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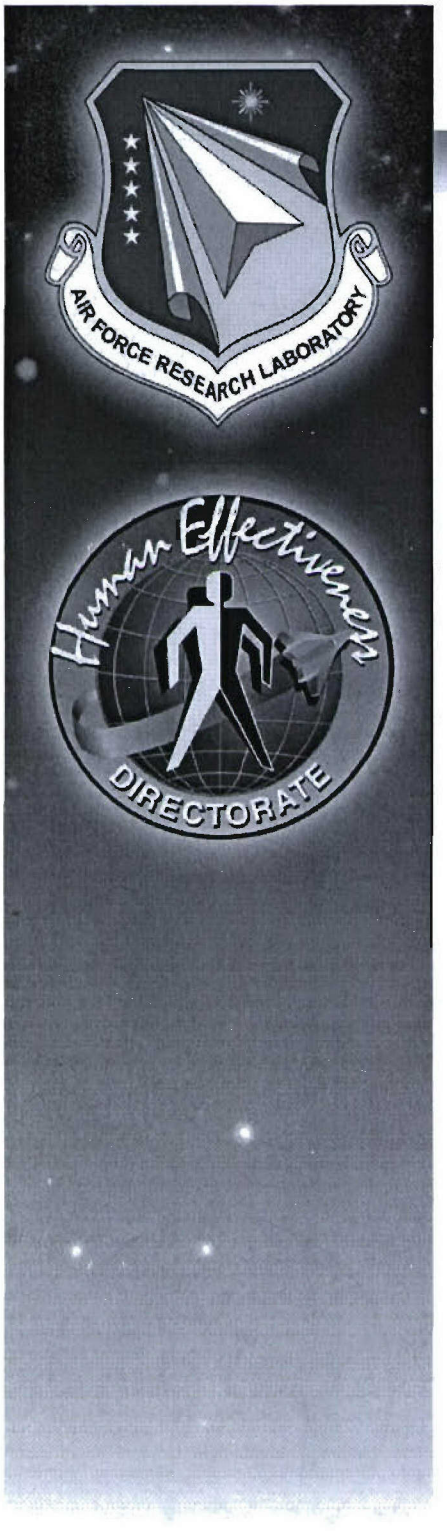

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Using Human Life Stage PBPK/PD Model Predictions of Perchlorate-Induced Iodide Inhibition to Inform Risk Assessment in Sensitive Populations

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14. ABSTRACT

Iodide inhibition was considered to be the key biochemical event preceding disruption of thyroid hormone homeostasis. The RfD was based on the No Observable Effect Level (NOEL) of 0.007 mg/kg-day, which resulted in no significant iodide inhibition in normal adults. An uncertainty factor of 10 was applied to the NOEL to account for intraspecies variability, including life-stage specific susceptibility. Recently, existing physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) models across life-stages in rat and in adult human were expanded to describe inhibition kinetics during perinatal development in humans. Chemical-specific parameters were estimated from life-stage and species-specific relationships established in previously published PBPK/PD models. The human perinatal models successfully simulate literature radioiodide data for gestation and lactation, as well as data from populations exposed to perchlorate contaminated drinking water. These validated models were used to examine the effect of developmental stage on susceptibility to thyroid perturbation across a range of doses. At environmentally relevant doses, the perinatal woman, fetus and nursing infant are predicted to have higher blood perchlorate concentrations and greater thyroid iodide uptake inhibition than either the non-pregnant adult or older child. At exposure levels equal to the NOEL and RfD, the PBPK/PD model predicted iodide inhibition in fetuses is within normal variation (less than 10%) and insignificant (less than 1%), respectively, indicating that the newly adopted RfD is in fact protective of the population most sensitive to thyroid inhibition.

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Using Human Life Stage PBPK/PD Model Predictions of Perchlorate-Induced Iodide Inhibition to Inform Risk Assessment in Sensitive Populations.

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ABSTRACT

The January 2005 National Research Council report "Health Implications of Perchlorate Ingestion" and the adoption of its findings into the U.S. Environmental Protection Agency Integrated Risk Information System resulted in a perchlorate reference dose (RfD) of 0.0007 mg/kg-day. Iodide inhibition was considered to be the key biochemical event preceding disruption of thyroid hormone homeostasis. The RfD was based on the No Observable Effect Level (NOEL) of 0.007 mg/kg-day, which resulted in no significant iodide inhibition in normal adults. An uncertainty factor of 10 was applied to the NOEL to account for intraspecies variability, including life-stage specific susceptibility. Recently, existing physiologically based pharmacokinetic/ pharmacodynamic (PBPK/PD) models across life-stages in rat and in adult human were expanded to describe inhibition kinetics during perinatal development in humans. Chemical-specific parameters were estimated from life-stage and species-specific relationships established in previously published PBPK/PD models. The human perinatal models successfully simulate literature radioiodide data for gestation and lactation, as well as data from populations exposed to perchlorate contaminated drinking water. These validated models were used to examine the effect of developmental stage on susceptibility to thyroid perturbation across a range of doses. At environmentally relevant doses, the perinatal woman, fetus and nursing infant are predicted to have higher blood perchlorate concentrations and greater thyroid iodide uptake inhibition than either the non-pregnant adult or older child. At exposure levels equal to the NOEL and RfD, the PBPK/PD model predicted iodide inhibition in fetuses is within normal variation (less than 10%) and insignificant (less than 1%), respectively, indicating that the newly adopted RfD is in fact protective of the population most sensitive to thyroid inhibition.

INTRODUCTION

- Ammonium perchlorate is a key component of solid rocket fuel and has been found in the drinking water of 30+ states.
- The DoD, EPA, DOE and NASA asked the National Research Council (NRC) to address key scientific issues associated with perchlorate.
- The NRC Committee on the Health Implications of Perchlorate Ingestion consisted of 15 national experts. Their final report concluded (NRC, 2005):
    - **Iodide uptake inhibition by perchlorate is the key biochemical event preceding disruption of thyroid hormone homeostasis.**
    - A reduction of thyroid iodide uptake of at least 75% for a sustained period (several months or longer) would be required to decrease thyroid hormone production sufficiently to cause adverse health effects.
    - A reference dose (RfD), protective for all populations, could be established at 0.0007 mg/kg-day based on:

        - A NOEL of 0.007 mg/kg-day in a human perchlorate study (Greer *et al.*, 2002)
        - An uncertainty factor of 10 for intraspecies variability, including life stage specific susceptibility.
            - In pregnant women, infants and children, and people who have a low iodide intake or pre-existing thyroid dysfunction, the dose required to cause a decrease in thyroid hormone production may be lower than in the normal population.
    - "A dose that does not inhibit thyroid iodide uptake will not affect thyroid function, even in subjects with an abnormal thyroid gland or a very low iodide intake" (NRC, 2005)
        - Iodide inhibition is a precursor to changes in hormone production, which in turn, is a precursor to adverse effects.
- The U.S. Environmental Protection Agency accepted the recommendation of the NRC Committee and entered a perchlorate RfD of 0.0007 mg/kg-day into their Integrated Risk Information System (IRIS).

Perchlorate PBPK/PD Models

- Using PBPK models, we can account for kinetic and physiological differences across life stages and **quantitatively predict exposure and effect (thyroid inhibition) in the sensitive populations.**
- PBPK models of perchlorate and iodide were published for the adult human, as well as the adult male pregnant and lactating female, fetal and neonatal rat (Clewell *et al.*, 2003a, 2003b; Merrill *et al.*, 2003; 2005a).
- **Recently, these PBPK models were expanded to describe inhibition kinetics across life stages in the human, including the pregnant and lactating woman, fetal development and the child from birth to adulthood.**

HUMAN LIFE-STAGE MODEL DEVELOPMENT

- **Physiological Parameters:** Based on published data and published PBPK models for human gestation, lactation and childhood (Gentry *et al.*, 2002, Clewell *et al.*, 2004)
- **Chemical-specific Parameters:** Estimated from life-stage and species-specific relationships established in published PBPK/PD models (Clewell *et al.*, 2003a, 2003b; Merrill *et al.*, 2003, 2005a)
- **Model Structure:** Identical to those for perchlorate and iodide in the rat (Clewell *et al*, 2003a, 2003b) (Figure 1)
- **Model Validation:** Successful prediction of available human data (Clewell *et al.*, in press)
    - I^- in the mother and fetus throughout gestation (Figure 2)
    - I^- in the mother and breast-fed infant through the first year of life (Figure 2)
    - I^- in the growing child
    - ClO_4^- in the serum of the pregnant mother and newborn, and the milk of lactating women exposed via naturally contaminated groundwater (Tellez *et al.*, 2005) (Figure 3).

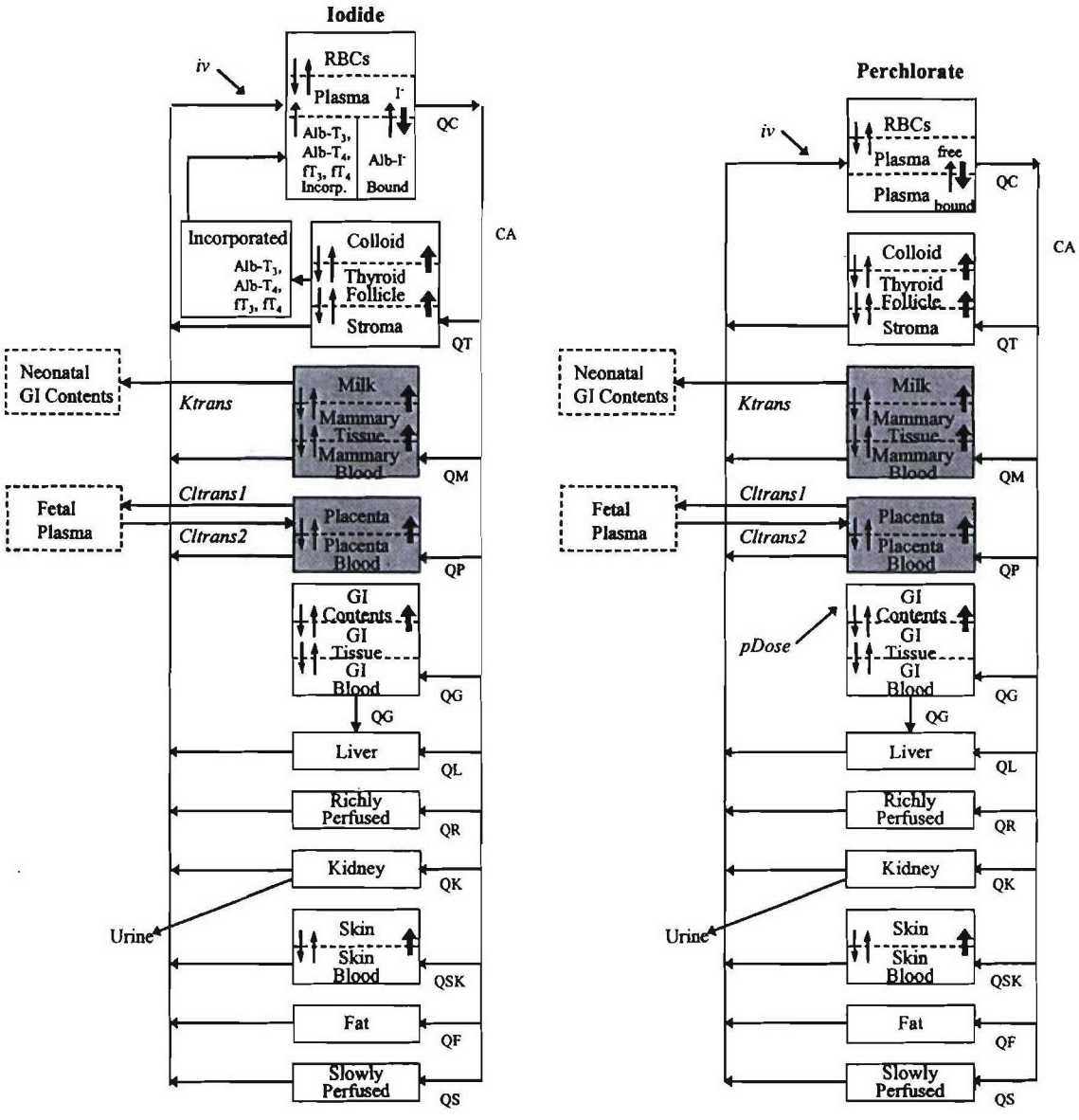

Figure 1. PBPK model schematic for radioiodide (left) and perchlorate (right) in the pregnant or lactating woman (Clewell *et al.*, in press). The fetal and neonatal models are identical, minus the shaded compartments. The fetal model does not include incorporation of iodide into thyroid hormones. Bold arrows indicate active transport, double arrows represent passive diffusion, and thin single arrows designate first order rates.

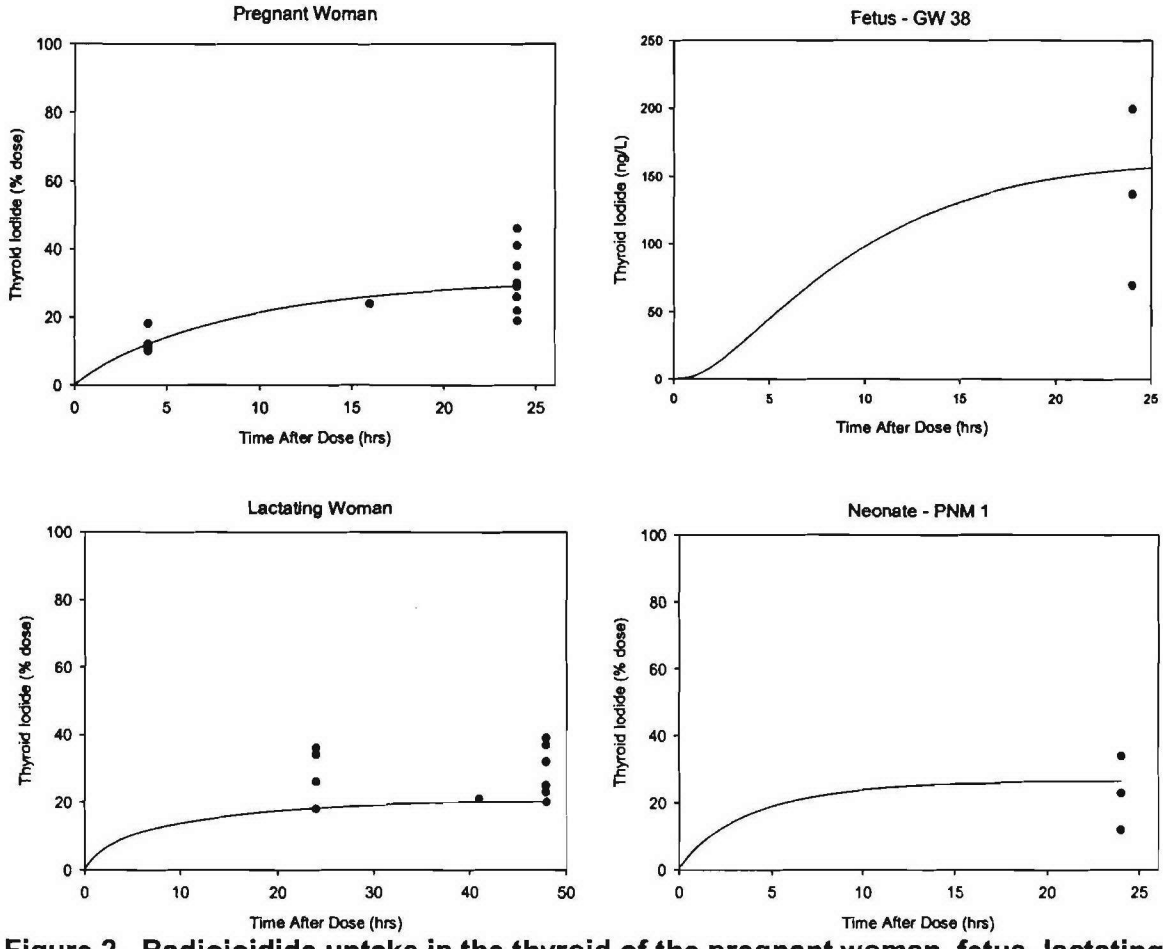

Figure 2. Radioiodide uptake in the thyroid of the pregnant woman, fetus, lactating woman and neonate after a single oral exposure. The solid lines indicate the model prediction and filled circles represent measured values in individual subjects from the literature (see references in Clewell *et al.*, in press). The fetus and pregnant woman were simulated at gestation week 38; serum levels and percent inhibition are constant across gestation. The lactating woman was simulated at post-natal week 2 and the infant was run at 1 month post-partum; these were determined to be the most sensitive time-points (greatest inhibition) for each life-stage by running the model repeatedly at different time-points.

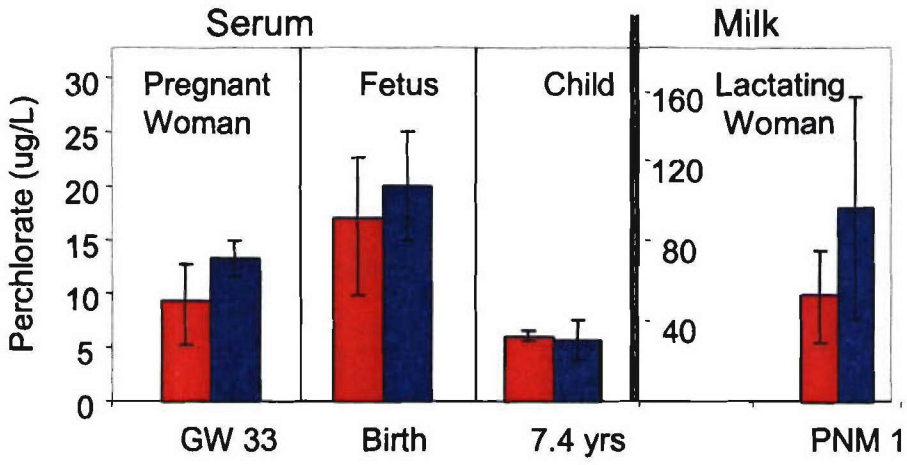

Figure 3. Perchlorate in serum of the pregnant woman, fetus and child, and milk of the lactating woman from environmental exposure. Red and blue bars represent model-predicted and measured perchlorate concentrations, respectively. Cross-bars represent ± one SD. Predicted values were simulated for average (± one SD) published doses (Gibbs *et al.*, 2004; Tellez *et al.*, 2005).

APPLICATION OF LIFE STAGE MODELS TO RISK ASSESSMENT

Determining Sensitive Population (Life-Stage):

- Susceptibility to chemical effect may be due to differences in exposure, pharmacokinetics or pharmacodynamics
- Models allow testing of the effects of different exposures (Figure 4) and pharmacokinetics (Figure 5) on the endpoint of interest
- Two ways to estimate susceptibility: Serum perchlorate AUC (area under the curve) and inhibition of thyroid uptake (% inhibition)
- **From predicted serum levels, the fetus is the most susceptible population based on pharmacokinetic and exposure differences (Figure 5)**
  - Models were run at constant water concentration (RfD: 25 ppb), assuming daily water intake for the 95th percentile (U.S. EPA, 1997, 2002).
  - Simulations performed across time-points in gestation, lactation, childhood and in the adult
  - Serum ClO_4^- AUC and % inhibition of thyroid were compared to determine most pharmacokinetically susceptible life-stage based on internal dose and estimated precursor effect

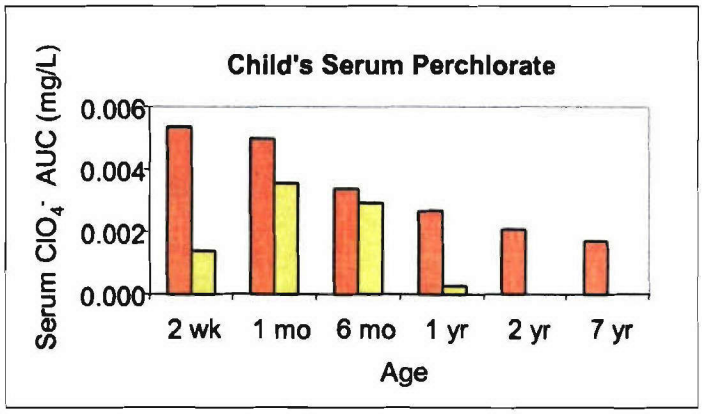

Figure 4. Serum perchlorate in breast-fed (yellow) vs. bottle-fed (orange) infant and the older child. Simulations in the breast-fed infant were performed at daily maternal water intake of 2 L (95th percentile for adults); the infant was exposed via maternal milk only. Simulations in the bottle-fed infant and in the older child assume daily water intake at 95th percentile for their age (1 L for <1 year of age). Perchlorate exposure for both simulations is assumed to occur exclusively through drinking water at a concentration of 25 ppb.

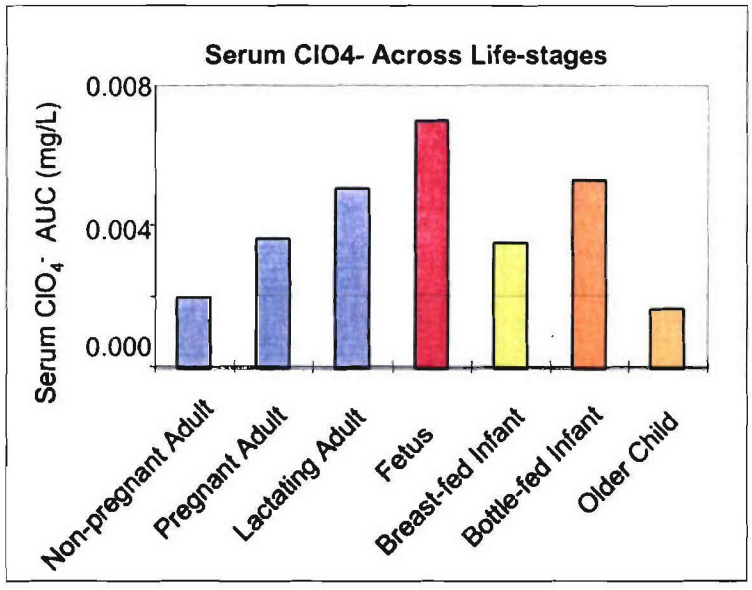

Figure 5. Serum perchlorate in the adult (purple), fetus (pink), breast-fed infant (yellow), bottle-fed infant (orange) and older child (yellow-orange). The dashed line is provided for comparison with the adult AUC. Simulations in adults, fetus (gestation week 38) and breast-fed infant (post-natal month 1) were performed at daily maternal water intake of 2 L (95th percentile for adults). Simulations in the bottle-fed infant (post-natal week 2) and older child (7 years) assume daily water intake at 95th percentile for their age. Perchlorate exposure for all simulations is assumed to occur exclusively through drinking water at a concentration of 25 ppb.

Estimating Risk Using PBPK Models:

- The most significant use of these models for risk assessment is the quantitative prediction of biological effect from perchlorate exposure.
- Based on NRC and EPA recommendations, preventing inhibition of iodide uptake in the thyroid will prevent downstream endocrine effects.
- The models can be used to determine a 'safe' perchlorate dose, below which thyroid inhibition is considered insignificant.
    - Because there are different concepts of 'insignificant inhibition', the model was run for several levels of inhibition, and the daily dose needed to reach the prescribed % inhibition was recorded across life-stages.

Table 1. Life stage models predicted dose resulting in levels of thyroid iodide uptake inhibition across life-stages.

	Normal Adult (M&F)	Pregnant Woman	Fetus (M&F)	Lactating Woman	Neonate (M&F)
	(mg/kg-d)	(mg/kg-d)	(mg/kg-d)	(mg/kg-d)	(mg/kg-d)
1% Inhibition	0.002	0.001	0.0008	0.001	0.001
5% Inhibition	0.01	0.005	0.004	0.005	0.006
10% Inhibition	0.02	0.01	0.008	0.01	0.01
75% Inhibition	0.7	0.3	0.4	0.3	2

Table 2. Life stage models predicted thyroid iodide uptake inhibition across life-stages at the EPA IRIS NOEL and RfD.

	Normal Adult (M&F)	Pregnant Woman	Human Fetus (M&F)	Lactating Woman	Human Neonate (M&F)
	% Inhibition	% Inhibition	% Inhibition	% Inhibition	% Inhibition
NOEL (0.007 mg/kg-day)	3.3	6.4	8.6	6.9	5.8
RfD (0.0007 mg/kg-day)	0.3	0.6	0.9	0.8	0.6

CONCLUSIONS

- PBPK models help bridge gaps between animal data and potential risk to humans at various life stages.
    - Using models that have been validated across life-stages in both the rat and human, we can predict safe exposure levels with more confidence and less uncertainty.
- At environmentally relevant doses, the perinatal woman, fetus and nursing infant are predicted to have higher blood perchlorate concentrations and greater thyroid iodide uptake inhibition than either the non-pregnant adult or older child.
- The models indicate that the fetus receives the greatest perchlorate dose (per kg BW) and is most susceptible to iodide inhibition at low doses.
- The model predicted daily dose estimated to disrupt thyroid hormone homeostasis in a normal adult (75% iodide inhibition (NRC, 2005)) is 0.7 mg/kg-day from model predictions.
    - The NRC estimated this dose would be more than 0.4 mg/kg-day perchlorate for a 70-kg adult, based on clinical studies (Gibbs *et al.*, 1998; Lamm *et al.*, 1999; Crump *et al.*, 2000).
- **Human exposure at the IRIS NOEL is predicted to result in 9% or less iodide inhibition across life stages.**
    - Normal human variation in iodide uptake was measured at approximately 10% (Greer *et al.*, 2002).
- **Human exposure at the RfD is predicted to result in insignificant (less than 1%) iodide inhibition across life stages.**
- **The life stage models predict iodide inhibition levels for both fetus and neonate that support the protectiveness of the RfD.**

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REFERENCES AVAILABLE UPON REQUEST