A Case Study on PBPK and Biologically Based Dose-Response Modeling for Safety Assessment Considerations: Utility and Challenges

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Conflict of Interest Statement

- I declare no conflict of interest
- All views expressed are those of the author and do not reflect the views of the FDA or its policies
Physiological Context and Endpoints of Concern

- Thyroid hormones play a critical role in growth and development
- Pregnant women support fetal thyroid hormone needs throughout gestation

Thyroid hormone insufficiencies during gestation:
- Neurodevelopment effects in the offsprings (Fetuses, Neonates, and Infants)
- Reproductive health effects in pregnant women
Thyroid Function and Means of Perturbations

- **Iodine deficiency:**
  - Less substrate
  - Depletion in iodide stores

- **Exposure to thyroid-active chemicals:**
  - NIS inhibition, common mode of action
    - Perchlorate ($\text{ClO}_4^-$)
    - Thiocyanate ($\text{SCN}^-$)
    - Nitrate ($\text{NO}_3^-$)

*Case Study*

![Thyroid Function Diagram](image)

- **Thyroidal Iodide Uptake**
- **Organification of Iodide to Thyroid Hormones**
- **Extra-thyroidal deiodination**

*NIS – Sodium Iodide Symporter*
Perchlorate

• Both naturally occurring and man-made chemical

• Excellent oxidizing properties

• Uses as an oxidizer
  – Rocket propellants and munitions
  – Fireworks
  – Car airbags
  – Matches and signal flares
Perchlorate Exposure Status

- Exposure to perchlorate is ubiquitous
- Found in food (FDA Total Diet Study data)
- Found in drinking water (EPA Unregulated Contaminant Monitoring Rule data)
- Human biomonitoring data show for the total population of the United States, the relative contribution to daily intake of perchlorate is estimated to be 80% from food and 20% from drinking water (Huber et al. 2011)
Iodine Nutritional Status

• The recommended daily intake of iodine in adults is 150 µg/day and 220 µg/day for pregnant women.

• According to WHO criteria, a population of pregnant women with median urinary iodine concentration (UIC) < 150 µg/L is considered iodine insufficient.

• Biomonitoring studies suggest marginal iodine sufficiency in pregnant women in the U.S. (National Children’s Study and NHANES).

SUPPLEMENTARY FIG. S1. Median urinary iodine concentration (UIC) values with 95% confidence limits for pregnant women, from National Health and Nutrition Examination Surveys (NHANES), United States. The median UIC categories and definitions are based on the World Health Organization recommendations (4).
Public Health Concern Related Questions

1) What level of perchlorate exposure can be associated with a decrease in thyroid hormone levels during gestation?

2) Based on the current perchlorate exposure and iodine nutritional status in the United States what is the effect of perchlorate on thyroid hormone levels in pregnant women?
Need for Alternative Methods in Data Scarce Populations

Computational tools for safety assessment applications in pregnant women:

- Physiologically Based Pharmacokinetic (PBPK) Modeling
- Biologically Based Dose-Response (BBDR) Modeling: PBPK + mode of action models

Clinical data in adults

In vivo data

In vitro and chemical specific data

SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety
Decade of Research on Iodide and Perchlorate: Series of Models Developed in Rats and Humans, Including Life Stages

- **PBPK Models in Rats and Rat Life-Stages for Tracer Radioiodide and Perchlorate:**
  - Merrill et al. 2003 (Toxicological Sciences)
  - Clewell et al. 2003 (Toxicological Sciences)
  - Clewell et al. 2003 (Toxicological Sciences)

- **PBPK Models in Humans and Human Life-Stages for Tracer Radioiodide and Perchlorate:**
  - Merrill et al. 2005 (Toxicological Sciences)
  - Clewell et al. 2007 (J. Toxic. Environ. Health, Part A)

- **BBDR Models in Adult Rats for Dietary Iodide and Perchlorate at Steady State:**
  - McLanahan et al. 2008 (Toxicological Sciences)
  - McLanahan et al. 2009 (Environmental Health Perspectives)

- **BBDR Models in Rat Life-Stages for Dietary Iodide Alone at Steady State:**
  - Fisher et al. 2013 (Toxicological Sciences)

- **BBDR Models in Human Life-Stages for Dietary Iodide and Perchlorate at Steady State:**
  - Lumen et al. 2013 (Toxicological Sciences)
Deterministic BBDR Model  [Proof-of-Concept]

**Goal:**
What is the effect of perchlorate on thyroid hormone levels given the iodine nutritional status during gestation?

**Lumen et al. 2013:**
A BBDR model framework for an “average” near-term pregnant woman was developed to evaluate perturbations in serum thyroid hormones for varying iodide intake conditions and perchlorate exposure scenarios.

**Modeling Approach**
- Choice of Near-Term Life Stage
- Euthyroid Conditions
- Lower Iodide Intake Conditions
- Perchlorate Exposure Conditions
- Interaction and Dose-Response Assessment
<table>
<thead>
<tr>
<th>Increase in maternal cardiac output</th>
<th>Decrease in plasma iodide concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in urinary clearance of iodide</td>
<td></td>
</tr>
<tr>
<td>Increase in plasma volume</td>
<td></td>
</tr>
<tr>
<td>Increase in thyroxine binding globulin (TBG)</td>
<td>Decrease in fT4 and fT3</td>
</tr>
<tr>
<td>Increase in TT4 and TT3</td>
<td></td>
</tr>
<tr>
<td>Increase in thyroidal uptake of iodide</td>
<td>Offset the urinary loss of iodide</td>
</tr>
<tr>
<td>Increase in hormonal output &amp; degradation</td>
<td>Increased hormone demands and role of placenta in deiodination</td>
</tr>
<tr>
<td>Increase in placental weight</td>
<td></td>
</tr>
<tr>
<td>Increase in blood flow to placenta</td>
<td>Placental transfer of fT4 and anions to fetus</td>
</tr>
<tr>
<td>Increase in fetal cardiac output</td>
<td></td>
</tr>
<tr>
<td>Increase in the fraction of cord blood flow to fetal cardiac output</td>
<td></td>
</tr>
</tbody>
</table>
Thyroid Hormone Homeostasis At Near Term
Model Parameterized to Describe Thyroid Function
Perchlorate Exposure Conditions
Model Parameterized to Describe Perchlorate Disposition

Non-Pregnant
(Greer et al., 2002)
(Merrill et al., 2005)

Pregnant
(Tellez et al., 2005)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Tellez et al 2005 (High exposure ‘Tall’ group)</th>
<th>Model Predictions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maternal</td>
<td>Fetal</td>
</tr>
<tr>
<td>Urine Iodide (µg/L)</td>
<td>217 ±109</td>
<td>NA</td>
</tr>
<tr>
<td>Serum perchlorate (µg/L)</td>
<td>13.2 ± 1.7</td>
<td>19.9 ± 5.0</td>
</tr>
<tr>
<td>Urine perchlorate (µg/L)</td>
<td>128.9 ± 127</td>
<td>NA</td>
</tr>
<tr>
<td>Free T4 (pmol/L)</td>
<td>10.7 ± 1.5</td>
<td>13.3 ± 1.8</td>
</tr>
<tr>
<td>Total T3 (nmol/L)</td>
<td>2.7 ± 0.6</td>
<td>1.3 ± 0.3</td>
</tr>
</tbody>
</table>
Application of BBDR Pregnancy Model (Theoretical Exposure Scenario)

Lumen et al. 2013
Application of BBDR Pregnancy Model (Real Life Exposure Scenario)

- Exposure scenarios: drinking water only and water+food [perchlorate food intake dose set to the 90th percentile as observed in biomonitoring studies during pregnancy in the United States]

<table>
<thead>
<tr>
<th>Life stages</th>
<th>Body weight (kg)</th>
<th>Percent decrease in serum $fT_2$ at different drinking water levels of perchlorate</th>
<th>POD$^a$ (µg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>15 µg/l (µg/kg/day)</td>
<td>20 µg/l (µg/kg/day)</td>
</tr>
<tr>
<td>Mother</td>
<td>72.3</td>
<td>0.494% Water only</td>
<td>0.692% Water only</td>
</tr>
<tr>
<td>Fetus</td>
<td>3.4</td>
<td>0.98% Water only</td>
<td>1.37% Water only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.76% Water only</td>
<td>0.99% Water only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.93% Water only</td>
<td>1.59% Water only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. $^a$POD, point of departure for perchlorate (NRC, 2005; USEPA, 2005).

$^b$Perchlorate intake dose with contribution from drinking water in the units of µg/kg/day were calculated using the 90th percentile drinking water intake rate of 0.033 l/kg/day estimated for pregnant women (USEPA, 2009, 2011) and a body weight of 72.3 kg.

$^c$Contributions from food to the total perchlorate intake dose were calculated using the estimated 90th percentile perchlorate food intake dose of 0.198 µg/kg/day for pregnancy conditions by Huber et al. (2011).
Goal: What is the effect of perchlorate on thyroid hormone levels at a population-level in pregnant women of the United States?

Modeling Approach:
- Global sensitivity analysis
  - Identify the sub-set of the most influential model input parameters and their interactions
- Probabilistic analysis using Monte-Carlo methods
  - Capture population-based responses in pregnant women with perchlorate exposures
Global Sensitivity Analysis

What are the most important model input parameters and their interaction effects?

- ~90% variance in model output is found to be explained by capturing variances in the top 10 input parameters

Lumen, McNally et al. 2015
Probabilistic Framework of BBDR Pregnancy Model
Monte Carlo Methods

Model input
Influential parameters

GSA

Lumen et al. 2015

Model output
Maternal Thyroid Hormone Levels
Specific for United States Pregnant Women Population
Reverse Dosimetry Methods

• To determine distribution of iodine intake for pregnant women in the US

Lumen et al. 2015

• Can we make use of available biomonitoring data?
Exposure Reconstruction from Biomonitoring Studies: Iodine Intake Distribution in US Pregnant Women Population

Modeling Approach:

• Reverse dosimetry using probabilistic BBDR pregnancy Model

• **Input:** measured biomonitoring data of urinary iodide concentrations in late-gestation United States pregnant women population

• **Output:** reconstructed iodine intake distribution estimated to yield the observed urinary biomonitoring data

• **Catch:** Urine concentration are from spot samples. Can spot urine measurements reliably help predict daily intake estimates?
Exposure Reconstruction from Biomonitoring Studies: Iodine Intake Distribution in US Pregnant Women Population

Not for all but plausible for iodide due to the following reasons:

- Most of the ingested iodine is readily absorbed and eliminated in urine without any secondary metabolism.
- Diet is the primary route of intake for iodine.
- Evidence that 24-hour urinary iodide concentration values, on average, did not differ from the spot urinary iodide concentration measurements.
- Minimal day-to-day variation between the timed-spot urine samples observed.
- Within-subject variance less than between-subject variance.
Use of Available Biomonitoring Data

Maternal Urinary Flow Rates
NHANES (2009-2012)

Maternal Urinary Iodide Concentrations
National Children’s Study (2009-2010)

Urinary flow rate (L/day) \times \text{Urinary iodide concentration (µg/L)}

= \text{Amount of iodide excreted (µg/day)}

PBPK/BBDR

\text{Reverse dosimetry}

\text{Amount of iodide intake (µg/day)}

Lumen and George 2017a
Model Performance Verification Endpoints Include:

- Distribution of thyroidal iodide stores
- Distribution of thyroid hormone levels
Iodine Nutrition estimates in US Pregnant Women Population (Late-gestation)

- Estimated population median iodine intake (220 ug/day) in agreement with WHO recommended intake for pregnant women.
- 21% to 44% of late-gestation U.S. pregnant women population predicted to have iodine intake needs unmet

Lumen and George 2017a
Estimates of Perchlorate Exposure in the US Population
Model Verification in Late-gestation Pregnant Women

Distribution of perchlorate food intake (Huber et al. 2011)

Model predicted distribution of perchlorate urinary concentration

Observed distribution of perchlorate urinary concentration (NHANES; NCS)

Predictions is good agreement with observations

Model ready for probabilistic dose-response analysis
Lumen and George 2017b

<table>
<thead>
<tr>
<th>Urinary Perchlorate Conc. Late-gestation (µg/L)</th>
<th>Geometric Mean (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model Prediction</td>
<td>3.75 (3.66, 3.84)</td>
</tr>
<tr>
<td>NCS Study</td>
<td>4.03 (3.72, 4.36)</td>
</tr>
<tr>
<td>NHANES Study</td>
<td>3.27 (2.59, 3.95)</td>
</tr>
</tbody>
</table>
Population-based BBDR model allows to address:

- What is the impact of current levels of perchlorate exposure at a population level?
- At what level of perchlorate exposure can we expect to see x-fold decrease in maternal thyroid hormone levels
- What % of the population is at an increased risk for a given level of perchlorate exposure
Population-Based Dose-Response Assessment
Application of Probabilistic BBDR Model

A. Lumen, N.J. George / Toxicology and Applied Pharmacology 322 (2017) 9–14

Table 5
Percentile distribution ($P_{2.5}$, $P_{25}$, $P_{50}$, $P_{75}$, $P_{97.5}$) and geometric mean (and 95% CI) of serum maternal thyroid hormone levels for various doses of perchlorate intake.

<table>
<thead>
<tr>
<th>Perchlorate dose (µg/kg/day)</th>
<th>Current levels of perchlorate</th>
<th>Median urinary perchlorate concentration (µg/L)</th>
<th>Serum concentration of maternal free thyroxine (pmol/L)</th>
<th>Geometric mean (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NA</td>
<td>5.4</td>
<td>7.4</td>
<td>8.8</td>
</tr>
<tr>
<td>2. No perchlorate exposure</td>
<td>3.58</td>
<td>5.3</td>
<td>7.4</td>
<td>8.8</td>
</tr>
<tr>
<td>3. LN(-2.8, 0.9)</td>
<td>(fitted distribution of perchlorate from food intake)</td>
<td>3.39</td>
<td>5.3</td>
<td>7.4</td>
</tr>
<tr>
<td>4. 0.060</td>
<td>($P_{90}$ of perchlorate from food intake)</td>
<td>11.15</td>
<td>5.3</td>
<td>7.4</td>
</tr>
<tr>
<td>5. 0.198</td>
<td>($P_{90}$ of perchlorate from food intake)</td>
<td>15.65</td>
<td>5.3</td>
<td>7.4</td>
</tr>
<tr>
<td>6. 0.278</td>
<td>($P_{90}$ of perchlorate from food intake)</td>
<td>39.04</td>
<td>5.3</td>
<td>7.3</td>
</tr>
<tr>
<td>7. 0.692</td>
<td>($P_{90}$ of perchlorate from food intake + 15 µg/L from drinking water)</td>
<td>48.36</td>
<td>5.3</td>
<td>7.3</td>
</tr>
<tr>
<td>8. 0.857</td>
<td>($P_{90}$ of perchlorate from food intake + 20 µg/L from drinking water)</td>
<td>56.72</td>
<td>5.3</td>
<td>7.2</td>
</tr>
<tr>
<td>9. 1.005</td>
<td>($P_{90}$ of perchlorate from food intake + 24.5 µg/L from drinking water)</td>
<td>395.00</td>
<td>4.8</td>
<td>6.5</td>
</tr>
</tbody>
</table>

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a Percentile estimates as reported in Huber et al. (2011).
b Estimates were computed assuming a drinking water intake rate of 0.033 L/kg/day for pregnant women (U.S. EPA, 2012) and a body weight of 72.3 kg.
c Statistically significant different from scenario 1 (no perchlorate exposure).

Lumen and George 2017b

No statistical difference
In response to dose-response questions for the effects of perchlorate on pregnant women population in the United States:

- Model predicted no statistically significant difference in thyroid hormone levels in late-gestation pregnant women considering current iodine nutritional status and known population perchlorate exposure from food intake alone.

- Model predicted a daily intake of 0.45 to 0.5 µg/kg/day of perchlorate necessary to produce statistically significant change in thyroid hormone levels of the evaluated population.
Summary
Utility of *In Silico* Tools for Safety Assessment

Computational models such as PBPK and BBDR pregnancy model:

- Allow for dose-response assessment for perchlorate and thyroid function in an “average” late-gestation pregnant woman
- Allow for estimation iodine nutritional status in the United States population of late-gestation pregnant women using biomonitoring data
- Allow for dose-response assessment for perchlorate and thyroid function at a population level for late-gestation pregnant women in the United States
Summary
Challenges of *In Silico* Tools for Safety Assessment

Computational models such as PBPK and BBDR pregnancy model:

- Still a very simplified depiction of a complex biological system and chemical interaction. Built on several model assumptions which could contribute to uncertainties.

- Early phases of pregnancy can still be challenging to model.

- Even with the best tools and techniques, can only go as far as the data allows us before hitting a wall.


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