How should EPA consider PBPK modeling to derive an MCLG for perchlorate?

- EPA should utilize a mode of action (MOA) framework for developing the MCLG that links the different steps in the proposed mechanism leading from perchlorate exposure through NIS inhibition to thyroid hormone changes and finally neurodevelopmental impacts.
- Within this MOA framework, the PBPK model provides a tool for integrating aspects of exposure (e.g., different drinking water consumption rates) with the biological changes occurring at the different lifestages to obtain predictions of inhibition as would be observed if a radiolabeled iodide uptake inhibition study were done.
- The PBPK model describes inhibition of NIS (as observed in RAIU inhibition study), so it includes the first key pharmacodynamic step, target modulation, and is therefore appropriately described as a PBPK-PD model.
- This approach starts to answer questions about sensitivity at lifestages that otherwise are only qualitative justifications for the UF of 10 for protecting sensitive populations.
- Documenting and making the PBPK-PD model accessible to non-modelers will be an important challenge for EPA since by comparison with the very simple algebraic default equation, the model can appear opaque despite the fact that it captures much scientific information.

What are the strengths and limitations of the two PBPK model results described in this effort?

- The first analysis (Table A3) evaluates the predicted RAIU inhibition for the same perchlorate dose (7 ug/kg/day) that arises from biological variations captured in the PBPK model for different lifestages. This analysis helps support the use of the UF in deriving the RfD.
- The second analysis (Table A4) evaluates the combined impacts of the differences in exposure (e.g., drinking water consumption) with the biological variability by assessing the predicted RAIU inhibition at fixed drinking water concentrations.
- A limitation of the first analysis is the selection of the urinary excretion rate for perchlorate. Literature for iodide excretion indicates the rate is faster in neonate/infants than at later ages, which might then be expected to be the case for perchlorate. This needs to be carefully assessed and justified.
- While the model addresses life-stage variations, it is a model of the average human at each life stage. Extension of the model to a full population description would be useful, but it is recognized that this would be a major effort.
- The human biological modeling uses life-stage specific uptake rates mediated by NIS levels but does not reflect changes in NIS in response to TSH regulation or chronic perchlorate exposure.

- A strength of the first analysis is that EPA modified the model to describe both perchlorate transport into breast milk as well as descreased iodide due to transporter inhibition, so that predictions for inhibition in breast fed infants account for both these aspects.
- The second analysis is the most valuable for asking what extent of NIS inhibition woud be predicted for different potential MCLG concentrations. It provides perspective on the protection offered by different concentrations. Since it uses 90th percentile drinking water consumption rates, it also starts to address population issues, though the biological aspects of the model are for an average individual.
- Extension of models to incorporate dietary iodide intake and thyroid hormone synthesis is underway in Dr. Fisher's lab and would be desirable to improve the quantitative linkages in the MOA framework. This would strengthen both the analysis of the biological variability and the combined impact of exposure differences with the biological variability.
- Future model developments that would be valuable include i) extending the model to describe iodide intake and thyroid hormone regulation, and ii) population variability beyond lifestage differences. These would be longer term efforts for improved analyses to support the MCLG.