Statistical analysis of association between urinary perchlorate and serum levels of TSH and T4 in the NHANES cohort: Consideration of gender, iodine status, smoking, and thiocyanate

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Office of Environmental Health Hazard Assessment

• Mission: to protect and enhance public health and the environment by scientific evaluation of risks posed by hazardous substances.

• OEHHA develops guidance values for air, water, soil, and exposure to carcinogens and reproductive toxicants (Prop 65)
Public Health Goal Program

- Public Health Goals (PHGs) are developed for all regulated water contaminants
- PHGs are based entirely on public health protection, without consideration of cost or feasibility
- PHGs must be protective of the health of individuals drinking the water for a lifetime and must take into account sensitive populations including pregnant women and their fetuses, infants, and the elderly
Perchlorate

Blocks the NIS

Inhibits iodine uptake

Decreases thyroid hormone production

Increases TSH

Cognitive and other effects, especially in susceptible people (iodine deficient, pregnancy, fetus)

Do environmental perchlorate exposures cause adverse thyroid effects?
Perchlorate PHG

• Completed in 2004, based on the study of Greer et al. in human volunteers
• PHG intended to avoid any detectable inhibition of iodine uptake, with adequate margin of safety
• PHG level = 6 ppb
Objectives:

• Assess the impact of various factors on the relationship between urinary perchlorate and serum thyroxine (T4) and thyroid stimulating hormone (TSH)

• Evaluate females with urinary iodide <100 μg/L (35% of the females in this sample) to compare our results with those of Blount et al. (2006)
Methods

• Univariate and multiple regression models of the NHANES data were developed in SAS 9.1
• Major parameters analyzed:
  – Urinary perchlorate, iodide, creatinine, nitrate, thiocyanate
  – Serum T4 and TSH
  – Smoking status
Methods, continued

- Other parameters evaluated:
  - sex, age, race, serum albumin, body mass index, 24-hr caloric intake
  - pregnancy, menopause, menarche, lactation status
  - serum c-reactive protein, hours of fasting before serum collection, use of thyroid-related medications
Methods, continued

- Urinary perchlorate and creatinine, and serum TSH were log10 transformed to normalize their distributions.
- Urinary creatinine added to all regression models involving urinary perchlorate, nitrate, and thiocyanate to adjust for variations in urinary output.
- In univariate analyses, urinary perchlorate residuals adjusted for creatinine calculated by method described by Willet and Stampfer (1998).
Perchlorate (NHANES 2001-2002)
Results

• Univariate and multivariate analyses on all men and all women showed no clear effects or interactions with serum thyroid hormones

• Women with urinary iodide <100 μg/L showed substantial evidence of interactions of interest

• Interactions of urinary perchlorate, cotinine, and thiocyanate, and smoking, with serum T4 or log TSH levels were most prominent
## Parameters of interest in women with urinary iodine < 100 μg/L

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Current smokers</th>
<th>Non-smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>66</td>
<td>260</td>
</tr>
<tr>
<td>Perchlorate (μg/L)</td>
<td>2.5 (0.55)</td>
<td>3.2 (0.88)</td>
</tr>
<tr>
<td>Iodine (μg/L)</td>
<td>51.7 (3.7)</td>
<td>54.3 (2.2)</td>
</tr>
<tr>
<td>Thiocyanate (μg/L)</td>
<td>4344 (646)</td>
<td>813 (64)</td>
</tr>
<tr>
<td>Cotinine (ng/ml)</td>
<td>201 (15.7)</td>
<td>1.1 (0.60)</td>
</tr>
<tr>
<td>T4 (μg/dL)</td>
<td>8.6 (0.22)</td>
<td>8.2 (0.18)</td>
</tr>
<tr>
<td>logTSH (μg/dL)</td>
<td>0.12 (0.06)</td>
<td>0.14 (0.03)</td>
</tr>
</tbody>
</table>
### Associations between log perchlorate and serum T4 and log TSH in women with urinary iodine < 100 μg/L

<table>
<thead>
<tr>
<th></th>
<th>T4a</th>
<th>logTSHb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>b</td>
</tr>
<tr>
<td>All</td>
<td>362</td>
<td>-0.73</td>
</tr>
<tr>
<td>Smokingc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>63</td>
<td>-1.66</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>245</td>
<td>-0.54</td>
</tr>
<tr>
<td>Cotinine in serum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (&gt;10 ng/ml)</td>
<td>64</td>
<td>-1.47</td>
</tr>
<tr>
<td>Mediumd</td>
<td>185</td>
<td>-0.57</td>
</tr>
<tr>
<td>Low (ND)</td>
<td>101</td>
<td>-0.16</td>
</tr>
<tr>
<td>Thiocyanate in urine (tertiles)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (&gt;1800 μg/L)</td>
<td>78</td>
<td>-1.67</td>
</tr>
<tr>
<td>Medium</td>
<td>107</td>
<td>-0.68</td>
</tr>
<tr>
<td>Low (&lt;751 μg/L)</td>
<td>176</td>
<td>-0.49</td>
</tr>
</tbody>
</table>
Results summary

• Perchlorate negatively associated with T4 and positively associated with logTSH in women with urinary iodine < 100 μg/L
• The T4 negative association much greater in smokers
• The logTSH positive association not much affected by smoking
Smoking, urinary cotinine, and urinary thiocyanate were not associated with serum T4 or TSH in women with urinary iodine <100 μg/L

Example:

- Cotinine with T4, $b = 0.03$, $p = 0.73$; with log TSH, $b = -0.02$, $p = 0.26$ ($n = 382$)
- Cotinine, adjusted for creatinine T4, $b = -0.17$, $p = 0.46$; for logTSH, $b = -0.05$, $p = 0.21$ ($n = 384$)
Combined Factor Analysis

Compare mean T4 and log TSH in women:

- **Group 1:** Current smokers, perchlorate residual > median, and urinary iodine < 100 µg/L
- **Group 2:** Never smokers, perchlorate residual ≤ median, and urinary iodine ≥ 100 µg/L
## Combined Factor Analysis

<table>
<thead>
<tr>
<th>Group</th>
<th>T4</th>
<th>Log TSH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>95% CI</td>
</tr>
<tr>
<td>Group 1 (n=21)</td>
<td>7.16</td>
<td>6.28-8.05</td>
</tr>
<tr>
<td>Group 2 (n=161)</td>
<td>8.41</td>
<td>7.96-8.86</td>
</tr>
<tr>
<td>Difference</td>
<td>1.25</td>
<td>0.13</td>
</tr>
<tr>
<td>p-value</td>
<td>0.04</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Summary

• Observations of Blount et al. (2006) for low-iodide women have been confirmed.
• The relationship of perchlorate with T4 is greater in smokers than in nonsmokers, and in women with higher thiocyanate excretion.
• The strength of the associations makes them unlikely to be due to chance.
• The results seem biologically plausible.
Using the Data

• How should this effect be used in risk assessment?
• How should other effects and associations discovered with this technology be used in risk assessment?
Using the Data

- Waiting for confirmation
- Need to decide on threshold effect of concern
- Need principles applicable to other alterations of homeostasis
- Need to allow for combined effects
- Need to address the sensitive subpopulation issues
Risk Communication

• This is a perchlorate exposure issue, not just a food or drinking water issue
• Should recommendations for use of iodine supplements be strengthened?
• Should iodinization of salt be mandated?
• Should these results be mentioned in anti-smoking campaigns?
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