SUMMARY OF EXTERNAL PEER REVIEW COMMENTS AND DISPOSITION
for the 2008 external review draft of the report
Inhibition of the Sodium-Iodide Symporter by Perchlorate: An Evaluation of Lifestage Sensitivity Using Physiologically-based Pharmacokinetic (PBPK) Modeling

The draft report, *Inhibition of the Sodium-Iodide Symporter by Perchlorate: An Evaluation of Lifestage Sensitivity Using Physiologically-based Pharmacokinetic (PBPK) Modeling*, has undergone a formal external peer review performed by scientists in accordance with the U.S. EPA guidance on peer review (U.S. EPA, 2006). The external peer reviewers were tasked with providing written answers to general questions on the overall analysis and on parameter-specific questions in areas of scientific controversy or uncertainty. A summary of significant comments made by the external reviewers and the U.S. EPA's responses to these comments arranged by charge question follow. In many cases the comments of the individual reviewers have been synthesized and paraphrased.

The final external peer review report, including the charge to peer reviewers, (November 12, 2008) is available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=199347.

EXTERNAL PEER REVIEWER COMMENTS

The reviewers made several editorial suggestions to clarify specific portions of the text. These changes were incorporated in the document as appropriate and are not discussed further.

General Comments

Charge Question G1. ***Is EPA's analysis logical, clear and appropriate in depth and length? Has EPA accurately, clearly and objectively represented and synthesized the scientific evidence for the changes made to or specification of the model code and input parameters?***

Comment G1-a: All eight reviewers indicated that the U.S. EPA's analysis was logical, clear, and appropriate in length. Three reviewers explicitly indicated that the U.S. EPA provided an accurate, clear, and objective representation and synthesis of the scientific evidence for the changes made to or specification of the model code and input parameters. One reviewer recommended additional consideration and discussion of intra-human variability and quantitative and statistical approaches to address uncertainty.

> Response G1-a: In predicting perchlorate dosimetry and radioactive iodide uptake (RAIU) inhibition for the average individual in each lifestage, use of the model provides information for only a portion of the total human population variability. To characterize the full inter-individual variability within each lifestage would require specification of population distributions for each model parameter in each lifestage, including the distribution of sodium/iodide symporter (NIS) expression in each tissue where it occurs. Such data are not currently available. Further, the task of gathering all the requisite information, integrating it into a population parameter model (computer code), and

simulating the parameter distributions to estimate dose-response distributions is beyond the scope of the current effort.

Sweeney et al. (2003) is an example of using a physiologically-based pharmacokinetic (PBPK) model to evaluate overall population uncertainty, which is similar to what was suggested for perchlorate by the reviewer. Sweeney et al. (2003) performed an analysis for acrylonitrile (AN), where estimates of parameter variability were combined with model-prediction sensitivity coefficients (for each parameter) to estimate overall population uncertainty. Considering internal dose metrics of peak or average blood concentrations of AN or the key oxidative metabolite, cyanoethylene oxide, the ratio of exposure metric in the 99th percentile of the population to the average individual was found to be no greater than 2.2. This is similar to the default inter-individual uncertainty factor for toxicokinetics of 3.

While the Sweeney et al. (2003) result is a single analysis, for a metabolized VOC, the intrinsic variability in human physiology incorporated by Sweeney et al. would be the same for perchlorate. However, to fully account for variability in the perchlorate analysis, one would also need to consider several additional factors across and within lifestages, such as variability in NIS levels and urinary clearance.

Comment G1-b: One reviewer noted that the draft report states that calculations were made for "subgroups, including potentially sensitive subgroups" although population-based modeling (with considerations of inter-individual and intra-individual variability) was not performed.

Response G1-b: A paragraph was added at the end of the introduction (Section 1) to clarify that the model predictions provided what could be considered central tendencies for specific subgroups.

Comment G1-c: One reviewer recommended considering the extent to which the gestation week 40 fetus may or may not represent the first and second trimester fetus.

Response G1-c: Text was added to the document (Section 4.2) to describe the rationale for using the model to predict %RAIU inhibition for only the gestation week (GW) 40 fetus. Briefly, the GW 40 fetus is not intended to represent the first or second trimester fetus. Key fetal parameters are too uncertain for quantitative application of the model to earlier GWs. There are no data to support model predictions of %RAIU inhibition in the fetus at the earlier GWs.

Comment G1-d: One reviewer asked for an expanded discussion of the motivation for some of the statistical fits to the data.

Response G1-d: Text was added to the beginning of Section 3 to provide a discussion and motivation for the methods used to estimate model parameters.

In short, the U.S. EPA's approach was to generate algebraic functions, through curve-fitting, that would provide good approximations of time- or BW-dependent changes in parameter behavior, using a relatively small number of parameters and simple

analytic tools (curve-fitting in Microsoft Excel) that could be readily applied. We believe that differences in the quantitative PBPK model predictions between using these curve-fits and what one might obtain by more extensive analyses would be small.

Charge Question G2. ***Please identify any additional studies or other data sources that should be considered in the assessment of the specific parameters addressed below, including urinary clearance (of iodide and/or perchlorate) and ingestion rates (breast milk, formula and water), especially in neonates.***

Comment G2-a: Five reviewers identified additional studies for the U.S. EPA to consider. One reviewer recommended that the U.S. EPA seek additional data to re-affirm the water ingestion rates, "particularly the use of the 90th percentile values in which the situations exceed the expectation of the fundamental knowledge." However, this reviewer was not aware of any studies or data sources that the U.S. EPA could use. One reviewer suggested that additional data collection could be done in the future, but noted that the U.S. EPA's use of DeWoskin and Thompson's data for scaling renal excretion for infants by body weight and extrapolating to a 60-day-old, 5 kg child is reasonable. One reviewer could not identify the reference Gentry et al. 2001 and suggested an alternative data source (Dewey et al., 1991) for the residual milk volume parameter.

Response G2-a: The Agency evaluated Dewey et al. (1991) and agrees that this reference provided a value (0.109 L) for residual milk volume that may be appropriate for use in the Clewell et al. (2007) model. Gentry et al. (2001) was referenced in the model code by the model authors for the original value used in the model (VMk = 0.632 L), but not in the corresponding manuscript and a Gentry et al. (2001) reference with this value could not be located. The value for residual milk volume (VMk) was changed from 0.632 to 0.109 L. Model sensitivity to VMk was tested and an 83% decrease from 0.632 to 0.109 L for VMk resulted in less than 3% change in model calculated percent inhibition of radioiodide uptake. Thus, the model is not sensitive to this parameter. This revision is documented in Appendix A, Section A.3, and an example of the impact of this change on model predictions is shown in A.7.

Comment G2-b: One reviewer recommended including a compartment analysis figure for the current model used by the U.S. EPA.

Response G2-b: Figures of the PBPK model structures, as they appeared in Merrill et al. (2005) and Clewell et al. (2007) for perchlorate and radioiodide were added to the report as Figures 1-1 and 1-2. Modifications to the model code did not alter the primary model structure shown in these figures, as originally published. However, the blood flow rates have been corrected to be blood plasma flow rates, rather than total blood flow rates, as described in detail in Appendix A, Section A.5.

Charge Question G3. ***Besides the specific parameters identified below, please comment on any other parameter or model choices described in the document that you think are incorrect or require further explanation or where other available information could provide better estimates.***

Comment G3-a: Two reviewers agreed with the U.S. EPA's parameter and model choices; one noted that the parameter values used by the U.S. EPA are supported by the literature. One reviewer stated that the methods used for scaling of clearance to body weight, age and surface area are appropriate; however, such scaling is most accurate when the substance is not reabsorbed or secreted. This reviewer recommended that the U.S. EPA consider alterations in NIS expression (Faggino et al., 2004) and whether other formulas could be used to more accurately reflect GFR in children and suggested two references (Check et al., 1977; Schrier, 2001). One reviewer declined to comment.

> Response G3-a: The PBPK models were originally developed to simply describe the alterations in NIS expression for different lifestages. A change in NIS expression is assumed to be described by a change in the NIS maximum velocity (Vmax) which is scaled by $BW^{0.75}$. Using allometric scaling of Vmax, there is greater activity per tissue volume at a lower BW. Faggino et al. (2004) describes the use of immunohistochemistry to compare NIS (and Pendrin) expression in children less than 12 years to children greater than 12 years, and shows a higher percentage of stained cells in younger children (with intensity of staining ~ constant across age). In fact, this is what one expects/predicts from allometric scaling as currently used in the model: higher activity/tissue volume with lower BW. However, histochemistry only provides qualitative information. Also, because Faggino et al. (2004) only reported data for children in two categories (less than or greater than 12 years), the published results could not be used to evaluate the appropriate shape for an age-dependent function. The NIS expression data in Faggino et al. (2004) are not sufficiently detailed (vs. age or BW) to quantitatively inform the age-dependence of NIS.
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> The Agency also evaluated Cheek et al. (1977) for information to describe GFR in children. Cheek et al. (1977) indicates that creatinine serves as an indicator of tissue mass, and specifically, clearance would scale with muscle mass. The current PBPK model calculates muscle mass, as a constant fraction of body weight (BW). Therefore, to simply replace BW with muscle mass as the explanatory variable on which scaling is based would simply result in a change in the multiplicative constants with no change in the model predictions. Cheek et al. (1977) also states that intracellular water (ICW) correlates linearly with muscle mass, provides data on individual age, BW and ICW, and points to an earlier reference demonstrating that relationship. If the relationship is direct proportionality, then the results in Cheek et al. (1977) for ICW could be used directly to correlate muscle mass with age—age being the independent variable in the PBPK model. Otherwise (i.e., if the relationship includes a non-zero constant term), these data would need to be combined with those of the earlier paper to obtain the correct relationship for muscle mass vs. age, and clearance could be varied in proportion to muscle mass changes with age.
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> The general trend indicated – muscle mass increasing as a fraction of BW with age – means that scaling urinary clearance in proportion to muscle mass would lead to a prediction of *lower* clearance per unit BW in children of all ages, which would increase

the predicted dose-response (risk) relative to the current model application. The magnitude of this change cannot be determined without a complete data analysis but is likely to be most significant in younger children, where the difference in percent muscle mass is greatest. In addition, Clewell et al. (2002, Crit. Rev. Toxicol., 32:329-389), citing a physiology textbook, show a table with skeletal muscle increasing from 25% of BW in neonates to 40% in adults, which indicates that scaling urinary clearance with muscle mass would give results qualitatively in agreement with the current ones, though with a more mechanistic basis.

The reviewer also provided a reference on scaling clearance with creatinine levels, but use of such a formula would require a relationship between age or BW and creatinine levels. The pages in the Schrier (2001) reference noted by the reviewer are in a chapter by Clark and Chantler and describe the correlation of GFR with height and creatinine. Since Cheek et al. (1977) indicates that creatinine is an index for muscle mass, such an approach would likely lead to the same results as directly correlating clearance with muscle mass or ICW. So, there does not appear to be additional value in also evaluating an explicit correlation with creatinine levels. Therefore, while the U.S. EPA does not dispute the suggestion that scaling clearance with muscle mass is preferable in general, no such change has been made since the data or specific, quantitative information that would lead to substantive changes in model predictions for perchlorate and iodide are not available.

Comment G3-b: One of the reviewers stated the value used for the residual milk volume seemed unrealistically high and provided information and references for consideration. This reviewer recommended that the U.S. EPA conduct a sensitivity analysis to decide if and how this issue should be addressed.

Response G3-b: See response to comment G2-a. The residual milk volume parameter (VMk) was further evaluated by the U.S. EPA. VMk was changed from 0.632 to 0.109 L based on data from Dewey et al. (1991), as suggested by the reviewer, and is discussed in detail in Appendix A, Section A.3.

Comment G3-c: One reviewer noted that focused data collection might facilitate the improvement of the partition coefficient (PC) values used in the model as well as the urinary clearance values for perchlorate and iodide.

Response G3-c: Considering variation in PC values between species is usually modest, it is unlikely that age-dependent changes within a species (humans) will be large enough to substantially alter model predictions. The U.S. EPA agrees that additional data on the variation in perchlorate and iodide urinary clearance among humans would be valuable.

Comment G3-d: One reviewer requested that the rationale for using the 90^{th} percentile value be provided in the report. The reviewer noted that this value seems to be used as an upper bound limit, although the U.S. EPA states in the document that this is not the case.

Response G3-d: Additional rationale for using the 90th percentile value was added to Section 3.3 and 4.3. While the 90th percentile water ingestion rate characterizes a high-end drinking water exposure, the model prediction is not considered to be an 'upper-bound' because of the use of mean or average lifestage parameter values.

Comment G3-e: One reviewer stated that the U.S. EPA's analysis partially addressed biological susceptibility and coexposures; however, the Agency needs to consider additional susceptible subgroups (i.e., those with clinical and subclinical hypothyroidism, the genetically predisposed, and those that are iodine deficient) and the coexposures with thiocyanate and nitrate.

Response G3-e: The U.S. EPA's Office of Research and Development (ORD) was tasked with evaluating the effects of perchlorate on radioiodide uptake in different human lifestages using the Clewell et al. (2007) and Merrill et al. (2005) PBPK models and as noted by the reviewer, the U.S. EPA has accounted for perchlorate coexposure through both food and drinking water. Evaluating the impact of coexposure to other iodide uptake inhibitors (e.g. thiocyanate or nitrate) was not within the scope of this analysis.

Additionally, terms to account for co-exposures to thiocyanate and nitrate would have to be added to the models developed by Clewell, Merrill, and colleagues, and appropriately parameterized to represent their interactions with NIS. At a minimum such terms would have to include estimates of internal concentrations of these compounds and binding or inhibition constants for their interactions with NIS. This degree of model revision is beyond the scope of the current effort, and the data necessary to set the requisite model parameters may not even be available.

Likewise the models have not been specifically parameterized to describe hypothyroid or iodine deficient individuals. While the figure provided by the reviewer may in some ways be qualitatively correct, accounting for the impact of iodide deficiency would require a knowledge of the degree to which NIS levels change in the deficient person and also would require an understanding of the significance or impact of a change in iodide uptake. The current knowledge of thyroid function is insufficient to predict the impact of such incremental changes. Additionally, there are many factors (e.g. production and metabolism of thyroid hormones) that could affect iodide kinetics in a hypothyroid state, thus adjusting the PBPK models to accurately predict effects in hypothyroid/iodine deficient individuals would likely require an extensive amount of additional data collection, research and model development beyond the scope of this analysis.

The U.S. EPA's rationale for not evaluating these subgroups was added to the document in Section 5.1.

Comment G3-f: One reviewer identified a need to develop and thoroughly test a consistent framework for modeling [urinary clearance] processes for different lifestages. The reviewer stated that correcting the inconsistencies, identified in Appendix B of the document, would be a first step towards implementing such a framework.

Response G3-f: A more detailed response is provided under comment A1-e below (section on urinary clearance). The primary inconsistency identified by the U.S. EPA

was that urinary clearance of iodide and perchlorate were varied independently, sometimes quite differently, when the mechanism by which they are cleared is presumed to be the same. Based on that assumed common mechanism, the U.S. EPA concluded that when iodide clearance is decreased by 60%, for example, perchlorate clearance should also be reduced by 60%. The changes in the model implemented by the U.S. EPA corrected all such inconsistencies.

The significant physiological changes occurring in the mother at childbirth could result in a significant change in clearance between pregnancy and the postpartum period, so no further "consistency" in treatment of clearance across lifestages was assumed.

Charge Question G4. ***Please discuss research that you think would be likely to increase confidence in these models and their use in predicting RAIU inhibition by perchlorate in different life stages (for an average individual within each life-stage).***

Comment G4-a: Three reviewers provided recommendations for future research including assessing the effect of perchlorate on the clearance of NIS substrates, studying the mechanisms of perchlorate inhibition of NIS, investigating the toxicity of NIS substrates in the presence and absence of perchlorate, estimating urinary clearances of environmental pollutants in infants and neonates, biomonitoring of perchlorate, iodide, thiocyanate and thyroid hormone during and after pregnancy and during lactation in smoking and no-smoking women, measuring perchlorate in non-composited baby formula samples, and studying renal clearance of iodine and perchlorate during pregnancy and postpartum.

Response G4-a: The U.S. EPA agrees that additional information would be valuable to future revisions of the PBPK models.

Comment G4-b: Two reviewers recommended that the Agency consider additional methods. One suggested a probabilistic sensitivity/uncertainty analysis and eventually the feasibility of population-based PBPK modeling. The other reviewer asked the U.S. EPA to consider the possibility of simulating iodine-deficiency (or hypothyroidism) in pregnant women.

Response G4-b: The U.S. EPA recognizes that a powerful aspect of PBPK models is that they provide an excellent framework for parameterizing and simulating the effects of population distributions in physiological, biochemical, and metabolic parameters; however, this is outside the scope of the current analysis.

The reasons why the models were not extended to describe hypothyroid or iodine deficient individuals were outlined above in G3-e.

Comment G4-c: One reviewer noted that if model output is sensitive to the residual milk volume parameter (see questions G2 and G3), confidence in the modeling could be increased by a better description of this parameter. Another reviewer stated that using real-world data like those from Blount et al. (2006) with the model would increase confidence, but acknowledged that the Blount et al. study does not include children ages 6 and younger. Another reviewer recommended evaluating newer estimates of renal function by Schwartz.

Response G4-c: The PBPK model output for the lactating woman and breast-fed neonates were not sensitive to the residual milk volume parameter (VMk) value; however, the parameter value was changed to reflect the data in Dewey et al. (1991) (as explained in responses G2-a and G3-b and discussed in detail in Appendix A, Section A.3.).

Blount et al. (2006) provide data relating urinary levels of perchlorate to changes in T4 and TSH. Since the model does not predict T4 and TSH, these results could only be used qualitatively; i.e., if the urinary levels are converted to exposure rates, then the RAIU changes predicted over that range may be similarly significant. This would not provide significant support for the current analysis and was not explored further.

A paper for which Schwartz was the first author was not located; however, a recent publication by Work and Schwartz (2008) describes a clinical approach for measuring GFR in children, but it does not provide data that could be used to estimate values of GFR in children of different ages or BWs.

Comment G4-d: One reviewer recommended that the U.S. EPA state that the modeling effort is theoretical because it has not been validated; however, this reviewer suggested using existing data to help test the model predictions and validate the model. The reviewer noted that the U.S. EPA's report did not include information about concentrations of perchlorate and iodine in milk as a function of perchlorate dose and suggested reviewing Pearce et al. (2007) which provided the relevant information. The reviewer noted that without this information it is impossible to determine whether the U.S. EPA's results are consistent with the literature showing no correlation between perchlorate and iodine in breast milk samples.

Response G4-d: The model does predict inhibition of radioiodide transfer into breast milk, although those specific predictions were not included in the report. Pearce et al. (2007) showed no significant reduction (trend) in breast-milk iodide with perchlorate exposure, which is qualitatively in agreement with model-predictions, where inhibition of transfer to breast milk was found to be no more than a few percent – low enough to be insignificant relative the amount of variability in breast-milk iodide. The U.S. EPA plotted model predictions against the data of Pearce et al. (2007) to more clearly demonstrate the level of agreement between the two sets of results. This is now described in section 4.1.1.2 and shown in Figure 4-2 of the document.

Comment G4-e: One reviewer noted that the models use arterial plasma concentration and whole blood flow rates and recommends either the influx in all mass balance equations should correspond to whole blood concentrations or the flow rate should correspond to plasma flows. The reviewer suggested evaluating the assumption to see whether this change would have any consequence.

Response G4-e: As the reviewer suggested, plasma flow, instead of blood flow, should have been used to describe delivery of perchlorate and radioiodide to the tissues in conjunction with the concentration of perchlorate or radioiodide in the plasma. Cardiac output (total blood flow) was adjusted to reflect plasma flow by multiplying by the plasma:whole blood volume ratio (PBratio=Volume_of_Plasma / Volume_of_Blood =

~0.557), thereby decreasing the flow to the tissues. This had a minimal impact on model output within the experimental error for the average adult (at 7 μg/kg-day changed from 2.1% RAIU inhibition to 1.6%); however, the use of plasma flow was retained to increase physiological accuracy of the model. A description of this change was added to Appendix A, Section A.5.

Charge Question G5. ***Does EPA accurately characterize the strengths and limitations of the analysis? Please comment on any particular strengths that may not be mentioned or adequately characterized for the estimates of RAIU for different life stages. Please also comment on any specific sources of uncertainty that you believe have been overlooked in EPA's analysis or that require further discussion, and which might be significant to EPA's estimates of RAIU for different life stages.***

Comment G5-a: Four reviewers indicated that the U.S. EPA adequately characterized the strengths and limitations. One of these reviewers suggested that the U.S. EPA's modeling analysis could be improved by including comparisons of the model simulations to experimental data. Another reviewer agreed that the strengths and weaknesses of the analysis were adequately highlighted but noted that the limitations associated with the lack of validation were not addressed.

Response G5-a: Section 4.1.1 was added to include several comparisons of model predictions with published data.

Comment G5-b: Two reviewers did not specifically address whether the characterization of strengths and weaknesses was adequate. One reviewer identified the explicit listing of unresolved issues and inconsistencies in the modeling as the main strength of the analysis and description in the document. This reviewer listed the main limitations as the use of point estimates rather than a distributional approach to characterize exposures, the emphasis on "average" individuals rather than populations, and the lack of consideration of NIS inhibitors other than iodide and perchlorate. The other reviewer considered use of the PBPK model to assess life-stage sensitivity, use of the fetus to evaluate relative sensitivity, and consideration of relevant route/source of exposure as strengths of the analysis, whereas the exclusion of certain subgroups (e.g., the elderly, early gestation fetuses, iodine-deficient or hypothyroid pregnant women) and not considering parameter value variability within subgroups were weaknesses.

Response G5-b: The reviewers note observations about the limitations and weaknesses in the analysis of lifestage relative sensitivity of percent inhibition of thyroid radioiodide uptake using the Clewell et al. (2007) and Merrill et al. (2005) PBPK models. These observations and suggestions by the reviewers would provide for a strong population analysis, coexposure analysis, or analysis of other potentially sensitive subgroups (e.g. elderly, early gestation fetuses, iodine-deficient, or hypothyroid individuals). Incorporating these suggestions into the analysis would expand the scope of the lifestage comparison, but would not directly strengthen the current approach examining "average" individuals in the subgroups. Additional work beyond the scope of the current exercise and data collection would be necessary to improve upon the weaknesses mentioned by

the reviewers. For example, to accurately predict effects of perchlorate in populations exposed to other iodide uptake inhibitors would require additional PBPK models for the compounds of interest and additional data on the potential variability of parameters across populations would need to be obtained. Currently, urinary clearance is the only parameter for which we had sufficient data to test model sensitivity to several biological plausible values.

Comment G5-c: One reviewer recommended conducting an uncertainty analysis to look at the implications of using direct IV dose of radioiodide (rather than oral ingestion) for bottle-fed infants to determine iodide uptake inhibition.

Response G5-c: The models as developed by the authors were not intended to simulate the effect or to estimate the impact of perchlorate on inhibition of dietary iodide uptake, nor are the models capable of describing the large mass flux of dietary iodide. Additionally, the model developers (Clewell and Merrill) primarily used IV doses of radioiodide because the data in literature available on perchlorate's effect on thyroidal iodide uptake was predominantly from radioiodide given as an IV dose. This was maintained for all lifestages (except breast-fed infant) in this analysis to provide for determination of relative lifestage sensitivity. The Agency did not simulate an IV dose of radioiodide to the breast-fed infant, but rather accounted for the diminished amount of iodide the infant would receive through breast milk. This approach was used to also reflects a decrease in the external dose of iodide that a breast-fed infant would receive. For all other lifestages, perchlorate is assumed not to reduce the external dose of iodide.

Comment G5-d: One reviewer recommended additional discussion of the limitations of focusing on "healthy" individuals and of not considering large susceptible populations, and adding a scenario analyses to ascertain inhibition levels for plausible cases of higher susceptibility.

Response G5-d: A discussion of why the U.S. EPA focused on "average" or "healthy" individuals was added to Sections 5.1 and 5.2. Data are lacking to derive model parameters and validate model predictions of radioiodide uptake inhibition for individuals that may potentially be more susceptible. See response to G3-e for more detail regarding susceptible subpopulations.

Charge Question G6. ***As recommended in EPA's 2000 Risk Characterization Handbook, is the analysis transparent in terms of the steps, logic, key assumptions, limitations, and decisions? Specifically, does characterization of the results of EPA's work fully explain: a) the analysis approach employed; b) the use of assumptions and their impact on the analysis; c) the use of extrapolations and their impact on the analysis; d) plausible alternatives and the choices made among those alternatives; e) the impacts of one choice vs. another on the analysis; f) significant data gaps and their implications for the analysis; g) the scientific conclusions identified separately from default assumptions and policy decisions, if any; and h) the major conclusions, and the discussions of EPA's confidence and uncertainties in the conclusions?***

Comment G6-a: All reviewers agreed the analysis complied with the Risk Characterization Handbook and was transparent. Two reviewers recommended adding a separate section with a summary of the limitations and uncertainties, one of these reviewers also recommended adding lists of the data gaps and of the major perceived weaknesses. One reviewer recommended clearly listing plausible alternatives for some of the parameters and how these alternatives will affect the model.

> Response G6-a: A separate section (5.2) was added to the document that specifically addressed the limitations and uncertainties of the PBPK modeling. Alternatives and effects on model output for urinary clearance parameter estimates were listed in Table 4-2 of the document. No other alternatives were tested due to lack of information for possible alternatives.

Comment G6-b: One reviewer questioned the availability of additional data in the literature that could be used to further validate the model.

> Response G6-b: The U.S. EPA agrees that the existing data provide only limited potential for validation and additional data would be beneficial.

Comment G6-c: One reviewer stated that some of the justifications in the document are weak, especially with respect to inconsistencies in modeling urinary clearance processes. The reviewer acknowledged that correcting the inconsistencies may not substantively affect the calculated outcomes but a fully defensible model should incorporate up-to-date scientific information and assumptions that are consistent across lifestages.

> Response G6-c: As stated in responses above, the U.S. EPA identified and corrected inconsistencies in the treatment of urinary clearance, where possible. The U.S. EPA determined that the current approach is appropriately consistent with the assumed mechanisms and known differences in urinary clearance of perchlorate and iodide, and generally known changes in renal function across ages and lifestages.

Comment G6-d: One reviewer suggested clarifying why the elderly and teens were not included in the subgroups and why the results of the analysis are also applicable to chronic exposure situations. This reviewer recommended the U.S. EPA provide justification for the choice of 24-hr RAIU, and not 24-hr AUC (area under the plasma concentration versus time curve), as the endpoint and further discuss the sensitivity of key input parameters as a function of age to the use of a single RAIU value in infants and adults.

> Response G6-d: The NRC (2005) noted that fetuses, infants, and developing children are the most sensitive lifestages. When exposure from food and water is considered, infants and young children receive relatively higher doses than adults and fetuses. Thus, EPA chose to focus on these groups, as well pregnant and lactating women. Available data do not indicate that the elderly and teens are relatively more sensitive or highly exposed when compared with other lifestages. The results of this PBPK analysis are applicable to

chronic exposure situations because the perchlorate pharmacokinetics are such that steady-state is reached within a few days to a week. Longer-term changes in physiological variables associated with aging will result in changes in perchlorate pharmacokinetics, but those longer-term changed are largely bracketed by the specific ages and situations considered in this analysis. The National Academy of Sciences (NRC, 2005) concluded that if the perchlorate exposure is sufficiently low that the acute effect of RAIU inhibition is kept safely below the identified NOEL, then the risk of chronic exposure to perchlorate will be minimal. The U.S. EPA considers it unlikely that, at the levels of inhibition which occur at the RfD, there will be a cumulative long-term effect.

Justification for using 24-hr RAIU inhibition as the dose metric was added to the introduction (Section 1). Briefly, the series of PBPK models developed by Merrill and Clewell used RAIU inhibition as the primary dose metric. 24-hr RAIU inhibition was the dose metric chosen by EPA as opposed to a 24-hr AUC of perchlorate because the amount of RAIU inhibition was defined as a precursor to a critical effect and as the point of departure for the derivation of the RfD.

Comment G6-e: One reviewer recommended additional discussion on the forms for statistical fits, the use of 90th percentile versus mean values for parameters, the failure to address certain large susceptible populations, and the use of the GW 40 fetus. This reviewer requested more quantitative and rigorous treatment of uncertainty.

Response G6-e: Use of GW 40 fetus was described in G1-c response and text was added to the document in Section 4.2. The rationale for the use of 90th percentile for water ingestion was detailed in responses (G3-d, B1-d, C1-e, and C2-d) and additional rationale was added to Section 4.3 of the document. A discussion of other susceptible subgroups and the challenges in using the current PBPK models to evaluate these subgroups was added to Section 5.1 of the document.

Parameter-Specific Charge Questions

A. Urinary Clearance

Parameter-Specific Charge Question A1: ***Please comment on the appropriateness of the input values selected for maternal urinary clearance during pregnancy and lactation in EPA's analysis. Are the available data and rationale for the values selected transparently and objectively described? Are you aware of other publications or data that could be used to guide these choices or which provide alternative input values that are equally valid or more appropriate? Likewise, are the values selected for urinary clearance for the infant and older child the best estimates, given the available science and data? Are there other data that would provide better (or equally valid alternative) guidance or estimates? Is there any reason to believe that urinary clearance might not be a limiting factor in the elimination of perchlorate for infants?***

Comment A1-a: Regarding maternal urinary clearance, seven reviewers agreed that the input values were appropriate. The other reviewer disagreed with the rationale for the maternal

urinary clearance values but agreed with the value used for the lactating mother. This reviewer asserted that the available human data, which shows no measurable or consistent difference in urinary clearance between pregnant and non-pregnant women, should be used.

Response A1-a: The discussion of urinary clearance in the primary document has been expanded (Section 3.1) to more fully explain the U.S. EPA's rationale for selecting the urinary clearance rates used. Information is limited to derive maternal (during pregnancy and lactation) and infant clearance values; thus given the available information, the U.S. EPA believes the values used to be both appropriate for sensitive individuals and within the range of biological realism.

The available data and information are inconsistent and not clear to determine urinary clearance of perchlorate and iodide during pregnancy. General information on the clearance of metabolized compounds is considered a weak indicator for potential changes in iodide and perchlorate clearance because different mechanisms are involved.

Also, since clearance is the ratio of the urinary excretion rate to blood concentration, it is entirely possible for excretion to remain approximately constant, or even increase, while clearance is decreased. On average, excretion of iodide must equal its ingestion rate, independent of how clearance may vary. So, data in humans which show little or no changes in the clearance of other compounds, or little or no changes in iodide *excretion,* may still be consistent with a decrease in the urinary clearance of iodide and perchlorate. The PBPK modeling in rats, however, showed a decrease in the clearance of both perchlorate and iodide (both decreasing approximately the same amount).

Finally, while Aboul-Khair et al. (1964) measured iodide clearance directly, the methods used to measure blood iodide levels at that time were not the methods used to generate the more recent data available for rats. Thus the evidence for each of the three urinary clearance rate possibilities has both strengths and weaknesses, and the U.S. EPA concluded that none of the three was clearly superior. The U.S. EPA is not aware of newer data for urinary clearance of iodide or another entity with a similar clearance mechanism (e.g., bromate) that it could have used for pregnancy in humans.

Comment A1-b: Five reviewers specifically noted that the data and rationale were transparently and objectively described. One reviewer stated that the clearance rate choices for the mother during pregnancy and lactation were arbitrary and the rationale was not provided. One reviewer suggested the U.S. EPA improve the discussion of maternal urinary clearance values, and one reviewer also questioned the curve fit and data shown in Figure B-6.

Response A1-b: Additional explanation of the rationale for U.S. EPA's choice of maternal urinary clearance values has been added to Section 3.1. A general statement on the approach used for curve fitting was added to Section 3 (see response to comment G1-d) to address the reviewer's comment about Figure B-6.

Clewell et al. (2007) had estimated reduced urinary clearance of perchlorate during lactation (based on lactational rat:average adult differences) but assumed that iodide clearance was unchanged from the average adult. The U.S. EPA considers this option to be inconsistent, since changes in renal function that reduce perchlorate clearance are likely to have a similar effect on iodide clearance. Therefore this option

was not considered a plausible alternative for use during lactation. Further, the male rat PBPK model (Merrill et al., 2003) used urinary clearance rate (CLUC) values of 0.07 and 0.05 L/hr/kg$^{0.75}$, respectively, with virtually identical values in lactating rats (0.07 and 0.06 L/hr/kg$^{0.75}$, respectively; Clewell et al., 2003). Thus, the application of a "parallelogram" approach to extrapolate the rat results to humans indicates that clearance during human lactation should be the same as for the average adult (male) human, rather than having *both* perchlorate and iodide clearance reduced from the average adult, as was indicated during pregnancy. Therefore, the existing data support only two options for perchlorate and iodide clearance during lactation: increased clearance relative to the average adult, based on the results of Aboul-Khair et al. (1964) and equal clearance relative to the average adult, based on the PBPK modeling in rats. The U.S. EPA considers the two alternatives to have equivalent likelihood. Given this uncertainty, the U.S. EPA then chose the lower clearance (more sensitive) option: clearance equal to that of the average adult. Alternatives for clearance during lactation differ from pregnancy because the rat-based PBPK results do *not* indicate reduced clearance during lactation as they did for pregnancy; thus, reduced clearance during lactation was not considered for the lactating women subgroup.

Regarding Figure B-6, since use of the PBPK model versions for pregnancy and lactation involve integrating exposure and dosimetry over the weeks from conception and/or birth, it is helpful to use a smooth function with a simple form which captures the primary time-dependent changes in the various parameters, including clearance. The U.S. EPA decided that it would be efficient and reasonable to only consider simple, non-mechanistic functions, balancing the desire to capture the primary time-dependent changes against the potential problems in identifying parameters that can occur with more complex equations. A quadratic equation appears to satisfy these criteria appropriately, and the U.S. EPA does not believe that more meaningful information could have been extracted with an alternate function form.

It is not clear whether the apparent "dip" in clearance observed late in pregnancy (week 36 vs. weeks 32 and 38) is due to real changes in clearance or if it is due to experimental variability and measurement error. Consequently, without a supporting biological mechanism, the U.S. EPA considers the current model, which captures the long-term trend although not the shorter-term variation, to be appropriate.

The post-partum data in Figure B-6 are also taken from Aboul-Khair et al. (1964) – the same post-partum data shown in Figure B-5 just above. From the Aboul-Khair et al. (1964) data and figure, it appeared to the U.S. EPA that there is an overall downward trend in clearance starting around GW 30 and continuing through birth into the post-partum period. So, the data were included to guide the quadratic curve-fit to capture that trend.

It is clear to the U.S. EPA that increased iodide clearance during pregnancy is widely believed to occur, and the data of Aboul-Khair et al. (1964) are consistent with that assumption. However iodide clearance, per se, can only be determined by simultaneously measuring iodide blood levels and urine concentration or excretion rate in the same individual, and the literature search conducted by the U.S. EPA only identified the Aboul-Khair et al. (1964) paper with clearance data. However, the review of DeLange (2004) questions that assumption and instead suggests that clearance does not change during pregnancy.

While GFR may be related to cardiac output (QC) in general, it seems likely that it is the rate of kidney perfusion (QK) that is the actual determining factor. As currently formulated the model *QK does not change* during pregnancy. Increases in QC primarily serve the developing fetus, uterus, and breast tissues.

Comment A1-c: None of the reviews identified other publications or data; however, one reviewer recommended obtaining data on differences in urinary clearance data outside the perchlorate and iodide literature, and another reviewer suggested obtaining additional data to cross check assumptions regarding iodide uptake and renal clearance during pregnancy and early postpartum. No specific references were provided.

Response A1-c: The U.S. EPA agrees that changes in clearance of other substances would be informative, provided that such clearance was GFR-mediated or -determined. The U.S. EPA did seek to identify such data but no additional data were found, and therefore no additional data were included in the document. It is noted that data on clearance of pharmaceuticals is often proprietary and therefore not readily available in the open literature. Also, many if not most pharmaceuticals have rates of clearance that are determined by metabolism that would not be appropriate for extrapolating in this case.

Comment A1-d: With respect to urinary clearance rates for the infant and older child, six of the reviewers agreed with the values used and none of the reviewers disagreed or suggested alternative values. One reviewer referred U.S. EPA to alternative guidance for urinary clearance in neonates, infants, and children but did not find any evidence to contradict the assumptions used. Another reviewer noted that the estimates used for urinary clearance in infants and children reflect published GFR values. One reviewer recommended emphasizing inter-individual variability in the discussion and describing it quantitatively.

Response A1-d: It is clear that an explicit analysis of inter-individual variation would be informative. See response to G3-a for a discussion on possible alternate approaches to estimating clearance rates.

Comment A1-e: One reviewer identified inconsistencies to be clarified, particularly with respect to scaling, and areas for future research, e.g., a consistent treatment of the urinary clearance process for various life stages.

Response A1-e: The U.S. EPA's goal was to assure consistency in handling iodide and perchlorate clearance. A clarification was added to the beginning of Section 3. For example, when considering reduced clearance during lactation, if iodide clearance was reduced by 60% then the U.S. EPA also reduced perchlorate clearance by 60%. In this regard the U.S. EPA was indeed consistent in changing the perchlorate and iodide clearance parameters. However, Clewell et al. (2007) reduced perchlorate clearance during lactation 60% from the "average adult" value found by Merrill et al. (2005), but did *not* reduce iodide clearance. The U.S. EPA chose not to consider that option as it appears inconsistent.

On units of clearance, when simulating an individual the rate of urinary clearance of "x" is:

$$RAU_x \text{ (mg/hr)} = CLU_x \cdot CVK_x,$$

where the (scaled) clearance constant, CLU_x, has units of L/hr (equivalent to volume of blood cleared per time), and CVK_x is the concentration in the kidney venous blood and has units of mg/L. Thus the units of the clearance rate (RAU), clearance constant (CLU) and blood concentration are all consistent.

However, as is often the case in PBPK modeling, the clearance rate constant is assumed to scale allometrically, by $BW^{0.75}$, and is therefore defined as:

$$CLU_x \text{ (L/hr)} = CLUC_x \cdot BW^{0.75}.$$

In fact this equation defines $CLUC_x$ and in no way contradicts the physics of the problem, which is appropriately represented by the equation for RAU. Further, given the units of CLU as shown, and that BW has units of kg, it follows that the units of CLUC *must be* $L/h/kg^{0.75}$. Since the model code describes urinary clearance using these two equations, with $BW^{0.75}$ scaling, it follows that the listing of CLUC by Clewell et al. (2007) and Merrill et al. (2005) as having units of L/h/kg is a simple typographical error.

The U.S. EPA does not believe that the document will be improved by including this exposition, since the key points area already included, so no changes have been made.

Furthermore, the U.S. EPA considers use of $BW^{0.75}$ to be a good rule-of-thumb, both for scaling across species and among individuals within a species, in the absence of other data. However, very young children are not the same as small monkeys (despite euphemistic references) and even the data for basal metabolic rate variation across species shows scatter around the primary allometric relationship that cannot be completely described by a simple power function. Therefore species- or substance-specific data may well depart from this general relationship, and therefore we choose to use the more specific data over the generality when such data are available. The suggested paper by Johnson (2008) provides data which strongly indicate a departure from this scaling in neonates, which supports the use of clearance data in human children that departs from this relationship.

Regarding the "GFR-based scaling" in Figure B-2, this scaling is defined by equation B3, not B1 as the draft document erroneously indicated. The scaling involves a combination of scaling by $BW^{2/3}$ to approximate dependence on body surface area (SA) and a correction factor, the specific growth rate (SGR), to account for the fact that infant excretion falls below what one would predict based on SA alone, with SGR being a function of infant age. Since there is variation in individual BW at any given age, when this function is applied to a set of individual data with known ages and BW, the result is not a smooth function of age but reflects the variation in BW with age. Appendix B, Section B.3 has been modified slightly to correct this error and clarify these points.

Comment A1-f: One reviewer requested clarification on Figure B-4 and for the statement that the U.S. EPA considers its urinary clearance estimates in infants and children to be scientific estimates and not bounds.

Response A1-f: General statements have been added to the Introduction (section 1) to explain the reasons and approach for describing population average behavior, and details about the handling of urinary clearance also have been added to section 3.1. In addition, the text under Figure B-4 has been expanded to include further explanation.

If the normalized Lloyd et al. (1985) data (yellow diamonds in Figure B-4) are simply taken as a collection of values, assumed to be independent of BW, then one can estimate a mean, standard deviation, etc. The "Lower 95% of Lloyd et al.(1985) " line is simply a horizontal line plotted at a y-value equal to lower 95% confidence limit on the mean of the data. The data average line is likewise determined by combining the normalized Lloyd et al. (1985) and Chin et al. (1982) data, irrespective of BW, calculating the average of those values, and plotting a horizontal line with that value.

The primary point of this plot is to show that, while the normalized data (Clu/BW values) show some downward trend with BW, the error between the data and assuming BW^1 scaling, which corresponds to the horizontal line (when normalized to BW) is not substantially worse than using $BW^{2/3}$ or $BW^{0.75}$. There is not a strong BW-dependent trend in the data such that one of the later scaling curves better describes the data, and in fact those two curves substantially over-predict clearance for many of the individuals (data points) shown.

The scaling used by the U.S. EPA corresponds to the "~ Adult average" line in the plot. As shown, this scaling comes quite close to the data average and is above the 95% confidence limit on the mean of the Lloyd et al. (1985) data. Thus, it is considered an estimate of the population average, rather than a (lower) bound.

B. Breast-milk ingestion

Parameter-Specific Charge Question B1. **Infants are generally known to consume very little milk or formula on the first day of life, with ingestion quickly increasing over time. However the first time-point for which ingestion data are available for infants is at 7 days, which EPA extrapolated back to 0 ingestion at time=0 in its analysis (birth; Figure 1). The breast-milk ingestion rate was estimated based on mean values reported in Arcus-Arth et al. (2005), while the water ingestion used for the breast-feeding mother was the 90th percentile value from U.S. EPA (2004).**

Is EPA's extrapolation and rationale transparently and objectively described? Does this function appropriately characterize the available data and information? Are there other data that could be used to obtain a better or equally valid alternative estimate of mean breast-milk ingestion rate for infants in the first few days of life? Should an estimate other than the mean be used to determine the breast-milk ingestion rate?

Comment B1-a: None of the reviewers disagreed with the U.S. EPA's extrapolation. Five reviewers explicitly stated that the U.S. EPA's explanation was objective, and three noted that it was transparent. One reviewer pointed out that the modeling of perchlorate and iodine kinetics

in the neonate is highly uncertain, making this one of the weakest parts of the analysis. The reviewer recommended that this uncertainty be more clearly articulated in the document. One reviewer noted that the characterization would be confusing for readers that were not modelers.

> Response B1-a: Additional discussion of the uncertainty surrounding model predictions for neonates and fetuses was added to the document (Section 5.2). The reviewer is correct that modeling of perchlorate and iodine in the neonate is more uncertain than the adult. No data are available for the validation of the percent RAIU inhibition in the neonate or fetus. However, a small amount of data available for neonates was compared to model predictions of urinary radioiodide excretion (Clewell et al., 2007 – Figure 9). In the fetus, data were available to compare with model predictions of thyroid and blood radioiodide (Clewell et al., 2007 – Table 3) and serum perchlorate (Clewell et al., 2007 – Figure 10).

Comment B1-b: None of the reviewers disagreed with the use of the data in Arcus-Arth et al. (2005). One reviewer suggested that there are data in the literature for intake on days 1, 2, 3, 4, and 5, and that the values on days 4 and 5 are consistent with what was reported in Arcus-Arth, et al. However, no specific additional references were provided. Another reviewer asked that the decision to use Arcus-Arth et al. be clarified.

> Response B1-b: Further explanation on the use of Arcus-Arth et al. (2005) was added to Section 3.3.1. Data for days 1-5 (tabulated in Arcus-Arth et al., (2005) and originally reported in Casey et al., (1986)), in addition to other data for the first two months after birth, were used to derive the equation for the breast-milk ingestion rate. This approach is described in detail in Section 3.3.1 of the document. Data reported by Arcus-Arth et al. (2005) were chosen as the most complete and most recent data available that could be used to derive breast-milk ingestion rates and that included data for very young infants. The Arcus-Arth et al. (2005) study was designed to represent the infant population whose mothers follow the American Academy of Pediatrics (AAP) recommendations. It was a meta-analysis using data from various studies in the peer-reviewed literature, and intake was calculated on a body weight basis.

Comment B1-c: Two reviewers agreed with the extrapolation from day 7 to day 0, while three expressed questions or concerns about it. One reviewer stated that the extrapolation was not warranted because the newborn was not a subgroup used in the assessment of relative sensitivity of lifestages. The second questioned the abrupt increase in milk ingestion during day 1 and between days 1 and 7; however, that reviewer concluded that the mean breast-milk ingestion rate might be robust enough for use. Another reviewer stated that the use of body weight as a surrogate for age is illogical and recommended developing an expression for milk ingestion in terms of volume per body weight per day as a function of age. That expression could then be used to convert to the model parameter for the milk ingestion rate.

> Response B1-c: As a result of reviewer comments, the U.S. EPA has moved from using a power function to relate BW to breast-milk ingestion to using a Hill-function that describes breast-milk ingestion as a function of age. This change is shown in Section 3.3.

Briefly, while the newborn infant (< 7 days old) was not explicitly considered in this analysis, it is necessary to describe breast-milk ingestion the first 7 days of life as accurately as possible because the perchlorate ingested during this timeframe affects the %RAIU inhibition at 7 days of age, the neonate age that was first considered in this analysis. Additionally, the data tabulated in Arcus-Arth et al. (2005) for these few days after birth were first reported in Casey et al. (1986). Using these additional data, (now included in Figure 3-1), a Hill-function describing breast-milk ingestion rate (mL/hr) as a function of age (days) was derived and used in the PBPK model in place of the initial U.S. EPA power function relating BW (kg) to breast-milk ingestion (mL/hr). The Hill-function is a better predictor of the data, especially during the first 7 days after birth, than the table function originally implemented in the model by Clewell et al. (2007) and was easily implemented in the PBPK model code.

Comment B1-d: Two reviewers questioned the use of a mean value for infants and recommended further explanation of the rationale. One reviewer stated that using the 90th percentile for intake would lead to an unrealistically high estimate for milk consumption. Another reviewer thought that if the purpose was to determine the relative difference in iodide uptake inhibition for various subgroups, then the mean should be used consistently for all exposure and pharmacokinetic parameters throughout the analysis. Two reviewers recommended better accounting for variability. One noted that whether the mean should be used depends on steps later in the process and how variability is considered. This reviewer added that using mean values and the approach to computing the milk ingestion rate parameter precluded a fuller description of variability in iodide uptake inhibition. The other reviewer recommended using a distributional rather than a point calculation approach due to the large population above the 90th percentile and the potential "spread" of exposure factors above that percentile.

Response B1-d: The relative sensitivity analysis reported in Table 4-3 was conducted using a fixed dose-rate, 7 μg/kg-day, rather than any particular water ingestion value. The subsequent analysis (Table 4-5) where % RAIU inhibition is estimated for each lifestage does use upper percentile ingestion rates because the U.S. EPA's intent is to protect the entire population. However, as now stated in section 3.3 ("Post-natal PBPK Modeling") an average ingestion rate is used for breast-milk ingestion because in that case the neonate's exposure to perchlorate is due to the mother's ingestion, and an upper bound is used for the mother's ingestion. Assuming that the infant's ingestion of breast milk and the mother's ingestion of tap water vary independently, using an upper bound for both would be using a "double" upper bound for this lifestage alone, and therefore inconsistent with the bound used for other lifestages. Considering the breast-feeding mother and child as a unit, breast-milk ingestion may be thought of as an "internal" flow, for which the model represents the biological average rather than a distribution.

The U.S. EPA selected the 90th percentile drinking water intake value for most of the subpopulations evaluated in this report in order to explore the potential effects of high end exposure to perchlorate from public water systems. The approach is consistent with the Agency's *Guidelines for Exposure Assessment* (1992) and with the U.S. EPA policies and procedures for deriving health based drinking water values including Maximum Contaminant Level Goals (MCLG), Health Advisory values (HA), and Health Reference

Levels (HRL). The U.S. EPA acknowledges that modeling a complete distribution of water ingestion would be informative; however, due to time and data constraints the U.S. EPA selected a high-end exposure estimate as the most appropriate means to explore the potential effects of drinking water exposure on subpopulations.

The U.S. EPA does not believe that using mean drinking water intakes would characterize the high end exposures to perchlorate that may occur as a result of drinking water consumption. Similarly, the use values in excess of the 90th percentile would be inconsistent with the Agency's policy to focus on realistic exposure scenarios and to avoid worst-case scenarios. The U.S. EPA further notes that less than one percent of public water systems reported detecting perchlorate at concentrations greater than 15 μg/L. Therefore, by evaluating populations consuming the 90th percentile of drinking water with concentrations of perchlorate at 15, 20 and 24.5 μg/L, the U.S. EPA is providing a realistic high-end exposure estimate. See also the response to comment C1-c.

The primary points from this explanation have been added to Section 4.3.

C. Water ingestion

Parameter-Specific Charge Question C1. **For pregnancy, EPA used a normalized (90th percentile) water ingestion rate of 33 mL/kg-day (U.S. EPA 2004), which was multiplied by the maternal BW as described by the PBPK model growth-functions during pregnancy to obtain total water ingestion for the mother.**

Is EPA's approach and rationale transparently and objectively described? Is this approach appropriate for characterizing the upper-bound for ingestion of pregnant women? Are there other approaches or data that could be used to obtain a better or equally valid alternative estimate for this parameter? (Note that the self-reported body weight values in U.S. EPA (2004) indicate the same average body weight for pregnant women as for non-pregnant; data appears inaccurate, so the PBPK model body-weight description was used instead.)

Comment C1-a: Four reviewers agreed with the U.S. EPA's approach, and three reviewers explicitly stated that the approach was objectively described and transparent. One reviewer noted that the water ingestion was not extensively discussed and questioned if modifications were made to the variable in the Clewell et al. model. One reviewer stated that the U.S. EPA was inconsistent in choosing upper bounds or means for various parameters and thought that if the purpose was to determine the relative difference in iodide uptake inhibition for various subgroups, then the mean should be used consistently for all exposure and pharmacokinetic parameters throughout the analysis. One reviewer recommended a distributed zonal analysis rather than point calculations.

Response C1-a: See response to B1-d. Additionally, Clewell et al. (2007) did not describe water ingestion rates explicitly, but rather utilized constant dose rates (mg/kg-day), thus the water ingestion variables added by the U.S. EPA were new. As noted above and already clearly stated in the document, relative sensitivities were evaluated at a fixed dose-rate 7 μg/kg-day. Using such a fixed dose-rate provides a consistent basis for

evaluating relative sensitivity. The dose-rate might otherwise be calculated as the product of the water ingestion rate and water concentration, but for the relative sensitivity analysis it was set directly.

Comment C1-b: Four reviewers requested further explanation for how the 90th percentile value was derived and why it was used. Two of these reviewers recommended explaining why the 90th percentile value, rather than other values (such as the median or 95th percentile), was chosen for the computations.

Response C1-b: See response B1-d.

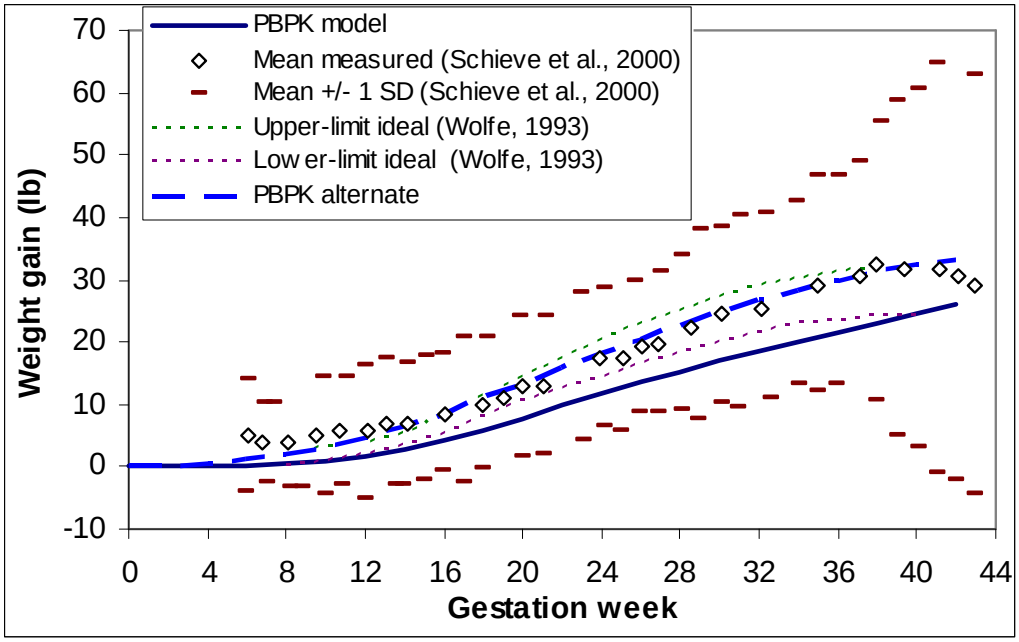
Comment C1-c: Two reviewers noted that the 90th percentile value was associated with a relatively small sample size (n = 65). One reviewer suggested this may be an underestimate and questioned the importance of the assumption and the sensitivity to the results. The other reviewer suggested using ingestion rates from Ershow et al. (1991), or to justify why they should not be used. This reviewer also questioned why the U.S. EPA specified total water ingestion rate but actually used the community water ingestion rate.

Response C1-c: The U.S. EPA selected community water ingestion for the analysis to characterize the high end exposure to perchlorate from public water systems (as opposed to bottled water or private well water which is captured in the total water ingestion). For a regulatory action under SDWA, the U.S. EPA's interest is in the impact of perchlorate in direct and indirect water. The reviewer is correct and this correction to the text has been made, as the analysis reflects that focus and that portion of water intake only. The U.S. EPA believes Kahn and Stralka (2008) and U.S. EPA (2004) are more recent and more appropriate data by which to evaluate the sensitive subpopulations of concern than is Ershow et al. (1991). The data from Ershow et al. (1991) were derived using data from the 1977-78 USDA Nationwide Food Consumption Survey, which is now 30 years old. . See also the response to B1-d.

Comment C1-d: One reviewer questioned the accuracy of the model growth-functions during pregnancy for estimating the body weight of pregnant women and suggested the U.S. EPA validate the weight estimates using NHANES data.

Response C1-d: While the CDC collects data on maternal weight gain and other health indicators for pregnancy, these appear to be just reported as total weight gain (from conception to just before birth), reported in the form of percent of population falling into various categories ("Under weight", "Normal weight," etc.), and do not include information on specific growth. However Schieve et al. (2000) reports BW gains during pregnancy from data for 3,511 mother-infant pairs from the 1988 National Maternal and Infant Health Survey, and Wolfe (1993) provides "upper-limit" and "lower-limit" values for ideal weight gain during pregnancy. Model-predicted BW gain is plotted against these published values below (the solid, dark-blue line is with the original model; the long-dashed, light-blue line is with PBPK model growth curves adjusted upward; the

mean and mean ± 1 SD are data from Schieve et al. (2000), and the "Upper/Lower-limit ideal" are from Wolfe (1993)).



Except for the apparent plateau in the data starting around GW 38, the shape of the model growth curve matches the observed growth curve quite well. While the curve falls somewhat below the observed mean (Schieve et al., 2000), it is well within one standard deviation of the mean, and since these were data not used in specifying the model, the agreement appears to be quite good.

Note that the data for the last few time points represent women who had not already given birth by that point; e.g., women who gave birth at GW 40 would not be included in the population represented at GW 42. So, the apparent plateau should not be construed as meaning that an individual woman's body weight would plateau or begin to decline in the last few GWs, but likely indicates that women who had the highest increase in BW by GW 38 (when the peak in the mean value occurs) gave birth in that week and so were not included in the population analyzed at later weeks. Since there is a tendency to induce labor before the child becomes too large to be safely delivered, the downward trend is then explained as a population shift, whereas the model growth-curve represents the change in a particular individual.

Finally, to test the sensitivity to BW, an alternate model version with the growth curve shifted upward was tested and compared to the original model. RAIU inhibition was evaluated at GW 40, given an exposure to 7 µg/kg-day (the POD). With the model as specified by the authors the RAIU inhibition predicted for the mother and fetus were 6.10 and 11.0%, respectively, and with the BW increased to better match the observed mean, the model predicted 6.14 and 11.1%, respectively. Thus the sensitivity of model predictions to changes in this range is negligible.

This information and figure were added to Section 4.1.1.1, Figure 4-1.

Comment C1-e: One reviewer recommended considering other approaches for estimating water ingestion for pregnant women. One suggestion was to consider water requirements for women in hot climates and choose a value somewhat above the 3.0 L/d considered an "adequate intake" by the Institute of Medicine (2004). The other suggestion was to pick a plausible upper bound from a cumulative distribution, and the reviewer offered that a value between 3.5 and 4 L/d seemed reasonable.

> Response C1-e: See response B1-d. The U.S. EPA recognizes that many women also drink bottled water and other beverages, for which any contribution to perchlorate exposure would be included in the "TDS" value. Thus the actual tap water ingestion is likely to represent only a fraction of the liquids ingested. Further, the U.S. EPA's objective is to estimate *actual* tap water ingestion in the U.S. population and the U.S. EPA believes the values currently used in the document are representative of the U.S. population exposure to tap water.

Parameter-Specific Charge Question C2**. For lactation, EPA used a fixed total (90th percentile) water ingestion rate of 2959 mL/day (U.S. EPA 2004), with the rationale that while the woman's weight and self-water demand are expected to drop after pregnancy (as described by the PBPK model time-dependent weight equations), the demand for milk production would be increasing, and the reported value was not for a specific age-range of child.**

Is EPA's approach and rationale transparently and objectively described? Is this an appropriate value to use for the ingestion rate of lactating women? Are there other better or equally valid alternative approaches or values that could be used?

Comment C2-a: Six reviewers agreed with the U.S. EPA's approach and five of these stated that the approach was transparent and adequately described. One reviewer requested clarification of the objectives of the analysis and reiterated that, if the purpose is to determine the relative difference in iodide uptake inhibition for different subgroups, then the mean should be used consistently for parameters throughout the analysis to avoid bias. One reviewer suggested that a probabilistic analysis would provide further insight and that a population/distribution-level analysis could be used to test the model in relation to data from Pearce et al. (2007) and Kirk et al. (2005, 2007).

> Response C2-a: The fixed ingestion rate of 7 μg/kg-day was used evaluating relative sensitivities, which is consistent in that the results show the differences in biological sensitivity, rather than differences due to changes in ingestion rates. As described in Response G1-a, sufficient data on NIS distributions that would be needed for a probabilistic analysis are not available at this time and the task of collecting and integrating the requisite information is beyond the scope of the current effort. The objectives of this analysis were elaborated upon in Section 1 of the document as well as

rationale for obtaining model predictions for the average individual, but using 90th percentile water ingestion, in each subgroup.

Comment C2-b: One reviewer questioned why the ingestion rate was substantially higher during lactation than pregnancy and recommended adding rationale for using a fixed ingestion rate. Another reviewer requested a better explanation for why a fixed ingestion rate was used, given the higher ingestion rate in lactating women on a mL/kg-day basis.

Response C2-b: As reported in Tables 6.3A-C in U.S. EPA (2004), the water ingestion rate of a lactating mother is greater than that of a non-pregnant or pregnant woman. This analysis reflects the recent data collected such that the water ingestion rate for the lactating woman (2.96 L/day) is greater than the non-pregnant (0.032 L/kg-day x 66kg = 2.11 L/day) and pregnant woman (0.033L/kg-day x 69-78kg = 2.18-2.57 L/day). Furthermore, instead of adjusting the lactating mother's water ingestion based on BW, which would decrease over time as the mother lost her weight gained during pregnancy, the water ingestion rate was kept constant. It is not known how the lactating mother's water ingestion changes over the first few months after giving birth. While it is possible that the mother's water ingestion may simply drop in proportion to her body weight, the U.S. EPA also considered the possibility that as the growing infant ingests an increasing volume of milk this would offset the reduced water consumption that would otherwise be expected to accompany a reduction in body weight. Therefore total water ingestion was kept constant, in the face of this uncertainty. This assumption leads to a higher predicted perchlorate dose, and hence effect, than if the mother's ingestion were assumed to decrease with her body weight.

Comment C2-c: Three reviewers questioned the use of the 90th percentile rather than the 95th percentile and asked for further explanation. One reviewer was concerned that a large number of mother-infant pairs are above the 90th percentile. Another reviewer suggested the U.S. EPA provide the rationale for selecting 2,959 mL/day at the 90th percentile and thought that providing the complete distribution of the water ingestion estimates would be helpful. The third reviewer asked why the U.S. EPA specified total water ingestion but used direct and indirect community water ingestion. This reviewer, noting the small sample size for the current value, also recommended using ingestion rates from Ershow et al. (1991), or justifying why they should not be used.

Response C2-c: See response B1-d.

Comment C2-d: One reviewer acknowledged that there are few data on the water needs of lactating women but presented the IOM (2004) argument that the intake of non-pregnant women added to the fluid output in breastfeeding provides a reality check on water ingestion rate. This reviewer recommended considering other approaches for estimating water ingestion for pregnant women. One suggestion was to consider water requirements for women in hot climates and choose a value somewhat above the 3.8 L/d considered an "adequate intake" by IOM (2004). The other suggestion was to pick a plausible upper bound from a cumulative distribution, and the reviewer offered that a value around 4 L/d seemed reasonable.

Response C2-d: See responses C1-e and B1-d.

The U.S. EPA seeks to identify a reasonable upper bound on tap-water consumption by women in the U.S. This ingestion rate may be less than an "adequate" intake, especially for women of warmer climates, since most of the U.S. has a moderate to cool climate and most people ingest beverages in addition to tap water to fulfill their water needs.

Breast-milk ingestion rises to an average of 25 ml/hr or 0.6 L/day in the first couple of weeks after birth, and continues rising to about 30 ml/hr or 0.72 L/day by 2 months. This is somewhat less than the exposure estimate change from 2.57 L/day for the GW 40 mother to 2.96 L/day for the lactating mother, but since a significant portion of breast milk will be lipids, an increase of 0.4 L/day appears appropriate.

Parameter-Specific Charge Question C3. **For bottle-fed infants, EPA made extrapolations of the 90th percentile water-ingestion in early life based on measurements made for the age ranges: 0-30 days, 1-3 months, and 6-12 months (points in Figure 2, upper panel). For the purposes of this analysis, bottle-fed implies feeding with formula requiring the addition of water.**

Is EPA's extrapolation and rationale transparently and objectively described? Does the overall function used to represent the changes in ingestion with age (and body weight) appropriately characterize the available data and information? Are there other data that could be used to obtain a better or equally valid alternative estimate of water ingestion rate for infants in the first few days of life (e.g., 7-day old)? The water ingestion rates used by EPA are based on 90th percentile ingestion data and thus are likely to exceed (minimal) physiological needs of infants as defined in nutritional guidelines. Are the water ingestion rates used by EPA reasonable in comparison to the physiological needs of infants at these various life stages? Are there other approaches or data (e.g., see the FDA memo) that could be used to obtain a better or equally valid alternative estimate for this parameter?

Comment C3-a: Seven reviewers agreed with the U.S. EPA's approach, and four of these reviewers stated that it was transparently and objectively described. One reviewer requested clarification of the objectives of the analysis and reiterated that, if the purpose is to determine the relative difference in iodide uptake inhibition for different subgroups, then the mean should be used consistently for parameters throughout the analysis to avoid bias. One reviewer noted that the reason for using a quadratic equation was not provided. Another reviewer stated that it was doubtful that using a single point estimate would provide an adequate understanding of the potential range of exposures and corresponding doses for bottle-fed infants.

Response C3-a: The fixed ingestion rate of 7 μg/kg-day was used for the relative sensitivity evaluation, thereby eliminating dependence on water ingestion for that calculation. Because data are not available for every age, it was necessary to fit a smooth curve to the data to predict water ingestion at the "in-between" ages. A quadratic equation was determined to provide an adequate fit to the data, consistent with the objective of performing a rapid and relatively simple analysis, and thus was used to estimate the ingestions at different ages. The U.S. EPA does not believe that using a 90th percentile ingestion rate provides an understanding of the range of potential effects from

different exposure scenarios, but rather characterizes the realistic, high-end exposure to perchlorate that may occur as a result of drinking water consumption.

Comment C3-b: One reviewer asked why the calculation was not scaled to 2 and 3 years and whether 0-7 days should represent another group or be removed (i.e., use 0-7 days or 7-30 days). Another reviewer questioned why the emphasis is placed on the section of the curve (i.e., the first few days after birth) that is not used in the lifestage analysis or supported by data.

Response C3-b: As stated in Response B1-c the first few days after birth are important in determining the infant's perchlorate concentration at day 7, and thus some estimate of intake must be used. Emphasis was not intended to be placed on the first 7 days following birth; however, it was necessary to make an estimate of ingestion during this timeframe. It did not seem logical to extrapolate the curve fit to data from Kahn and Stralka (2008) (shown in Figure 3-2A) such that the 1 day old infant consumes almost as much as the 7 day. Thus, the extrapolation was made back to 0, as shown in Figure 3-2B.

Additionally, a distinct set of computer files is used to simulate perchlorate dosimetry in older children (age 1 year and above), and dosimetry in older children is expected to have no dependence on exposures during infancy. Thus, the infant exposure calculation was not scaled to older children, and the two age ranges were analyzed separately.

Comment C3-c: One reviewer suggested that the U.S. EPA look at a report from a public health agency in Québec that has data on water ingestion rates for infants 8 weeks of age. One reviewer agreed that it was reasonable to use nutritional guidelines and that it would be useful to compare water consumption with what one would expect given nutritional guidelines and typical formula recipes, the nutritional guidelines would not lead to a reliable upper bound value for water consumption. None of the reviewers recommended using the approach outlined in the FDA memo as a better alternative to what was presented in the report.

Response C3-c: The values reported in a document published in Québec (Direction Risques biologiques, environnementaux et occupationnels, Institute national de santé, and Unité de recherché en santé publique, 2004) for bottle-fed only infants of 8 weeks (56 days) of age are slightly less than the values used by the U.S. EPA in this analysis. The 90^{th} percentile water ingestion values in the Québec report were 981 mL/day or 179 mL/kg-day for 8-week-old bottle-fed infants. The U.S. EPA did not estimate percent inhibition of radioiodide uptake for the 8-week old bottle-fed infant. These data provide support for the use of the 90^{th} percentile estimates from Kahn and Stralka (2008), but do not suggest a need to change the estimate for bottle-fed infants.

Comment C3-d: One reviewer recommended using nutritional guidelines to estimate the total water-ingestion rate. One reviewer offered an alternative approach for estimating ingestion rates for the first few days of life in which the data on breast milk consumption for the first few days (e.g., from Casey et al., 1986; Neubauer et al., 1993) are used. This reviewer suggested comparing literature values for breast milk consumption on days 1-7 to the values predicted for bottle-fed infants using the $1\text{-}e^{-day}$ function.

Response C3-d: Breast milk consumption for the first few days of life was tabulated in Arcus-Arth et al. (2005) from data reported by Casey et al. (1986). These data were considered in determining the breast milk ingestion rate for the breast-fed infants. Since individual ingestion can vary above or below nutritional guidelines and the U.S. EPA's goal was to estimate actual ingestion, the values from Kahn and Stalka (2008) were used in this analysis.

D. Perchlorate concentrations in formula

Parameter-Specific Charge Question D1. **EPA used 1.42 µg/L as the concentration of perchlorate in formula for bottle-fed infants. This estimate was based on information from FDA's Total Diet Study, supported by Pearce et al.'s (2007) findings.**

Is EPA's approach and rationale transparently and objectively described? Is 1.42 µg/L an appropriate value to use for the concentration of perchlorate in infant formula? Are there other better or equally valid alternative approaches or values that could be used?

Comment D1-a: Seven reviewers agreed with the U.S. EPA's approach, and five of these stated it was transparently and objectively described. One reviewer recommended adjusting the intake of perchlorate from infant formula to result in a daily exposure at the point of departure in order to provide results for a consistent comparison across all subgroups. Another reviewer recommended making the description more transparent and providing a sample calculation for Table 4 to show how perchlorate intake for bottle-fed infants was estimated.

Response D1-a: The bottle-fed infant formula contribution to perchlorate exposure was not set to result in a daily exposure equal to the point of departure (POD) because the concentration in infant formula should be reflective of the concentration in formula rather than the POD. The POD (7000 ng/kg-day or 7 µg/kg-day) was used in Table 4-3 for each lifestage to provide for a consistent comparison across lifestages. The FDA TDS data was added to the document and is shown in Table 4-4 along with the market basket averages and the overall average. A more detailed description of the calculation that yielded 1.42 ppb was added to Section 4.3.

Comment D1-b: One reviewer recommended that the U.S. EPA provide additional rationale for the selection of 1.42 µg/L, note in the document that the concentration values in Pearce et al. ranged from 0.2 to 4.1 ppb, and examine the sensitivity in uptake for a range rather than an average value. Another reviewer expressed concerns that the composite samples and detection limit (1 µg/L) of the FDA data do not provide an indication of higher end exposures. The reviewer also argued against using data on ready-to-eat formulas because the infants receiving that type of formula would not be part of the population drinking tap water. The reviewer recommended using either the highest value from the FDA study (3.6 µg/L) or a high value from the Pearce et al. (2007) study, based on measurements of undiluted (but intended to be diluted) formula (~3 µg/L). The reviewer added that better and more extensive measurements of perchlorate in infant formula are desirable.

Response D1-b: Additional rationale for the use of the 1.42 μg/L (ppb) from the FDA TDS study (Murray et al., 2008) was added to the document in Section 4.3. The U.S. EPA selected the Total Diet Study data (Murray et. al, 2008) to represent the dietary intake of perchlorate because TDS is the best available, nationally representative estimate of dietary exposure to perchlorate for the majority of the sensitive subpopulations of concern, including infants and children.

Model simulations were performed to examine the effect of using 1 ppb or 3.6 ppb (an upper end value from Pearce et al. (2007) instead of 1.42 ppb. Results of this sensitivity analysis were added to the document in Section 4.3.

The contribution of concern under SDWA is represented by the consumption of drinking water used to reconstitute powdered formula and formula concentrate. However, the U.S. EPA believes it is reasonable to compare the TDS data to an average value from Pearce et al. (2007) that included both ready-to-eat and concentrated formulas. After powdered formula is reconstituted with water, the concentration in the final product will be the sum of the amount in the powdered formula and that in the tap water. Since the perchlorate concentration in un-reconstituted powdered formula has not been reported, the U.S. EPA assumed that the contribution from the powdered formula after reconstitution (when the formula is ready for consumption) would be the same as the concentration in ready-to-eat formula. This is equivalent to assuming that ready-to-eat formula is made by reconstituting powdered formula with perchlorate-free water.

The U.S. EPA agrees that better and more extensive measurements of perchlorate in infant formula are desirable.

E. Radioiodide excretion into breast-milk by NIS

Parameter-Specific Charge Question E1. **In the model, EPA included perchlorate inhibition of NIS radioiodide excretion into breast milk, as well as inhibition of radioiodide transport by perchlorate for all NIS-containing tissues, thereby making the code consistent with the model description in Clewell et al. (2007).**

Is this inclusion appropriate? Are the impacts of this inclusion transparently and objectively described?

Comment E1-a: Seven reviewers agreed with the U.S. EPA's approach and stated that it was objectively and transparently described. One reviewer recommended reconsideration of Pearce et al. as these data do not suggest that there would be an effect of perchlorate on the excretion of iodine in breast milk; therefore, inclusion of this model feature may not be accurate. Another reviewer recommended adding a section towards the end that discusses the impacts of perchlorate inhibition.

Response E1-a: U.S. EPA is retaining in the model the perchlorate inhibition of radioiodide excretion in breast milk and believes it is consistent with the data in Pearce et al. (2007). The impact of including NIS inhibition of iodide transport into breast milk the model-predicted iodide concentration in breast milk by ~3% at a maternal dose equal to the point-of-departure (7 μg/kg-day). This small decrement is consistent with the

observations of Pearce et al. (2007), since the change is less than the variability seen in those samples. However, it should be noted that this reduction is essentially additive. That is, if the effect of the perchlorate alone on the infant is ~3% and the reduction in breast-milk iodide is ~3%, then the net effect on the amount of iodide taken up by the infant thyroid will be a ~6% reduction.

Published data have not shown a decrease in breast-milk iodide at low levels of perchlorate exposure. However, high-level perchlorate exposures (Kirk et al., 2005) and exposures to thyiocyanate (Laurberg et al. 2004) have been shown to decrease breast milk iodide. A full discussion of the impacts of perchlorate inhibition is beyond the scope of this document, but is available in the National Academy of Sciences review (NCR, 2005).

Comment E1-b: One reviewer noted that the rationale for scaling NIS levels to body weight was not clear and recommended review of studies (Faggino et al. and others) that suggest that scaling may not be appropriate as NIS expression changes over the course of development.

Response E1-b: See response to G3-a. U.S. EPA has reviewed the information recommended by the reviewer and has decided to retain the NIS scaling as originally described by the models' authors (Clewell et al. 2007 and Merrill et al. 2005).

Additional Reviewer Comments

Comment 1: One reviewer stated that the U.S. EPA should have considered easier and more straightforward approaches, e.g., Lorber (2008).

Response 1: While the Lorber (2008) model is able to predict perchlorate kinetics for the lactating woman and average adult, it was not developed to predict percent inhibition of radioiodide uptake by perchlorate and does not describe dosimetry in the pregnant mother, fetus, or child. Thus, the PBPK models by Clewell et al. (2007) and Merrill et al. (2005) were chosen to be the most appropriate tool for this analysis.

Comment 2: One reviewer noted that the water intake rates presented in Section 4.3 for 6- to 12-month olds and 1- to 2-year-olds do not appear logical or consistent with the values presented in Kahn and Stralka (2008). The reviewer recommended that they be checked.

Response 2: The reviewer is correct. The values were checked and found to be a typographical error. The values were corrected to reflect those from Table 4 of Kahn and Stralka (2008) that were used in the model.

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