**ASSOCIATION OF
METROPOLITAN
WATER AGENCIES**

November 20, 2017

Samuel Hernandez
USEPA Headquarters
Office of Ground Water and Drinking
Water, Standards and Risk Management
Division, (Mail Code 4607M)
1200 Pennsylvania Avenue, N. W.
Washington, DC 20460

Re: Docket ID No. EPA-HQ-OW-2016-0438, Request for Public Comments To Be Sent to EPA
on Peer Review Materials To Inform the Safe Drinking Water Act Decision Making on
Perchlorate

Dear Mr. Hernandez:

The Association of Metropolitan Agencies (AMWA) is an organization representing the largest
publically owned drinking water utilities in the United States. Any changes in the development
of national primary drinking water regulations significantly impact our members. EPA has
published a request for comment on the draft report: *Proposed Approaches to Inform the
Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water.* AMWA
has been involved with the issue of perchlorate since EPA first began pursuing a regulatory
determination.

AMWA appreciates the work that EPA has done in order to make a scientifically sound decision
on the regulation of perchlorate. The multiple reviews and drafts that EPA has compiled in order
to develop a reliable and precise model for determining the impact of perchlorate is a valuable
scientific approach. While AMWA agrees that there is a possible correlation between perchlorate
exposure and iodine uptake, which in turn may impact thyroid hormone levels, the association
has concerns with the methodology of the model and its use to extrapolate possible neurological
outcomes in children. AMWA is not certain that the model is precise and reliable enough to
determine a thyroid hormone level that corresponds/correlates with perchlorate exposure and is
concerned with the possible biases that are introduced by using the model's output with already
existing neurodevelopment data from the literature in order to make conclusions on the impact of
perchlorate on neurodevelopment. Due to the reasons stated above, AMWA is concerned that the
methods shown in this report set a worrying precedent for regulatory determination decisions to

follow.

Due to the importance of this report as it relates to the development of a maximum contaminant level goal for perchlorate, AMWA is pleased to submit these comments for the Safe Drinking Water Act decision making on perchlorate. Our specific comments are provided as an attachment. If you have any questions, please contact Stephanie Hayes Schlea (schlea@amwa.net), AMWA's Manager of Regulatory and Scientific Affairs.

Sincerely,

Diane VanDe Hei
Chief Executive Officer

Attachment

CC: Eric Burneson; Michael Shapiro

**AMWA's Comments to EPA on Peer Review Materials To Inform the Safe
Drinking Water Act Decision Making on Perchlorate**

General Comments

1. The peer review panel in January 2017 advised EPA to include first trimester, but
    not to exclude the other life stages. EPA focused on only the first trimester for
    their revised model due to the lack of data for other stages and the stronger
    relationship between hormone levels and neurodevelopmental outcomes in early
    pregnancy. However, the original model encompassed late trimester and infancy,
    particularly in regards to bottle and breast-feeding infants. EPA states that
    excluding these stages allows for a simplified model. AMWA requests that EPA
    give more explanation as to why the model was limited to the first trimester
    instead of just expanding the original model in order to evaluate all stages.
    AMWA also suggests that EPA discuss the biases and uncertainties that are added
    to EPA's analysis by only looking at this life stage.

2. Although this has been stated in previous discussions, AMWA reiterates that a
    lack of iodine may be the larger factor contributing to thyroid dysfunction
    regardless of perchlorate exposure. According to the report, one six month study
    found no changes to thyroid function, but the subjects had higher than average
    concentrations of iodine, which the report suggests may have been protective.
    AMWA recommends EPA discuss the possibilities for why no change in thyroid
    function was found and if iodine deficiency may be the larger factor in thyroid
    dysfunction.

3. A second statement in the report (p. 3-13) mentions that "there is little predicted
    change in the percentage drop in fT4 or percentage increase in TSH between
    gestational weeks due to perchlorate exposure, although baseline TSH and total
    T4 levels do vary significantly with gestation. However, there is a significant drop
    in fT4 and increase in TSH with decreased iodide intake in the absence of
    perchlorate exposure. AMWA recommends that EPA discuss possibilities for why
    there is little change in fT4 due to perchlorate exposure and if the major factor
    again might be iodine intake.

4. According to Huber et al. (2011), drinking water contributes 20% to perchlorate
    intake and food contributes 80%. For the studies cited, is food intake accounted
    for and if so, how much effect from perchlorate is due to solely drinking water?

5. In section 8, the report lists many other possible health concerns regarding
    perchlorate. In particular, in section 8.3 (p. 8-2) it is stated that the Comparative
    Toxicogenomics Database (CTD) "identified 455 diseases potentially associated
    with perchlorate." However, in the paragraph below (p. 8-3) this statement it is
    said "connecting perchlorate with other adverse outcomes such as
    neurodegenerative diseases is highly uncertain at this time. Until more detailed
    information is collected that will allow the CTD to be used for hazard
    assessments, it is currently limited to hypothesizing adverse outcome pathways
    and designing additional studies to more completely understand the range of

adverse health effects associated with perchlorate." What is the reasoning for including these statements linking perchlorate to a variety of conditions if it is limited to only hypothesizing?

6. There seems to be a variety of studies that conclude perchlorate does affect TSH and fT4 levels, particularly the studies used in this report, but there are also many studies that have found no correlation. For example, Pearce et al. (2010, p. 3321) found that there was "no association between urinary perchlorate levels and first-trimester serum TSH or FT4 levels." A second study by Brent (2014, p. 4066) stated, "Perchlorate was detected in the urine of all women studied, but there was no correlation of perchlorate levels in the urine with maternal thyroid function. This finding was especially significant because the median iodine intake in Cardiff and Turin, 98 and 52 μg/L, respectively, was relatively low. Individuals with lower iodine intake are thought to be more susceptible to the negative effects of perchlorate exposure." In one of the more recent perchlorate studies (Leung, Pearce and Braverman 2014, p. 376), the conclusion was as follows; "Available data thus far have been inconsistent in demonstrating a correlation between low-level perchlorate exposure and thyroid dysfunction, particularly among those most vulnerable to even mild thyroid dysfunction. Ongoing research is needed to help better understand the potentially adverse effects of human perchlorate exposure, especially in light of recent discussion to proceed with costly longterm perchlorate regulation in U.S. drinking water."

   What reasoning does EPA have for the variation in findings from these studies? AMWA recommends that EPA discuss if there is sufficient data to determine a relationship between perchlorate and hormone levels during pregnancy, particularly at lower levels within sensitive populations.

Precision and Reliability of the Model

1. In section 3.5, it is stated that the incorporation of a feedback loop in the model introduces uncertainties. Fitzgerald and Bean (2016) are cited within the report stating that increasing TSH levels do not have a consistently predictable impact on T4 levels. The report goes on to cite Hadlow et al (2013), which indicates the relationship between TSH and T4 levels is consistently a decreasing function but that it is variable with many factors. AMWA recommends that EPA discuss how the uncertainty of this relationship impacts the reliability and precision on the model.

2. A significant portion of this report relies on the correlation between low thyroid hormone in the first trimester of pregnancy and decreased neurodevelopment. There are recent studies that have shown a high concentration of thyroid hormone may have similar detrimental effects on neurodevelopment, including one of the five case studies used for this report, Korevaar et al. (2016). AMWA recommends that EPA discuss how certain and reliable the correlation is between thyroid hormone in pregnancy and its impacts on neurodevelopment.

3. In section 3.3.1, the report indicates that NHANES 2007-2012 data for non-pregnant women was used as part of a parameter calibration procedure to simulate population percentiles of fT4, T4, T3, and TSH due to limited data in the range of iodine intake levels of below 75 μg/day. With limited data below 75 μg/day and no data for pregnant women, AMWA recommends that EPA discuss the reliability of this data for use as a calibration for a parameter within the model.

Isolating Perchlorate as the Main Contributing Factor

1. In section 3.5 it is stated that clinical toxicology and occupational studies in high dose subjects showed minimal changes in hormone levels. These populations are not sensitive, nor are they the life stage that the model attempts to study, however, how does EPA explain the lack of a hormonal response at even high doses?

2. This report states that iron deficiency may also cause hypothyroxinemia. A study by Yu et al. (2015) found an association between iron deficiency and isolated hypothyroxinemia in both pregnant and non-pregnant childbearing-aged women, independent of the effects of iodine. A second study (Chang et al. 2013) found a possible correlation between iron deficiency and psychomotor development index (PDI), a factor that two of the studies in this report use to determine the effects of perchlorate exposure. The U.S. Preventative Services Task Force stated in a 2015 report (Siu 2015) that there is little data for the percentage of individuals in the U.S. with iron deficiency. With this in mind, how do you isolate the impacts of perchlorate and account for the possibility of iron deficiency?

3. Figure 5 in section 3.4 (p. 3-13), states the figure "shows that 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." How does this model account for the possibility that perchlorate exposure's impact on iodine uptake is determined by the years leading up to pregnancy? If considering perchlorate impacts years before pregnancy, how would you exclude other possible factors? AMWA recommends that EPA discuss how these uncertainties impact the reliability and output of the model.

Uncertainties within the Model and Study

1. In section 1.1.2, the report states that the adult thyroid contains several months of T4 stored in the colloid and that it is not expected to see a result in thyroid status in only a two-week study. The five studies selected only looked at thyroid hormone levels at certain points during pregnancy. Some only used hormone values taken at one point during gestation. AMWA recommends that EPA discuss how much uncertainty this brings to the model's output.

2. The report states that the relationship between fT4 and neurodevelopment is still very much evolving. AMWA recommends that the panel discuss the reliability

and certainty of fT4 level impacts on neurodevelopment. AMWA also recommends that EPA discuss any variations in recent findings related to the relationship between fT4 levels and neurodevelopment.

3. Of the five studies used with the model, only two assessed iodine status. With the large impact that iodine has on thyroid hormone levels, AMWA recommends that EPA discuss how much uncertainty this lack of data brings into the results of the report.

4. The populations from the studies used with the model are not from the US, but instead are from the Netherlands and Italy. The report says there is no reason to believe that the impact of fT4 would vary by country unless there is a substantial difference in iodine intake and that three studies showed that iodine intake was similar between the Netherlands and the US. How sure is EPA of this statement, in particular in light of the case studies reviewed, as only two gave data on iodine status? Does EPA have more data to support this postulate?

   Are there other environmental factors that could be influenced based on geographic location? In particular, how does the Vermiglio (2004) study, one of the five studies used, which is in northern Sicily, compare to iodine levels in the U.S.? Two studies (Andersson, Karumbunathan, & Zimmermann 2012; Lazarus 2014) looked at trends in iodine deficiency and found that Europe tended to be iodine deficient, accounting for over a third of the iodine deficient countries in the world, and that the U.S. was, as a whole, iodine sufficient. Zimmermann's 2012 study specifically stated that Italy was iodine deficient including within the pregnant population. Although this study did mention that the Netherlands, where the other four studies have occurred, had levels of iodine within pregnant women that was deemed sufficient.

   AMWA recommends that EPA discuss the possible uncertainties and bias that this assumption brings into the study.

5. The model was limited to using fT4 levels at 12-16 weeks gestation based on a recommendation from the Science Advisory Board (SAB) during the initial review of the model. In section 2.6, the report states that fT4 levels aren't as impactful after 16 weeks, but are still involved in some measure. AMWA recommends that EPA discuss in more detail how much impact fT4 levels can have past 16 weeks gestation and how this might impact the results of the study in relation to neurodevelopment.

6. In section 6.5.2 (p. 6-16) it is stated that "it is difficult to ascertain the true implications of a change in the standard deviation of reaction time, the endpoint with which there is a significant association with maternal fT4 levels." If the implications are so uncertain, why use this study? AMWA recommends that EPA discuss how this uncertainty may impact the interpretation of the results of the report.

7. In section 6.5.5 (p. 6-18) it is mentioned that thyroid tests have yet to be standardized, but that this shouldn't pose a problem "because all individuals in the papers were assessed using the same techniques, any bias resulting from this

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source of uncertainty would likely be random and would tend to bias toward the null." This appears to suggest that the same tests are used within each single study, but not necessarily throughout all five chosen studies. AMWA recommends that EPA explain why using different tests among studies wouldn't bring any uncertainty to the results.

8. One study that is referenced for showing significantly increased adverse health affects, particularly in regards to IQ (Taylor et al. 2014, p. 4296) explicitly states in the paper that their "results should be interpreted with caution and analysis viewed in the context of hypothesis generation, although the observed deleterious effects principally on VIQ are in keeping with a recent study of maternal iodine deficiency and subsequent offspring cognitive development. We would not recommend action on perchlorate levels from this study alone, although our report highlights a pressing need for larger studies of perchlorate levels from the general pregnant population and those with undetected hypothyroidism. Future studies should utilize samples taken at several stages of pregnancy with subsequent neonatal thyroid function and more detailed cognitive development of offspring, in particular VIQ." VIQ meaning verbal IQ.

   In light of the author's recommendation, AMWA recommends that EPA discuss whether or not the science has come far enough since this study to make a conclusive determination that perchlorate has an effect on IQ in offspring, particularly since hormone levels are only being considered during weeks 12-16 of gestation.

9. Three of the studies (Pop et al. 1999; Pop et al. 2003; Vermiglio et al. 2004) all had very small sample sizes at 22, 57, and 27 individual children respectively. In comparison, the other two studies used significantly larger sample sizes at 3,839 and 1,765. AMWA recommends that EPA discuss the reliability of the conclusions for the three smaller studies.

Possible Bias

1. In section 5.1, the literature review procedure is discussed. It is mentioned that "search strings" were used in order to find studies that may work best within the model EPA has created (i.e. neurodevelopment AND hypothyroxinemia; hypothyroxinemia AND autism; etc.). AMWA recommends that EPA discuss the biases, if any, that this method brings into determining the effect of hypothyroxinemia on neurodevelopment.
2. The procedure utilized to determine which studies were to be used were only ones that found significance between fT4 and neurodevelopment, the reasoning for this being that only these studies would work within the model. In section 6.5 (p. 6-14) the report states, "one global uncertainty in this analysis is that the state of the science on the relationship between maternal fT4 levels and offspring neurodevelopment is constantly evolving." AMWA recommends that EPA discuss the biases introduced into this report by only using these five studies and the method utilized to select them.

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3. Hypothyroxinemia is defined in the report (p. 2-4) by the Science Advisory Board's definition of "a variety of cutoffs….ranging from fT4 below the 10th or 5th percentiles to below the 2.5[th] percentile." This report used the 10th percentile. According to Dosiou and Medici (2017, p. R24), "there are substantial differences in the definition of IMH between studies, which significantly affect the interpretation of prevalence data for this condition." Why was the 10th percentile chosen? When looking at the "shift" of women who become hypothyroxinemic due to perchlorate, how might these numbers be different if using the 2.5[th] percentile? AMWA recommends that EPA discuss the biases, if any, this may bring to the report.

4. Different neurodevelopment measurements are used with the model; two studies look at PDI, two look at IQ, and one looks at reaction time. As a whole there are five studies, but in actuality there are three different unknowns between them. This inherently leaves smaller sample sizes for each parameter and, as discussed above, some of these data sets are already quite small. With the amount of data on each single factor, AMWA recommends that EPA discuss whether or not there is enough data to support the findings and if more studies should be analyzed before drawing a conclusion.

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