External Peer Review Meeting for EPA's
Revised BBDR Model and
Draft MCLG Approaches Report for Perchlorate in Drinking Water

Crystal City Marriott at Reagan National Airport
1999 Jefferson Davis Highway
Arlington, VA, 22202-3526

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PEER REVIEWER CHARGE QUESTIONS

Introduction

EPA is developing approaches to inform the derivation of a Maximum Contaminant Level Goal (MCLG) for perchlorate. In January 2017, EPA's contractor (Versar, Inc.) conducted an independent, external, scientific peer review of the draft biologically-based dose-response (BBDR; also known as a PBPK/PD) model and report titled: *BBDR Models for the Effect of Perchlorate on Thyroid Hormones in the Infant, Breast Feeding Mother, Pregnant Mother, and Fetus: Model Development, Revision, and Preliminary Dose-Response Analyses*. The model predicts the relationship between perchlorate exposure and thyroid hormone levels in sensitive life stages and has been revised based on peer reviewer recommendations.

The purpose of this review is to seek guidance from expert peer reviewers on the scientific assessment titled: *Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water* (e.g., draft MCLG Approaches Report), which links the revised perchlorate BBDR model predictions to neurodevelopmental effects, to inform decision-making for perchlorate under the Safe Drinking Water Act. The outcome of this peer review is not the derivation of an MCLG; rather, it is to solicit expert comment on the proposed approaches that might be used to inform future decisions on the derivation of an MCLG.

MCLGs are non-enforceable, health-based goals that EPA sets for each regulated drinking water contaminant. In accordance with the Safe Drinking Water Act (SDWA), they are set at a level at which no known or anticipated adverse human health effect occurs and to allow for an adequate margin of safety. MCLGs consider only public health, and not limits of analytical measurement and treatment technology effectiveness. The SDWA requires that EPA establish the enforceable Maximum Contaminant Level (MCL) as close as feasible to the MCLG taking costs and benefits into consideration.

Peer Review History

In 2012, as a part of the national primary drinking water regulation development process for perchlorate and in accordance with the requirements of the SDWA, EPA sought recommendations from EPA's Science Advisory Board (SAB) on approaches to inform the derivation of a perchlorate MCLG.

In 2013, the SAB recommended the following:
- derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic modeling (PBPK);
- expand the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;
- utilize a mode of action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition to thyroid hormone changes and finally neurodevelopmental impacts; and
- extend the [BBDR] model expeditiously to…provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages.

The SAB stated that this data-driven approach represents a more rigorous way to address differences in biology and exposure between adults and sensitive life stages than is possible with the default approach for deriving an MCLG, and that EPA should also consider available data on potential adverse health effects (neurodevelopmental outcomes) due to thyroid hormone level perturbations regardless of the cause of those perturbations. See Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate, EPA-SAB-13-004.

Based on the SAB's recommendations, EPA, with contributions from the Food and Drug Administration, developed a BBDR model to predict the effect of perchlorate on the thyroid gland in formula-fed and breast-fed infants, and in lactating women. This draft model was integrated with a previously published model that similarly predicted the effects of perchlorate on serum thyroid hormone concentrations in the third trimester pregnant woman and her fetus. The model was subjected to external peer review in January 2017. The final peer review report titled *External Peer Review for EPA's Draft Biologically Based Dose-Response (BBDR) Model and Draft BBDR Model Report for Perchlorate in Drinking Water* is available through the docket at https://www.regulations.gov/docket?D=EPA-HQ-OW-2016-0439

Revisions to the BBDR Model Following the January 2017 Peer Review
EPA considered all of the peer reviewers' recommendations from the January 2017 peer review and focused on those that were anticipated to be most important for increasing the scientific rigor of the model and modeling results. These revisions are summarized in Chapter 3 of the draft MCLG Approaches Report; additional detail is available in Appendix A. Model revisions focused on the following key recommendations:
- extending the model to early pregnancy;
- incorporating biological feedback control of hormone production via TSH signaling, such that the model can describe lower levels of iodide nutrition;
- calibrating the model and evaluating its behavior for upper and lower percentiles of the population, as well as the population median; and
- conducting an uncertainty analysis for key parameters.

The revised BBDR model does not explicitly address consideration of other goitrogens. Previous peer reviewers (2017) were mixed on their recommendations regarding the issue of consideration of other goitrogens. A recent review of thiocyanate pharmacokinetics and modes of action

indicates that an attempt to address other goitrogens in the model would involve significant uncertainty (Willemin & Lumen, 2017). However, it is expected that the model predictions may, in fact, incorporate the effect of perchlorate along with exposure to other goitrogens because the model predictions for zero perchlorate exposure are calibrated to National Health and Nutrition Examination Survey (NHANES) data, which are from a population with an exposure distribution to other goitrogens that is assumed to be independent of perchlorate.

EPA's Approaches for Informing the Derivation of an MCLG
EPA has developed a two-stage approach linking the revised BBDR model results with quantitative information on neurodevelopmental outcomes from epidemiological studies. EPA has also developed an alternative population-based approach that uses the revised BBDR model to evaluate a shift in the population of pregnant women who could be hypothyroxinemic.

The first stage of the two-stage approach is the development of the revised BBDR model that describes thyroidal hormone production in women of childbearing age with low/adequate iodide intake, and predicts the relationship between perchlorate exposure and changes in thyroid hormone levels in early pregnancy. The available data for the second stage of the analysis comes from epidemiological studies that evaluated maternal thyroid hormone levels in early pregnancy and neurodevelopmental outcomes (these are not studies evaluating perchlorate exposure). Based on the recommendations of previous peer review panels, EPA assumed that changes in thyroid hormone levels would be expected to lead to neurodevelopmental outcomes. For this reason, EPA did not conduct a complete, systematic review of the body of literature on this topic. However, EPA conducted a focused review of the published literature and identified 29 epidemiological studies that examined thyroid hormone levels and neurodevelopmental outcomes. Of these 29 studies, 14 provide categorical data that assist in understanding the implications of altered thyroid hormones, and 15 provide more detailed dose-response characterizations via regression analyses to inform the relationship between low thyroid hormone levels and neurodevelopmental effects in offspring.

EPA focused on the latter set of 15 studies due to their more robust dose-response analyses, which included studies that found statistically significant changes and studies that did not find a statistically significant correlation. Among these studies, the number of subjects ranged from 22 to 3,839. In many of these studies the general outcomes, though not statistically significant, showed a positive relationship that was consistent with the studies used for quantitative analyses. In some instances, the studies had results that were negative or inconsistent with the studies that were used for the quantitative analyses. EPA presents and characterizes all of these studies in Chapter 5 of the report.

Five studies in this group of 15 were identified (Pop et al., 1999; 2003; Finken et al., 2013; Korevaar et al., 2016; and Vermiglio et al., 2004) that included data that were used to quantitatively describe the relationship between thyroid hormone levels in early pregnancy (the focus of the analysis) and changes in neurodevelopment in offspring. Neurodevelopmental outcomes associated with these studies included assessment of Bayley Scales of Infant Development, Weschler Intelligence Scales for Children, a Dutch non-verbal intelligence test (the Snijders-Oomen Niet-Verbale Intelligentie Test) and Standard Deviation of Reaction Time

Using the output from the revised BBDR model (stage 1 of the analysis) and the quantitative relationships between thyroid hormone levels and neurodevelopmental effects from the published epidemiological studies (stage 2 of the analysis), EPA characterized the relationship between perchlorate exposure on fT4 levels in pregnant mothers during early gestation and the potential for changes in neurodevelopmental outcomes in their offspring.

EPA's alternative population-based approach estimates the shift in the population of hypothyroxinemic, pregnant women that would result from perchlorate exposure. EPA used the BBDR model predictions to estimate the proportion of hypothyroxinemic pregnant mothers in the population, assuming a distribution of fT4 levels with a consistent iodide intake.

Charge Questions
Topic #1: General Questions

1. Please comment on the appropriateness of focusing the current evaluation on perchlorate's potential impact on the fetuses of hypothyroxinemic pregnant women during early gestation for the purposes of informing a perchlorate MCLG.

2. Please identify any additional peer-reviewed studies that could inform the BBDR modeling or the quantitative relationship of thyroid hormone levels to neurodevelopmental outcomes. If an alternative study data set would be more appropriate, please outline how such data might be used.

Topic #2: BBDR Modeling to Predict Changes in Thyroid Hormone Levels in Early Pregnancy

The revised BBDR model seeks to predict the pharmacokinetics and pharmacodynamics of iodide and perchlorate, as well as the thyroid hormones T3, T4 and TSH in non-pregnant and pregnant women, including those with low iodide intake, and changes in thyroid hormone levels.

3. Please comment on the assumptions, strengths and limitations of methods and parameters by trimester for:

    a. determining the quantitative relationships between oral intake and serum levels of perchlorate during pregnancy under continuous exposure assumptions, and

    b. estimating statistical distributions of specific biochemical parameters that determine serum perchlorate concentrations, urine clearance of iodide and perchlorate, and thyroid iodide uptake for purposes of estimating the effect of environmental levels of perchlorate on maternal fT4 concentrations.

4. Please comment on the assumptions, strengths and limitations of the uncertainty analyses of the parameters, particularly with regard to availability of data supporting parameter assumptions.

5. Please comment on the utility of the BBDR model for predicting variability in fT4 levels in the population (e.g., percentiles for different thyroid hormone levels) at varying levels of iodide intake.

6. Please comment on the robustness, precision and sensitivity of the model, and how these factors affect the model's ability to predict changes in fT4 at low perchlorate doses. Consider whether a perchlorate dose range exists for which the modeling predictions would be highly uncertain.

7. The revised BBDR model incorporates a TSH feedback loop defined by an equation from Hadlow et al. (2013) (J Clin Endocrinol Metab, 98(7): 2936-2943), with an adjustment factor to match specific data sets or population percentiles, to describe the relationship between fT4 and TSH.

    a. Please comment on the assumptions, strengths and limitations of this approach to incorporate a TSH feedback loop into the BBDR model.

    b. Noting the reliance on the Hadlow et al. (2013) study, please comment on whether there are other studies that should be considered and describe how they would improve the analysis.

    c. Please comment on the approach for characterizing inter-individual variability in relevant populations from which the epidemiological data were obtained.

8. Since the observational thyroid hormone data that are used to calibrate the model derive from populations exposed to goitrogens other than perchlorate, EPA has made an assumption that the model parameters may implicitly account for exposures to these other goitrogens. As such, the exposure to perchlorate is assumed to be effectively added to this background goitrogen exposure as discussed in Section 3.5 of the report.

    a. Please comment on the validity of this assumption and the extent of uncertainty associated with this assumption.

Topic #3: Identification of Published Literature and Quantitative Relationship of Thyroid Hormone Levels to Neurodevelopmental Outcomes

9. EPA conducted a three-step literature review, which identified 15 studies with information that could inform the quantitative relationship between thyroid hormone levels and neurodevelopmental outcomes.

    a. Please comment on whether EPA has clearly identified the criteria to identify studies through each of the three steps of the literature review, and the adequacy of the strategy for conducting the literature search. Are these criteria scientifically supportable, and did EPA apply them properly?

    b. Please also comment on the summary and characterization of the literature in Chapter 5 of the draft MCLG Approaches Report and identify any inaccuracies or mischaracterization of the studies.

10. EPA focused on 5 studies that evaluated the relationship of maternal fT4 and several neurodevelopmental endpoints (IQ, MDI, PDI and reaction time) based on the measurement of fT4 during early pregnancy at weeks 12, 13 and 16.

    a. Please comment on the assumptions, strengths and limitations of focusing on the five studies and associated neurodevelopmental end points to inform an

MCLG, including but not limited to study design, evaluation of neurological endpoints, sample size, iodide nutrition status, potential confounders such as smoking, and study population.

b. Please comment on whether the chosen studies are sufficient in number, quality, and robustness for the purpose of informing the derivation of an MCLG.

c. Please provide advice on reducing any identified limitations.

11. EPA used regression analyses to predict the magnitude of change in each of the neurodevelopmental endpoints given a change in fT4 as a result of increased perchlorate exposure at different iodide intakes.

a. Please comment on the assumptions, strengths, and limitations of using the regression analyses to inform the relationship between thyroid hormone levels and neurodevelopmental outcomes. Please also comment on the various functional forms of the regression equations (e.g., linear, log-linear, quadratic) in each of the relationships.

b. Please identify additional data or analyses EPA could use to quantify the relationship between thyroid hormone levels and neurodevelopmental effects, including how this information would be expected to improve the analysis.

c. Please comment on whether there is a magnitude of change in fT4 below which the relationship between fT4 and neurodevelopmental effects should not be used because it is too uncertain.

d. Please comment on whether other studies that were identified in the literature search (e.g., studies that found categorical relationships between fT4 and neurodevelopmental outcomes, studies that found effects but lacked statistical significance, studies that did not find an effect) could be utilized to quantitatively characterize the relationship between fT4 and neurodevelopmental outcomes or inform uncertainty associated with the analysis presented.

Topic #4: Alternative Population-Based Approach and Comparison to the Two-Stage Approach Linking Thyroid Hormone Levels to Neurodevelopmental Outcomes

12. Please comment on the assumptions, strengths and limitations associated with the population-based approach that is focused on a shift in the proportion of the population that could be considered hypothyroxinemic.

13. Hypothyroxinemia is the condition of having an abnormally low level of T4 in the blood and TSH is in the normal range, and in diagnosing this condition the threshold for "abnormally low" is often selected to be the 2.5^{th}, 5th or 10th percentile of the population fT4 distribution. Because the BBDR model can be calibrated to any given percentile, but does not predict the distribution of fT4 levels, it was necessary to derive a fT4 distribution to identify a hypothyroxinemic threshold. EPA assumed a lognormal distribution with a Geometric Standard Deviation based on two to three studies, depending on the gestational week. There is uncertainty regarding the true fT4 levels at various percentiles in the distribution around the median output from the BBDR model. For example, some of the analyses show larger

unit changes with increasing percentiles of fT4 in most analyses (See tables 24, 30, 31, 32, 33 and Section 6.5.6 of the draft MCLG Approaches Report). Please comment on the assumptions, strengths and limitations of the derived fT4 distribution for the purposes of this analysis.

14. Please comment on the strengths and limitations of the two-stage approach versus the alternative population-based approach to inform the derivation of an MCLG.

15. EPA has developed a two-stage approach linking the revised BBDR model results with quantitative information on neurodevelopmental outcomes from epidemiological studies. Please comment on the utility of this two-stage approach for predicting potential impact of perchlorate exposure in early pregnancy on neurodevelopmental outcomes in the population at varying levels of iodide intake. Please comment on whether there are better strategies for estimating the potential impact of perchlorate exposure in early pregnancy on neurodevelopmental outcomes that are likely to be more scientifically defensible than the approaches presented (e.g., Appendix C estimates IQ impact directly from perchlorate exposure using Steinmaus et al. and Korevaar et al., or potentially some alternative studies). If an alternative approach would be more appropriate, please outline specifically how the approach might be developed given the current available state-of-the-science and data.