ppb, 3500 ppb, and 17,500 ppb.

In a second study led by Braverman, workers at an ammonium perchlorate plant were compared to workers not in the plant for perchlorate exposure. While some workers absorbed 20 mg or more of perchlorate (10,000 ppb) in a single shift and iodine uptake was reduced, circulating thyroid hormone levels were not affected. This corroborates the population studies and research using human subjects discussed in our summary.

A third study by Rafael Tellez, MD is similar to Crump *et. al.* 2000. In this case pregnant women living in a region in Chile with high levels of naturally occurring perchlorate (113

ppb) were compared to women living where levels were low (6 ppb) or undetectable. Tellez and his team found that levels as high as 114 µg/l (ppb) during pregnancy did not affect maternal thyroid status, fetal thyroid status, or breast milk iodine concentrations.

UC Irvines Urban Water Research Center published a science and policy review in June, 2004 (Bull, *et al* 2004). In it they conclude that while the current public health goal in California is 6 parts per billion, exposure to perchlorate at levels below 100 ppb would likely cause no harm to healthy adults. They recommend more study of those groups who might be more susceptible to low iodine levels such as pregnant women and their offspring.

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The following documents provide excellent reviews of the literature available at the time of their preparation:

1. Draft Public Health Goal for Perchlorate in Drinking Water. Pesticide and Environmental Toxicology Section. 2002 Office of Environmental Health Hazard Assessment. California Environmental Protection Agency March.
2. Report on the Peer Review of the U.S. Environmental Protection Agency's Draft External Review Document "Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization" 2002,
3. Soldin, O. P.; Braverman, L. E.; Lamm, S. H. "Perchlorate clinical pharmacology and human health: a review." *Ther. Drug Monit.* 23: 316-331. 2001
4. Zoeller, R Thomas "Challenges Confronting Risk Analysis of Potential Thyroid Toxicants" *Risk Analysis* Vol 23, No.1, 2003

These documents present additional information in a more agenda driven format:

1. "Perchlorate and the Toxic Legacy of the Cold War" Environmental Working Group, Wash DC; Available at [www.ewg.org](http://www.ewg.org) 2001.
2. Juberg, D.R. "Perchlorate in Drinking Water - Scientific Collaboration in Defining Safety" The American Council on Science and Health (ASCH) Special Report January 2002

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