American Water Works Association

Dedicated to the World's Most Important Resource®

Government Affairs Office
1300 Eye Street NW, Suite 701W
Washington, DC 20005-3314
T 202.628.8303
F 202.628.2846

November 20, 2017

SUBMITTED VIA E-MAIL

Mr. Michael H. Shapiro
Acting Assistant Administrator
USEPA, Office of Water
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

RE: Comments on the draft Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water (82 FR 43354, EPA–HQ–OW–2016–0438)

Dear Mr. Shapiro:

The American Water Works Association (AWWA) appreciates the opportunity to review and comment on the Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal (MCLG) for Perchlorate in Drinking Water (82 FR 43354, EPA–HQ–OW–2016–0438).

We recognize and support EPA's efforts to address the recommendations made by the Science Advisory Board in 2013. Our review of the proposed MCLG approach and biologically based dose-response (BBDR) modeling for perchlorate has identified several areas of concern that should be considered closely by the Agency and the selected peer reviewers. A detailed assessment is attached, but in general terms the results of our review yielded the following overall conclusions:

1. The BBDR is not capable of adequately predicting iodine uptake or free thyroxine (fT4) based on attempts to simulate multiple key studies measuring perchlorate inhibition of iodine uptake, which is a necessary precursor to thyroid effects.
2. Several modeling assumptions are not appropriately documented or are based on insufficient data. This results in increased uncertainty associated with the scientific integrity of the model required to support the proposed MCLG approach.
3. EPA's process for selecting key studies linking changes in fT4 levels and neurodevelopmental effects in the proposed MCLG approach was (a) not transparent

and (b) introduced additional uncertainty, especially when confounding variables (e.g., hCG, iron deficiency) are not controlled.

In summary, while EPA's efforts to address the SAB recommendations are laudable, we believe the proposed approach contains significant uncertainties and is, therefore, insufficient for supporting a risk assessment. Until the uncertainties in the current MCLG approach can be addressed, EPA should continue to rely on the RfD recommended by the National Academy of Sciences for considering further regulatory action. The results of the modeling simulation we prepared for this review of the MCLG approach confirmed the conclusions of prior studies that low levels of perchlorate have no demonstrated health consequence that can be scientifically validated with the confidence necessary to support the proposed MCLG approach.

Should you have questions or would like to discuss this matter, please contact me (tmehan@awwa.org) or Kevin Morley (kmorley@awwa.org).

Sincerely,

G. Tracy Mehan, III
Executive Director – Government Affairs

cc: Peter Grevatt – EPA/OW/OGWDW
Eric Burneson – EPA/OW/OGWDW/SRMD
Samuel Hernandez – EPA/OW/OGWDW/SRMD

Prepared for
The American Water Works Association

Date
November 2017

By
Robinan Gentry, PhD, DABT
Tracy Greene, BS
Ramboll Environ US Corporation, Monroe, Louisiana

Harvey J. Clewell, III, PhD, DABT, FATS
C. Eric Hack, MS
ScitoVation, Research Triangle Park, North Carolina

COMMENTS ON USEPA 2017:

"PROPOSED APPROACHES TO INFORM THE DERIVATION OF A MAXIMUM CONTAMINANT LEVEL GOAL FOR PERCHLORATE IN DRINKING WATER"

RAMBOLL ENVIRON

CONTENTS

EXECUTIVE SUMMARY

The document provides comments on the US Environmental Protection Agency's (USEPA) 2017 report entitled "Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water", which was prepared by the USEPA's Office of Ground Water and Drinking Water (USEPA 2017). In this report, USEPA (2017) is proposing approaches to inform the derivation of a Maximum Contaminant Level Goal (MCLG) for perchlorate in accordance with recommendations made from previous reviews conducted by the USEPA's Science Advisory Board (SAB). This MCLG approach (USEPA 2017) includes revisions to a previously developed and peer reviewed biologically-based dose-response (BBDR) model that has been extended to predict the relationship between perchlorate exposure and thyroid hormone levels in sensitive life stages. These revisions, suggested by the SAB (2013), include the following:

- Derivation of a perchlorate MCLG that addresses sensitive life stages through PBPK/PD modeling;
- Expansion of the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;
- Utilization of 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
- Extension of "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" (SAB 2013, p. 19).

USEPA's (2017) attempts to address SAB's recommendations should be applauded. Revisions presented in the report include methods that extend the model to early pregnancy and incorporate biological feedback control of hormone production via TSH signaling, adding a description of the impact of lower levels of iodide nutrition. In addition, an attempt has been made to calibrate the model's behavior for upper and lower percentiles of the population, as well as the population median for thyroid hormone production. Finally, an uncertainty analysis for key parameters was conducted.

For the development of the MCLG, USEPA has proposed a two-stage approach linking the revised BBDR model results ("Stage 1") with quantitative information on neurodevelopmental outcomes from epidemiological studies ("Stage 2"). Stage 1 describes the thyroidal hormone levels in women of childbearing age with low to adequate iodide intake. In this stage, the revised BBDR model is applied to predict the relationship between perchlorate exposure and changes in thyroid hormone levels in early pregnancy. Data for Stage 2 of the approach is provided from epidemiological studies evaluating maternal thyroid hormone levels in early pregnancy and the relationship between changes in these levels and the observation of neurodevelopmental outcomes. USEPA (2017) has also developed an alternative population-based approach that uses the revised BBDR model to estimate changes levels of selected thyroid hormones, specifically free T4, resulting from perchlorate exposure that may result in a shift in the population of hypothyroxinemic pregnant women.

Following a review of USEPA (2017), comments were prepared and organized around three main topics:

- USEPA model revisions including those for extending the model to early pregnancy, incorporating biological feedback control of hormone production via TSH signaling, calibrating the model and evaluating its behavior, and conducting an uncertainty analysis for key parameters. This includes comparison of model output to results from key studies, including

those identified in previous assessments, including results reported by Greer et al. (2002), Braverman et al. (2006), and Téllez Téllez et al. (2005a, 2005b);

- Linking BBDR results to neurodevelopmental outcomes focusing on the identification of published literature to develop the quantitative relationship between thyroid hormone levels and neurodevelopmental outcomes; and
- Comparison of the results from the BBDR modeling and MCLG approach with results and key studies from previous USEPA assessments.

The results of our review of the EPA's proposed MCLG approach (EPA 2017) and BBDR modeling for perchlorate yielded the following overall conclusions:

- While we applaud the EPA for the application of a BBDR model in the MCLG approach, as these models integrate the available science for a compound of interest, there is some concern that uncertainties inherit in the model call into question its proposed application in the risk assessment for perchlorate and whether it is fit for that purpose. While the hormone component of the model is a definite scientific improvement in terms of incorporating the available biology, there is a lack of data to provide validation of multiple steps in the proposed approach and of the assumptions/parameters within the biologically based dose-response (BBDR) model.
- Many of the changes in free thyroxine (fT4) that are predicted by the MCLG approach to impact the population distribution of fT4 and therefore result in per unit changes in neurodevelopmental outcomes are small percent changes (some as low as a 1.3-4.3% change). This would appear to suggest that the extended version of the BBDR model has a capability to estimate small changes in fT4 with precision that is not demonstrated by any adequate validation. Further, the model predictions of fT4 underpredict observed data in various clinical studies by substantially more than 1.3-4.3%. This suggests that the model is not precise enough to predict such small changes in fT4. Moreover, considering the variability of fT4 in the populations of interest, there is uncertainty as to whether these slight changes could be measured clinically, considering the greater impact of iodine intake on hormone levels.
- Until additional data are available to validate current extensions of the BBDR model to the pregnant woman, the Greer et al. (2002) and Braverman et al. (2006) studies provide the critical information in determining concentrations of perchlorate that do not result in significant inhibition of iodide uptake and, therefore, impacts on fT4. Based on recommendations from the National Research Council (2005), points of departure provided by these studies used in combination with uncertainty factors were considered to be protective of sensitive subpopulations, and provides a basis for future risk management decisions.

Therefore, we conclude that while the MCLG approach as proposed by USEPA incorporates additional science into the process, it still contains significant uncertainties that call into question the use of this approach to support a regulatory decision. Until the uncertainties in the current MCLG approach can be addressed, USEPA should continue to rely on the RfD recommended by the NAS for considering further regulatory action.

1. MODEL REVISIONS

1.1 Extending the Model to Early Pregnancy

The MCLG approach (USEPA 2017) is based on a hypothesized mode of action for neurodevelopmental outcomes associated with the development of hypothyroxinemia as a result of perchlorate exposure. The sensitive populations of concern for exposure to perchlorate are the fetuses of hypothyroxinemic pregnant women. Extending the model to predict the impact of perchlorate exposure on fT4 during early pregnancy is complicated by the significant variability in the levels of fT4 in the general population and the challenges in measuring fT4, as well as by the uncertainty in the identification of an alteration that may over time change fT4 from an individual's "set-point" and therefore potentially impact circulating levels in both the mother and the fetus.

According to the "American Thyroid Association Task force on Thyroid Disease During Pregnancy and Postpartum", isolated hypothyroxinemia is defined as a normal maternal TSH concentration in conjunction with fT4 concentrations in the lower 5th or 10th percentile of the reference range (Stagnaro-Green et al. 2011). USEPA (2017) has also focused on selected percentiles of the reference range; however, reference ranges can vary from population to population (Alexander et al. 2017). Even within US populations and across ethnic groups, the 2.5th percentile can vary by up to 2 pmol/L or approximately 20% (9.3-11.4 pmol/L as reported by Alexander et al. (2017)).

The variation in fT4 reported in the published literature during early pregnancy is provided in USEPA (2017), Appendix A, Figure A-33. The levels of fT4 during early pregnancy, based on the studies identified by USEPA (2017), appear to range from approximately 12-16 pmol/L. This range is consistent with the range of fT4 means reported in the Greer et al. (2002) study at baseline of approximately 1.2 ng/dL (15.5 pmol/L). However, the 50th percentile model predictions at zero dose perchlorate and 170 µg/day iodine intake (approximately 10 pmol/L at gestation weeks 12, 13, and 16) are much lower than these reported values.

Measuring fT4 in the presence of high concentrations of bound T4 is challenging, especially in conditions where binding proteins are altered such as during pregnancy (Alexander et al. 2017). Measurement techniques are prone to inaccuracy during pregnancy due to disruption of the original equilibrium. The 95% fT4 reference intervals decrease gradually with advancing gestational age: from 1.08– 1.82 ng/dL (approximately 13.9 – 23.5 pmol/L) in week 14 to 0.86–1.53 ng/dL (approximately 11.1 – 19.8 pmol/L) in week 20.

In addition, as noted in USEPA (2017):

> *"Circulating T3 and T4 levels in an individual are maintained within a narrow range by a negative feedback loop with TSH from the pituitary and TRH from the hypothalamus (see Figure 2) that operates around a "set-point." This set-point is different from individual to individual, which generates a population variance in blood levels of thyroid hormone that is considerably broader than the individual variance (Andersen, Pedersen, Bruun, & Laurberg, 2002). Therefore, in euthyroid individuals, serum T4 and T3 fluctuate within a fairly narrow range (about 10% of the population variance), maintained by the negative feedback relationship with serum TSH from the pituitary gland. This normal variation creates a situation where single measures of free or total T4 and TSH are a somewhat imprecise measure of an individual's average T4 and TSH concentrations (Andersen et al. 2002)."*

Extending the thyroid BBDR model to address early gestation is a significant challenge due to the complex interaction between thyroid homeostasis and gestational development. While the model appears to accurately simulate average fT4 in early gestation in the absence of perchlorate exposure, (Figure A57 in Appendix A), a previous peer review panel noted that

the model of early 2017 was most appropriate for higher iodide and lower or zero perchlorate exposures. Considering the addition of TSH feedback dynamics, and an adjustment factor to match specific population percentiles, there is reason for concern regarding the uncertainty of the revised model predictions under low iodide intake conditions. Some of these concerns are highlighted below:

- In addition to regulation by TSH, hCG levels rise in early pregnancy and this increases NIS uptake activity and T4 production. hCG is structurally similar to TSH, and stimulates iodide transport and thyroid hormone synthesis through stimulation of the TSHR. In the model, the Vmax for NIS-mediated uptake is increased during pregnancy based on independent data, but that change is not described as a function of hCG. "VmaxNISF_thy_I is scaled to increase with pregnancy based on an empirical relationship between gestational age and radioactive iodide uptake." hCG is calculated as a function of gestational age, and is then used to increase T3 and T4 production, but the increase in thyroidal iodine uptake is mistakenly ascribed by the model to TSH. This suggests that the model structure is not true to the biology, introducing uncertainty to predictions of T4 during pregnancy.
- The current model uses a baseline first-order constant calibrated to NHANES 2007-2012 median, 10th, or 90th percentile non-pregnant data. The KProdT4F value for the median NHANES calibration is 6.25*10-7 /hr/kg$^{0.75}$ (Table A-2), which is lower than 2.45 x 10-6 used by Lumen et al. (2013) based on fitting to data of Nicoloff et al. (1972). This value is scaled in pregnancy with increasing KProdT4 through GW 16 (peak occurring ~ GW 9) based upon placental hCG increase over this time according to the linear relationship from Glinoer (1997): hCGreg = 1 + 0.00354 x hCG. However, the use of a T4 production rate that is lower than the published value is not adequately justified, given the importance of this parameter, which has a direct impact on predictions of fT4 changes, for the intended application of the model.
- The current model uses a Km for perchlorate binding to the NIS (KmNIS_P) that is 3-fold lower than Lumen et al. (2013) (i.e. a 3-fold higher affinity). Specifically, Km is the 2.5th percentile lower confidence limit of the population median based upon USEPA reanalysis of Greer et al. (2002). The value (50th percentile = 0.73 µM) is similar to that obtained from re-analysis of in vitro binding data, 0.59 µM (Schlosser 2016); use of KmNIS_P = 0.489 µM makes perchlorate 3 times more effective at competitive inhibition of NIS versus Lumen et al. (2013).
- Plots of NHANES 2007-2012 data for non-pregnant women demonstrated little relationship between iodine intake and fT4, even at iodide intake levels below 75 µg/day (Figure A-54). Given limited data in this range, USEPA has used the relationship between thyroidal iodide stores (mg) and iodine intake, which shows depletion of fT4 at iodide intake levels below 100 µg/day (Delange, 2000). It is clear from Figure A-54, this is inconsistent with the NHANES data. This relationship was used as part of a parameter calibration procedure to simulate population percentiles of fT4, T4, T3, and TSH identified from NHANES data (see Appendix A, Figures 54-56)." However, script files included with the BBDR model use an iodine intake of 90 µg/day. The model is much more sensitive to iodine intake than perchlorate dose, with minimal changes to hormone levels due to perchlorate exposure at high iodine intake levels. The various iodine intake levels used for model simulations need to be more clearly presented and justified.

1.2 Calibrating the Model and Evaluating its Behavior

In development of these comments, multiple studies were independently simulated to an attempt to duplicate datasets that were reported by USEPA (2017) to calibrate the model. This included studies

to evaluate the model's behavior and determine if the results were consistent with the final values reported in the draft MCLG approach. This included:

- Comparison to the Steinmaus et al. 2016 results
- Other key studies noted in previous assessments:
  - Greer et al. 2002 – 14 day worker study
  - Braverman et al. 2006 – 6 month study
  - Téllez Téllez et al. 2005a, 2005b – Chile study (see attached)

In efforts to produce these simulations, it was noted that instructions for running the model for different scenarios, and documentation of the rationale for the model parameter values associated with them, are inadequate and lack transparency; this deficiency is exacerbated by the number of permutations of parameter settings used to generate the figures in the document. As a result it is difficult to have confidence in the results of a model evaluation, even by an experienced modeler, due to the significant uncertainties regarding the steps necessary to reproduce the figures and tables in the report, or to perform comparisons of model predictions to data for alternative exposure scenarios or studies.

1.2.1 Comparison to the Steinmaus et al. 2016 Results

In Appendix B of USEPA (2017), a comparison of the predicted changes in both fT4 and TSH from the BBDR model were compared to the results reported by Steinmaus et al. (2016). The Steinmaus et al. (2016) study was conducted to evaluate the potential for perchlorate exposure to impact thyroid hormone levels in pregnant women in San Diego. They reported an effect of perchlorate on fT4 levels to be similar among women with both low iodine (<100 µg/day) and normal (100-300 µg/day), with a greater effect of perchlorate observed among pregnant women in the high iodine intake group (>300 µg/day). They noted that this effect has been observed in NHANES evaluations

The comparison of the predicted fT4 changes from the BBDR model and the Steinmaus et al. (2016) results associated with changes in perchlorate dose are reported in Figure B-1. Duplication of this BBDR modeling output was possible using the USEPA provided modeling code, with additional instruction from USEPA staff. However, this comparison clearly highlights the differences between the model predictions and those from a published study. The baseline simulations with normal iodine intake (170 µg/day) demonstrate no change in fT4, which is consistent with other studies in which no impact on fT4 has been observed at doses up to 7 µg/kg/day (Greer et al. 2002; Braverman et al. 2006). The model underpredicts the changes in fT4, even in the scenario with low dietary iodine intake (75 µg/day), in comparison to the changes reported by Steinmaus et al. (2016). This discrepancy demonstrates the significant uncertainty in the ability of the model to predict changes in fT4 associated with perchlorate exposure. In particular, the current MCLG approach results in small changes in fT4 as low as approximately 1% being predicted to result in unit changes in neurodevelopmental endpoints. Predictions of this precision would require a level of model precision that has not been demonstrated by comparison to existing data.

1.2.2 Other Key Studies Noted in Previous Assessments:

Greer et al. 2002 – 14 day study

The Greer et al. (2002) study was conducted to establish the dose-response in humans for perchlorate inhibition of thyroidal iodide uptake and any short-term effects on thyroid hormones following exposure for male and female volunteers to perchlorate in drinking water at doses of 7, 20, 100 or 500 µg/kg/day for 14 days. The results of this study have previously been relied upon by the USEPA (2005) to derive a reference dose (RfD) and to determine health reference levels (HRLs). The results of this study indicate a decrease in iodide uptake following exposure to a dose of 20

µg/kg/day, but no effect on hormone levels, including fT4 and TSH, at the highest dose tested. A No Observed Effect Level of 7 µg/kg/day was determined based on these results, and an RfD of 0.7 µg/kg/day was adopted, based on NRC recommendations, with the application of an uncertainty factor of 10 for intraspecies variability or sensitive subpopulations.

Consistent with the results of the study, simulating the exposure of the Greer et al. (2002) with the BBDR model indicated no significant change in fT4 at doses up to 500 µg/kg/day. However, predicted concentrations of fT4 are lower than those measured by Greer et al. 2002. The model simulation was run with an iodine intake of 90 µg/day, as this was the value USEPA used in the Greer_test.m script. However, 90 µg/day is not consistent with the 170 µg/day value EPA reports as representing a sufficient intake and USEPA's documentation does not indicate why a lower value was used for the individuals in the Greer study. Simulation of iodide uptake inhibition (RAIU) appears to over-predict the measured values, though the qualitative increasing trend of inhibition with dose behaves appropriately. This discrepancy may result from the low iodine intake chosen by USEPA.

Table 1. Simulation of the Greer et al. (2002) Perchlorate Study

Dose	RAIU (%)		fT4 (pM)	
(ug/kg/d)	Simulated	Measured	Simulated	Measured
0	100	100	10.33	-
7	89	98.2	10.33	-
20	74	83.6	10.32	16.09
100	37	55.3	10.31	15.26
500	11	32.9	10.30	15.44

Braverman et al. 2006 – 6 month study

The Braverman et al. (2006) study was conducted to determine whether prolonged exposure (6 months) to low levels of perchlorate (0.5, 1.0 or 3.0 mg/day) would perturb thyroid function. The study included a small number of individuals; however, iodine levels were comparable with those of the general population. The authors noted the limitations of the small sample size, but concluded that the results suggested that healthy, euthyroid individuals, with normal levels of iodine intake, can tolerate chronic exposure to perchlorate at doses of up to 3 mg/day (approximately 40 µg/kg/day) without any effects on thyroid function, including inhibition of iodine uptake.

The Braverman et al. study was simulated using the BBDR model, and predicted T3 and TSH levels were compared to the reported measurements. fT4 was not compared because it was not clear how to convert the T4 index to a concentration and vice versa. As with the Greer simulation, 90 ug/day was used for iodine intake. Baseline T3 and TSH are similar to the measured values. But, as was seen with fT4, the simulated change in hormone levels is severely dampened compared to the measured values.

Table 2. Simulation of Braverman et al. (2006) perchlorate study.

Dose	T3 (nM)		TSH (mIU/L)	
(ug/kg/d)	Simulated	Measured	Simulated	Measured
0	2.63	2.49	1.51	1.20
7	2.63	2.51	1.52	1.60
43	2.62	1.77	1.53	2.60

Téllez Téllez et al. 2005a, 2005b – Chile study in pregnant women

Téllez Téllez et al. (2005a, 2005b) reports the results of a longitudinal epidemiological study among pregnant women from three cities in Chile exposed to concentrations of perchlorate as high as 114

µg/L in the public drinking water. The focus of the study was to evaluate maternal thyroid function during pregnancy, neonatal thyroid function and developmental status at birth, and breast milk iodine and perchlorate levels during lactation. The National Academy of Sciences (2005) has reviewed this study in the context of health implications for perchlorate ingestion and concluded this study should be considered in the evaluation of the U.S. experience with perchlorate in drinking water. The total iodine nutrition among this cohort was also noted to be similar to that of U.S. pregnant women (Téllez Téllez et al. 2005a); therefore, this study should be a key consideration in evaluating the relationship between perchlorate exposure, changes in fT4 in pregnant women and developmental status.

Results from this study, relied upon for BBDR model parameters (specifically the elimination to urine parameter – CLFUP), indicated no effect on thyroid levels in early pregnancy, late pregnancy, or neonates at birth related to perchlorate in drinking water at concentrations up to 114 µg/L. It seems this study should provide a validation dataset for the impact of high concentrations of perchlorate exposure in drinking water on potential changes in fT4 or TSH.

The BBDR model was used to simulate the drinking water study. The predictions of fT4 are consistent with the negative results of the study, though the concentrations are again smaller than those observed. This is not a strong validation of the model given the weak trend of changes in hormone levels seen in comparisons to other studies.

Table 3. Simulation of the Tellez et al. study of pregnant women exposed to perchlorate via drinking water.

Dose	fT4 (pM)	
(ug/kg/d)	Simulated	Measured
0.01	9.74	12.5
0.08	9.73	12.2
2	9.69	12.7

Overall, the BBDR model reproduces the key elements of the findings from these three studies, which indicate that thyroid hormone levels are relatively insensitive to inhibition of thyroid iodine uptake by perchlorate concentrations several orders of magnitude higher than those predicted by the BBDR to affect fT4 in early pregnancy. In particular, it seems biologically implausible that concentrations of perchlorate up to 2 ug/kg/d were demonstrated to be without effect to pregnant women in the Tellez study, while the BBDR model predicts that perchlorate concentrations nearly an order of magnitude lower could result in changes in fT4 during the first trimester. During the first trimester, hCG increases the iodine uptake capacity of the thyroid and the T4 production rate so significantly that TSH concentrations are typically reduced. The BBDR model assumes that during the first trimester thyroid hormone production is controlled by both TSH and hCG but thyroid uptake is controlled by TSH only. However, hCG controls both organification and uptake. During pregnancy, hCG stimulates iodide transport and thyroid hormone synthesis through stimulation of the TSH receptor due to the structural similarity of hCG to TSH. This increase typically results in lower TSH levels (Pesce and Kopp 2014). Thus, during the first trimester, the thyroid is actually in a better position to respond to inhibition of iodine uptake through a direct TSH-mediated response if needed.

2. LINKING BBDR RESULTS TO NEURODEVELOPMENT OUTCOMES

Chapter 5 of USEPA (2017) focuses on the SAB's recommendation to "Identify literature and conduct analyses to support the model outputs for the downstream steps" from the BBDR's predicted changes in thyroid hormones following exposure to perchlorate. Specifically, Chapter 5 was developed to present the process USEPA used to identify literature to support the approach for derivation of the MCLG for perchlorate. USEPA (2017) states, "Based on the recommendations of previous peer review panels, USEPA assumed that changes in thyroid hormone levels would be expected to lead to neurodevelopmental outcomes", and because of this assumption, a complete systematic review of the body of literature on this topic was not performed. Instead, a "focused review of the published literature" was conducted.

The approach is inconsistent with recent recommendations from the National Research Council regarding systematic review and evidence integration (NRC 2014). These recommendations are currently being incorporated into the USEPA's Integrated Risk Information System (IRIS) process and USEPA has recently released scoping and problem formulation materials for several new Integrated Risk Information System (IRIS) assessments, including ethylbenzene (USEPA 2014a), and naphthalene (USEPA 2014b). The approach applied in these assessments is intended to follow recommendations provided by the National Research Council (NRC 2013). While development of MCLGs are not part of the IRIS process, the application of systematic review principles in the identification of studies to define the relationship between fT4 and neurodevelopmental effects, is needed. The application of these principles will not only assist in defining the highest quality studies to address a specific research question, they provide a way to integrate all of the available evidence for the specific research questions raised by the SAB. Systematic reviews include the formulation of a specific question to be addressed and developing a protocol that specifies the methods that will be used to address the question. While a broad research question can lead to a large systematic review, if the research question is limited, such as in the case of perchlorate, then the systematic review becomes more focused.

For the USEPA (2017) MCLG approach, a systematic review question could have been easily developed based on the SAB recommendation (i.e. "Identify literature and conduct analyses to support the model outputs for the downstream steps") and the protocol would simply be focused on the methods for conducting the systematic review to address this very focused systematic review question in a transparent manner. Transparency being defined by USEPA as "sufficient information will be available to understand the scientific rational behind decisions, as well as, reproduce methods used to identify and evaluate data". However, in the case of the literature identified for consideration in the MCLG approach for perchlorate, a well-defined protocol for all steps of the process has not been developed and therefore is inconsistent with the recommendations of the NRC (2013):

> *"A priori decisions and a predefined protocol are critical during the systematic review process (Berlin and Colditz 1999; Dickersin 2002); the protocol should describe the following steps: the research question, the search strategy and data sources, the study inclusion and exclusion criteria, the data to be abstracted and derived from the original studies (such as sample size, exposure and outcome assessment methods, and confounders evaluated), the criteria and methods for pooling effect estimates and measures of variability among studies. Systematic reviews and meta-analyses need to be replicable; other investigators following the same steps should be able to identify the same articles, abstract the same data, and reach similar conclusions."*

At each step of the process for identifying studies for use in the development of the MCLG approach for perchlorate, a detailed set of criteria is needed. For example, if decisions are made to include or exclude any studies, there should be very detailed criteria indicating why studies were included or excluded and it should be specified prior to the initiation of the literature searching process. The criteria for each step should be described in such a way that an independent reviewer could use it to replicate the results of the literature search and review; however, there are several areas in the USEPA (2017) MCLG approach for perchlorate where this level of detail is lacking, making it difficult for an independent reviewer to replicate the results.

2.1 Systematic Review Research Questions

An overall hypothesis or systematic review research question should be developed that is based on the SAB recommendation to clarify the focus of the review and the linkage between altered maternal fT4 (as predicted by the BBDR model) and the potential for adverse neurodevelopmental effects in offspring. Some additional explanation as to how USEPA arrived at the specific neurodevelopmental outcomes of concern should be provided.

2.2 Searching the Published Literature

While the literature search key words are presented in the USEPA (2017) report, there is a lack of explanation as to the reasoning behind the focus on the outcome of concern. The research question should be used to develop the literature search. The major points used or considered in developing the literature search strategy should be presented. In addition, there should be a detailed explanation of the screening criteria used to screen the literature search results. Furthermore, USEPA (2017) does not report the details of the literature search results. For each search string reported in Table 9 of the USEPA (2017) report, a total number of citations identified should be reported. In addition, the criteria used to screen the original search results should be clearly reported in the document. Essentially, each step of the literature search and review should be reported in such a way that any independent party could easily reproduce the results reported in Chapter 5 of USEPA (2017). The lack of this type of information does not allow the reader to determine if any key studies may have been removed from consideration.

2.3 Literature Screening Approach and Selection of Key Studies

USEPA (2017) states that a 3 step approach was used to identify studies for consideration in the development of the approach for derivation of the MCLG for perchlorate. The approaches utilized by USEPA (2017) to identify the epidemiological studies for this evaluation were strictly focused on the appropriateness of the quantitative data for consideration in combination with the output of the BBDR model. Group 2 (studies with categorical analyses only) and Group 3 (studies with analyses not directly compatible with BBDR output) studies were apparently eliminated from consideration in the assessment. While not directly compatible with BBDR modeling output, it is possible that these studies may provide information important in understanding the potential relationship between changes in thyroid hormones and the potential for neurodevelopmental effects, as well as potential key confounders.

While 15 studies were identified in Group 1, only 5 of these were determined by USEPA to include analyses that could be used to connect the results of the BBDR model to incremental changes in adverse neurodevelopmental effects. A clearly defined set of inclusion and exclusion criteria should be developed to clearly convey to the reader why the other 40 studies in Groups 1, 2, and 3 were not considered. In addition, studies that provide no evidence of an inverse relationship between perchlorate exposure and serum thyroid function (e.g. Ghassabian et al. 2014; Modesto et al. 2015; Moleti et al. 2016; Noten et al. 2015) should also be considered to not only understand why these

results are in contrast to the potential research question, but also that the overall weight of evidence can be determined. It is possible that the majority of studies provide evidence that critical factors that are not reported in some of the available studies may explain the reported changes in serum thyroid function.

2.4 Assessment of Study Quality and Risk of Bias

According to recent recommendations from the National Research Council (NRC 2014), the National Toxicology Program's (NTP) Office of Health Assessment and Translation (OHAT) method for the assessment of study quality and risk of bias of the literature (NTP 2015) is one method that should be considered for qualitative and quantitative assessments. "An assessment of study quality evaluates the extent to which the researchers conducted their research to the highest possible standards and how a study is reported. Risk of bias is related to the internal validity of a study and reflects study-design characteristics that can introduce a systematic error (or deviation from the true effect) that might affect the magnitude and even the direction of the apparent effect" (NRC 2014). Each study meeting inclusion criteria in Group 1, 2, and 3, should be evaluated against a predetermined set of study quality and risk of bias criteria and the results of this evaluation should be presented in the perchlorate MCLG approach report.

2.5 Uncertainties Critical to Characterizing Changes in Thyroid Hormone Levels in Pregnant Women Associated with Neurodevelopmental Changes in Offspring

The MCLG approach presented in USEPA (2017) to predict doses of perchlorate that would result in per unit changes in neurodevelopmental measures, is, as noted by USEPA (2017), "...dependent upon predictions from the BBDR model, the derivation of the distribution of fT4, and the evaluations of the relationship between fT4 and neurodevelopment. Each of these steps has inherent uncertainties associated with it."

A major source of uncertainty is related to the five studies in Group 1 with data that could be used to quantitatively describe the relationship between thyroid hormone levels in early pregnancy and changes in neurodevelopment (Pop et al. 1999, 2003; Finken et al. 2013; Korevaar et al. 2016; Vermiglio et al. 2004). None of these five studies relied upon data from US populations or have been demonstrated to have iodine intake similar to US populations. Yet according to Alexander et al. (2017) the reference range of both TSH and fT4 in pregnant women varies depending upon ethnicity. While two studies in Group 1 focused on population groups within the United States, neither were considered for the model because T4 and not fT4 was measured in the pregnant females (Oken et al. 2009) and the relationship between fT4 and neurodevelopment was evaluated in late pregnancy and did not reach statistical significance (Chevrier et al. 2011). USEPA (2017) (Section 6.5.1) states "there is no reason to believe that the impact of fT4 on neurodevelopment would differ by country, unless there is a substantial difference in iodine intake". While USEPA (2017) does make an effort to evaluate changes in iodine intake in women from various populations, including the US, there are not substantial data reported to validate the conclusions that the impact of fT4 on neurodevelopment would differ by population or uncertainty in iodine intake levels would have an impact on the derivation of the MCLG. This is inconsistent with data from the American Thyroid Association (Alexander et al. 2017) that suggest variability in the distribution of thyroid hormone levels across populations and even within ethnicities within a single population.

USEPA (2017) also notes that all five studies used for quantitative analysis relied on a one-time fT4 level during pregnancy (Section 6.5.5). The influence of changes in maternal fT4 on fetal brain development is likely greatest during early pregnancy. The variability in maternal fT4 levels during pregnancy and the lack of measurement of fT4 at time points throughout pregnancy in the studies relied upon introduces a significant amount of uncertainty to the assessment. As stated in USEPA (2017),

> *"Circulating T3 and T4 levels in an individual are maintained within a narrow range by a negative feedback loop with TSH from the pituitary and TRH from the hypothalamus (see Figure 2) that operates around a "set-point." This set-point is different from individual to individual, which generates a population variance in blood levels of thyroid hormone that is considerably broader than the individual variance (Andersen, Pedersen, Bruun, & Laurberg, 2002). Therefore, in euthyroid individuals, serum T4 and T3 fluctuate within a fairly narrow range (about 10% of the population variance), maintained by the negative feedback relationship with serum TSH from the pituitary gland. This normal variation creates a situation where single measures of free or total T4 and TSH are a somewhat imprecise measure of an individual's average T4 and TSH concentrations (Andersen et al., 2002)."*

Several other areas of uncertainty are also highlighted by USEPA (2017). Specifically, USEPA (2017) noted that none of the five studies carried forward provided iodine intake levels (Section 6.5.3), which adds significant uncertainty to the estimates. Three of the 5 studies (Pop et al. 1999, 2003; Vermiglio et al. 2004) also have populations of less than 30 decreasing the statistical power of the studies (section 6.5.4) relied upon for establishing the relationship between changes in fT4 and neurodevelopmental changes. USEPA (2017) also noted uncertainties in regards to the analytical methods used to evaluate fT4 levels and while approaches are being introduced to standardize analytical methods, results at different time points and from different countries may vary considerably due to differences in analytical procedures (USEPA 2017). USEPA (2017) also notes that "there is uncertainty regarding the true fT4 levels at various percentiles in the distribution around the median output from the BBDR model. This is exemplified by the fact that in this analysis larger unit changes are being seen with increasing percentiles of fT4 in most analyses." Finally, other confounders such as iron deficiency were not considered in the analysis. Iron deficiency in pregnant mothers may also be associated with hypothyroxinemia (Yu et al., 2015) and failing to directly account for a relationship between iron deficiency and hypothyroxinemia may introduce an uncertainty into this analysis.

While all of these uncertainties are noted by USEPA (2017), there is no attempt to adjust the MCLG approach in any way to account for these uncertainties. Many of these, especially confounders such as iron deficiency in the study population and a lack of information on iodide intake, can have a significant effect in characterizing changes in thyroid hormone levels associated with changes in neurodevelopmental outcomes. In the absence of adequately accounting for these uncertainties, it is difficult to conclude that small changes in a specific thyroid hormone (e.g. fT4) may accurately predict the potential for neurodevelopmental effects.

3. COMPARISON TO PREVIOUS ASSESSMENTS

In the MCLG approach, USEPA (2017) has focused on five studies that evaluated the relationship of maternal fT4 and several neurodevelopmental endpoints (IQ, mental development index (MDI), psychomotor development index (PDI), standard deviation of reaction time) based on the measurement of fT4 during early pregnancy. Results from previous studies have provided the basis for No Observed Effect Levels (NOELs) for health effects of perchlorate in the development of Reference Doses and currently recommended Health Reference Levels (HRLs), including Greer et al. (2002) which reported results similar to the BBDR model in human test subjects. Results reported by Greer et al. (2002) in which subjects were exposed to perchlorate in drinking water at doses of 0.007, 0.02, 0.1, or 0.5 mg/kg/day for 14 days demonstrated a NOEL for perchlorate inhibition of radioiodide uptake by the thyroid NIS following exposure to 7 µg/kg/day. The point of departure from the Greer et al. (2002) study represents a perchlorate level that precedes the inhibition of iodine uptake by the thyroid. The NAS RfD developed based on the point of departure (POD) from this study is a departure from the Agency's traditional approach of using a No Observed Adverse Effect Level (NOAEL) for regulatory actions. The NAS's use of a No Observed Effect Level (NOEL) is based on "using a nonadverse effect that is upstream of the adverse effect [which] is a more conservative and health protective approach".

While these studies have not been conducted in pregnant women (the population of interest for the MCLG approach), as noted by in USEPA (2017):

> *"...the BBDR model predicts very little difference in non-pregnant and first-trimester response to perchlorate. This likely occurs because the half-life of (organified) iodine in the adult thyroid is around six months, hence the availability of thyroidal iodine in the first trimester pregnant woman is determined to a very large extent by her nutrition and perchlorate exposure several years preceding pregnancy."*

This suggests comparison of the current modeling results to those from studies conducted in adults should provide insight into the predictions of the model and the conclusions regarding the changes in thyroid hormone levels that may result in neurodevelopmental effects.

The current approach for deriving the MCLG assumes any exposure to perchlorate reduces fT4 to some extent (p. 3-17 of USEPA doc). In addition, linear regression analyses conducted to evaluate the relationship between changes in fT4 and neurodevelopmental effects further assumes any change in fT4 results in some risk of neurodevelopmental effects. These assumptions are in contrast to the results from the Greer et al. (2002) in which exposures to perchlorate were as high as 500 µg/kg/day and no impact on thyroid hormone levels was observed. This was true for both men and women. In addition, in a study conducted by Braverman et al. (2006), 6 months of exposure to perchlorate in capsules at doses up to 3 mg/day (approximately 40 µg/kg/day) was reported to have no effect on thyroid function, including inhibition of thyroid iodide uptake as well as serum levels of thyroid hormones, TSH, and Tg in a small group of volunteers.

USEPA (2017) notes (p. 6-16) that from results of the literature review, it appears the relationship between maternal fT4 and fetal brain development has a temporal relationship, with this influence likely being greatest in early pregnancy (i.e. prior to mid-gestation). The focus of the evaluation is on gestational weeks 12, 13, and 16, where the mother's fT4 levels will have the greatest impact on the fetus. This should allow for comparison to the model results in pregnant women to results from previous studies focused on identification of perchlorate concentrations that would impact fT4 levels in adult women, such as the Greer et al. (2002) study.

In comparing the current BBDR model predictions to previous assessments, in Tables 35 and 40 of USEPA (2017) a perchlorate dose of 0.3-0.4 µg/kg/day would result in a 1% increase in the

proportion of the population with hypothyroxinemia and a perchlorate dose of 2.1-2.2 µg/kg/day would result in a 5% increase in proportion of the population with hypothyroxinemia. These modeling results suggest a potential for a significant change in thyroid hormones, as well as adverse effects on neurodevelopment at doses of perchlorate exposure for which there is evidence that decreases in fT4 are not observed. Based on the mode of action proposed by USEPA (2017), decreases in fT4 and increases in TSH would be prerequisite steps for the potential for neurodevelopmental effects. These changes in hormone levels are not observed in workers in the Greer et al. study following exposure up to 500 µg/kg/day. The current assessment suggests population changes in fT4 would be observed that would shift the proportion of pregnant women that would be hypothyroxinemic at doses of perchlorate below the previously defined NOEL (7 µg/kg/day).

Table 39 of USEPA (2017) provides the predicted dose of perchlorate per unit change in neurodevelopmental measure for low iodine intake individuals. Considering multiple neurodevelopmental endpoints (IQ, mental development index (MDI), psychomotor development index (PDI), standard deviation of reaction time), those for IQ are approximately at or above (6.5 – 45 µg/kg/day) the NOEL from Greer et al. (2002) and are associated with decreases in fT4 of 4.3 to 18.7%. The remaining doses associated with the other neurodevelopmental endpoints are 1.7 to 3.0 µg/kg/day and associated with decreases in fT4 of 1.3 to 2.4%. These percent changes in fT4 are very small and considering the potential uncertainty and variability in measuring fT4 levels, may not be detectable in the clinical setting. The dose of perchlorate estimated to result in a 1% or 5% increase in the proportion of hypothyroxinemic pregnant women is even lower, ranging from 0.3 to 2.2 µg/kg/day. Multiple studies in adults and pregnant women (Greer et al. 2002; Braverman et al. 2006; Téllez Téllez et al. 2005) provide evidence that no impact on iodine uptake or thyroid hormone levels would be expected at these dose levels. Based on the mode of action proposed by USEPA (2017), these events would be precursors necessary for the development of neurodevelopmental effects.

4. OVERALL CONCLUSIONS/COMMENTS

- While we applaud the EPA for the application of a BBDR model in the MCLG approach, as these models integrate the available science for a compound of interest, there is some concern that uncertainties inherent in the model call into question its proposed application in the risk assessment for perchlorate and whether it is fit for that purpose. While the hormone component of the model is a definite scientific improvement in terms of incorporating the available biology, there is a lack of data to provide validation of multiple steps in the proposed approach and of the assumptions/parameters within the BBDR model.
- Many of the changes in fT4 that are predicted by the MCLG approach to impact the population distribution of fT4 and therefore result in per unit changes in neurodevelopmental outcomes are small percent changes (some as low as a 1.3-4.3% change). This would appear to suggest that the extended version of the BBDR model has a capability to estimate small changes in fT4 with precision that is not demonstrated by any adequate validation. Further, the model predictions of fT4 underpredict observed data in various clinical studies by substantially more than 1.3-4.3%. This suggests that the model is not precise enough to predict such small changes in fT4. Moreover, considering the variability of fT4 in the populations of interest, there is uncertainty as to whether these slight changes could be measured clinically, considering the greater impact of iodine intake on hormone levels.
- Until additional data are available to validate current extensions of the BBDR model to the pregnant woman, the Greer et al. (2002) and Braverman et al. (2006) studies provide the critical information in determining concentrations of perchlorate that do not result in significant inhibition of iodide uptake and, therefore, impacts on fT4. Based on recommendations from the National Research Council (2005), points of departure provided by these studies used in combination with uncertainty factors were considered to be protective of sensitive subpopulations, and provides a basis for future risk management decisions.

5. REFERENCES

Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. 2017. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid, 27(3): 315-389.

Andersen S, Pedersen KM, Bruun NH, Laurberg P. 2002. Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease. The Journal of Clinical Endocrinology and Metabolism, 87(3): 1068-1072.

Berlin JA, Colditz GA. 1999. The role of meta-analysis in the regulatory process for foods, drugs, and devices. JAMA 281(9): 830-834 (As cited in NRC 2013).

Braverman L, Pearce EN, He X, Pino S, Seeley M, Beck B, Magnani B, Bleunt BC, Firek A. 2006. Effects of six months of daily low-dose perchlorate exposure on thyroid function in healthy volunteers. The Journal of Clinical Endocrinology and Metabolism, 91(7): 2721-2794.

Chevrier J, Harley KG, Kogut K, Holland N, Johnson C, Eskenazi B. 2011. Maternal thyroid function during the second half of pregnancy and child neurodevelopment at 6, 12, 24, and 60 months of age. Journal of Thyroid Research, 2011: 426427.

Delange FM. (Editor). 2000. Iodine deficiency (8th edition). Philadelphia, PA: Lippincott, Williams, and Wilkins (As cited in USEPA 2017).

Dickersin K. 2002. Systematic reviews in epidemiology: Why are we so far behind? International Journal of Epidemiology, 31(1): 6-12 (As cited in NRC 2013).

Finken MJJ, van Eijsden M, Loomans EM, Vrijkotte TGM, Rotteveel J. 2013. Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5- to 6-year-old offspring. Journal of Clinical Endocrinology and Metabolism, 98(4): 1417-1426.

Ghassabian A, Henrichs J, Tiemeier H. 2014. Impact of mild thyroid hormone deficiency in pregnancy on cognitive function in children: lessons from the Generation R Study. Clinical Endocrinology and Metabolism, 28(2): 221-232.

Glinoer D. 1997. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocrine Reviews, 18(3): 404-433 (As cited in USEPA 2017).

Greer MA, Goodman G, Pleus RC, Greer SE. 2002. Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans. Environmental Health Perspectives, 110(9): 927-937.

Korevaar TIM, Muetzel R, Medici M, Chaker L, Jaddoe VWV, de Rijke YB, Steegers EAP, Visser TJ, White T, Tiemeier H, Peeters RP. 2016. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: A population-based prospective cohort study. The Lancet Diabetes and Endocrinology, 4(1): 35-43.

Lumen A, Mattie DR, Fisher JW. 2013. Evaluation of perturbations in serum thyroid hormones during human pregnancy due to dietary iodide and perchlorate exposure using a biologically based dose-response model. Toxicological Sciences, 133(2): 320-341 (As cited in USEPA 2017).

Modesto T, Tiemeier H, Peeters RP, Jaddoe VW, Hofman A, Verhulst FC, Ghassabian A. 2015. Maternal mild thyroid hormone insufficiency in early pregnancy and attention deficit/hyperactivity disorder symptoms in children. JAMA, 169(9): 838-845.

Moleti M, Trimarchi F, Tortorella G, Candia Longo A, Giorgianni G, Sturniolo G, Alibrandi A, Vermiglio F. 2016. Effects of maternal iodine nutrition and thyroid status on cognitive development in offspring: A pilot study. Thyroid, 26(2): 296-305.

National Academy of Sciences. 2005. Health Implications of Perchlorate Ingestion. National Academy Press, Washington DC.

Nicoloff JT, Low JC, Dussault JH, Fisher DA. 1972. Simultaneous measurement of thyroxine and triiodothyronine peripheral turnover kinetics in man. Journal of Clinical Investigation, 51(3): 473-483 (As cited in USEPA 2017).

Noten AM, Loomans EM, Vrijkotte TG, van de Ven PM, van Trotsenburg AS, Rotteveel J, van Eijsden M, Finken MJ. 2015. Maternal hypothyroxinaemia in early pregnancy and school performance in 5-year-old offspring. European Journal of Endocrinology, 173(5): 563-571.

NRC. 2013. Critical Aspects of USEPA's IRIS Assessment of Inorganic Arsenic: Interim Report. National Research Council, Division on Earth and Life Studies, Board on Environmental Studies and Toxicology, Committee on Inorganic Arsenic. Available at: https://books.google.com/books?id=PflhCwAAQBAJ&lpg=PP1&dq=Critical%20Aspects%20of%20EPA's%20IRIS%20Assessment%20of%20Inorganic%20Arsenic%3A%20Interim%20Report&pg=PR10#v=onepage&q=Critical%20Aspects%20of%20EPA's%20IRIS%20Assessment%20of%20Inorganic%20Arsenic:%20Interim%20Report&f=false.

NRC. 2014. Review of USEPA's Integrated Risk Information System (IRIS) Process. National Research Council. Washington, DC: The National Academies Press. Available online: http://www.nap.edu/catalog/18764/review-of-epas-integrated-risk-information-system-iris-process

NTP. 2015. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. National Toxicology Program, United States Department of Health and Human Services. Office of Health Assessment and Translation (OHAT), Division of the National Toxicology Program, National Institute of Environmental Health Sciences.

Oken E, Braverman L, Platek D, Mitchell ML, Lee SL, Pearce EN. 2009. Neonatal thyroxine, maternal thyroid function, and child cognition. The Journal of Clinical Endocrinology and Metabolism, 94(2): 497-503.

Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ. 2003. Maternal hypothyroxinemia during early pregnancy and subsequent child development: A 3-year follow-up study. Clinical Endocrinology, 59: 282-288.

Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga WM, Drexhage HA, Vader HL. 1999. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clinical Endocrinology, 50: 149-155.

SAB. 2013. SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate. EPA-SAB-13-004. Washington, DC.

Schlosser PM. 2016. Revision of the affinity constant for perchlorate binding to the sodium-iodide symporter based on in vitro and human in vivo data. Journal of Applied Toxicology, 36(12): 1531-1535 (As cited in USEPA 2017).

Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce E, Soldin O, Sullivan S, Wiersinga W. 2011. Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and Postpartum. The American Thyroid Association Taskforce on Thyroid Disease during Pregnancy and postpartum. Thyroid, 21(10): 1081-1125.

Steinmaus C, Pearl M, Kharrazi M, Blount BC, Miller MD, Pearce EN, Valentin-Blasini L, DeLorenze G, Hoofnagle AN, Liaw J. 2016. Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in Southern California. Environmental Health Perspectives, 124(6): 861-867.

Téllez Téllez R, Michaud Chacón P, Reyes Abarca C, Blount BC, Van Landingham CB, Crump KS, Gibbs JP. 2005a. Long-term environmental exposure to perchlorate through drinking water and thyroid function during pregnancy and the neonatal period. Thyroid, 15(9), 963-975.

Téllez Téllez R, Michaud Chacón P, Reyes Abarca C, Blount BC, Van Landingham CB, Crump KS, Gibbs JP. 2005b. Chronic environmental exposure to perchlorate through drinking water and thyroid function during pregnancy and the neonatal period. Thyroid, 15(X).

USEPA. 2005. Integrated Risk Information System Chemical Assessment Summary: Perchlorate and Perchlorate Salts.

USEPA. 2014a. Scoping and problem formulation for the identification of potential health hazards for the Integrated Risk Information System (IRIS) Toxicological Review of ethylbenzene [CASRN 100-41-4]. National Center Environmental Assessment, Office of Research and Development, United States Environmental Protection Agency, Washington, DC. EPA/635/R-14/198.

USEPA. 2014b. Scoping and problem formulation for the identification of potential health hazards for the Integrated Risk Information System (IRIS) Toxicological Review of naphthalene [CASRN 91-20-3]. National Center Environmental Assessment, Office of Research and Development, United States Environmental Protection Agency, Washington, DC. EPA/635/R-14/199.

USEPA. 2017. Draft Report: Proposed approaches to inform the derivation of a maximum contaminant level foal for perchlorate in drinking water. Volume 1. Office of Ground Water and Drinking Water. United States Environmental Protection Agency. EPA-OGWDW. September 2017.

Vermiglio F, Lo Presti VP, Moleti M, Sidoti M, Tortorella G, Scaffidi G, Castagna MG, Mattina F, Violi MA, Crisà A, Artemisia A, Trimarchi F. 2004. Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: A possible novel iodine deficiency disorder in developed countries. The Journal of Clinical Endocrinology and Metabolism, 89(12): 6054-6060.

Yu X, Shan Z, Li C, Mao J, Wang W, Xie X, Liu A, Teng X, Zhou W, Li C, Xu B, Bi L, Meng T, Du J, Zhang S, Gao Z, Zhang X, Yang L, Fan C, Teng W. 2015. Iron deficiency, an independent risk factor for isolated hypothyroxinemia in pregnant and nonpregnant women of childbearing age in China. The Journal of Clinical Endocrinology and Metabolism, 100(4):1594-601.