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Emerging Science Supporting The 2005 National Research Council Perchlorate Risk Assessment

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Abstract: In sufficient amounts, perchlorate can inhibit iodine uptake by the thyroid, ultimately leading to diminished thyroid function. Recent studies in Europe and the United States have determined that maternal hypothyroidism during pregnancy, even when mild and considered subclinical, may be associated with impairment of normal brain development and intelligence in offspring. Concern about the possibility that iodine uptake inhibition from environmental perchlorate could result in impaired maternal thyroid function during pregnancy and adverse neurodevelopmental effects in the fetus, has led to proposed a proposed reference dose (RfD) as low as 0.00003 mg/kg-day. For 18 months during 2003 and 2004, a committee of the National Research Council (NRC) reviewed the science available in order to assess the risk of perchlorate ingestion. In the committee’s January 2005 report, it concluded that the no-observed-adverse-effect level (NOAEL) is 0.4 mg/kg-day and that the no-observed-effect-level (NOEL) is 0.007 mg/kg-day. Based on the NOEL, the committee recommended an RfD of 0.0007 mg/kg-day. Subsequent to the NRC committee deliberations, five new scientific studies have been completed that strongly support the committee’s NOAEL and NOEL and support that the recommended RfD is safe for even the most susceptible populations – fetuses of pregnant women with insufficient iodine consumption.

1. INTRODUCTION

Perchlorate is known to inhibit the thyroid’s uptake of iodine, necessary for the production of thyroid hormones. Since medical doses of 4 to10
mg/kg-day were given in the 1950s and 60s, to treat overactive thyroid conditions, it is clear that these doses, perchlorate can inhibit iodine uptake by the thyroid sufficiently to lead to diminished thyroid function (hypothyroidism). Recent studies in Europe and the United States have determined that maternal hypothyroidism during pregnancy, even when mild and considered subclinical, may be associated with impairment of normal brain development and intelligence in offspring. The recent detection of perchlorate in drinking water and in foods has led to concern that iodine uptake inhibition from environmental exposure – typically thousands of times lower than doses given medically – could result in impaired maternal thyroid function during pregnancy and adverse neurodevelopmental effects in the fetus.

Because of these concerns, and because of controversies regarding previous risk estimates, the U.S. Environmental Protection Agency (EPA) requested in 2003 that the NRC review the available science regarding possible risks from ingestion of perchlorate from environmental sources. In January 2005, the NRC published its report on the Health Implications of Perchlorate Ingestion. Relying primarily upon published, peer-reviewed studies in humans, the NRC committee identified three key risk assessment parameters for perchlorate:

- The **NOAEL** [no-observed-adverse-effect-level - the highest dose at which no adverse health effects have been observed]

- The **NOEL** [no-observed-effect-level - the highest dose at which there are no statistically or biologically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control]

- The **RfD** [reference dose - an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral dose delivered to the human population (including sensitive groups) that is likely to have no appreciable risk of harmful effects during a lifetime]

In establishing a NOAEL from the literature, the committee observed that “it is highly likely that in people with a normal iodide intake the dose of perchlorate would have to reduce thyroid iodide uptake by at least 75% for a sustained period (several months or longer) for iodide uptake and thyroid hormone production to decline enough to cause adverse health effects … In adults, that is likely to require sustained exposure to more than 30 mg of perchlorate per day (0.4 mg/kg per day for a 70-kg person), on the basis of
the clinical studies in healthy subjects and the studies of long-term treatment of hyperthyroidism.”

Based on a 14-day clinical study of adults by Greer et al., the committee “identified a NOEL for inhibition of iodide uptake by the thyroid at 0.007 mg/kg per day”. They further went on to assert that “…chronic exposure will have no greater effect than that resulting from short-term exposure. In fact, it may well have less effect because of the capacity of the pituitary-thyroid system to compensate for iodide deficiency by increasing iodide uptake.”

The committee then departed from the traditional risk assessment approach of starting with a NOAEL in deriving the RfD. The committee applied the more conservative NOEL as the starting point and then applied an additional safety factor of 10 to protect the most sensitive population identified by the committee – fetuses of pregnant women who might have hypothyroidism or iodide deficiency. Thus, they adjusted the NOEL downward from 0.007 to 0.0007 mg/kg-day to derive the RfD. They went on to state that “using a nonadverse effect that is upstream of the adverse effects is a conservative, health-protective approach to the perchlorate risk assessment,” and that this RfD “should protect the health of even the most sensitive populations.”

Five additional human studies relevant to perchlorate risk assessment were underway at the time the committee was deliberating, but were not yet peer reviewed. Those studies now have been completed and peer reviewed. The purpose of this paper is to examine whether the results of these five studies support the NOAEL, NOEL and RfD derived by the NRC panel.

2. REVIEW OF NEW STUDIES AND SIGNIFICANT FINDINGS


It has been known for more than half a century that perchlorate is the most potent of several common substances such as nitrate and thiocyanate that also inhibit iodine uptake by the thyroid. Research in the 1950s and 60s indicated that perchlorate was about 10 to 20 times more potent than thiocyanate and about 100 to 200 times more potent than nitrate in blocking iodine uptake by the thyroid. Whether these relative potencies held
throughout all concentrations or how the effects might combine was not known.

In 2001, Tonacchera and colleagues at the University of Pisa in Italy successfully inserted the gene that codes for the human NIS into a standard laboratory cell culture line. (The NIS, or sodium-iodide-symporter, is the receptor that actively transports iodine into the thyroid). They developed a new tool suitable to further explore how perchlorate, thiocyanate and nitrate interact and inhibit iodine uptake. In 2003-2004, the same researchers measured iodine uptake in the special cell culture with varying concentrations of perchlorate, thiocyanate and nitrate in the serum surrounding the cells. All in all, they conducted 776 separate measurements of iodine uptake and found that the relative potencies of perchlorate, thiocyanate and nitrate were constant over all concentrations and that the effects of combinations of these ions were simply additive. The dose-response curves as shown in Figure 1 are parallel over orders of magnitude of concentrations. Perchlorate is 9 and 150 times more potent than thiocyanate and nitrate respectively, in inhibiting iodine uptake by the thyroid.

![Figure 1. Dose – Response for iodine uptake and serum perchlorate, thiocyanate and nitrate concentrations (based on Tonacchera et al, 2004)](https://scholarworks.umass.edu/soilsproceedings/vol11/iss1/17)

While the NRC committee NOEL and NOAEL are doses (mg/kg-day), the Tonacchera et al study relates serum concentrations (µg/L). Human data
relating perchlorate dose (over four orders of magnitude) with serum perchlorate concentration have recently been published \cite{7,8,9,10} and correlated \cite{4}. The resulting correlation is presented as Figure 2. Using the correlation in Figure 2 and the *Tonacchera et al* relationship in Figure 1, the NRC-derived NOAEL of 0.4mg/kg-day would correspond to 72% inhibition of iodine uptake (compared with 75% in the committee report).

![Figure 2: Relationship between perchlorate dose and serum perchlorate concentration from recently published studies, from Gibbs 2005\cite{5}](image)

Nitrate is common in green leafy vegetables as well as a common pollutant in drinking water. The maximum contaminant level (MCL) for nitrate is 10 mg/L as nitrate-nitrogen, which is equivalent to 45 mg/L as nitrate. Using standard assumptions, a 70 kg adult drinking 2 liters of water daily would ingest a nitrate dose of 1.3 mg/kg-day. This dose is equivalent to 0.0055 mg/kg-day of perchlorate in iodine uptake inhibition. Thus, although nitrate is common in our drinking water, the nitrate MCL is similar to the perchlorate NOEL. Thyroid effects from nitrate in drinking water are therefore unlikely, and none have been reported in the U.S.
2.2 Gibbs 2005. A Comparative Risk assessment of Perchlorate and Thiocyanate Based on Competitive Inhibition of Iodide Uptake as the Common Mode of Action

Sixteen published and peer-reviewed human studies relating serum thiocyanate concentrations and thyroid function were evaluated. These studies included chronic exposure among pregnant women and infants, exposure in regions with varying degrees of iodine deficiency, and exposure resulting in a wide range of serum thiocyanate concentrations. Sources of thiocyanate included medications, occupational exposures, milk preservatives, cassava and cigarette smoking. These studies, by proxy, fill many of the gaps in the perchlorate literature.

Table 1. Serum Thiocyanate Concentration Effect on Human Thyroid Function and Perchlorate Dose Required to Achieve an Equivalent Inhibition of Iodine Uptake

<table>
<thead>
<tr>
<th>Observed Thyroid Effects from Thiocyanate in Published Studies</th>
<th>Serum Thiocyanate Concentration µg/L</th>
<th>Calculated Inhibition of Iodine Uptake¹</th>
<th>Equivalent Perchlorate Serum Concentration µg/L¹</th>
<th>Equivalent Perchlorate Dose, mg/kg-day²</th>
</tr>
</thead>
<tbody>
<tr>
<td>No thyroid effects, even in regions with mild to moderate iodine deficiency</td>
<td>2,500</td>
<td>70%</td>
<td>290</td>
<td>0.2</td>
</tr>
<tr>
<td>Adaptive thyroid effects (but not hypothyroid effects) in regions with iodine sufficiency or iodine deficiency</td>
<td>5,000</td>
<td>86%</td>
<td>580</td>
<td>0.5</td>
</tr>
<tr>
<td>Measurable hypothyroid effects regardless of iodine status</td>
<td>10,000</td>
<td>93%</td>
<td>1,150</td>
<td>1</td>
</tr>
<tr>
<td>Profound hypothyroid effects regardless of iodine status</td>
<td>50,000</td>
<td>99.9%</td>
<td>5,750</td>
<td>6</td>
</tr>
</tbody>
</table>

¹Based on Figure 1
²Based on Figure 2

A summary of the key findings from the thiocyanate scientific literature is presented in Table 1. No adverse thyroid effects were observed at thiocyanate levels equivalent to 0.2 mg/kg-day or less of perchlorate (half the NRC NOAEL), even among pregnant women and neonates in regions...
with mild to moderate iodine deficiency. Adaptive but not hypothyroid effects were seen at perchlorate-equivalent doses slightly above the NRC NOAEL, and hypothyroid effects were clearly seen at perchlorate-equivalent doses 2½ times the NRC NOAEL. Profound hypothyroid effects were seen at perchlorate-equivalent doses that are in the range used pharmacologically to treat overactive thyroid conditions. Therefore, for the most sensitive subpopulation identified by the NRC panel, fetuses of pregnant women with insufficient iodine consumption, the thiocyanate literature shows that the NRC recommended RfD is many times lower than levels seen to be without any effects seen in these studies.

2.3 Braverman et al, 2005. The Effect of Perchlorate, Thiocyanate, and Nitrate on Thyroid Function in Workers Exposed to Perchlorate Long-Term

Twenty-nine perchlorate workers and 12 volunteer community controls in southern Utah were studied in 2004. This is the same perchlorate manufacturing facility in which the workers were studied by Lamm et al. in 1999, and the two study cohorts overlapped somewhat. The workers had all worked a minimum of two years at the facility and most had worked there much longer. Their work schedules are structured with three 12-hour shifts in a row followed by three days off. Important differences between the Braverman et al. study and the Lamm et al. study include:

- estimating work shift perchlorate doses from serum perchlorate concentrations,
- measuring concurrent serum nitrate and thiocyanate concentrations,
- measuring iodine uptake just before and just after the three 12-hour shifts,
- measuring thyroid volume by ultrasound, and
- including volunteer community controls for comparison.

About half of the workers had 12-hour shift perchlorate doses above the NRC NOAEL of 0.4 mg/kg-day and about half had doses below this level. All workers and community controls were healthy white adult males with iodine-sufficient diets. Although there was significant reduction in iodine uptake among the workers related to their perchlorate doses, there were no hypothyroid changes in the workers compared to the community controls or related to their individual perchlorate doses. Additionally, there was no
increased thyroid volume among workers related to perchlorate dose or in comparison to community controls.

The significant findings in this study as it relates to the NRC committee report are:

- The perchlorate dose-response relationship for the workers for relative iodine uptake was nearly identical to that found in the two-week volunteer study by Greer et al, the study on which the NRC committee based the NOEL.
- The absolute iodine uptake of the perchlorate workers after three full days off was significantly higher than that of the community controls, and their absolute iodine uptake after three 12-hour shifts was about the same as the community controls.
- The workers' relative iodine uptake correlated very strongly with the relative iodine uptake predicted by Tonacchera et al (Figure 1).

Thus the Braverman et al. study demonstrated that with long-term perchlorate exposure, the thyroid adjusts by taking in iodine more efficiently. This observation substantiates the NRC committee assertion that with regard to inhibition of iodine uptake, “…chronic exposure will have no greater effect than that resulting from short-term exposure. In fact, it may well have less effect because of the capacity of the pituitary-thyroid system to compensate for iodide deficiency by increasing iodide uptake.” This study also confirmed that the cell-culture-derived relative potencies for perchlorate, thiocyanate and nitrate from Tonacchera et al. are valid in living human subjects.

2.4 Crump and Gibbs 2005. Benchmark Calculations for Perchlorate from Three Human Cohorts

It is beyond the scope of this paper to fully discuss benchmark methodology, but in recent years, the statistical lower bound on a benchmark dose calculation (BMDL) has been accepted by the U.S. EPA as an equivalent to a NOAEL for risk assessment purposes. In Crump and Gibbs 2005, the authors performed benchmark calculations based on combined raw data from Braverman et al 2005 and Lamm et al, 1999. Although both these studies are “negative” in the sense that no adverse effect was found and thus a NOAEL could not be established, BMDLs calculated from such negative results represent valid statistical lower bounds on the dose that accounts for a potential, but unobserved, adverse effect of perchlorate. Two standard indicators of hypothyroidism were selected for analysis: free thyroxine index
(FTI) and thyroid stimulating hormone (TSH). BMDLs ranged from 0.21 to 0.56 mg/kg-day based on FTI changes, and from 0.36 to 0.92 mg/kg-day based on TSH changes. Thus, these combined datasets are generally supportive of the 0.4 mg/kg-day NOAEL in the NRC committee report.


It has been known for many years that perchlorate is present naturally in nitrate fertilizer mined in the Atacama Desert in northern Chile. Crump et al. 2000\textsuperscript{12} characterized the water supplies in the region and studied thyroid function among school children and infants in three cities with varying perchlorate in their municipal water supplies. There were no hypothyroid changes attributable to 110 to 115 ppb perchlorate in municipal drinking water relative to cities with non-detectable or much lower perchlorate concentrations. A follow-up study among pregnant women in the same region was then undertaken in 2002-2004.

![Figure 3. Study region in northern Chile. The primary study city, Taltal, obtains its municipal water from a well field in Agua Verde containing 110-115 ppb perchlorate. Antofagasta obtains its municipal water from snowmelt piped from the Andes. Chañaral obtains its municipal water from a well field in Copiapo to the south.](image-url)
Tellez et al., of the Catholic University in Santiago, studied approximately 60 women during pregnancy and post partum in Taltal, a city in northern Chile where the entire municipal drinking water supply contains 110 to 115 ppb perchlorate. They compared these women’s thyroid function during pregnancy and post partum with that of a similar number of pregnant women in each of two nearby cities: Antofagasta, with non-detectable perchlorate levels; and Chañaral, with 6 ppb perchlorate in the municipal drinking water. Neonatal thyroid function at birth was also evaluated via cord blood testing in each of the three cities. A map of the study region is shown as Figure 3.

Although iodine nutrition in this region has previously been excessive, changes in salt iodination were instituted in 2000, and the pregnant women studied in Tellez et al. had median urinary iodine levels of 269 µg/L, very similar to those in pregnant women in the U.S. surveyed by the Centers for Disease Control and Prevention (CDC) in the early 1970s and 1990s.

All maternal urine samples were analyzed for perchlorate by the CDC in 2004 using their latest technology (ion chromatography coupled with tandem mass spectrometry). A reliable estimate of the perchlorate excretion rate can be made by expressing the urine perchlorate as a ratio with urine creatinine, and thus a reliable estimate of each woman’s perchlorate dose over the preceding day or so also can be made. Cumulative distribution of perchlorate doses for women from the three cities was clearly different, as shown in Figure 4.
Figure 4. Cumulative distribution of maternal perchlorate doses as estimated from urinary perchlorate/creatinine ratios from three cities studied by Tellez et al. The NRC NOEL (0.007 mg/kg-day) and RfD (0.0007 mg/kg-day) are shown superimposed.

It is apparent from Figure 4 that perchlorate dose is highly variable within each city. The women self-reported drinking a median of about one liter of tap water daily in addition to about 700 ml as sodas or bottled water. Using the median doses from Figure 4, it appears that in each city, the women were ingesting a median of about 20 to 30 µg perchlorate daily from sources other than tap water – most likely from food sources. No specific food sources of perchlorate were identified in this study. It also is apparent that only a few of the women were exceeding the NOEL as established by the NRC and none were exceeding the NOAEL. On the other hand, 15%, 35% and 90% of the women were exceeding the RfD in Antofagasta, Chañaral and Taltal respectively.

Tellez et al. evaluated maternal thyroid function in early (~16 weeks) and late (~33 weeks) pregnancy, and again post partum (~12 weeks). Newborn thyroid function was assessed from cord blood samples at birth. There were no maternal or neonatal hypothyroid effects attributable to perchlorate in Taltal relative to the two control cities, while typical thyroid changes associated with pregnancy were observed.

Perchlorate and iodine were assessed from breast milk samples obtained at the postpartum visit. Median breast milk perchlorate levels in each city were similar to the drinking water concentrations in the respective cities but the levels were highly variable. The levels ranged from < 4 µg/L in each
city to a maximum of 1042, 61 and 204 in Antofagasta, Chañaral and Taltal respectively. The subject from Antofagasta with the highest breast milk perchlorate had non-detectable perchlorate in her home tap water but elevated urine perchlorate, suggesting a perchlorate source other than tap water. Mean breast milk iodine concentrations were 45, 33 and 38 µg/dL in Antofagasta, Chañaral and Taltal respectively. These levels were not statistically different and indicated acceptable iodine nutrition for the infants. No significant correlations could be established between breast milk perchlorate and either urine perchlorate or breast milk iodine concentrations.

3. DISCUSSION

Although they were not considered by the committee in their recommendation, taken together, the five new studies described herein are strongly supportive of the NRC committee report on the potential health effects of perchlorate. The new studies give more confidence to policy officials and the public by providing more evidence that environmental exposures to perchlorate are not likely to have any adverse effect, including to the most sensitive members of the population.

The subjects in the Braverman et al. occupational study had long-term perchlorate doses similar to the NOAEL, yet had no demonstrable hypothyroid findings. Benchmark dose analysis of the Braverman et al. and Lamm et al. study results yielded BMDLs that are generally in the range of the NOAEL and represent a valid statistical lower bound on a potential, but unobserved, effect of perchlorate. Comparative analysis of the thiocyanate literature, using relative potencies of perchlorate and thiocyanate from cell culture experiments, indicates that perchlorate doses of ½ the NOAEL do not cause any hypothyroid effects, even in sensitive subpopulations, while doses 2½ times the NOAEL cause hypothyroid effects in all populations. Thus, the NOAEL is very consistent with results of the newer studies.

The Braverman et al. occupational study demonstrated a long-term dose-response relationship between perchlorate ingestion and iodine uptake that is nearly identical with that from the two week study by Greer et al. Furthermore, Braverman et al. demonstrated that the workers had adjusted to the perchlorate and were actually more efficient at absorbing iodide than were community controls without exposure. Although only a few of the pregnant women studied by Tellez et al. had perchlorate doses exceeding the NOEL, many had doses approaching the NOEL, and there was no discernable tendency toward hypothyroid findings as perchlorate dose increased.
The RfD is intended to be a conservative concentration that protects even the most sensitive subpopulations for a lifetime. Among the pregnant women studied by Tellez et al., 90% of the women from Taltal exceeded the RfD, yet there was no tendency toward hypothyroid findings in either mothers during pregnancy or the infants at birth. Thus the RfD, although conservative, is clearly protective of these most sensitive subpopulations.

REFERENCES