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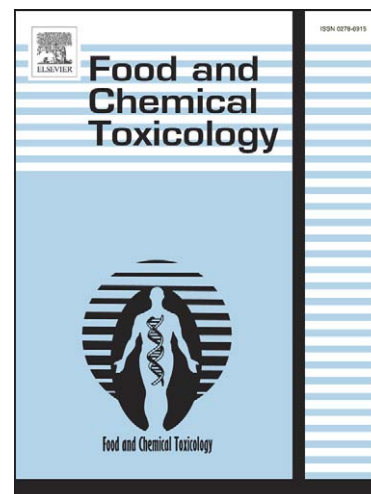
Perchlorate: Overview of Risks and Regulation

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CONFIDENTIAL DRAFT**Perchlorate: Overview of Risks and Regulation**

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Abbreviations: DDE, *p,p'*-dichlorophenyldichloroethylene; NAS, National Academy of Sciences; NHANES, National Health and Nutrition Evaluation Survey; PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzo-*p*-dioxins; PCDFs, polychlorinated dibenzofurans; T₃, triiodothyronine; T₄, thyroxine; TEQ, toxic equivalent; TSH, thyroid stimulating hormone; RfD, reference dose; US EPA, US Environmental Protection Agency; US FDA, US Food and Drug Administration

ABSTRACT

The extent to which perchlorate, which occurs naturally and as an industrial contaminant, should or should not be regulated has become controversial. This review examines a number of inconsistent conclusions that have been drawn based on thyroid hormone serum concentrations, urinary iodine concentrations, and perchlorate exposure among women participating in the 2000-2001 National Health and Nutrition Examination Survey (NHANES) and based on the body of epidemiologic and clinical evidence reporting no associations between effects on thyroid hormones and similar or much higher levels of perchlorate exposure. For example, studies associating perchlorate with thyroid effects at low exposures did not control for anti-thyroid agents with modes of action that differ from that of perchlorate, such as some organochlorines. Available evidence does not support a causal relationship between changes in thyroid hormone levels and current environmental levels of perchlorate exposure but does support the conclusion that the US Environmental Protection Agency's reference dose (RfD) for perchlorate is conservatively health-protective. However, potential perchlorate risks are unlikely to be distinguishable from the ubiquitous background of naturally occurring substances present at much higher exposures that can affect the thyroid via the same biological mode of action as perchlorate, such as nitrate and thiocyanate. Risk management approaches that account for both aggregate and cumulative exposures and that consider the larger public health context in which exposures are occurring are desirable.

Introduction

Perchlorate is a substance that has recently been receiving prominent legislative and regulatory attention in the US by both federal and state governments. Initially identified as a groundwater contaminant associated primarily with rocket fuel spillage, perchlorate is now found to be ubiquitous. Widespread human exposure to both anthropogenic and naturally occurring perchlorate occurs primarily via ingestion. Like several other dietary goitrogens, perchlorate can interfere with iodine uptake by the thyroid gland, potentially disrupting thyroid hormone levels responsible for regulating many of the body's metabolic and developmental functions. Because thyroid hormones are critical for normal fetal and neonatal development, perchlorate has the potential to pose a risk to children although no specific cases have been identified, even in areas where exposure occurs to high levels of naturally occurring perchlorate. Because there are incomplete data on perchlorate's potential risks, however, the US Environmental Protection Agency (US EPA) has developed a precautionary limit on lifetime exposure intended to prevent adverse effects that might have an impact on the developing child. The adequacy of that exposure limit is debated, with some stakeholders believing it is too stringent and others believing it is not stringent enough.

This article provides an overview of the scientific basis for the controversy, exploring what is known about perchlorate exposure and effects and describing its risks in the context of potential risks from other iodine-uptake-inhibiting goitrogens as well as goitrogens that do not inhibit iodine uptake. In particular, the apparent discrepancy between the reported associations

between exposure and effects at current low, background levels of exposure in the US and the reported absence of effects at much higher levels of exposure is discussed.

Hazard and dose-response assessment

Concern about potential human health risks from perchlorate in food and drinking water results from the observation that perchlorate has a great affinity for the sodium (Na^+)/iodide (I^-) symporter, the protein responsible for transporting iodide into the thyroid gland for the purpose of synthesizing thyroid hormones. As a result of that affinity, perchlorate can block the transport of iodide into thyroid follicular cells. When less iodide is available with which the thyroid can generate the hormones thyroxine (T_4) and triiodothyronine (T_3), the production of thyroid stimulating hormone (TSH) by the pituitary is increased. This homeostatic mechanism in turn stimulates the production of more T_3 and T_4 so that concentrations of thyroid hormones sufficient for the body's needs are maintained, even in situations with reduced levels of available iodide. According to a National Academy of Sciences (NAS) report evaluating the effects of perchlorate, "Compensation for iodide deficiency or other perturbations in thyroid hormone production . . . is the rule" (NAS/NRC 2005).

If the thyroid gland is deprived of adequate iodide over a long period of time, as occurs in areas where dietary iodide intake is insufficient, conditions such as goiter (enlarged thyroid) and even mental retardation may result. In particular, thyroid hormones are essential for skeletal and neurodevelopment and severe iodide intake deficiency during pregnancy ($< 20 \mu\text{g}/\text{day}$) or during

infancy can result in children with profound neurodevelopmental and physical deficits. By competing with iodide for the sodium/iodide symporter, perchlorate can interfere with thyroid function, leading to increased TSH and decreased T_3 and T_4 , which—if not compensated for—has the potential to interfere with fetal development. There have been no reports indicating that perchlorate exposure has harmed public health or interfered with fetal development—that relationship is inferential—but epidemiologic studies demonstrating or refuting a causal relationship between perchlorate exposure and fetal harm are lacking for women with inadequate dietary iodine.

Nonetheless, a number of epidemiologic studies suggest that, at current environmental perchlorate levels, exposure is unlikely to pose developmental or other risks for women with adequate dietary iodine. For example, a prospective longitudinal study of drinking water perchlorate exposure and pregnancy outcomes for 307 women in Chile failed to show an effect on thyroid hormone serum concentrations, milk iodine concentrations, or fetal development at perchlorate concentrations up to 114 $\mu\text{g/L}$ drinking water (Télez Télez et al. 2005). A study of 313 women from areas in Israel where well water perchlorate contamination was between 42-340 $\mu\text{g/L}$ and mean serum perchlorate concentrations were about 1-6 $\mu\text{g/L}$ found no effect on serum T_4 concentrations in newborns compared to 843 women in areas with lower serum perchlorate concentrations (Amitai et al. 2007). An ecological study of 342,257 newborns in California also failed to find an association between perchlorate concentrations in drinking water and the prevalence of congenital hypothyroidism or increased serum TSH concentrations (Buffler et al. 2006). Crump et al. (2000) evaluated thyroid hormone concentrations and TSH

production in 9,784 newborns and 162 school-age children in three cities in Chile with no, some (5-7 $\mu\text{g/L}$), or high (100-120 $\mu\text{g/L}$) drinking-water perchlorate concentrations and with similar characteristics in terms of socioeconomic status, ethnicity, and urinary iodine levels. No effects attributable to perchlorate exposure were observed.

A number of occupational studies have evaluated the effects of adult perchlorate exposure on thyroid hormone concentrations and reported no effects, but generally involved small numbers of subjects with adequate dietary iodine. For example, a study of 29 male workers exposed occupationally to high concentrations of airborne perchlorate demonstrated average iodide uptake inhibition of 38% but no effect on thyroid hormones (Braverman et al. 2005). A similar study evaluated 37 workers in the same plant and also reported no effect of long-term perchlorate exposure on a variety of determinants of thyroid health at doses up to about 0.5 mg/kg (Lamm et al. 1999). Intentional dosing studies involving short-term perchlorate exposure (up to two weeks) have also produced iodine uptake inhibition with no effect on serum hormone concentrations. For example, a study involving 21 healthy female volunteers and 16 healthy male volunteers saw a dose-dependent decrease in thyroid radioiodide uptake during two weeks of daily perchlorate administration, but no effect on thyroid hormone serum concentrations, even with a 67% reduction in iodide uptake (Greer et al. 2002). A no-observed-effect level of 0.007 mg/kg/day (equivalent to about 240 μg perchlorate/liter drinking water) based on iodide uptake inhibition was identified from that study. A more recent prospective, double-blind, randomized trial involving 17 healthy male and female volunteers saw no effect on thyroid function, including iodide uptake or serum concentrations of thyroid hormones,

following six months of perchlorate administration at doses up to 3 mg/day (Braverman et al. 2006).

Perchlorate has been used therapeutically to treat hyperthyroidism, including 12 pregnant women who received doses of 600-1,000 mg/day throughout most of their pregnancies. One infant had a slightly enlarged thyroid gland but the effect disappeared shortly after birth; no other effects on the infants were observed (Wenzel & Lente, 1984). Evidence from therapeutic use of perchlorate for more than a year supports the conclusion that moderate doses of perchlorate given chronically do not cause hypothyroidism (NAS/NRC 2005).

Other ecological, occupational, and clinical studies have also failed to support an association between perchlorate concentrations in water supplies and adverse thyroid effects in children or adults. Several more detailed reviews of studies evaluating the potential effects of perchlorate exposure on human health are available (Braverman 2007, NAS/NRC 2005, Soldin et al 2001). The National Academy of Sciences perchlorate report concluded, based on studies involving both clinical and environmental exposures, that long-term, sustained exposure to more than 30 mg/day (equivalent to about 15,000 $\mu\text{g/L}$ drinking water) would be required to produce adverse effects in healthy adults (NAS/NRC 2005).

Until recently no studies have specifically evaluated thyroid function related to perchlorate exposure in iodine-deficient or hypothyroid women, the groups that would be expected to be most vulnerable (NAS/NRC 2005). In a recent study, Pearce et al. (2007a)

evaluated 398 European women with lower urinary iodine concentrations ($< 100 \mu\text{g}/\text{liter}$) during the first trimester of pregnancy who were exposed to perchlorate at levels similar to those in the US and found no effects on maternal thyroid function associated with perchlorate. That result suggests that urinary iodine concentrations $< 100 \mu\text{g}/\text{liter}$ do not confer susceptibility to perchlorate. The urinary concentration of iodine considered deficient is $< 50 \mu\text{g}/\text{liter}$ and the most recent NHANES data indicate that about 7% of pregnant women in the US have urinary iodine concentrations $< 50 \mu\text{g}/\text{liter}$ (Caldwell et al. 2005). However, NHANES data also showed no differences in thyroid hormone levels when women with urinary iodine concentrations $< 50 \mu\text{g}/\text{L}$ were compared to women with higher urinary iodine concentrations (based on serum TSH and T_4 concentrations) (Soldin et al. 2005). That observation is consistent with the fact that even large reductions in iodine intake are adequately compensated for by the thyroid.

More recent concerns about perchlorate result from a study suggesting that there might be an interaction between iodine deficiency and the effects of perchlorate. In that study, Blount et al. (2006a) reported statistical correlations between increasing urinary perchlorate concentrations, increasing serum concentrations of TSH, and decreasing serum concentrations of T_4 in women but not in men. The authors used multiple regression analysis to evaluate data on urinary perchlorate and iodine concentrations and on serum concentrations of TSH and T_4 for 2,299 men and women who participated in the National Health and Nutrition Examination Survey (NHANES) during 2001-2002.

When Blount et al. (2006a) separated the women into higher ($\geq 100 \mu\text{g}/\text{L}$) and lower ($<$

100 µg/L, n ≈ 350) iodine groups, they found a significant positive association between perchlorate and TSH and a significant negative association between perchlorate and T₄ in the low iodine group only, although both hormone concentrations remained within the normal range. The directions of those associations are consistent with perchlorate's anti-thyroid activity but are surprising given the low levels of perchlorate involved and the studies described above reporting no effects at much higher exposure levels. However, statistically significant associations were also reported between serum hormone concentrations and a variety of other independent variables, indicating that thyroid function is likely to be affected by many important factors. For example, the R² value reported by Blount et al. for the association between T₄, perchlorate, and other covariates for lower-iodine women, 0.240, indicates that of the covariates evaluated showing associations with significance < 0.05, perchlorate accounts for only about 3% of the variation seen in T₄ values for that population. Significantly, a recent reanalysis of the same data adjusted urinary iodine concentrations for creatinine, which better reflects 24-hour urine iodine excretion than do the unadjusted urinary iodine concentrations used by Blount et al. (2006a). After that adjustment, the lower-urinary-iodine-status women no longer showed a negative association between urinary perchlorate concentrations and T₄ (Lamm et al. 2007).

The positive association of perchlorate with TSH for all women regardless of iodine status reported by Blount et al. (2006a) is also surprising and, if causal, is inconsistent with the idea that adequate iodine intake prevents effects associated with sodium/iodide symporter competitors. The NHANES data also show a positive association between perchlorate and iodine (Figure 1) and between iodine and TSH (Soldin et al. 2005). The positive association

between perchlorate and TSH reported by Blount et al. (2006a) is thus to be expected because natural sources of iodine co-occur with natural sources of perchlorate (hence the positive association, see exposure discussion below) until synthetic sources of perchlorate predominate and a plateau is reached. So, because there is a positive association between urinary iodine and perchlorate at lower levels because they co-occur naturally, and there happens to be a positive association between urinary iodine and serum TSH in the NHANES data, it is logical that there would be a positive association between urinary perchlorate and serum TSH but no particular reason to conclude that perchlorate is causally responsible for the increase in TSH. Furthermore, the R^2 value of 0.061 reported by Blount et al. (2006a) for the association between TSH, perchlorate, and other significant covariates for lower-iodine women indicates that perchlorate accounts for only about 1% of the variation seen for TSH in that population.

Even the lower-iodine women in the NHANES database have adequate iodine for normal thyroid function. Because adequate iodine intake would be expected to ameliorate any potential effects of perchlorate, even in the lower-iodine women, another possibility is that an antithyroid agent with a mechanism unrelated to iodine uptake inhibition could explain the associations observed by Blount et al. (2006a). Blount et al. did not control for goitrogens with non-iodine-related modes of action so it is possible, given the adequate iodine status of the women in the NHANES study, that the presence of goitrogens with a mode of action unrelated to iodine uptake inhibition, such as some organochlorines, is responsible for the effects seen.

A number of widespread contaminants such as bisphenol A, polychlorinated biphenyls

(PCBs), and polybrominated diphenyl ethers have been characterized as goitrogens and reported to have anti-thyroid activity via mechanisms unrelated to iodine uptake (Brucker-Davis 1998, McLanahan et al. 2007, Talsness et al. 2007). Those substances' anti-thyroid activity has been attributed to their ability to react with thyroid hormone receptors and affect thyroid-hormone-regulated gene expression (Zoeller 2007) or with aryl hydrocarbon hydroxylase receptors and induce enzymes associated with T₄ metabolism (Chevrier et al. 2007). Turyk et al. (2007) used the same NHANES database as Blount et al. but added the data from 1999-2000 and evaluated the relationships between total PCBs or total toxic equivalents [TEQs; includes PCBs, polychlorinated dibenzo-*p*-dioxins (PCDDs), and polychlorinated dibenzofurans (PCDFs)] with thyroid hormones. A negative association was reported for PCB/PCDD/PCDF TEQs with T₄, with stronger effects seen in women than in men. A positive association with TSH was seen in women over 60 only. Chevrier et al. (2007) measured 34 PCB congeners in the serum of 285 pregnant women and TSH concentrations in their children's blood shortly after birth. A positive association was observed for neonatal TSH and maternal levels of PCB congeners grouped by their ability to induce microsomal enzymes, but not total PCBs or dioxin-like PCB TEQs. Schell et al. (2008) found a positive association between TSH and persistent PCBs and a negative association with free T₄ and PCBs among adolescents from the Akwesasne Mohawk Nation who had not been breastfed. Despite higher postnatal PCB exposures, no such relationships were seen among those who had been breastfed. A positive relationship between DDE and TSH has been reported in some studies (e.g., Rylander et al. 2006) but not others (e.g., Schell et al. 2008). Figure 2 compares the NHANES relationships between TSH and DDE, total dioxin-like compounds (primarily PCBs), and perchlorate. In each case, a positive correlation is seen for

women.

The reports of associations between thyroid hormone concentrations and PCBs, TEQs, other organochlorines, or perchlorate are subject to similar limitations. As with perchlorate, earlier studies of PCBs, PCDDs, and PCDFs generally reported associations with changes in thyroid hormone concentrations only at exposure levels much higher than those evaluated by Turyk et al. (2007) and Chevrier et al. (2007), although those reported associations are inconsistent and involve increasing hormone concentrations associated with exposure in some studies and decreases in others. Blount et al. (2006a) did not control for non-iodine-inhibiting goitrogens and the PCB/TEQ studies did not control for iodine-inhibiting goitrogens. None of the studies demonstrate a causal relationship between PCBs, PCDDs, PCDFs, or perchlorate and changes in thyroid hormone concentrations because all three are cross-sectional studies reflecting a single point in time. Such studies are appropriate for estimating mean values but lead to overestimation of the number of people at the tails of the distribution (Andersen et al. 2001, Givens et al. 2007), distorting the true dose-response relationship. All three studies conflict with the weight of the evidence based on results of a significant number of studies involving much higher levels of exposure. All three studies are uncontrolled for the normal fluctuations in hormone concentrations that occur throughout the day in response to various stimuli, although that shortcoming may be compensated for by the large sample sizes. Finally, in all three studies, the changes reported remained within the normal range for thyroid hormones so do not constitute adverse effects and are unlikely to have clinical significance. Nonetheless, those studies are useful for hypothesis generation and suggest the need for additional mechanistic and dose-

response research.

Exposure assessment

Perchlorate occurs both naturally and as an environmental contaminant. Most environmental perchlorate has been attributed to its use as an oxidizer in propellants used by solid fuel rockets and missiles (US EPA 2002). Since the 1950s poor disposal practices have resulted in soil and groundwater contamination. Perchlorate is also used in air bag inflators, lubricating oils, leather finishing, electroplating, rubber manufacture, and other manufacturing processes (US EPA 2002). Massachusetts reported that the primary contributors of perchlorate to environmental media in that state were blasting agents, military munitions, fireworks, and, to a lesser extent, hypochlorite (bleach) solutions (MA DEP 2005). Traces of perchlorate are found in natural materials used as fertilizers, such as Chilean saltpeter, kelp, fishmeal, hanksite, potash ore (sylvinitite), and playa crust (Orris et al. 2003).

Detection of perchlorate in groundwater in regions with no historical use of rocket fuels or other potential anthropogenic sources, its occurrence in parallel with iodate, and its presence in rain and snow samples led to the suspicion that perchlorate is formed atmospherically. Dasgupta et al. (2005) demonstrated perchlorate formation by a number of atmospheric processes and concluded that a natural perchlorate background of atmospheric origin must exist.

Whether of natural or anthropogenic origin, human exposure to perchlorate is thought to

occur primarily through ingestion (NAS/NRC 2005). Perchlorate has been detected in public water systems (US EPA 2005a) and also in groundwater, including groundwater in areas with no history of industrial or agricultural use (Dasgupta et al. 2005). Low levels of perchlorate can also be found in drinking water supplies disinfected with sodium hypochlorite (MA DEP 2005). Biomonitoring data evaluating the relative contributions of different sources to perchlorate exposure suggest that the diet is an important source, however (Blount and Valentin-Blasini 2007). El Aribi et al. (2006) tested food and water samples from around the world and found detectable levels of perchlorate in all foods tested. In the US, perchlorate concentrations in foods sampled ranged from 0.094 to 19.29 $\mu\text{g}/\text{kg}$ (mean, 0.252) and tap water samples ranged from 0.072 to 2.983 $\mu\text{g}/\text{L}$. California-grown lettuce and spinach have been reported to contain perchlorate at levels ranging from 0.6 to 6.4 $\mu\text{g}/\text{kg}$ (Seyfferth and Parker 2006). Mean concentrations of perchlorate in cow's milk from US supermarkets in 11 states and human milk samples from 18 states were reported to be 11 and 92 $\mu\text{g}/\text{L}$, respectively (Kirk et al. 2005). In a sample of lactating women in Boston, milk perchlorate concentrations ranged from 1.3 to 411 $\mu\text{g}/\text{L}$ and no correlation with milk iodine levels was seen (Pearce et al. 2007b). Groundwater monitoring data from California show concentrations ranging from below the limit of detection to 100 $\mu\text{g}/\text{L}$ (CA DPH 2007). A number of other reports can be found describing perchlorate concentrations in various foods and beverages, many of which are described in detail in US EPA (2006).

The 2006 Total Diet Study conducted by the US Food and Drug Administration (US FDA), which involves analysis of nutrients and chemical contaminants in 280 different foods,

now includes perchlorate as one of the analytes, so is expected to provide data supporting comprehensive dietary intake estimates. Based on data from 27 foods, the US FDA has made a preliminary estimate of average daily perchlorate intake in the US of 0.053 $\mu\text{g}/\text{kg}/\text{day}$ (US FDA 2007), similar to that estimated on the basis of urinary perchlorate measurements, 0.066 $\mu\text{g}/\text{kg}/\text{day}$ (Blount et al. 2006a), and 10,000 times less than the daily intake concluded by the National Academy of Sciences perchlorate report to be required to produce adverse effects in healthy adults following long-term exposure (NAS/NRC 2005). The extent to which perchlorate intake can be attributed to natural versus anthropogenic sources is not known.

Risk characterization and regulation

Due to its biological mode of action, exposure to perchlorate during pregnancy in the absence of adequate iodine nutrition at doses high enough to result in insufficient maternal thyroid hormone concentrations could pose a risk of fetal developmental toxicity. To prevent such a risk, the 2005 National Academy of Sciences report evaluating human health risks from perchlorate recommended an exposure limit considered to be without adverse effects over a lifetime of oral exposure, or reference dose (RfD), of 0.0007 $\text{mg}/\text{kg}/\text{day}$ (NAS/NRC 2005). That RfD was adopted by US EPA in February 2005 (US EPA 2005b) and was based on the study of Greer et al. (2002) involving perchlorate-induced inhibition of radioactive iodide uptake in human volunteers. The no-observed-effect level in that study, 0.007 $\text{mg}/\text{kg}/\text{day}$, was divided by an uncertainty factor of 10 to protect the most vulnerable individuals, the fetuses of hypothyroid pregnant women. Other uncertainty factors were considered unnecessary because of the

conservative (i.e., health-protective) choice of an outcome that does not constitute an adverse effect. The NAS report reasoned that inhibition of iodide uptake by the thyroid is the key biochemical event in the continuum of possible effects of perchlorate exposure and would precede any adverse effects of perchlorate exposure. That reasoning has been challenged on the basis that because iodide uptake inhibition is not in itself an adverse effect and that no adverse effect on thyroid hormones had been seen by Greer et al. (2002), its choice as the basis of the RfD is inconsistent with established reference dose methodology (M. Dourson, personal communication; Barnes & Dourson 1988). A more supportable RfD might be developed using the data from pregnant women in Chile and Israel, the potentially susceptible group of interest, which produced a no-observed-adverse-effect level of approximately 0.03 mg/kg/day.

Despite its having adopted an RfD, US EPA has not yet chosen to regulate perchlorate in drinking water by developing a maximum contaminant level, explaining that more information on sources of perchlorate exposure is needed to determine the relative source contribution of drinking water to total exposure (US EPA 2006). The US Congress is considering two pieces of legislation, one that would compel US EPA to establish a drinking water standard for perchlorate and one that would compel US EPA to determine whether perchlorate should be regulated. Meanwhile, the states of Massachusetts and California have adopted drinking water standards for perchlorate of 2 µg/L and 6 µg/L, respectively.

Understanding the apparent inconsistencies between the associations observed for perchlorate and thyroid hormone levels at low concentrations reported by Blount et al. (2006a)

using the NHANES data and the absence of effects at much higher perchlorate exposure levels in the epidemiologic and other human studies is critical to assessing risk for the purpose of establishing regulatory limits on perchlorate exposure. Upon closer examination, however, there apparently are no significant inconsistencies between those observations. The changes reported by Blount et al. remained within the normal range of thyroid hormone concentrations and are unlikely to be causally related to perchlorate at those levels of exposure for the reasons discussed above. The absence of a causal relationship is supported by the results of Lamm et al. (2007), who found no association between perchlorate and T₄ when urinary iodine concentrations were adjusted for creatinine, by the results of Pearce et al. (2007a), who failed to find associations between thyroid hormone serum concentrations and urinary perchlorate in low-iodine-status pregnant women in Europe, and by the weight of evidence provided by previous epidemiologic and clinical studies reporting effects only at much higher levels of exposure, albeit in healthy adults. The women in the NHANES database do not appear to be representative of hypothyroid or subclinically hypothyroid women, however, as evidenced by the fact that there are no differences in thyroid hormone concentrations when women with urinary iodine concentrations < 50 µg/L are compared to women with higher urinary iodine concentrations (Soldin et al. 2005).

It is also interesting to note that the perchlorate doses derived from the NHANES data compare favorably with the US EPA RfD; that is, the majority of perchlorate doses in the general US population do not exceed the RfD. Blount et al. (2006b) estimated a total daily perchlorate dose for each adult in the NHANES database they evaluated, finding a median dose of 0.066 : g/kg/day (about one tenth of the US EPA RfD) and a 95th percentile of 0.234 : g/kg/day (about

one third of the US EPA RfD). Eleven adults (0.7%) in that study had estimated perchlorate exposures in excess of the RfD (0.7 : g/kg/day). Of course, exceeding an RfD does not indicate that a person is “at risk”. Reference doses are not bright lines or threshold values for adverse effects; they are set far below exposure levels associated with adverse effects. US EPA is careful to point out that, while exposure at or below a reference dose indicates that a health risk is unlikely, people who are exposed to a substance above its reference dose should not be considered at risk: “. . . exceeding the [reference dose] is not a statement of risk” (US EPA 2004) and “. . . It is . . . important to note that the [reference dose] does not define a bright line, above which individuals are at risk of adverse effect” (US EPA 2005c). In any case, the RfD was derived from a non-adverse effect. Based on US EPA’s RfD, current environmental exposures to perchlorate in the US thus do not appear to pose a risk of developmental toxicity.

Because hypothyroid pregnant women are the sensitive group of interest in terms of potential perchlorate risk, it is useful to determine the extent to which hypothyroidism is prevalent. In the United Kingdom about 1-2% of pregnant women are reported to be overtly hypothyroid and another 2.5% have subclinical hypothyroidism, defined as raised TSH but normal T₄ (Anonymous 2006). The prevalence of subclinical hypothyroidism among US women in the general population has been reported to be 4-10%, with 2-5% of those cases progressing to overt hypothyroidism annually (Papi et al. 2007). Casey et al. (2005) reported that 2.3% of a cohort of 17,298 pregnant women in Texas tested before 20 weeks’ gestation had subclinical hypothyroidism, while 0.2% of those had overt hypothyroidism. Between 50-80% of hypothyroidism is attributed to chronic autoimmune thyroiditis (Papi et al. 2007), however, not

iodine insufficiency; because of its mode of action, perchlorate would not be expected to contribute to risk in such cases. Of course, hypothyroid pregnant women are already at risk of effects on the fetus due to the fact of their hypothyroidism alone; measurable additional risk from normal background intakes of perchlorate (around 4 $\mu\text{g}/\text{day}$, see previous discussion of exposure) seems unlikely.

Complicating attempts to assess risks from or establish regulatory limits for perchlorate is the fact that perchlorate exposure does not occur in isolation from exposure to other goitrogens, or anti-thyroid agents, that have the same iodine uptake inhibition mode of action as perchlorate. In particular, nitrates and thiocyanates are ubiquitous in the diet and occur in such quantities and with such potencies that determining the additional contribution to risk made by small exposures to environmental perchlorate is potentially impossible (De Groef et al. 2006).

In vitro studies comparing the relative abilities of perchlorate, nitrate, and thiocyanate to inhibit cellular iodine uptake show that, after adjusting for biological half-life, perchlorate is half as potent as thiocyanate and 240 times as potent as nitrate (De Groef et al. 2006). Given those relative potency estimates, comparing perchlorate's RfD to those for nitrates and thiocyanates is instructive. Nitrate's RfD is 1.6 mg/kg/day (US EPA 1991) and cyanide's (the active portion of thiocyanates) is 0.02 mg/kg/day (US EPA 1993). Taking into account their relative potencies, the RfDs for nitrate and thiocyanate are 100 times and 50 times higher than the perchlorate RfD, respectively. Those differences could be interpreted to imply that perchlorate is 50 to 100 times safer than suggested by its RfD or that nitrate and thiocyanate are 50 to 100 times more

dangerous than implied by their RfDs. On that basis, for an adult in the US eating a US Department of Agriculture recommended diet, the average daily intake of nitrates and thiocyanates combined is equivalent to 0.5 mg/kg/day perchlorate (De Groef et al. 2006), 1,000 times greater than the perchlorate RfD.

Of course, RfDs are determined based on many factors in addition to the level of exposure anticipated to produce adverse effects, reflecting the nature and adequacy of the underlying data, so comparing them can be misleading. Comparing RfDs for perchlorate, cyanide, and nitrate highlights an unreasonable regulatory inconsistency but is not really the appropriate comparison for the purposes of drawing conclusions about relative and cumulative risks. The RfDs for the three goitrogens are derived from different biological effects—reduced iodine uptake by the human thyroid for perchlorate (not in itself an adverse effect), blue baby syndrome for nitrate, and a 1955 study in rats that produced no adverse effects for cyanide. The highest doses of each goitrogen that failed to produce an effect were divided by different “uncertainty factors”—intended to protect sensitive individuals or to compensate for the use of animal instead of human data—to derive their RfDs. As a result, the respective RfDs are not really comparable. A more appropriate comparison might be based on the highest doses that fail to produce adverse effects on the thyroid, which themselves will vary according to iodine status. Nonetheless, any potential effects of low exposures to perchlorate are likely to be undetectable against a natural goitrogen background exposure 1,000 times higher than perchlorate’s exposure limit. As yet, however, human health risk assessment continues to focus on single chemicals in isolation, with the notable exceptions of PCBs, dioxins, some pesticides, and polycyclic aromatic

hydrocarbons.

Discussion

It is generally the case that data useful for evaluating a substance's human health risks are incomplete. As a result, regulatory decisions about limiting risks are based on science to the extent feasible but, of necessity, also on policy judgments. Regulatory limits are thus neither "right" nor "wrong" scientifically, although some may reflect the weight of the scientific evidence better than others. The data available on perchlorate risks appear at first to be inconsistent, with thyroid effects associated with current low levels of exposure from the NHANES data but no effects seen in other studies at much higher levels of exposure. Three explanations for the discrepancy are possible. One explanation is that the effect seen in the NHANES data is attributable to another substance that co-occurs with perchlorate but affects the thyroid via a different biological mode of action, perhaps PCB/PCDD/PCDF TEQs or some other substance as yet to be identified, for which evaluations of the NHANES data were not controlled. Another explanation is that the reported effects are statistical artifacts because perchlorate naturally co-occurs with iodine and there is an association between iodine and TSH in the NHANES data and because the negative association with T_4 cannot be detected when urinary iodine concentrations are adjusted for creatinine. Of course, despite numerous indications to the contrary, a third explanation is that the cross-sectional NHANES associations are causally related after all and, for as-yet-to-be-determined reasons, the large and consistent body of clinical and epidemiologic evidence that failed to detect similar associations or detected

them only at much higher exposures is wrong. All three explanations are consistent with the conclusion that the US EPA RfD for perchlorate is conservatively health-protective.

While a conservatively health-protective perchlorate RfD is desirable as a precautionary matter, considering perchlorate's RfD in the context of the other iodine-uptake-inhibiting goitrogens to which we are exposed ubiquitously, also primarily through the diet, suggests that it may be unnecessarily stringent. The relative exposure levels and potencies of nitrate and thiocyanate, in particular, are likely to swamp any effects potentially attributable to perchlorate. That inconsistency illustrates the need for risk assessment approaches that can account for both aggregate and cumulative exposures and for risk management approaches that can consider the larger public health context in which exposures are occurring.

In its Framework for Cumulative Risk Assessment, US EPA expresses the hope that attempts focus on the combined effects of more than one agent or stressor may generate interest in a wider variety of nonchemical stressors than do traditional risk assessments (US EPA 2003a). In other words, instead of focusing on the potential effects of individual chemical exposures in isolation, we may start looking at public health in terms of the broader definition of environment. The World Health Organization defines environment as including "both the direct pathological effects of chemicals, radiation and some biological agents, and the effects (often indirect) on health and well-being of the broad physical, psychological, social and aesthetic environment which includes housing, urban development, land use and transport" (WHO 1989). The proportion of disease that is attributable to chemical exposures is thought to be relatively small

against the backdrop of socioeconomic conditions, behavioral factors, psychological factors, infectious agents, nutrition, and other considerations. Indeed, US EPA acknowledges that “One of the greatest challenges to elucidating the connection between environmental exposure and disease is the fact that exposure to an environmental pollutant or stressor is rarely the sole cause of an adverse health outcome . . . Other factors include, for example, diet, exercise, alcohol consumption, heredity, medications, and whether other diseases are present . . . Also, different people have different vulnerabilities . . . All these factors make it difficult to establish a causal relationship between exposure to environmental pollutants and disease outcome . . .” (US EPA 2003b).

In view of our incomplete knowledge of the complex inter-relationships among multiple chemical and non-chemical, environmental and non-environmental stressors, a holistic approach to public health protection is a distant hope, probably dependent on our eventual understanding of how molecular and cellular pathways can be perturbed in ways that lead to toxicity (NAS/NRC 2007). While we eagerly anticipate that day, we can in the meantime evaluate health risks more holistically and with improved logic in the smaller spheres where it is currently possible to do so. Assessing and regulating potential risks from substances like perchlorate within the larger context of simultaneous exposure to the naturally occurring background of goitrogens with the same mode of action would be a logical start.

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The author has no conflict of interest related to the substance of this article.

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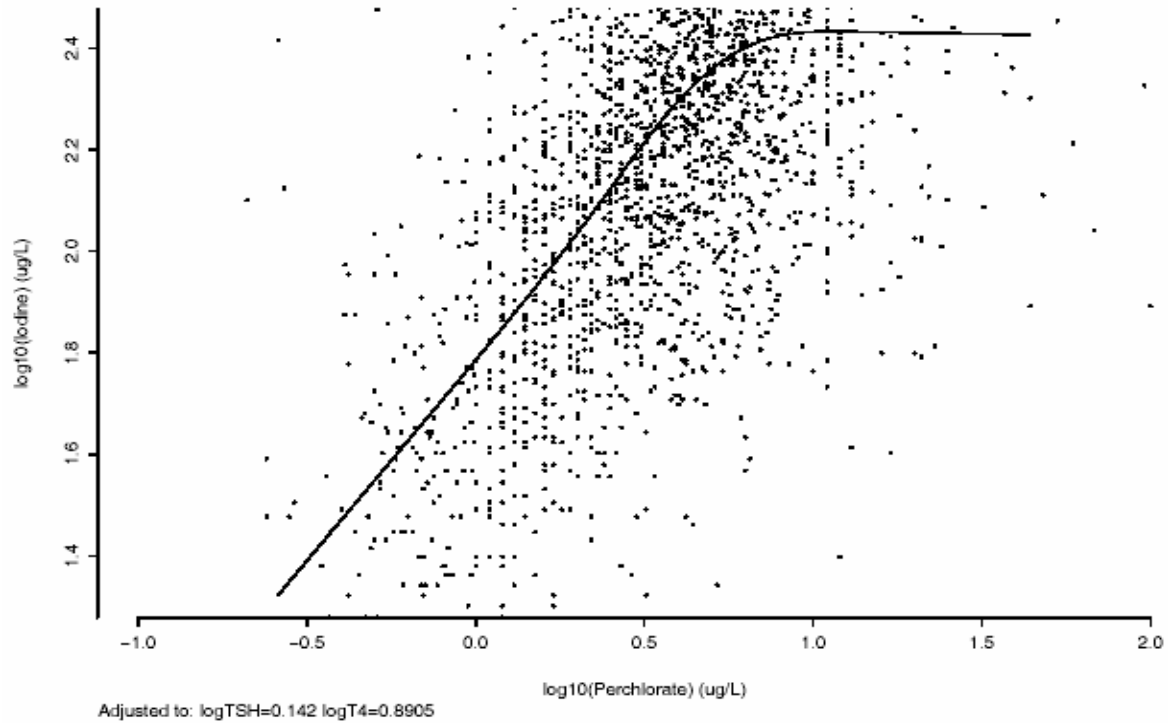
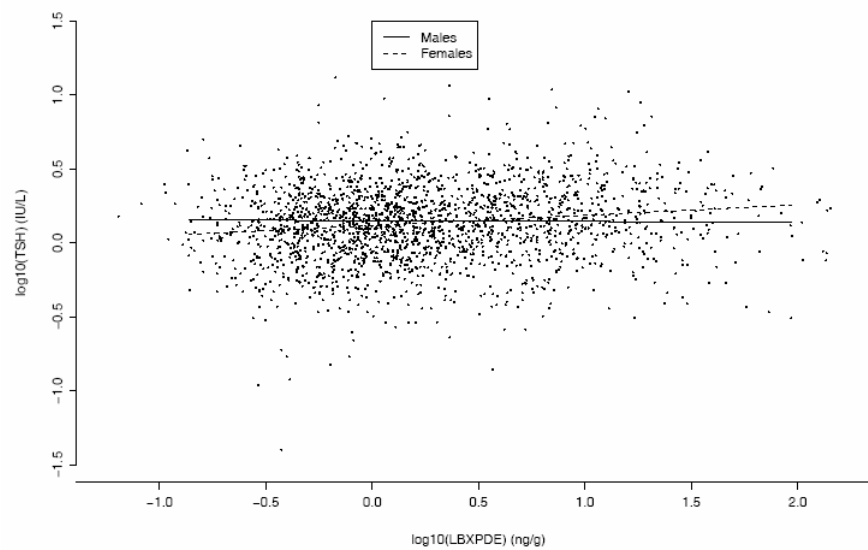
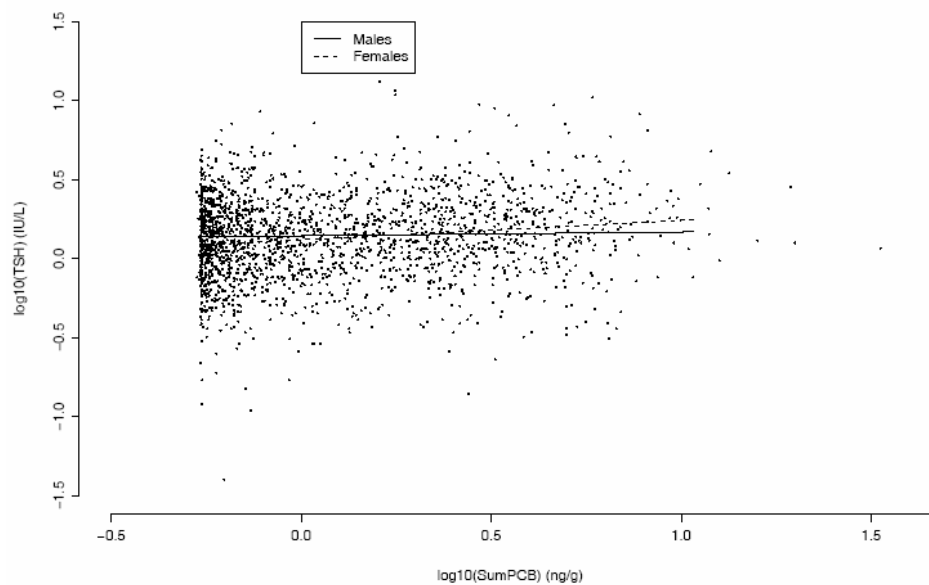


Figure 1. Relationship between iodine and perchlorate controlled for T_4 and TSH [$R^2 = 0.36$].

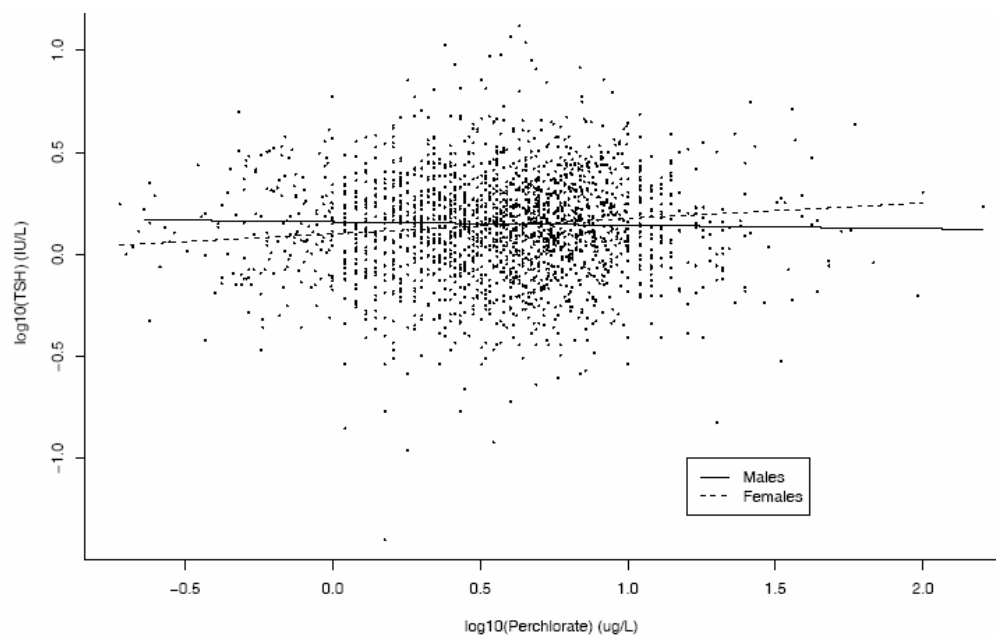
Source: Drawn from the original NHANES data by the Bio-Statistical Center of the Catholic University of Leuven



(a)



(b)



(c)

Figure 2. Relationship between TSH and DDE (a) [$R^2 = 0.01$], total PCBs (b) [$R^2 = 0.009$] or perchlorate (c) [$R^2 = 0.006$] by gender. Source: Drawn from the original NHANES data by the Bio-Statistical Center of the Catholic University of Leuven