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

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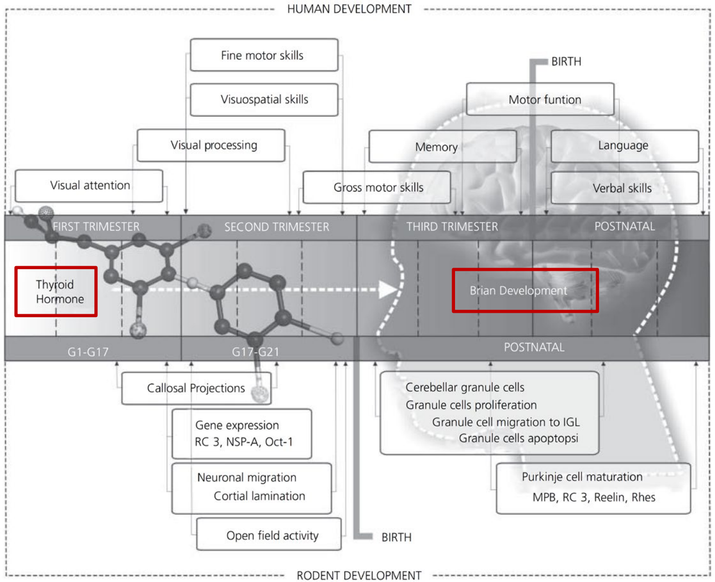
Conflict of Interest Statement

- 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

Timing of thyroid hormone action in the developing brain



Zoeller and Rovet, 2004

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

Thyroid hormone insufficiencies during gestation:

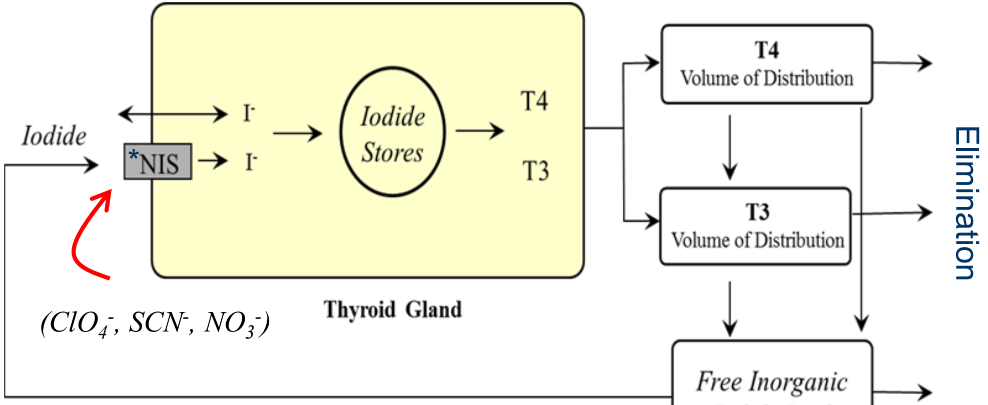
- Neurodevelopment effects in the offsprings (Fetuses, Neonates, and Infants)
- Reproductive health effects in pregnant women

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 (ClO_4^-)
  - Thiocyanate (SCN^-)
  - Nitrate (NO_3^-)

Case Study

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



*NIS – Sodium Iodide Symporter

Perchlorate

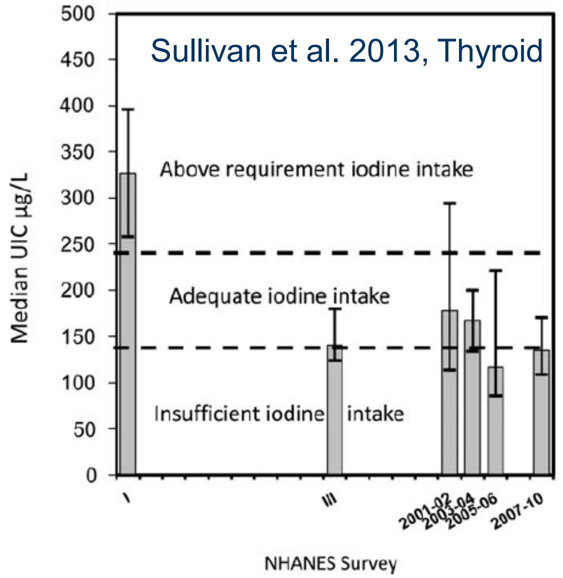
- Both naturally occurring and man-made chemical
- Excellent oxidizing properties
- Uses as an oxidizer
  - Rocket propellants and munitions
  - Fireworks
  - Car airbags
  - Matches and signal flares

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?

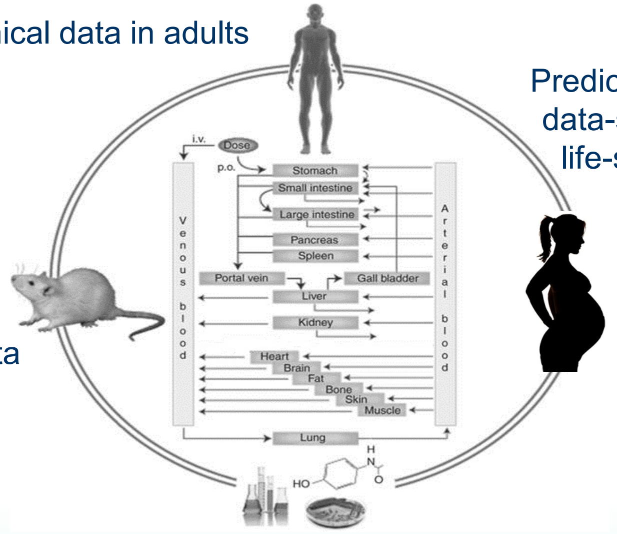
Need for Alternative Methods in Data Scarce Populations

Computational tools for safety assessment applications in pregnant women:

Clinical data in adults

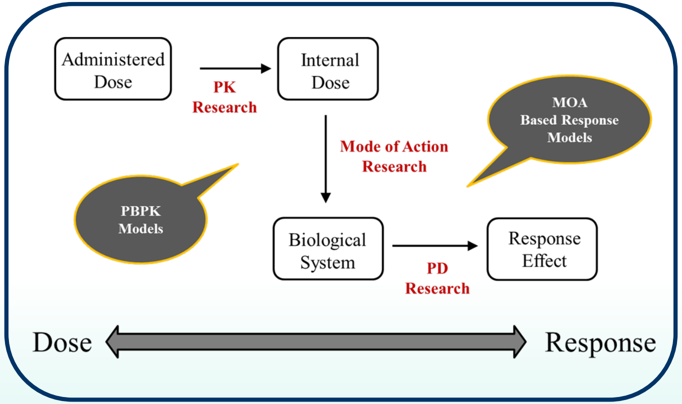
Predictions in data-scarce life-stage

In vivo data



In vitro and chemical specific data

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



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]

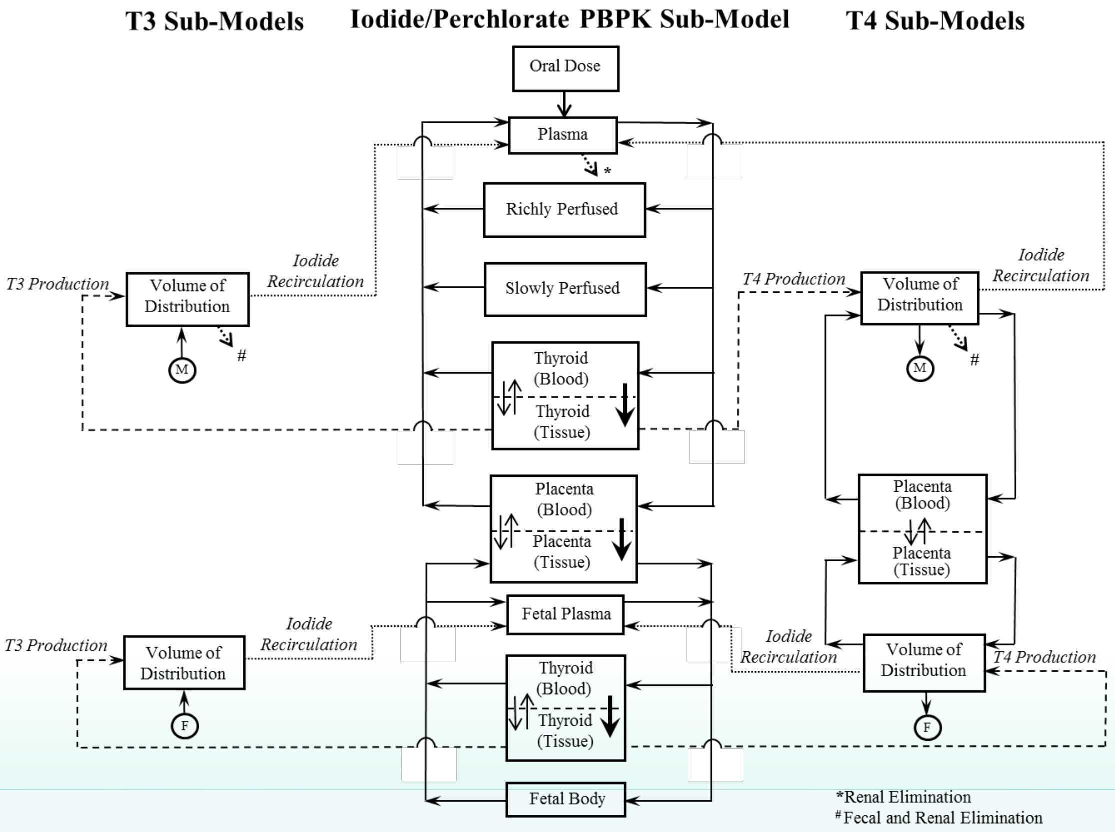
Goal:
What is the effect of perchlorate on thyroid hormone levels given the iodine nutritional status during gestation ?

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

Near-Term BBDR Pregnancy Model Structure

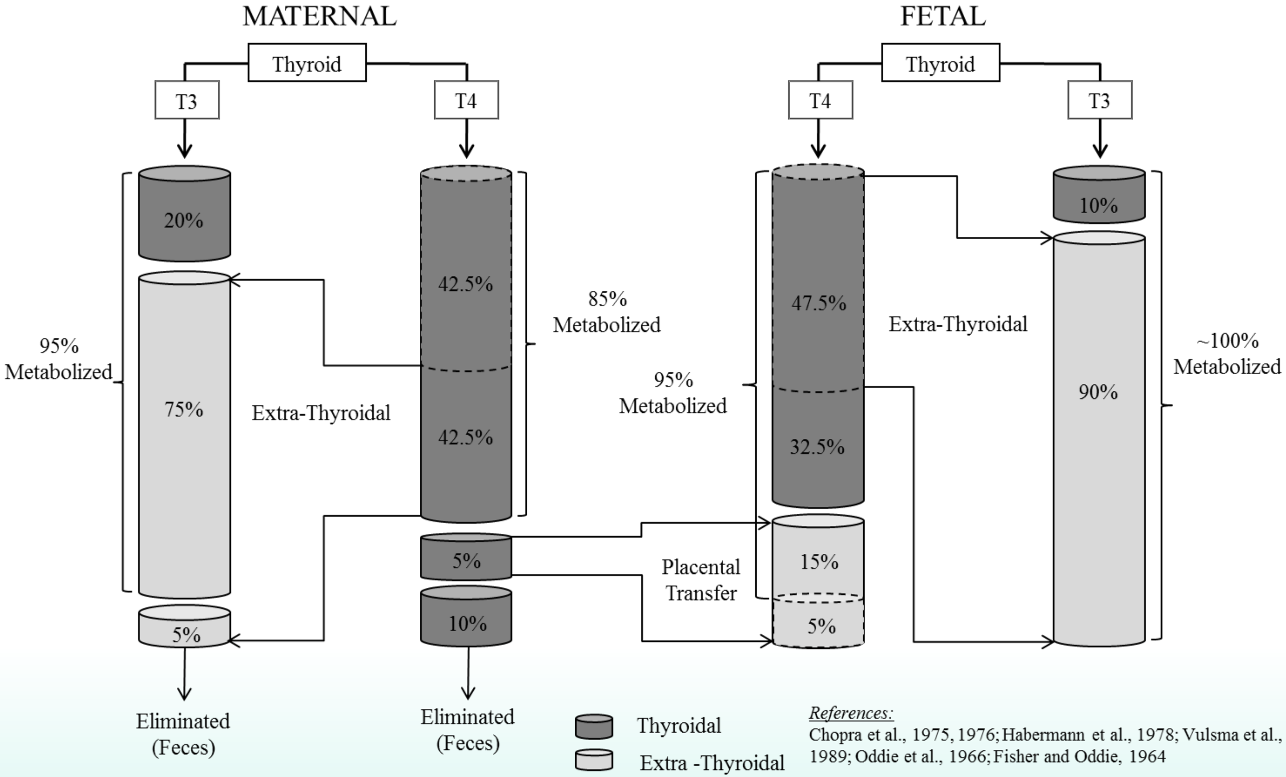


Lumen et al. 2013

Physiological and Thyroid Function Changes During Pregnancy Accounted for in the BBDR Model

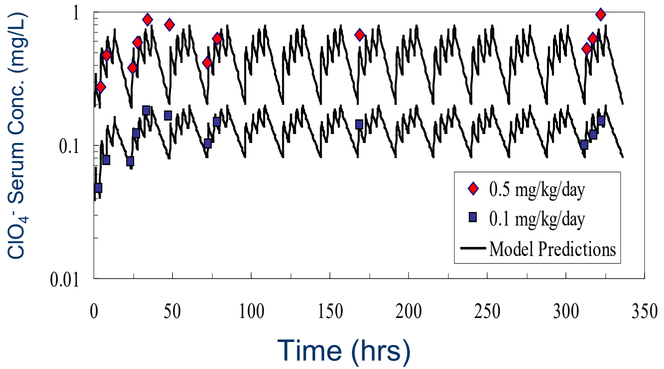
Increase in maternal cardiac output	Decrease in plasma iodide concentration
Increase in urinary clearance of iodide	
Increase in plasma volume	
Increase in thyroxine binding globulin (TBG)	Decrease in fT4 and fT3
Increase in TT4 and TT3	
Increase in thyroidal uptake of iodide	Offset the urinary loss of iodide
Increase in hormonal output & degradation	Increased hormone demands and role of placenta in deiodination
Increase in placental weight	Placental transfer of fT4 and anions to fetus
Increase in blood flow to placenta	
Increase in fetal cardiac output	
Increase in the fraction of cord blood flow to fetal cardiac output	

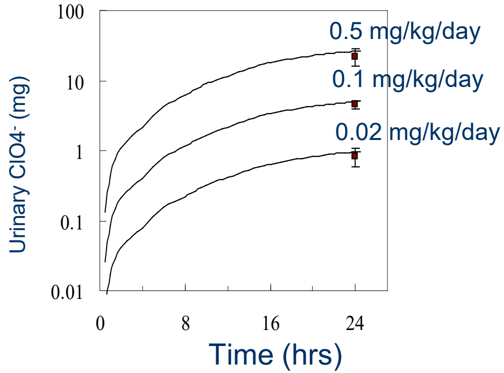
Thyroid Hormone Homeostasis At Near Term
Model Parameterized to Describe Thyroid Function



References:
Chopra et al., 1975, 1976; Habermann et al., 1978; Vulsma et al., 1989; Oddie et al., 1966; Fisher and Oddie, 1964

Perchlorate Exposure Conditions
Model Parameterized to Describe Perchlorate Disposition





Non-Pregnant

(Greer et al., 2002)

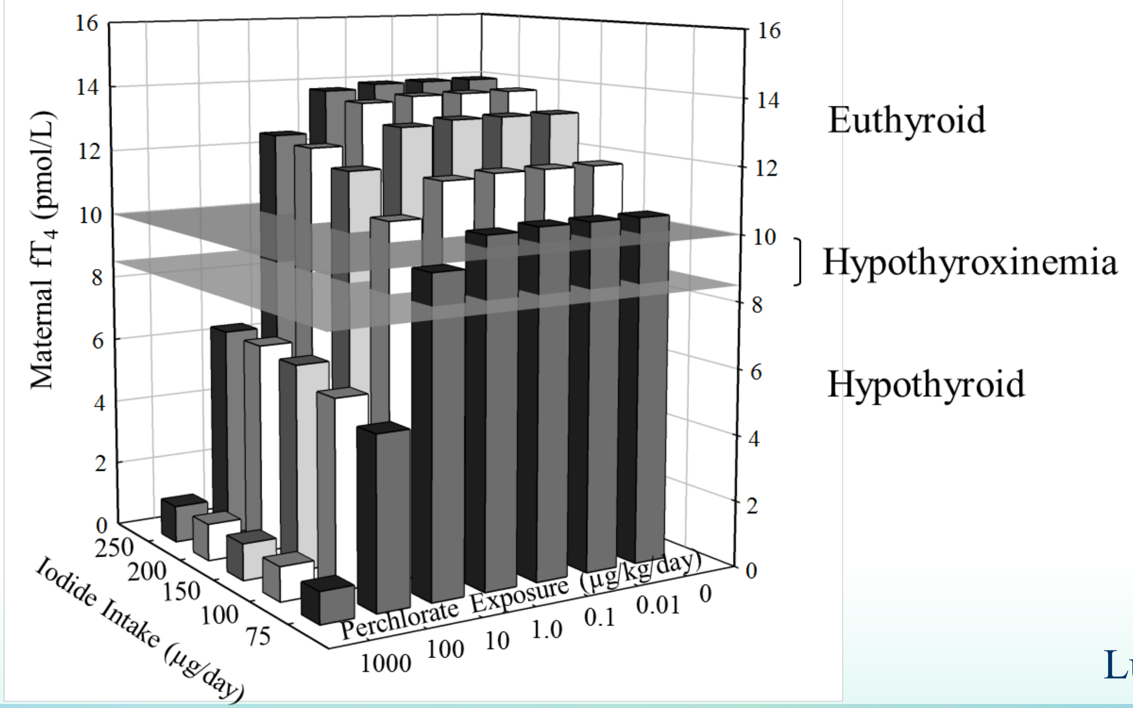
(Merrill et al., 2005)

Parameters	Tellez et al 2005 High exposure 'Taltal' group		Model Predictions	
	Maternal	Fetal	Maternal	Fetal
Urine Iodide (µg/L)	217 ±109	NA	218.1	-
Serum perchlorate (µg/L)	13.2 ± 1.7	19.9 ± 5.0	13.2	20.2
Urine perchlorate (µg/L)	128.9 ± 127	NA	176.8	-
Free T4 (pmol/L)	10.7 ± 1.5	13.3 ± 1.8	13.5	14.4
Total T3 (nmol/L)	2.7 ± 0.6	1.3 ± 0.3	2.5	1.0

Pregnant

(Tellez et al., 2005)

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 9

Model-Predicted Changes in the fT_4 Levels for Different Perchlorate Exposure Scenario With Contribution From Both Drinking Water and Food Compared With Model-Predicted fT_4 Levels for Euthyroid Conditions (200 µg of Iodide/Day) With No Perchlorate Exposure

		Percent decrease in serum fT_4 at different drinking water levels of perchlorate						
		15 µg/l		20 µg/l		24.5 µg/l		POD[a]
		0.494[b] (µg/kg/day)	0.692[c] (µg/kg/day)	0.659[b] (µg/kg/day)	0.857[c] (µg/kg/day)	0.807[b] (µg/kg/day)	1.005[c] (µg/kg/day)	7 (µg/kg/day)
Life stages	Body weight (kg)	Water only	Water + food	Water only	Water + food	Water only	Water + food	
Mother	72.3	0.57%	0.80%	0.76%	0.99%	0.93%	1.16%	7.5%
Fetus	3.4	0.98%	1.37%	1.31%	1.69%	1.59%	1.97%	11.92%

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).

Lumen et al. 2013

Model Expansion

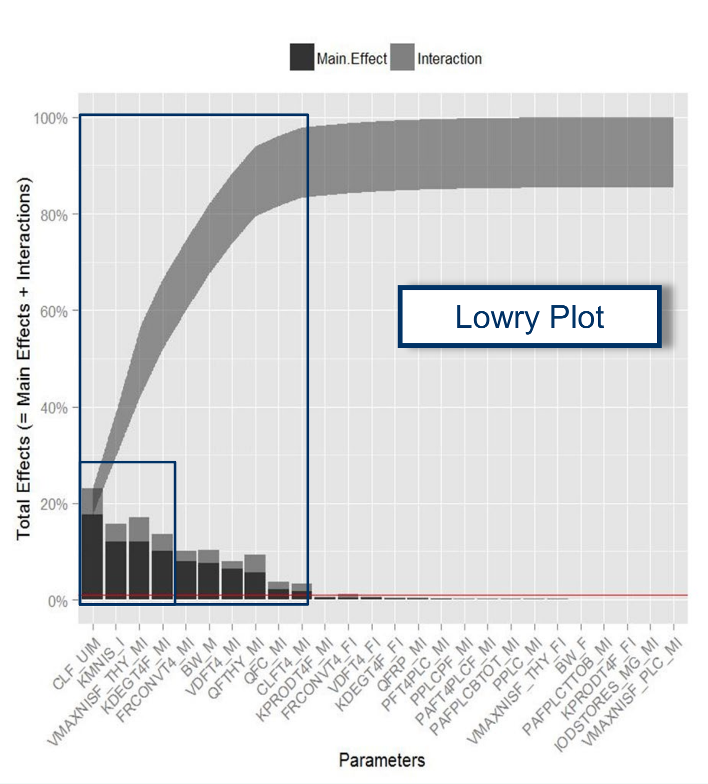
Deterministic → Probabilistic BBDR Pregnancy Model

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?

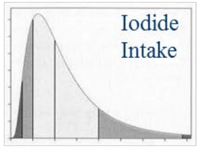
- ~90% variance in model output is found to be explained by capturing variances in the top 10 input parameters

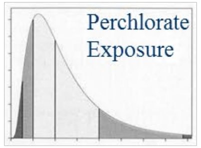
Lumen, McNally et al. 2015

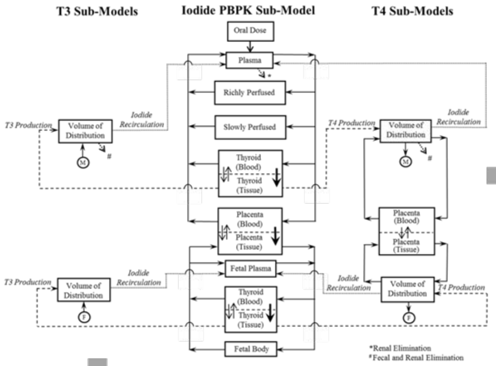
Probabilistic Framework of BBDR Pregnancy Model
Monte Carlo Methods

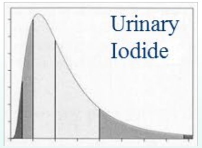
Model input
Influential parameters

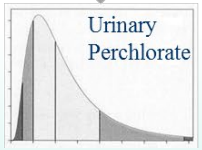
Lumen et al. 2015



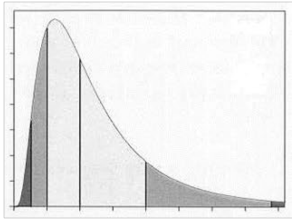








Model output
Maternal Thyroid
Hormone Levels

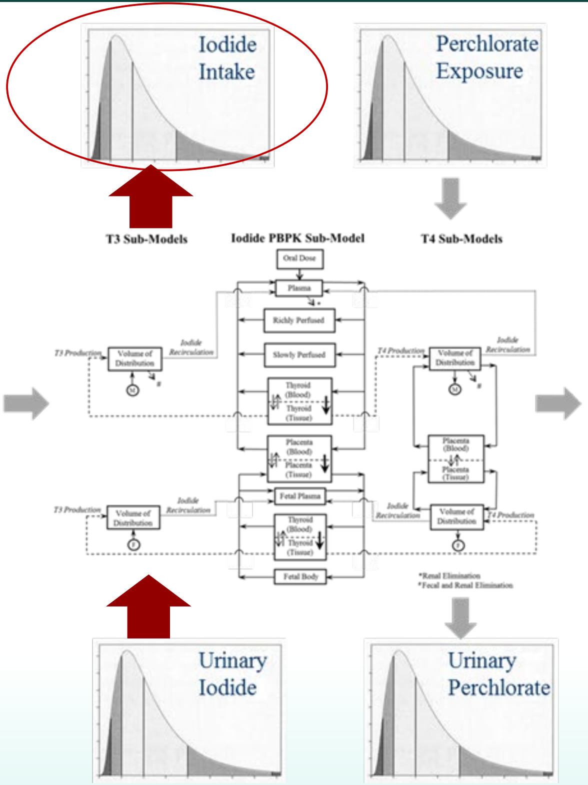


Specific for United States Pregnant Women Population
Reverse Dosimetry Methods

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

Model input
Influential parameters

Lumen et al. 2015



Model output
Maternal Thyroid
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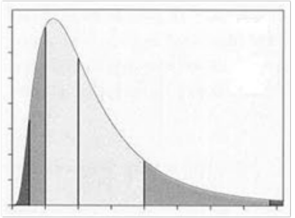


- Can we make use of available biomonitoring data?

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?

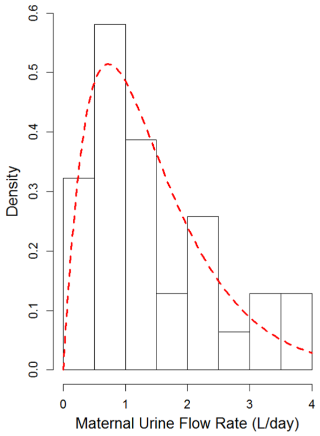
Exposure Reconstruction from Biomonitoring Studies: Iodine Intake Distribution in US Pregnant Women Population

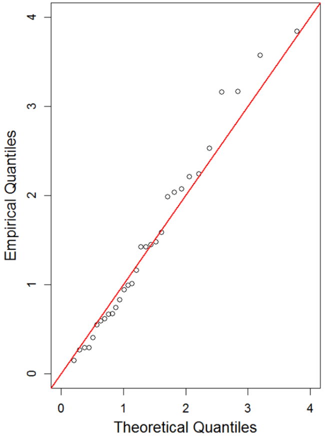
Not for all but plausible for iodide due to the following reasons:

- 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)





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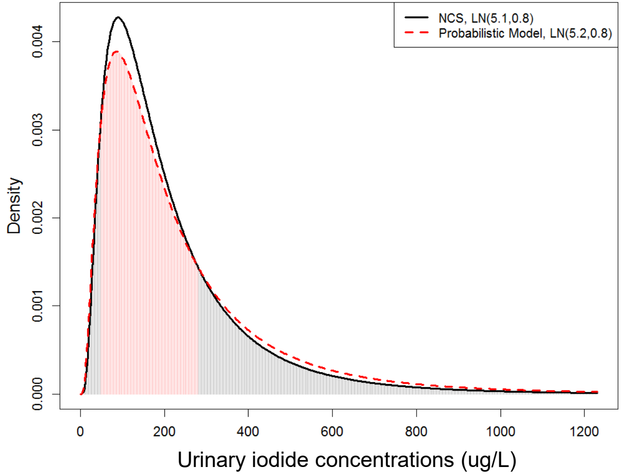
Maternal Urinary Iodide Concentrations
National Children's Study (2009-2010)



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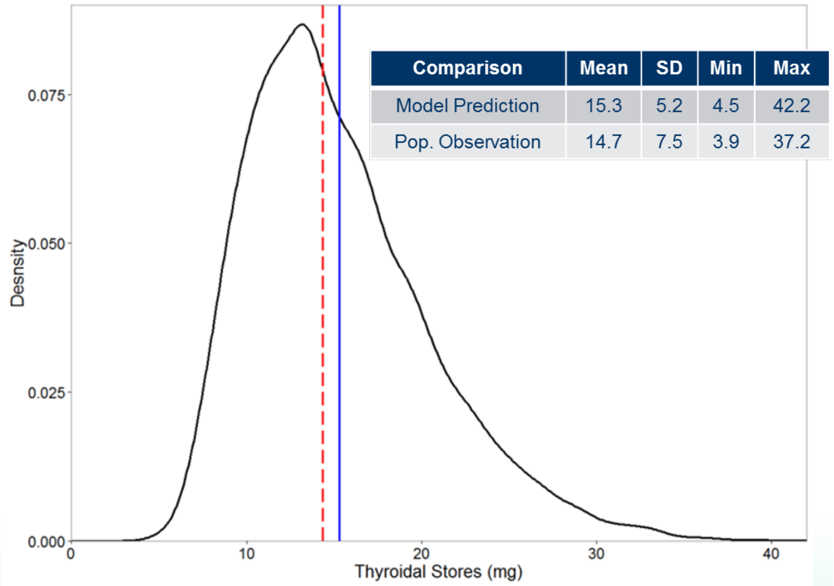
Urinary flow rate (L/day) X Urinary iodide concentration (μg/L)

= Amount of iodide excreted (μg/day) $\xrightarrow[\text{Reverse dosimetry}]{\text{PBPK/BBDR}}$ Amount of iodide intake (μg/day)

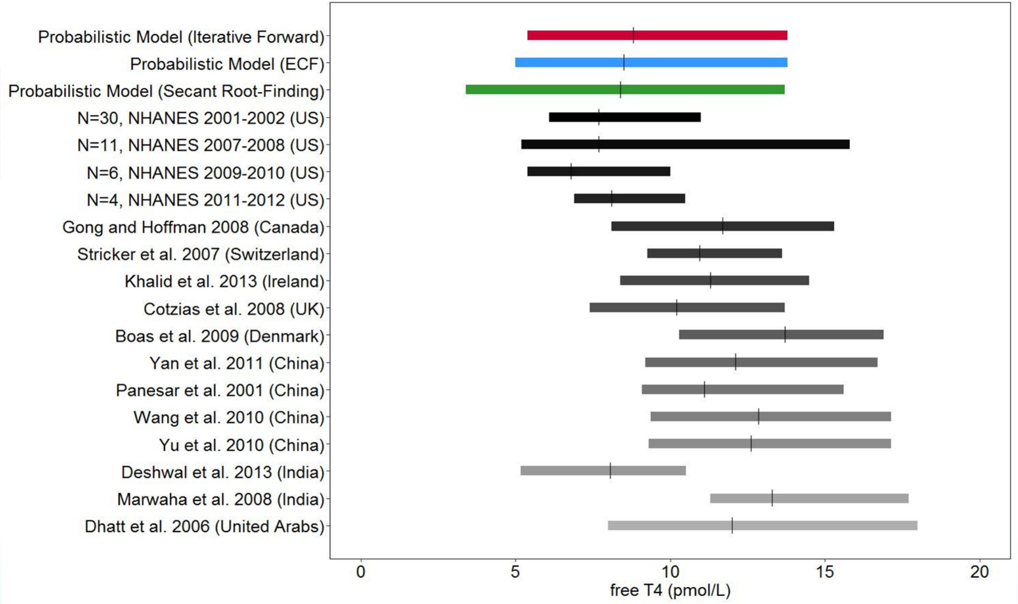
Model Performance Verification Endpoints Include:

Distribution of thyroidal iodide stores

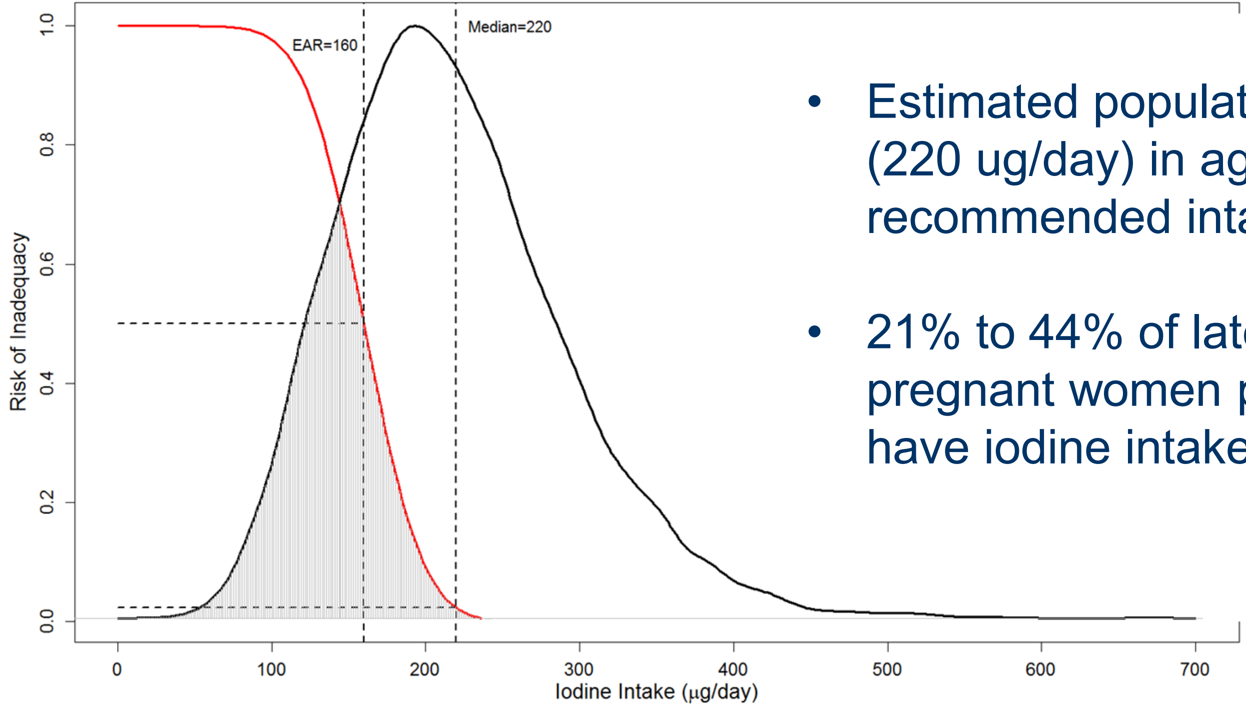


Comparison	Mean	SD	Min	Max
Model Prediction	15.3	5.2	4.5	42.2
Pop. Observation	14.7	7.5	3.9	37.2

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

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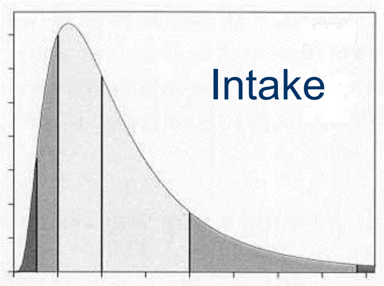
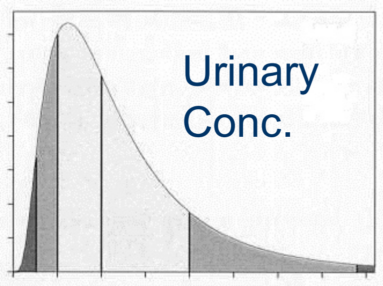
Estimates of Perchlorate Exposure in the US Population
Model Verification in Late-gestation Pregnant Women



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

PBPK/BBDR

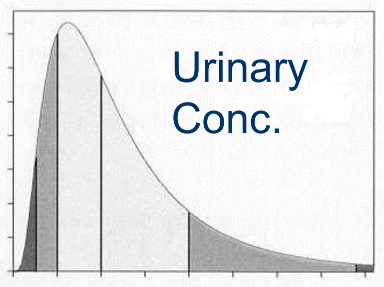
Forward Dosimetry



Model predicted distribution of perchlorate urinary concentration

Predictions is good agreement with observations

Observed distribution of perchlorate urinary concentration (NHANES; NCS)



Model ready for probabilistic dose-response analysis

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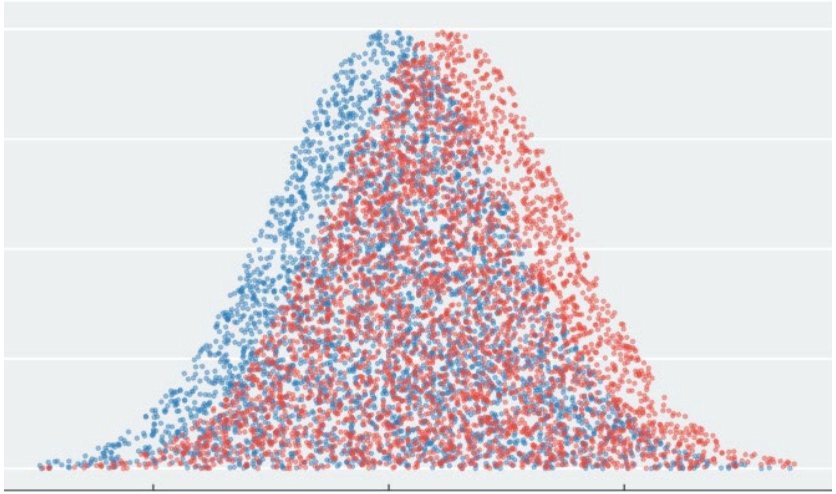
Urinary Perchlorate Conc. Late-gestation (µg/L)	Geometric Mean (95%CI)
Model Prediction	3.75 (3.66, 3.84)
NCS Study	4.03 (3.72, 4.36)
NHANES Study	3.27 (2.59, 3.95)

Population-Based Dose-Response Assessment
Illustration of Concept

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

Red: without perchlorate exposure
Blue: with perchlorate exposure



Thyroid hormone levels in
late-gestation pregnant women population in the US

Population-Based Dose-Response Assessment

Application of Probabilistic BBDR Model

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.

Current levels of perchlorate

Perchlorate dose (µg/kg/day)	Median urinary perchlorate concentration (µg/L)	Serum concentration of maternal free thyroxine (pmol/L)					
		$P_{2.5}$	P_{25}	P_{50}	P_{75}	$P_{97.5}$	Geometric mean (95%CI)
1. No perchlorate exposure	NA	5.4	7.4	8.8	10.4	13.8	8.73 (8.69, 8.77)
2. LN(−2.8, 0.9) (fitted distribution of perchlorate from food intake)	3.58	5.3	7.4	8.8	10.4	13.8	8.72 (8.68, 8.76)
3. 0.060 (P_{50} of perchlorate from food intake[a])	3.39	5.3	7.4	8.7	10.4	13.8	8.72 (8.68, 8.76)
4. 0.198 (P_{90} of perchlorate from food intake[a])	11.15	5.3	7.4	8.7	10.3	13.7	8.70 (8.65, 8.74)
5. 0.278 (P_{95} of perchlorate from food intake[a])	15.65	5.3	7.4	8.7	10.3	13.7	8.68 (8.64, 8.72)
6. 0.692 (P_{90} of perchlorate from food intake[a] + 15 µg/L from drinking water[b])	39.04	5.3	7.3	8.6	10.2	13.6	8.61 (8.56, 8.65)[c]
7. 0.857 (P_{90} of perchlorate from food intake[a] + 20 µg/L from drinking water[b])	48.36	5.3	7.3	8.6	10.2	13.6	8.58 (8.53, 8.62)[c]
8. 1.005 (P_{90} perchlorate from food intake[a] + 24.5 µg/L from drinking water[b])	56.72	5.3	7.2	8.6	10.2	13.5	8.55 (8.51, 8.60)[c]
9. 7.0 (NRC's point of departure; NRC, 2005)	395.00	4.8	6.5	7.7	9.2	12.4	7.67 (7.63, 7.71)[c]

No statistical difference

[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).

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Summary
Case Study (Perchlorate)

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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