

**NEW JERSEY DEPARTMENT OF ENVIRONMENTAL PROTECTION
SCIENCE ADVISORY BOARD**

**FINAL REPORT
REVIEW OF PROPOSED EPA MAXIMUM CONTAMINANT LEVEL FOR
PERCHLORATE**

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EXECUTIVE SUMMARY

On December 24, 2019, the Public Health Standing Committee (hereafter referred to as the Committee) of the New Jersey Department of Environmental Protection (NJDEP) Science Advisory Board was charged with examining the U.S. Environmental Protection Agency's (EPA, 2019a) proposal for adopting a Maximum Contaminant Level (MCL) for the chemical perchlorate. To address the charge questions developed by NJDEP, a Work Group consisting of most members of the Public Health Standing Committee and two experts invited to serve as external members was formed. All Committee members were given the opportunity to participate in the Work Group and to review and comment on the Work Group's report.

EPA's proposed MCL is based on a Maximum Contaminant Level Goal (MCLG; i.e. health-based drinking water concentration) of 56 µg/L. Perchlorate interferes with the transport of iodine into the thyroid gland, with the potential for decreased formation of thyroid hormone, reduced serum thyroid hormone concentration and adverse effects secondary to low thyroid hormone. This has effects at all human life stages, but particularly during early development when the nervous system is developing.

The Committee reviewed the EPA's overall approach for development of a Reference Dose (RfD) and MCLG for perchlorate, the selection of a sensitive period (first trimester of fetal development), and the use of data derived from a study by Korevaar et al. (2016). The Committee also reviewed earlier EPA perchlorate risk assessment documents (Appendix 1) and the basis for perchlorate drinking water guidelines previously developed by EPA and other states (Appendix 2). The Committee made the following determinations:

- 1) The modeling approach used by EPA links predictions of perchlorate's effect on thyroid hormone production in early-pregnancy women who have low iodide intake with epidemiologic data for effects of decreased early pregnancy thyroid hormone levels on neurodevelopment. This is an appropriate approach to risk assessment, but the models and their application are complex and not transparent, with many sources of large uncertainties at several points. The EPA approach is informative regarding effects from exposure in early pregnancy. However, it is not necessarily preferable to or less uncertain than the simpler and more straightforward approach previously used by the National Academy of Sciences (NAS), the EPA Integrated Risk Information System (IRIS) and several states based on a RfD derived from decreased thyroidal iodine uptake in adult volunteers (Greer et al., 2002). The Committee notes that the NJDEP Ground Water Quality Standard for perchlorate uses the RfD based on Greer et al. (2002) that was developed by the NAS and adopted by EPA IRIS.
- 2) Interference with maternal thyroid function and hormone production would seriously impact early neurodevelopment in the embryo/fetus, with the potential for cognitive

impairment. The Committee accepted EPA's choice of the first trimester as an appropriate critical period with adequate data, and it concluded that data appropriate for use in risk assessment are not available for other known sensitive periods during development including the neonatal period that could be as sensitive or more sensitive to perchlorate.

- 3) The Korevaar et al. (2016) data on the relationship between free thyroxine (fT4) in early pregnancy and decreased IQ in the offspring provide an appropriate starting point for the risk assessment. However, the EPA selectively re-analyzed the data, using a linear model which the Committee believes underestimated the slope of the lower portion of the dose-response curve as compared to the quadratic model presented by Korevaar et al. (2016).
- 4) The Committee accepted EPA's choice of IQ point loss as the critical endpoint, based on the availability of information on IQ loss that is suitable for risk assessment, although other neurodevelopmental endpoints might be more sensitive. The Committee was critical of the EPA's choice of a criterion of a loss of 2 IQ points, concluding that it is inadequately protective. Other agencies have based standards or regulations on a 1 IQ point loss. EPA offered 1 IQ point loss or 3 IQ point loss as alternative criteria with corresponding alternative MCLs and MCLGs of 18 µg/L and 90 µg/L. The Committee recommended that, of the IQ decrement options proposed by EPA, the IQ point value of 1 should be used in deriving an appropriate RfD.
- 5) The Committee's consensus was that EPA's decision to apply a total uncertainty factor (UF) of 3 to its point of departure is seriously inadequate. Considering that there may be more sensitive subpopulations and the many uncertainties and data gaps associated with the EPA approach, as discussed in detail in this report, the Committee determined that deriving a RfD from the existing data and models would require use of total UF in the range of 10 to 100 or greater, with the largest number of members endorsing a total UF of at least 30.
- 6) The Committee evaluated the Relative Source Contribution (RSC), which accounts for exposure from sources other than drinking water. It concluded that the approach used to determine the RSC is appropriate. However, the RSC would be more stringent (lower) if a more appropriate RfD (lower) was used, as recommended by the Committee. The assumed drinking water consumption rate was considered to be appropriate for the selected health endpoint.
- 7) In conclusion the Committee determined that, at several points in the MCLG derivation process, EPA chose non-conservative approaches or assumptions. Although the Committee was not charged with developing an MCL for NJ, the use of a RfD for a 1 IQ

point loss that includes a total UF of 10, 30, or 100, along with a 20% RSC appropriate with such a RfD, would yield MCLGs of 1.9, 0.6, and 0.19 $\mu\text{g/L}$, respectively. The Committee noted that these values are close to or below the range of health-based drinking water values (0.5 to 15 $\mu\text{g/L}$) that other agencies (including EPA and the NJ Drinking Water Quality Institute) and other states including (MA and CA) have developed using RfDs for decreased thyroidal iodine uptake in adult volunteers in Greer et al. (2002). The Committee concluded that 56 $\mu\text{g/L}$ would not be a protective MCL.

- 8) The Committee therefore concluded that health protective values based on the EPA modeling approach and an appropriate critical endpoint and UFs would fall in the range of approximately 0.2 to 2 $\mu\text{g/L}$.
- 9) On June 18, 2020, as the Committee was finalizing its report, EPA announced its decision not to regulate perchlorate in drinking water. While this possibility was included as an alternative in the EPA's proposal, NJDEP's charge questions did not ask the Committee to evaluate this issue and the committee proceeded under the assumption that regulation of perchlorate in drinking water is protective of public health.
- 10) In conclusion, the Committee unanimously concluded that addressing perchlorate in drinking water, by establishing an MCL, is an appropriate and needed environmental health action, protective of public health, by protecting thyroid hormone production and function. The Committee determined that the potential MCLs and MCLGs of 18 – 90 $\mu\text{g/L}$ proposed by the EPA were at least an order of magnitude too high to be sufficiently protective. The Committee concluded that perchlorate in drinking water represents a public health hazard and that an MCLG in the range of approximately 0.2 to 2 $\mu\text{g/L}$ would be an appropriate target for a health-protective standard. Based on the Committee's evaluation, the current EPA Health Advisory for perchlorate of 15 $\mu\text{g/L}$ is not sufficiently protective. The Committee was not charged with recommending an MCL and did not quantitatively evaluate occurrence data. The Committee concluded that EPA should not have abandoned the regulation of perchlorate in drinking water.

It should be noted that this report does not include a comprehensive review of the sources, environmental fate, and potential exposure to perchlorate (see, for example, Zoeller, 2006; ATSDR, 2008; Leung et al., 2014). The occurrence, concentrations, and geographic distribution of perchlorate in drinking water were likewise outside our scope.

BACKGROUND INFORMATION

A lengthy history of actions exists on EPA's efforts to determine an acceptable health-based maximum concentration of perchlorate in drinking water (Appendix 2). Going back to 2008, EPA (2008a) published a non-enforceable interim Health Advisory (HA) to provide guidance to state and local officials in their efforts to address this issue. The HA, based on a health reference level (HRL) of 15 µg/L, was derived from an RfD of 0.7 µg/kg/day, using the then current EPA default adult body weight (70 kg) and drinking water consumption rate (2 L/day)¹, and a perchlorate-specific RSC of 62% for a pregnant woman (EPA, 2008a). The EPA adopted the RfD of 0.7 µg/kg/day derived in 2005 by the National Research Council (NRC, 2005). The RfD was based on a reported no-observed effect level (NOEL) of 7 µg/kg/day for perchlorate's inhibition of radioactive iodine uptake (RAIU) into the thyroid in a study of healthy adults (Greer et al., 2002), and the subsequent application of an UF of 10 for intraspecies variability.

In 2009, EPA (2009a) published a supplemental request for comment with a new analysis that derived potential alternative HRLs for 14 life stages, including infants and children. The analysis used the RfD of 0.7 µg/kg/day and life stage-specific body weight and exposure information (i.e., drinking water intake, RSC).

EPA (2011a) made a regulatory determination that a National Primary Drinking Water Regulation (e.g. MCL) should be developed for perchlorate, under the criteria provided in the Safe Drinking Water Act.

A year later in 2012, EPA (2012) released a White Paper detailing a range of potential MCLGs based on life stages and using the RfD of 0.7 µg/kg/day. The MCLGs ranged from 2 µg/L for bottle-fed infants to 18 µg/L for non-pregnant females of childbearing age. The purpose of that report was to seek guidance from the EPA's Science Advisory Board (SAB) on how best to consider and interpret the life stage information, the epidemiologic and biomonitoring data that became available since the NRC (2005) report, and use of the physiologically based pharmacokinetic (PBPK) model presented earlier by NTP (2005) and EPA (2008b) to predict the effects of perchlorate on iodide uptake into the thyroid in the average adult, pregnant woman and fetus, lactating woman and neonate, and young child, and the totality of perchlorate health information relevant to the derivation of an MCLG for perchlorate.

In 2013, an EPA SAB (2013) review of "Approaches to Derive an MCLG for Perchlorate" made the following recommendations:

¹ EPA Office of Water and other parts of EPA (e.g. Superfund) have since updated these default assumptions to 80 kg and 2.4 L. See <https://www.epa.gov/sites/production/files/2015-10/documents/human-health-2015-update-factsheet.pdf>. In effect, this makes little difference because the relevant value is the drinking water ingestion rate which changed from 0.029 L/kg/day to 0.03 L/kg/day.

1. Derive a perchlorate MCLG that addresses sensitive life stages through PBPK/PD modeling
2. Expand the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure
3. 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
4. “Extend the [biologically-based dose-response (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”

It is within this context that EPA developed a 2-step approach for modeling the neurodevelopmental effects in offspring of women who are exposed to perchlorate in early pregnancy. This approach can be described as containing two main components: (1) a BBDR model of how perchlorate's inhibition of iodine uptake into thyroid gland affects thyroid hormone production in early pregnancy in women with low iodide intake; and (2) a pharmacodynamic model, which describes the relationship between decreased thyroid hormone (thyroxine [T4]) in early pregnancy and later neurodevelopmental effects (e.g. IQ decrease) in the offspring.

RESPONSE TO CHARGE QUESTIONS

Charge Question 1 - Overall approach

1A. Is the overall conceptual approach proposed by United States Environmental Protection Agency (EPA) (linking predictions of perchlorate's effect on thyroid hormone production in early-pregnancy women who have low/adequate iodide intake with epidemiology data for effects of decreased early pregnancy thyroid hormone levels on neurodevelopment) appropriate for MCLG development?

1B. Is the conceptual approach proposed by EPA preferable to the earlier approach using the EPA IRIS Reference Dose that was developed by the National Research Council (NRC) and is based on decreased thyroidal iodine uptake in human volunteers who ingested perchlorate? If so, why?

Response (Combined 1 A & B): This is a compound question that is addressed in more detail below in response to specific questions that follow.

The Committee believes the conceptual approach proposed by EPA for perchlorate MCLG development is one potentially valid approach. However, the Committee identified weaknesses

and a number of important uncertainties that affect the reliability of EPA's conclusions. The Committee concluded that the approach proposed by EPA (linking predictions of perchlorate's effect on thyroid hormone production in early-pregnancy women who have low iodide intake with epidemiology data for effects of decreased early pregnancy thyroid hormone levels on neurodevelopment) is not necessarily preferable to the approach based on the Greer et al. (2002) study of perchlorate's effect on thyroidal iodine uptake in human volunteers. The Committee noted that the complex modeling approach has not been independently validated to date, and it is unclear to the Committee whether validation would be possible.

As detailed in its rule proposed of an MCL for perchlorate published June 26th, 2019 in the Federal Register (EPA, 2019a), EPA linked deficiencies in T4 during early pregnancy to neurodevelopmental outcomes in the offspring - as reported by Korevaar et al. (2016). Identification of Korevaar et al. (2016) as the critical study which forms the basis for RfD derivation results in a *de facto* assumption by EPA of the first trimester as the most sensitive stage in the continuum from conception through the neonatal period.

A basic question in evaluating the EPA approach is: does it capture the most sensitive life stage? As discussed in more detail later in the response to this charge question, the first trimester is considered to be a sensitive life stage, especially since the fetal thyroid does not begin to function until about week 12 (Fisher et al., 1976; Contembre et al., 1993) and does not produce enough thyroid hormone for its own needs until about week 20 (Rovet, 2014). Additionally, there are inadequate data on the relationship between maternal thyroid hormone levels and offspring IQ during later trimesters until birth, and the results of neonatal screening for congenital hypothyroidism do not provide data adequate to assess potential impacts during the neonatal period or that are easily employed for the EPA's model.

The Committee concluded that the available data indicate that the first trimester is a sensitive life stage, but uncertainties exist as to whether other developmental periods may be more sensitive. The qualification is that this assessment does not compare impacts that may occur in early pregnancy with those that may occur over the entirety of gestation and during the neonatal period, although it is noted that early pregnancy could be expected to be a particularly sensitive period since fetal T4 production does not begin until the second trimester.

Moving beyond this basic comparison, the Committee identified a number of issues with the EPA modeling paradigm, not the least of which was the decision to use a 2 point IQ deficit as the point of departure (POD) for deriving the RfD (see response to Charge Question 6 below for more details). Questions also arose regarding the mathematical equation used by EPA to describe the dose-response for the relationship between decreased T4 in early pregnancy and decreased IQ in offspring in the critical study (Korevaar et al., 2016) that forms the basis of the RfD derivation.

The linear equation utilized by EPA to describe the dose-response for T4 in early pregnancy and decreased IQ in offspring differs from the quadratic equation employed by Korevaar et al. (2016). To drill down further into this issue, the Committee made arrangements to hold a conference call with Dr. Tim Korevaar, who is based in the Netherlands. Issues discussed included: the dose-response relationship between maternal T4 concentration during pregnancy and child IQ; the mathematical equation for describing this relationship; and the sensitivity of early pregnancy as a critical time period.

Regarding the dose-response, Dr. Korevaar noted that the direct relationship between maternal T4 and childhood IQ is represented by an inverted “U” shape. That is, both low and high maternal T4 concentrations are associated with lower IQ scores. He went on to note two concerns with EPA’s reanalysis of his study’s findings. First, that EPA modeled only the lower portion of the dose-response; and second, that EPA fitted this lower portion of the T4/IQ relationship to a linear dose-response model which underestimated the slope of the relationship in the lowest part of the curve due to a steep dose-response at the lowest T4 levels followed by a plateau effect beginning between the 25th – 35th percentile.

In the EPA (2019a) perchlorate MCL proposal, EPA cites the following reasons for using decreased IQ from Korevaar et al. (2016) as the critical endpoint:

“(1) There is sufficient quantitative data to derive a health impact function for the sensitive population of interest; (2) the analysis adjusts for an appropriate set of confounders, and (3) the neurodevelopmental endpoint— intelligence quotient (IQ)—is more straightforward to interpret because there is more national and cross-national data available (more on the selection of this endpoint below).”

The Committee’s concern with EPA’s use of a linear equation to model dose-response is clearly reflected in the table below from the EPA rule proposal for the perchlorate MCL (EPA, 2019a). Table 1 below demonstrates that the EPA independent analysis using the linear model results in a 1.6 to 1.8-fold higher (less protective) perchlorate dose (ug/kg/day) equating to each of the three selected endpoints (1, 2 or 3 point decrease in IQ) than the quadratic analysis presented in Korevaar et al. (2016). The Committee concluded that EPA’s explanation for using the linear model did not adequately address this discrepancy.

Table 1 (Table 9-3 from EPA, 2019b)

Table 9-3. Predicted Dose of Perchlorate per a 1% to 2% Change^a in Neurodevelopmental Measure for Low-Iodine Intake Individuals Based on Upper Effect Estimates at the 10th Percentile fT4 Level^{a, b}

Study	Endpoint	Dose-Response Function	β (95% CI)	Δ fT4 in pmol/L Associated with a 1% to 3% Decrease in Endpoint (% Δ fT4 from 0 dose perchlorate, iodine intake = 75 μ g/day) ^{a,b,c}			Dose of Perchlorate per 1% to 3% Decrease in Endpoint (μ g/kg/day) ^{a,b,c}		
				1%	2%	3%	1%	2%	3%
Korevaar et al. (2016) Quadratic	IQ	$\Delta IQ = (\beta_1 \times \ln fT4_2 + \beta_2 \times \ln(fT4_2)^2) - (\beta_1 \times \ln fT4_1 + \beta_2 \times \ln(fT4_1)^2)$	$\beta_1 = 33.8$ (9.8, 57.8) $\beta_2 = -6.2$ (-10.6, -1.9)	-0.13 (1.9%)	-0.25 (3.8%)	-0.38 (5.7%)	1.9	3.9	6.1
Korevaar et al. (2016) EPA independent analysis	IQ	$\Delta IQ = (\beta_1 \times \ln(fT4_2)) - (\beta_1 \times \ln(fT4_1))$	17.26 (3.77, 30.75)	-0.21 (3.1%)	-0.41 (6.2%)	-0.61 (9.2%)	3.1	6.7	10.8

The last issue that the Committee discussed with Dr. Korevaar related to whether the first trimester of pregnancy is the most sensitive time interval in protecting against adverse effects from decreased T4 levels, versus the entire course of the pregnancy or in neonates/infants. Dr. Korevaar stated that he believes that early pregnancy is most important, especially considering that the fetus does not make its own thyroid hormones until the 14th week of pregnancy. The first trimester is a critical period for central nervous system development. However, there are inadequate quantitative data on the relationship between maternal thyroid hormone levels and offspring IQ from later trimesters, until birth, and the results of neonatal screening for congenital hypothyroidism do not provide quantitative data adequate to assess potential impacts during the neonatal period or that are easily employed for the EPA’s model. The Committee concluded that, while it is clear that the neonatal period is very sensitive to thyroid hormone insufficiency, the available data for the neonatal stage are not adequate for EPA’s modeling effort for risk assessment with regard to identifying a POD for an RfD. This is addressed in the response to Charge Question 7 on uncertainties and UFs.

In summary, the EPA approach advances the science beyond the RfD previously developed from iodide uptake inhibition (Greer et al, 2002). It is a reasonable alternative approach that informs effects during the first trimester *in utero*, which Greer et al. (2002) clearly does not. However, it is fraught with uncertainties.

Charge Question 2 - Level of uncertainty in the proposed EPA MCL

Based on the considerations listed below, is the approach used in the EPA proposal appropriate to support MCLG development?

2A. What are the key parameters in each of the two linked models, and are the choices that were made for these parameters supportable?

The approach employs two linked models that are each complex with many assumptions. The key variables are perchlorate levels and iodine uptake on the one hand, and free T4 and cognitive development on the other. Going through each of the assumptions to evaluate whether they can be supported is outside the scope of this Report. However, several of the important assumptions were discussed in Committee as described below, and the Committee identified several points where a high level of uncertainty underlying EPA's models' assumptions exist. These include:

1. The degree of perchlorate exposure required to inhibit iodide uptake into the thyroid gland to cause a reduction in circulating levels of fT4. This is a very large uncertainty for two reasons.

First, how much perchlorate is required to inhibit iodide uptake into the thyroid gland such that thyroid hormone insufficiency results? The only direct measures that have been made for this were in healthy adult volunteers (Greer et al., 2002). Do the data from the healthy adults apply to women in early pregnancy, neonates, and older infants? EPA uses the observation that thyroid stimulating hormone (TSH) released from the pituitary stimulates the production and abundance of the Sodium/Iodide Symporter (NIS) in the thyroid gland and that, as serum TSH is increased during the first trimester, thyroidal NIS abundance would increase. However, these assumptions represent uncertainties in estimating the degree of iodide uptake required to support adequate thyroid hormone synthesis during pregnancy. These uncertainties are exacerbated by the fact that other factors can inhibit iodide uptake into the thyroid, including thiocyanate, chlorate, nitrate, and others.

Several issues are important with respect to the relationship between iodide uptake inhibition and the production of thyroid hormone insufficiency. Greer et al. (2002) estimated a true no effect level for perchlorate-induced iodide inhibition of 5.2 µg/kg-day, but the relationship between iodide uptake inhibition and serum thyroid hormone levels is complex and unknown. Specifically, the thyroid gland stores thyroid hormone in the form of iodinated thyroglobulin in the colloid and this amounts to what may be several months' worth of thyroid hormone (Greer et al., 2002). This estimate, however, is not consistent with the findings of Blount et al. (2006) who showed a concordant positive association between urinary perchlorate and serum TSH in adult women using CDC's National Health and Nutrition Evaluation Survey (NHANES) data, and this

association was stronger in women with low urinary iodide in addition to an inverse association with serum T4. In addition, Steinmaus et al. (2007) extended this by showing that the association between thyroid hormones and perchlorate exposure was enhanced in women who smoked. This is important because the estimated perchlorate consumption in these women is below the NOEL of Greer et al. (2002); thus, a major uncertainty is the quantitative relationship between perchlorate exposure and serum thyroid hormone, requiring assumptions built into the model that “make it work”.

2. An additional uncertainty is that the EPA did not build into their model that perchlorate not only inhibits iodide uptake into the thyroid gland but is also transported into the thyroid gland. This is important because perchlorate uptake into the thyroid causes iodine discharge from the gland (Targovnik et al. 2017), thereby potentially reducing intracellular iodine below that predicted by urinary iodine levels. Moreover, perchlorate has recently been shown to both inhibit iodide uptake by the NIS, and to block sodium binding to the NIS (Llorente-Esteban et al., 2020). This report was published after the EPA’s MCL proposal. However, because the effect on sodium binding occurs at low concentrations of perchlorate, the lack of consideration of this effect in the EPA model adds an additional uncertainty that EPA was not aware of when they developed this RfD and MCLG. Additionally, although beyond the scope of this discussion, it is notable that perchlorate concentrates directly in breast milk (Dohan et al., 2007).

3. The EPA (2019a) MCL proposal included TSH feedback in situations where maternal T4 was low because the 2017 peer review considered that this signaling was necessary to accurately predict responses of women with very low iodine intake. To model the relationship between serum TSH and T4, they used aggregate data of serum fT4 and TSH from NHANES and made estimates of the “strength” of TSH action on the thyroid gland. The EPA then selected an iodine intake level of 75 µg/day to simulate an individual with low-iodine intake. This value represents an intake between the 15th and 20th percentile of the women of child bearing age population distribution of estimated iodine intake from the NHANES.

The EPA considered using a lower iodine intake level of 50 µg/day, which represents approximately the 5th percentile of the NHANES distribution. However, at 50 µg/day of iodine intake, the BBDR model predicts TSH levels that would be elevated to within the clinically hypothyroid range before exposure to any perchlorate (TSH ranges between 4.51 and 5.41 milliinternational units per liter [mIU/L] at zero dose of perchlorate when evaluating gestational weeks 12 or 13). In contrast, at 75 µg/day iodine, the BBDR model predicted concentrations of serum fT4 and TSH that are significantly reduced from the population median but are still within the euthyroid range. Therefore, the EPA model

cannot be used to evaluate the effect of perchlorate on thyroid function of women with the lowest 5% of iodine intake.

TSH increases in response to decreases in T4 have been captured in numerous studies that document the relationship between these hormones (Blount et al., 2006; Steinmaus et al., 2013, 2016). The EPA designed the BBDR model to depict this feedback regulation by adjusting a set of three parameters: The number of NIS sites, the T4 synthesis rate, and the T3 synthesis rate. The BBDR model allows for variability in the strength of the TSH feedback by varying these parameters with a variable called “pTSH.” For the MCLG analysis, the EPA used a pTSH value of 0.398, which is the ratio of a median value for TSH from NHANES (non-pregnant women) to the 97.5 percentile value from NHANES (non-pregnant women). This value represents an assumption that sensitive individuals with high TSH and average fT4 levels exist, and that this is because the stimulus strength of TSH is proportionally weaker in these individuals. The EPA chose to use a low TSH feedback coefficient to ensure that the MCLG is protective of this sensitive population.

In other words, EPA added a component to the model (TSH feedback) in response to peer review. However, after the addition of the TSH feedback component, EPA needed to use a higher cutoff for iodine intake of 75 µg per day, which represents the 15th-20th percentile of women surveyed in NHANES. They were restricted in this value because if they parameterized the model with 50 µg per day, serum TSH would be in the hypothyroid range even in the absence of added perchlorate. Clinical studies do not show this relationship (e.g., Berg et al., 2017; Moreno-Reyes et al., 2013). In addition, the model predicts that at 75 µg/day iodine intake, both fT4 and TSH are reduced, which is also not observed in NHANES data. Thus, the assumptions built into the TSH feedback represent a level of uncertainty that is producing relationships that do not reflect empirical measurements and have restricted the analysis to the 15th and 20th percentile of pregnant women rather than a more traditional 5th to 10th percentile.

The Committee concluded that the model’s inability to predict empirical measurements in women with low iodine levels (5th percentile) illustrates a more general limitation with the EPA approach. While the EPA approach attempts to simulate the biological processes associated with perchlorate exposure in more detail than the simpler approach based on decreased thyroidal iodine uptake from Greer et al. (2002), both approaches are associated with a similar level of uncertainty.

4. EPA makes the statement that “individuals with low iodine intake have increased sensitivity to perchlorate’s impact on thyroid hormone levels because the functional iodide reserve of the hypothalamic-pituitary-thyroid (HPT) system is limited...,” citing Blount et al. (2006), Leung et al. (2014), and Steinmaus et al. (2007). None of these

references report the functional reserve of iodide. While it is difficult to know how EPA used this information – there is no mention of the functional reserve of iodide in either the EPA (2019a) MCL proposal or the description of the models in Appendix A of EPA (2019b) – there is uncertainty in the way that iodine “economy” was modeled. It should also be noted that the Greer et al. (2002) estimated that the adult thyroid gland contains several months’ worth of iodinated thyroglobulin. However, Blount et al. (2006) demonstrated a negative correlation between urinary perchlorate and serum T4 in adult women at estimated concentrations of exposure far below the perchlorate doses provided to the adult volunteers in Greer et al. (2002). Thus, there is empirical evidence indicating that the relationships between perchlorate exposure, iodide uptake into the thyroid gland, and serum T4 are not completely understood, increasing the assumptions required in the model and the uncertainties surrounding these assumptions.

2B. Is the level of uncertainty for the key parameters and for the overall model predictions too great to support MCLG development?

The Committee concludes that there is a high level of uncertainty for several important variables, that require expanding the UFs used in the final analysis. The key relationships being modeled by the EPA are 1) perchlorate inhibition of iodide uptake into the thyroid gland and its modification by the level of dietary iodine consumption, 2) the degree of thyroidal iodide inhibition required to reduce serum fT4 in first trimester pregnant women, and 3) the relationship between maternal serum fT4 and global IQ in the offspring.

This is a highly ambitious exercise. Imagine developing an Adverse Outcome Pathway (AOP) to describe the goal of these linked models, with a molecular initiating event (MIE) of the inhibition of iodide uptake into the maternal thyroid gland by perchlorate. The number of key events (KEs) that would link the MIE to IQ in the model would be very large, and while the EPA has recruited data reasonably to parameterize their linked models, the uncertainties surrounding each KE and assumptions made to produce a working model have created a situation where adjustments had to be made (e.g., the use of 75 µg/day iodide consumption as a low end – see point 3 in the response to Question 2A above) because the model was not predicting fT4 levels that are seen in the general population. Moreover, the models do not explain or provide insight into the paradox between the conclusions made by Greer et al. (2002) that a concentration of 200 µg/L perchlorate in drinking water would be required to “just begin” to inhibit iodide uptake into the thyroid gland, yet Blount et al., (2006) found that background levels of perchlorate were negatively associated with serum T4 in adult women. Thus, given that the model does not appear to predict the relationship between iodine and fT4 in pregnant women, the many assumptions introduce considerable uncertainty into the model outputs.

2C. Have the models been sufficiently validated to have the degree of confidence in their predictions needed to support MCLG development?

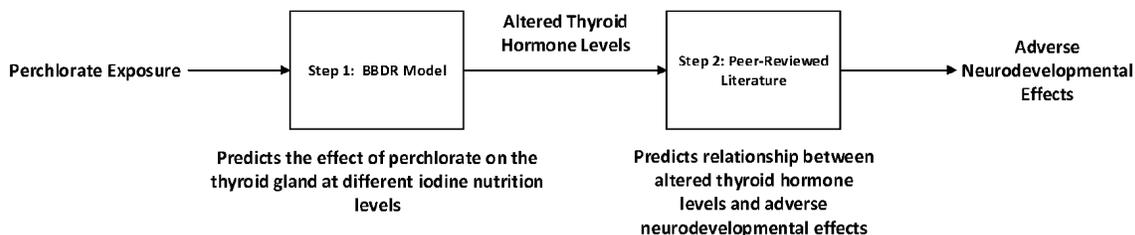


Figure 1. Summary of Modeling Approach for Estimating Measurable Adverse Neurodevelopmental Impacts in Offspring from Perchlorate Exposure in Pregnant Woman (Figure 9-1 from EPA, 2019b).

The EPA has developed two models shown in Figure 1 above to predict the effect of perchlorate on neurodevelopment at different levels of iodide intake. The models have unique features which do not lend themselves to independent validation. These are two very complex models (BBDR and pharmacodynamic) with three components that are designed to make predictions about the adverse outcome of perchlorate exposure in a particularly vulnerable population – first trimester pregnant women with low iodine consumption. These components include 1) the quantitative relationship between dietary iodide intake and effects of perchlorate exposure, 2) the quantitative relationship between iodide and fT4 levels in plasma of first trimester pregnant women and 3) the quantitative relationship between plasma fT4 in first trimester women and IQ in the offspring. EPA describes an enormous amount of work – including sensitivity analyses and model modifications – before employing these models to establish an MCLG. However, specific elements of the model are not predicting empirical relationships between urinary iodine and serum T4, although the empirical data are sparse. It is also noted that neither Volume 1 nor Volume 2 (Appendix A) of the EPA (2019b) perchlorate documents cite the EPA (2009b) document, “Guidance on the Development, Evaluation and Application of Environmental Models.” The Committee was uncomfortable with this omission.

Charge Question 3 – Consideration of peer reviewers’ comments

Did EPA adequately consider the comments from the 2017 peer review of its draft document when developing the proposed MCLG?

As reviewed in the introduction, the EPA process has gone through several iterations and at least two substantial peer reviews, which did not necessarily agree in terms of weaknesses and recommendations. Overall, the EPA performed a substantial amount of work in preparing the model(s) and subsequent reports. The EPA did a good job responding to the peer review comments and attempted to address the Peer Reviewer’s concerns as detailed below.

Since 2012, several reports pertaining to establishing an MCLG for perchlorate in drinking water were prepared by the EPA, and then peer reviewed. A chronological list of these reports and the corresponding peer review reports is presented below.

- *Life Stage Considerations and Interpretation of Recent Epidemiological Evidence to Develop a Maximum Contaminant Level Goal for Perchlorate*, EPA (2012) White Paper
 - *Review of Approaches to Derive an MCLG for Perchlorate*, EPA SAB (2013).
- *Biologically Based Dose Response 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*, EPA (2016)
 - External Peer Review of EPA’s Draft Biologically Based Dose-Response (BBDR) Model and Draft BBDR Model Report for Perchlorate in Drinking Water, EPA Peer Review (2017a)
- *Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water*, Volume 1-3, EPA (2017b)
 - Review of Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water, EPA Peer Review (2018a)
- Proposed Rule – National Primary Drinking Water Regulations: Perchlorate, EPA (2019a)
 - Comment period ended August 26, 2019

Several recommendations were issued by the EPA SAB (2013) on the review of *EPA 2012 Life Stage Considerations and Interpretation of Recent Epidemiological Evidence to Develop a Maximum Contaminant Level Goal for Perchlorate*, and most of them were addressed. However, it is unclear if adequate consideration was given to the SAB’s recommendation for “Investigating non-linear patterns of effect across low, moderate, and high exposure categories.” The final model developed by the EPA used a linear reanalysis of a portion of the Korevaar et al. (2016) data, which is discussed below and does not seem to adequately address the SAB recommendation.

In preparing the *Biologically Based Dose Response 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* (EPA, 2016), the prepared model focused on lactating mothers and breast-fed/formula-fed infants. The 2017 Peer Reviewers stated that the current model “neglected the sensitive life stage associated with 1st trimester pregnancy and possibly the 1st month of pregnancy before the mother knew she had conceived.” One panel member commented that the “prime effect of ultimate interest – changes in cognitive development measured as IQ” was needed (EPA Peer Review, 2017a).

Responding to the EPA Peer Review (2017a) report, the EPA prepared the *Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water*, Volume 1-3, EPA (2017b). The EPA Peer Review (2018a) offered the following comments/recommendations. It is noted that the EPA Peer Review process did not request consensus, and these points are based on responses from individual peer reviewers:

- The importance of also addressing other sensitive life stages beyond simply the 1st trimester of pregnancy.
- To re-evaluate the selected studies to expand and improve the information available for the assessment to include a broader range of endpoints (i.e.: autism and attention deficit hyperactivity disorder [ADHD]) not just IQ.
- To revisit using the full range of concentrations between fT4 and adverse neurodevelopmental outcomes as the choice of regression should fit all the data and make biological sense.
- A comment was issued by the peer reviewers that the model produces a counterintuitive result. Specifically, that the effect of perchlorate on first trimester pregnant women with higher fT4 appear greater than the effect for individuals with lower fT4. Peer reviews accounted for this counterintuitive result based on 1) the assumption of the lognormality of the data and suggested that right-skewed distributions or normal distributions should be explored, and 2) that the result could be an artifact produced by the model itself.

EPA did not respond to this particular concern.

With regard to addressing other sensitive life stages beyond simply the first^t trimester of pregnancy, the EPA developed the model to protect the embryo/fetus of a first trimester pregnant mother with low-iodine intake, low fT4, and low TSH feedback. The EPA believes that this approach would be protective of other sensitive populations due to the results of the EPA (2016) model that showed perchlorate would have minimal impact on thyroid hormone levels of formula-fed infants up to 90 days and breast-fed infants up to 60 days (EPA, 2019a). The EPA response seems to address the Peer Review comment.

With regard to the Peer Review recommendation to re-evaluate studies to expand and improve the information available for the assessment to include a broader range of endpoints (i.e. autism and ADHD) beyond just IQ, the EPA still chose to use IQ as the sole neurodevelopmental endpoint. Their reasoning for this choice was that an IQ measurement is more straightforward to interpret, and that more national and international data are available. EPA chose to model IQ instead of other neurodevelopmental endpoints for the following reasons:

- The studies using the Bayley Scale to evaluate Psychomotor Development Index (PDI) and Mental Development Index (MDI) were not adjusted for confounders and these studies had an N<50, while the Korevaar et al. (2016) EPA reanalysis has an N=3,609;
- Anxiety/depression scores are “not an intuitively interpretable endpoint”, EPA (2019a); and
- Evaluating the Standard Deviation (SD) of reaction time tests was not well received by the Peer Review (2018a) because “it is difficult to ascertain the true implications of a change in the SD of reaction time”, EPA (2019a).

In regard to revisiting the use of the full range of concentrations between fT4 and adverse neurodevelopmental outcomes as the choice of regression should fit all the data, the EPA (2019a) maintained their use of an independent reanalysis of the linear regression approach of the lower values (left side) of the Korevaar et al. (2016) data. One main finding represented by Korevaar et al. (2016) is that “both low and high free thyroxine concentrations during pregnancy were associated with lower child IQ...”. The independent linear reanalysis performed by the EPA does not account for the potential adverse neurological effects resulting from high maternal fT4 present as the “right” side of the Korevaar et al. (2016) data distribution, as these data have been omitted from their independent analysis. In performing the independent analysis, EPA determined that, in the original analysis, fT4 was estimated using multiple imputations, which could have affected the estimate of fT4 from data that were not directly measured. EPA’s linear reanalysis does not include these imputations.

While the omission of these data runs in opposition to the Peer Review recommendation, the Committee agrees with EPA’s decision to model only the data from the “left” (lower) part of the data since, as stated in the Response to Question 1, the intent of the proposed perchlorate MCLG is to define a daily dose of perchlorate below which adverse health effects would not, with an adequate margin of safety, occur. However, as discussed in the response to Charge Question 1, the Committee has concerns about EPA’s modeling of the left portion of the data from Korevaar et al. (2016), specifically that EPA fitted the lower portion of the data to a linear dose-response model which underestimated the slope of the relationship in the lowest part of the curve due to a steep dose-response at the lowest T4 levels followed by a plateau effect beginning between the 25th – 35th percentile.

Finally, one last recommendation of the Peer Review panel is related to the model producing a counterintuitive result. The panel specifically stated that the counterintuitive result was that the model predicted an effect of perchlorate on first trimester pregnant women with higher fT4 that was greater than in women with lower fT4. This finding is not predicted based on our understanding of the MOA of perchlorate. The peer reviewers suggested that right-skewed distributions or normal distributions should be explored. EPA explained that “overall the lognormal function demonstrated a better fit than a normal distribution” (EPA, 2019a).

However, it remains unclear whether the model's counterintuitive effect of perchlorate on individuals with higher fT4 appearing greater than for individuals with lower fT4 has been resolved. The Committee notes that this an additional uncertainty with the EPA approach.

Additionally, the final MCLG of 56 µg/L of perchlorate in drinking water recommended by the EPA ranges from approximately 4 to 100 times greater than previous health-based guidelines developed by other states, and even by the EPA itself, as the EPA (2008) Health Advisory was 15 µg/L. The recommendation of a higher concentration of 56 µg/L as an MCLG for perchlorate in drinking water than previous health-based concentrations developed by EPA (2008), New Jersey Drinking Water Quality Institute (2005), Massachusetts DEP (Zewdie et al., 2010), and California EPA (2015) appears to be, of itself, counterintuitive, especially with consideration of the issues raised by the Committee regarding choice of decreased of 2 IQ points and the need for additional UFs.

*Of note, no consensus was attempted to be sought during each of the two peer review panel documents (2017a, 2018a), and EPA considered comments made even by only one peer reviewer as a valid justification for decisions in development of the MCL proposed in EPA (2019a). For example, the EPA (2019a, p. 30535) MCL proposal states that EPA is “prompted to revisit the original Korevaar et al., (2016) model,” because one member made the suggestion to control for certain variables.

Question 4 – Consideration of additional life stages

Should evaluations based on other critical life stages (later pregnancy, bottle-fed infant, breastfed infant) be considered in addition to the evaluations based on early pregnancy used as the basis for the MCLG?

The committee discussed this issue extensively and ultimately concurred with the EPA that the first trimester of pregnancy offered a better quantitative data set upon which to develop this model. The Committee also noted that there remains considerable uncertainty regarding the sensitivity of neonates to perchlorate.

Other life stages were considered by EPA and the Committee. It is well-known that human neonates are very sensitive to thyroid hormone insufficiency. This is best documented in the clinical syndrome of congenital hypothyroidism (CH) (e.g., Bongers-Schokking et al., 2018; Clairman et al., 2015). EPA used the following argument to justify the use of Korevaar et al. (2016) and that other life stages would be protected by an MCLG based on perchlorate exposure in the first trimester of pregnancy:

The SAB pointed to two lines of evidence supporting their suggestion of the infant as a potentially sensitive population to perchlorate: Preterm infants that experience transient hypothyroxinemia of prematurity (THOP) and infants that experience congenital hypothyroidism (EPA SAB, 2013). Thus, sufficient thyroid

hormone levels in infancy are necessary for the infant brain to develop properly. However, the best evidence linking perturbations in thyroid hormone levels to disrupted neurodevelopment for infants are in individuals with significant thyroid deficiencies manifesting as clinical conditions (e.g., THOP and congenital hypothyroidism). It is unclear and unknown if minor perturbations in thyroid hormones in infants, such as those that could be caused by environmental levels of perchlorate, would result in adverse neurodevelopmental outcomes similar to those seen in the literature for the offspring of first trimester pregnant mothers with hypothyroxinemia. Given the lack of evidence demonstrating minor perturbations in infant fT4 levels as being associated with neurodevelopmental outcomes, the EPA has concluded that it is appropriate to derive the perchlorate MCLG to protect the first trimester fetus of a pregnant mother with low-iodine intake. The EPA concludes that an MCLG calculated to offer a margin of protection against adverse health effects to these fetuses targets the most sensitive life stage and will be protective of other potentially sensitive life stages as well.

While it is true that there is no evidence linking differences in circulating thyroid hormones with cognitive function in otherwise healthy neonates or infants, there is a large literature defining the optimal treatment strategy for neonates with congenital hypothyroidism. The Committee discussed this literature (e.g., Bongers-Schokking and de Muinck Keizer-Schrama, 2005; Rastogi and LaFranchi, 2010) and, while it is clear that this life stage is sensitive to thyroid hormone insufficiency, the quantitative relationship required for modelling is not available in this literature. This is both because the timing of the onset of treatment is as important as the circulating level of T4 achieved, and because different cognitive outcomes are associated with circulating T4 at different ages. Thus, the Committee agreed with EPA that the first trimester of pregnancy offered a better quantitative data set upon which to develop this model but also noted that there remains considerable uncertainty regarding the true sensitivity of neonates to perchlorate.

The Committee also raised this issue with Dr. Korevaar on the conference call. Specifically, is the first trimester of pregnancy the most sensitive time interval in protecting against adverse effects from decreased T4 levels, whether over the course of the pregnancy or in neonates/infants? As discussed above, Dr. Korevaar stated that he believes that early pregnancy is most important, especially considering that the fetus does not make its own thyroid hormones until the 14th week of pregnancy. However, he does not know for certain because the effects of thyroid function on cognitive function in other trimesters are not known because there are no data.

As discussed in the response to Charge Question 1, the POD for a decrease of 2 IQ points from the EPA reanalysis of Korevaar et al. (2016) is lower than the POD for decreased thyroidal iodine uptake from Greer et al. (2002). This supports the choice of this effect from exposure during early pregnancy, based on the available data. However, uncertainty remains about

whether the later trimesters of pregnancy and the neonatal period are more sensitive than the first trimester of pregnancy to thyroid hormone insufficiency. This uncertainty should be accounted for through the application of an appropriate **database** uncertainty factor.

Charge Question 5 – Choice of key study and modeling approach for neurodevelopmental effects

This is a compound question. Once the first trimester fetal response was identified as a critical endpoint, the Korevaar et al. (2016) study was the most appropriate study. Other studies with other endpoints were considered by the Committee, but it was concluded that the Korevaar study and IQ were appropriate. The issue of EPA’s re-analysis and re-interpretation of the Korevaar data are addressed here, and in greater detail in the response to Question 1.

5A. Is the study that was chosen as the basis for the quantitative predictions of neurodevelopmental effects (Korevaar et al., 2016) the most appropriate study?

EPA noted that there are also limited quantitative data to link the low fT4 with other adverse neurodevelopmental outcomes including ADHD, expressive language delay, reduced school performance, autism, and delayed cognitive development (Alexander et al., 2017; Ghassabian et al., 2011; Gyllenberg et al., 2016; Henrichs et al., 2010; Korevaar et al., 2016, Noten et al., 2015; Pop et al., 1999; Pop et al., 2003; EPA SAB, 2013; van Mil et al., 2012). Although based on limited data, some of these effects appeared more sensitive than IQ, but do not offer sufficient data for risk assessment. This is an additional uncertainty associated with the RfD based on decreased IQ from Korevaar et al. (2016).

However, EPA also argues that the difficulty in estimating the likelihood and magnitude of the potential implications of perchlorate’s mode of action on expressed neurodevelopmental health effects in humans exposed to perchlorate during development is the lack of robust epidemiological studies, especially in sensitive populations. Therefore, based on a known mode of action of perchlorate, the EPA estimated potential health risks using a novel approach suggested by the EPA’s SAB (SAB for the U.S. EPA, 2013). The EPA’s approach to estimating perchlorate risks has evolved over time with improved research and modeling capabilities.

Table III-2 of EPA (2019a) presents perchlorate doses predicted to result in 1, 2, and 3 point decreases of several neurodevelopmental endpoints offspring (IQ, Mental Development Index, Psychomotor Development Index, anxiety/depression score, reaction time) that have been associated with decreased fT4 in early pregnancy. As also stated in the response to Charge Question 1 above, EPA listed three reasons for selecting decreased IQ in offspring from Korevaar et al. (2016) instead of the other endpoints from the other studies mentioned above: (1) There are sufficient quantitative data to derive a health impact function for the sensitive population of interest; (2) the analysis adjusts for an appropriate set of confounders, and (3) Intelligence quotient (IQ) is more straightforward to interpret than the other endpoints because

more national and cross-national data are available. The other studies presented in Table III–2 do not provide one or more of these features. In general, the Committee felt that these arguments were reasonable.

5B. Should another study which suggests a lower perchlorate dose be used and/or should the risk assessment be based on data from multiple studies?

EPA’s arguments for the use of Korevaar et al. (2016) that are highlighted in the response to Question 5A justify the use of this particular study. Because the other studies evaluated different endpoints, it would likely be difficult to integrate them into a single risk assessment.

5C. Is the choice of “independent analysis” modeling of the Korevaar et al. (2016) data the most appropriate of the three modeling approaches presented? (See table III-2, pgs. 30533-34 of FR notice and Tables 25, 27, and 28 on pp. 6-5 to 6-9 of EPA, 2017).

No. As described by Dr. Korevaar in his personal communication and discussed in responses to Charge Question 1, the full dose-response between maternal serum fT4 and child IQ exhibited an “inverted U” shape. This dose-response shape means that at the apex of the “inverted U,” there is a null relationship between maternal fT4 concentration and childhood IQ. However, the relationship between maternal fT4 and child IQ up to about the 35th percentile of the population fT4 is very steep, followed by a plateau at higher fT4 levels and a decreasing curve at the highest fT4 levels. The EPA’s linear modeling included both the steep and plateau portions of the left (lower fT4) portion of the curve. Inclusion of the plateau portion of the curve in the linear modeling results in a flattening of the curve (i.e. a less steep slope) compared to modeling only the steeply increasing portion of the curve. The EPA linear model therefore underestimates the relationship of interest: maternal fT4 and child IQ in the most vulnerable segment of the population with the lowest maternal fT4 levels.

Charge Question 6 – Choice of critical effect

Is a decrease in IQ of 2 points in offspring of low iodine, hypothyroxinemic mothers an appropriate critical effect for the risk assessment? Is a different level of IQ decrease or another critical effect more appropriate?

As noted above, EPA selected decreased IQ as the critical effect for the RfD from several potential effects that were considered. The Committee did not address the issue of whether it is appropriate to use decreased IQ as the basis for regulatory standards in general, while noting that this endpoint has been used previously by regulatory agencies. The Committee does not support the choice of 2 IQ points as a criterion for risk, and instead, a 1 IQ point loss was considered more appropriate and in line with previous assessments from other agencies, including EPA itself.

EPA has derived three toxicity values (RfDs) for perchlorate based on “acceptable” modeled IQ losses of 1, 2 or 3 IQ points. An RfD is an “estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.” Determining the degree of IQ loss that is acceptable is a risk management decision rather than a scientific determination. For this reason, the Committee is uncomfortable with the implication that IQ decrements of 2 to 3 points attributable to exposure to a single toxic compound are not “deleterious.” Committee members noted that modest changes in overall population IQ can have more significant impacts in the tails of the distribution, increasing the proportion of low IQ individuals and decreasing the proportion of high IQ individuals. Committee members also stated that a 1 point IQ change is likely to be the smallest change that can be determined and that it provides a reasonable basis for deriving an RfD. Furthermore, to our knowledge there is no regulatory precedent for determining that IQ decrements of 2 or 3 points should be viewed as acceptable. This policy decision is inconsistent with conclusions of the EPA’s Clean Air Scientific Advisory Committee (CASAC) in its consideration of the National Ambient Air Quality Standard (NAAQS) for lead, another neurotoxin, where that Committee concluded that a “population loss of 1-2 IQ points is *highly significant* from a public health perspective” (EPA, undated). The California Office of Environmental and Human Health Assessment (OEHHA) selected a decrease of 1 IQ point as a benchmark target in deriving a health guidance value for lead in drinking water for use in health risk assessments at school sites (California EPA, 2006).

In conclusion, the Committee recommends that, of the IQ decrement options proposed by EPA, the 1 IQ point value be used in deriving an appropriate RfD.

Charge Question 7 – Uncertainty factors (UFs)

Is the total uncertainty factor (UF) of 3 for potentially more sensitive subpopulations appropriate? Is it too high or too low? Should additional UFs be applied?

The Committee agreed that given the complexity of the model, the limitations of IQ as an endpoint, the quality of the data and the other uncertainties discussed below, the total UF of 3 selected by EPA was not appropriate or sufficient. The Committee was not tasked with choosing a single best total UF, and, as explained below, several UFs of 3 or 10 were considered for different weaknesses, yielding a total UF ranging from 10 to 100, with most of the members who endorsed a specific value preferring a total UF of at least 30.

As discussed in the response to Question 6 above, the Committee concluded that a decrease of 1 IQ point, rather than 2 IQ points, is appropriate as the critical effect for the RfD, and the POD for a decrease of 1 IQ point in EPA (2019a) is 3.1 µg/kg/day. The RfDs based on this POD and a total UF of 10, 30, and 100 are 0.31, 0.10, and 0.03 µg/kg/day, respectively. As discussed in the response to Question 8 below, the RSC appropriate for these RfDs is 20%, rather than the RSC

of 80% used with the EPA RfD of 2.2 µg/kg/day. The MCLGs based on these RfDs of 0.03 to 0.31 µg/kg/day and an RSC of 20% range from 0.19 to 1.9 µg/L. These values are generally similar to or lower than the state and EPA drinking water values (0.5 to 15 µg/L; Appendix 1) based on the Greer et al. (2002) study of perchlorate's effect on thyroidal iodide uptake in adults.

Background

EPA (2002) has stated: "The exact value of the UFs chosen should depend on the quality of the studies available, the extent of the database, and scientific judgment." Non-cancer endpoints are evaluated using the RfD approach (Barnes and Dourson, 1988; Dourson, 1992; EPA, 1993; 2002; EPA, 2018b) which assumes that there is a threshold for these endpoints that will not be exceeded if appropriate UFs are applied to the POD (Dourson et al., 1996; EPA, 2002; WHO/IPCS, 2005). The POD can be a BMDL (lower confidence limit on the benchmark dose, which is the dose associated with a specified minimal change); No Observed Adverse Effect Level (NOAEL), or Lowest Observed Adverse Effect Level (LOAEL). The POD is derived from human exposure data when available. UFs are applied to the POD to address limitations in data sets and in order to ensure that the resulting RfD is sufficiently protective of public health for the entire population.

The factors that are typically applied for each type of uncertainty (i.e., human variation, animal to human extrapolation, LOAEL-to-NOAEL, subchronic-to-chronic exposure, incomplete database) are either 10 or the square root of 10 (which is rounded to 3). The general rationale for application of each of these UFs and the applicability of each UF as determined by the Committee are shown in Table 1. As shown in the table, the pertinent categories of UFs for the perchlorate RfD relate to human variation (protection of sensitive subpopulations) and incomplete data (potentially more sensitive effects not otherwise accounted for).

UFs in the EPA (2019a) Proposed Perchlorate MCLG

In its toxicity value derivation, EPA applied a total, or composite, UF of 3 to account for sensitive subpopulations (intraindividual variability). The rationale for EPA's UF selection was that the POD was derived from data on the developmental effects from human studies and modeling focused on effects during the first trimester, a sensitive period. EPA states that this UF was applied to "account for the uncertainties in modeling the impacts of perchlorate ingestion on the thyroid hormone levels for pregnant mothers with low iodide intake, and the uncertainties in predicting the neurodevelopmental effects of these thyroid hormone changes on their children." No other UF was applied despite a substantial list of uncertainties identified by EPA (see below) as well as some additional uncertainties that EPA did not note, related to the available database and the models used. As shown in the Table 2 below, the Committee reached a consensus that a composite or total UF of 3 is clearly insufficient for the approach used by EPA. Of the members who stated their choice for a total UF, the majority selected a total UF of 30, while some

members felt that the total UF could be in the 10-30 range and other members believed that the total UF should be 100 or higher.

Table 2. Uncertainty Factor (UF) considerations for perchlorate RfD

Factor	Application Rationale and Criteria	Pertinent to Perchlorate Proposed MCLG Review?	EPA Selection	Committee Recommendation
Human (intra-individual) variability	Account for differences among individuals and population subgroups that could result in some individuals being more sensitive to toxicity due to demographics, health status, life stages, innate physiology, diet, and other factors.	Yes. Pregnancy, gestation and perinatal stages are sensitive life stages. Variations in individual physiology of thyroid function and iodine in the diet may render some subpopulations more sensitive than others.	3 A full factor 10 not applied as POD based on sensitive life-stage.	3-10 Some members concurred with EPA. Others felt that uncertainties about most sensitive life-stage warranted full factor of 10.
Animal to human extrapolation	Rodents or other laboratory animals on which toxicology studies are conducted may not accurately represent human physiology.	No. Data were derived from human population studies.	Not pertinent.	Not pertinent
Lowest Observed Adverse Effect Level to No Observed Adverse Effect Level	The Point of Departure is derived from the LOAEL in a study in which a dose at which adverse effects are absent was not identified.	No. The RfD is based on a BMDL.	Not pertinent.	Not pertinent
Subchronic to Chronic exposure	The Point of Departure is based on an effect in a subchronic study that could occur at lower doses with longer exposures.	No. The RfD is based on an effect that occurs from exposure during the first trimester of pregnancy.	Not pertinent.	Not pertinent
Database Uncertainty	Data from which the Point of Departure is derived has gaps which could result in underestimation of risk.	Yes. Some of these gaps are listed and discussed in the Committee's response to Question 7 which identified many uncertainties, including substantial uncertainties in the model and the parameters used in the model.	Not applied.	3 – 10 The Committee concluded a database UF was necessary to reflect numerous modeling and data uncertainties identified by EPA and the Committee. Some members supported a value of 3, others 10, while some did not endorse a specific value.

Sensitive Subpopulations

The default UF for sensitive subpopulations (i.e. intraindividual variability) is 10. This value may be reduced if the POD used as the basis of the RfD is derived from sufficiently robust data on sensitive subgroups or life stages. In this case, the proposed RfD is based on results from the outputs of models derived based on, and validated to some degree against, limited data on sensitive subgroups. However, the Committee notes that the models address thyroid effects on the pregnant woman, which is an indirect measure of potential effects on the embryo/fetus. As noted previously, additional uncertainties exist with respect to other potentially sensitive periods later in pregnancy as well as the potential sensitivity of the neonate. In light of these issues, some members of the Committee concluded that the UF of 3 for sensitive subpopulations used by EPA (2019a) is adequate, while others felt that the full default UF of 10 for sensitive subpopulations should be used. Furthermore, the Committee concluded that the total UF=3 for sensitive subpopulations used by EPA (2019a) is not sufficient to capture other uncertainties in the data base (UF=3 or 10), and in the modeling approach (UF=3 to 10), as discussed further below.

Database Uncertainty

The database UF can be applied to account for deficiencies in the available dataset. The size of the UF may depend on the extent and nature of other data available. EPA (2018b) states that this UF is to be used as follows: "If there is concern that future studies may identify a more sensitive effect, target organ, population, or life stage, a database UF reflects the nature of the database deficiency." In other guidance (EPA, 2002), EPA states that, "The database UF is intended to account for the potential for deriving an underprotective RfD/RfC as a result of an incomplete characterization of the chemical's toxicity. In addition to the identification of toxicity information that is lacking, review of existing data may also suggest that a lower reference value might result if additional data were available."

For perchlorate, major gaps remain in our understanding of the mechanism, as well as the extent, of risk to neurodevelopment from prenatal and early childhood exposures. In its discussion of the proposed RfD options, EPA acknowledges numerous uncertainties inherent in its derivation of these values (see page 30537 - 30538 in the EPA, 2019a Federal Register notice of the MCL proposal). These uncertainties, listed below, are attributable to the many limitations of the complex biologically based dose response (BBDR) model used, deficiencies in the available database, and other factors.

1. "uncertainty in the relationship between perchlorate exposure and subsequent neurodevelopmental outcomes",
2. the fact that "very few toxicokinetic calibration data are available for the perchlorate to thyroid hormone relationship described in the BBDR model",
3. uncertainties relating to "aspects such as competitive inhibition at NIS, depletion of iodide stores under different iodine intake levels and physiological states, and

the ability of the TSH feedback loop to compensate for perturbations in thyroid function....”,

4. “uncertainties linking maternal fT4 levels to offspring IQ....(which) include the population for which dose-response information is available (i.e., no study is U.S. based), a lack of study information on the iodine intake status for the population for which the dose-response information is available, uncertainties around the methods used to assess maternal fT4 measurement during pregnancy, and uncertainties related to the true distribution of fT4 for a given iodine intake”,
5. “...some uncertainty due to the lack of information linking incremental changes in infant thyroid hormone levels to adverse neurodevelopmental outcomes”,
6. uncertainty relating to the fact that EPA’s “analysis is assuming that protecting a first trimester fetus from alterations in maternal fT4 will protect the fetus throughout pregnancy” and “...about the impact perchlorate may have on the fetal thyroid gland, and subsequent neurodevelopmental impacts, in later trimesters of pregnancy.”
7. uncertainty regarding potentially more sensitive effects beyond IQ that are not accounted for.
8. uncertainty regarding perchlorate’s mode of action, which may involve additional mechanisms such as effects on organification of iodine and thyroid hormone transport, allosteric effects and perchlorate induced discharge of iodide from the thyroid.
9. uncertainty about the health protectiveness of the EPA modeling approach that is highlighted by epidemiological data demonstrating associations between perchlorate and effects on thyroid hormone status at exposure levels predicted by the EPA model to have no effect.

Additionally, as indicated in the Committee’s reply to Question 5, the Korevaar et al. (2016) study on which EPA’s RfD is based found that the relationship between maternal fT4 and child IQ from the 20th to 25th percentile of the population fT4 is very steep, but the overall relationship is an inverted U-shaped, with a plateau near the middle of the exposure range. As a result, EPA’s extrapolation from the plateau region of the dose response to assess the lower dose relationship between fT4 and child IQ underestimates the risks of neurodevelopmental effects among the most vulnerable segment of the population – those at the 15th-20th percentile of fT4.

Given the above uncertainties and potential lifelong consequences of adverse effects on neurologic development, the Committee concludes that an additional UF of either 3 or 10 for database uncertainties is appropriate, with the majority of those who selected a specific value endorsing 10.

Recommended Composite UF

In summary, the Committee's consensus was that the composite UF should be increased from 3 if the EPA modeling approach is used to derive a toxicity value for perchlorate. Application of a UF of either 3 or 10 for sensitive subpopulations and either 3 or 10 for database uncertainties would yield a resulting composite UF of 10, 30 or 100 to be applied in the derivation of the RfD. Of the members who stated their choice for a total UF, the majority endorsed a total UF of 30, while some members felt that the total UF could be in the 10-30 range and other members believed that the total UF should be 100 or higher.

Charge Question 8 - Relative Source Contribution (RSC) factor

Is the approach used to develop the Relative Source Contribution (RSC) factor and the resulting RSC appropriate and sufficiently protective?

Although EPA applied an appropriate approach in its RSC determination, for the reasons detailed below, the final RSC selected is neither appropriate nor sufficiently protective. This results from EPA proposing three alternative RfD values that are not sufficiently protective. A more appropriately health protective RfD, which reflects the uncertainties in EPA's modeling approach, would lead to an RSC of 20%, well below that proposed by EPA.

The RSC is the percent of the Reference Dose allocated to exposure from drinking water at the guideline concentration. It is intended to ensure that total exposure from all sources (drinking water and non-drinking water) does not exceed the RfD. For example, when the RSC is 20%, the drinking water guideline is based on 20 percent of the RfD, with 80 percent of the RfD allocated to non-drinking water sources. Therefore, a lower RSC results in a more stringent (lower) drinking water guideline. Since the RSC represents daily exposure from non-drinking water sources as a fraction of the RfD, it is independent of the concentration that is present in contaminated drinking water, a concept that is often misunderstood by those who are unfamiliar with development of drinking water guidelines.

EPA's Office of Water follows the general principles for determination of the RSC from drinking water intake as outlined in the Ambient Water Quality Criteria Human Health Methodology (U.S. EPA, 2000). Additional organizations, including states and others who conduct independent risk assessments on drinking water contaminants, also follow a similar outline in deriving an RSC. The EPA risk assessment guidance specifies a RSC of 20 to 80 percent, with a default of 20 percent (the most stringent possible value) when adequate data on exposures from non-drinking water sources needed to derive a chemical-specific value are not available. If chemical-specific data shows that drinking water contributes less than 20 percent of the RfD, a "floor" RSC of 20 percent is used. The 20 percent floor is derived from the EPA guidance, which states "The 20 percent floor has been traditionally rationalized to prevent a situation where small fractional exposures are being controlled. That is, below that point, it is more appropriate to reduce other sources of exposure, rather than promulgating standards for de

minimus reductions in overall exposure.” If drinking water is known to contribute more than 80 percent of the RfD, the “ceiling” RSC value of 80 percent is used to protect for non-drinking water exposures that may not have been otherwise taken into account. For the perchlorate assessment, EPA followed the key features of the Human Health AWQC Decision Tree from the guidance noted above and concluded that food is the only significant non-drinking water source of perchlorate.

To calculate the proposed RSC, EPA (2019a) selected the 90th percentile dose of perchlorate from food, assuming a scenario where the food contained the 95th percentile perchlorate concentration. This corresponds to a perchlorate dose for food of 0.45 µg/kg/day, which is lower than the RfD proposed by EPA. The EPA chose to use the 90th percentile bodyweight-adjusted perchlorate consumption from food using the 95th percentile Total Diet Study results to estimate the perchlorate RSC from drinking water. The RSC of 80% for the RfD of 2.2 µg/kg/day based on a 2 point IQ loss proposed by EPA, was then calculated using the following equation:

$$\text{RSC (\%)} = (\text{RfD } [\mu\text{g/kg/day}] - \text{Food } [\mu\text{g/kg/day}]) / (\text{RfD } [\mu\text{g/kg/day}] \times 100\%)$$

This approach and RSC are appropriate for the RfD of 2.2 µg/kg/day proposed by EPA, which is based on a decrease of 2 IQ points and a total UF of 3.

However, as discussed in the Question 6 above, the Committee has concluded that the RfD should be based on a decrease of 1 IQ point rather than 2 IQ points. Additionally, as discussed in Question 7 above, because there are additional uncertainties regarding the data set (as was even acknowledged by EPA, 2019a) and concerns with the modeling approach used by EPA (2019a), a composite UF of 10 to 100, instead of the UF value of 3 used by EPA is appropriate. The RfDs based on a 1 IQ point decrease and a total UF of 10 to 100 range from 0.03 to 0.31 µg/kg/day. Even the largest of these RfDs, 0.31 µg/kg/day, falls below the estimated perchlorate intake from food of 0.45 µg/kg/day. In this case, the RSC would default to the recommended lower bound value of 20%. With a higher UF (e.g. 30 or 100), the RfD would be even further below the estimated intake from food.

Charge Question 9 – Drinking water ingestion rate

Is the assumed drinking water ingestion rate appropriate? Should the rate be based on other sensitive populations (e.g., formula-fed infant)?

Since EPA (2019a) determined that the critical effect from the human studies was the linkage in early pregnancy with low fT4 levels with adverse neurodevelopmental outcomes (Endendijk et al., 2017; Korevaar et al., 2016), the Committee concluded that the drinking water consumption rate of 0.03 L/kg/day (upper percentile rate for women of childbearing age) is appropriate, and that slight variations in this variable have little impact on the final MCLG estimate (a less certain

estimate for pregnant women of 0.033 L/kg/day is only 10% higher than the value used by EPA, 2019a).

While the RfD that EPA (2019a) derived is based upon the pregnant woman's dietary intake of water during early pregnancy, EPA (2019a) states that "EPA did not use water intake data for pregnant women because the sample sizes were too small to be statistically stable." Instead, EPA used the 90th percentile water ingestion rate for women of childbearing age (non-pregnant, non-lactating, age 15-44 years) of 0.032 L/kg-day, which is almost identical to the rate of 0.033 L/kg/day for a small group of pregnant women. EPA used the ingestion rate specific to women of childbearing age instead of EPA's current default assumptions for adults of 0.03 L/kg/day (mean body weight of 80 kg for adults 21 years and older; Table 8.1 of EPA Exposure Factors Handbook; EPA, 2011b), and water consumption of 2.4 L/day (per capita estimate of combined direct and indirect community water ingestion at the 90th percentile for adults ages 21 and older; EPA Exposure Factors Handbook, EPA 2011b, Table 3-23).

Given that the POD for deriving the RfD is based on a critical effect from a study of the pregnant woman, it is also appropriate that the drinking water ingestion rate of 0.032 L/kg/day intended to represent that of a pregnant woman is used. The agreement with the ingestion rate applies since the window of susceptibility is within the first trimester. If later data suggest additional susceptibility in the second or third trimester a higher ingestion rate should be considered as the general advice is to increase daily water ingestion by 0.5 liters later in the pregnancy. It would be inappropriate to use the drinking water ingestion rate for another subpopulation (e.g. infant) unless the RfD were based on the specific exposure and hazard data for the other subpopulation, as well.

Additional Issue: Should EPA withdraw its regulation of perchlorate?

The June 26, 2019 Federal Register notice proposing an MCL and MCLG of 0.056 mg/L (56 µg/L), EPA (2019a) states: "In addition to the proposed regulation, the EPA is requesting comment on three alternatives: (1) Whether the MCL and MCLG for perchlorate should be set at 0.018 mg/L (18 µg/L), (2) whether the MCL and MCLG for perchlorate should be set at 0.090 mg/L (90 µg/L), or (3) whether instead of issuing a national primary drinking water regulation, the EPA should withdraw the Agency's February 11, 2011, determination to regulate perchlorate in drinking water."

In the course of its deliberations, the Committee had considered EPA's proposed MCL of 56 µg/L, as well as the proposed alternative MCLs of 18 and 90 µg/L determining that none were adequately protective of health, and that the approach to arrive at these numbers was seriously flawed. As the Committee's work was concluding, EPA (2020a; EPA, 2020b) announced that it had opted to withdraw its proposed regulation (the third alternative listed in EPA, 2019a). The Committee then evaluated this third alternative as well.

EPA (2020) stated that it had determined that perchlorate does not meet the criteria for regulation as a drinking water contaminant under the SDWA. This decision represents a complete reversal of the EPA (2011a) positive regulatory determination. According to EPA (2020), its latest analysis (which the Committee concluded was flawed) yields perchlorate MCLG values (18-90 µg/L) that are higher than the concentrations considered in the EPA (2011a) regulatory determination. EPA (2020) used these higher values to rationalize its decision not to regulate, because perchlorate is not found in drinking water with a “frequency and at levels of public health concern to support a meaningful opportunity for health risk reduction through a national perchlorate drinking water regulation.”

Although it was not charged with recommending an MCL and did not quantitatively evaluate occurrence data, the Committee devoted part of its final meetings to specifically discussing a response to this alternative. The Committee concluded that perchlorate in drinking water is a significant health hazard, and that it should be regulated and an MCL is an appropriate tool. Based on its analysis and the members’ different views of uncertainties, the Committee agreed that a protective MCLG and MCL would be in the range of approximately 0.2 to 2 µg/L depending on the UFs adopted, with the modal estimate (assuming a composite UF=30) in the vicinity of 0.6 µg/L. Only two states have set MCLs for perchlorate, pending federal EPA action. Massachusetts derived an RfD of 0.07 µg/kg/day, which equates to a risk-based drinking water value of 0.49 µg/L, and set its MCL at 2 µg/L in consideration of practical factors related to water supply chlorination; these values are within the range of the Committee’s conclusion. California has set its MCL at 6 µg/L, and it subsequently reduced its Public Health Goal (analogous to an MCLG) from 6 µg/L to 1 µg/L but has not yet reduced its MCL to reflect this change.

Although the Committee did not quantitatively evaluate occurrence data, the Committee disagrees with EPA’s conclusion that perchlorate is not found in drinking water at a “frequency and at levels of public health concern to support a meaningful opportunity for health risk reduction through a national perchlorate drinking water regulation” when considering the much lower levels of health concern. This conclusion was informed by the EPA (2011a) regulatory determination and the EPA (2019c) update of national occurrence data for perchlorate in drinking water. In its 2011 determination, EPA (2011) determined that approximately 4% of public water supplies, serving from 5.1 – 16.6 million people, included in the Unregulated Contaminant Monitoring Rule 1 (UCMR1) had at least one detection of perchlorate above a drinking water threshold concentration of 4 µg/L, EPA’s reporting limit for UCMR 1 (note that reporting limits below 2 µg/L are now achievable²), and that this occurrence frequency was sufficient to support adoption of an MCL. The EPA (2020a; 2020b) conclusion not to regulate perchlorate relied on an EPA (2019c; Exhibit 9) update of the UCMR1 occurrence data. This update provides a similar estimate as EPA (2011a) of approximately 4% of public water systems

² E.g. MassDEP requires certified laboratories to meet an MRL of 1 µg/L or lower
<https://www.mass.gov/doc/letter-to-certified-labs-regarding-perchlorate-testing-0/download>

with at least one detection of perchlorate above of 4 µg/L. The Committee notes that the frequency of occurrence is expected to be much greater at the lower drinking water values (0.2 – 2 µg/L) recommended by the Committee. Thus, the Committee concludes, consistent with EPA’s own reasoning, that regulation of perchlorate in drinking water presents a meaningful opportunity for health risk reduction.

In summary, the Committee unanimously disagrees with EPA’s latest determination not to regulate perchlorate through adoption of a national MCL. As discussed extensively in this document, the Committee concluded that the perchlorate levels (18 -90 µg/L) used as benchmarks by EPA are not protective of public health. Therefore, the EPA analysis based on occurrence exceeding these levels is irrelevant and does not provide a sound rationale for EPA’s decision not to regulate perchlorate in drinking water. The Committee concludes that EPA should not abandon regulation of perchlorate in drinking water, but should use a more health protective approach in arriving at an MCLG, which should fall in the range of approximately 0.2 to 2 µg/L.

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APPENDIX 1 - COMPARISON OF NEW JERSEY, CALIFORNIA, MASSACHUSETTS, AND EPA HEALTH-BASED DRINKING WATER GUIDELINES AND REGULATORY STANDARDS FOR PERCHLORATE

	New Jersey Drinking Water Quality Institute (2005) https://www.state.nj.us/dep/watersupply/pdf/perchlorate_mcl_10_7_05.pdf	Massachusetts DEP (Zewdie et al., 2010) https://ehp.niehs.nih.gov/doi/pdf/10.1289/ehp.0900635	California EPA (2015) https://oehha.ca.gov/media/downloads/water/chemicals/phg/perchloratephgfeb2015.pdf	EPA Health Advisory (2008) https://www.epa.gov/sites/production/files/2019-03/documents/interim-dw-perchlorate.pdf	EPA Proposed Maximum Contaminant Level (2019) https://www.govinfo.gov/content/pkg/FR-2019-06-26/pdf/2019-12773.pdf
Study	Greer et al. (2002)	Greer et al. (2002)	Greer et al. (2002)	Greer et al. (2002)	Korevaar (2016); linked with EPA model
Basis	Human iodide uptake	Human iodide uptake	Human iodide uptake	Human iodide uptake	Predictions of perchlorate effect on thyroid hormone in early pregnancy woman with low/adequate iodide intake (EPA model) - linked with study of effects of decreased thyroid hormone in early pregnancy on IQ of offspring (EPA independent analysis of Korevaar, 2016).
Point of Departure	7 ug/kg/day) - NOEL	7 ug/kg/day - minimal LOAEL	3.7 ug/kg/day - BMDL for 5% decrease	7 ug/kg/day - NOEL	6.7 µg/kg/day - dose predicted to decrease IQ by 2 points in offspring of pregnant women with low iodine intake, ft4 levels and TSH feedback effectiveness.
Uncertainty Factors	10 – intrahuman (sensitive subpopulations)	100 - Total <ul style="list-style-type: none"> • 10 – intrahuman (sensitive subpopulations) • 10 – LOAEL to NOAEL 	10 – intrahuman (sensitive subpopulations, e.g. infants)	10 – intrahuman (sensitive subpopulations)	3 - intrahuman (sensitive subpopulations)
Reference Dose	0.7 ug/kg/day) (NAS/EPA IRIS)	0.07 ug/kg/day	0.37 ug/kg/day	0.7 ug/kg/day) (NAS/EPA IRIS)	2.2 µg/kg/day
Exposure Assumptions	Default adult – 70 kg body wt; 2 L/day water consumption	Default adult – 70 kg body wt; 2 L/day water consumption	Infant 0-6 months – 4.2 kg x day/L (0.24 L/kg/day)	Default adult – 70 kg body wt; 2 L/day water consumption	0.032 L/kg/day (90th percentile of women age 15-44; very close to 0.029 L/kg/day based on 2 L/day, 70 kg body weight).
Relative Source Contribution	20% - default	20% - default	73% - specific to infants	62% - Based on urinary data from 2001-20 NHANES and nationwide exposure based on UCMR occurrence data (90 th percentile)	80% - based on the 90th percentile of consumption of food containing the 95th percentile perchlorate concentration from FDA Total Diet Study.
Health-based Guideline	5 ug/L – Health-based MCL	0.49 ug/L – Health-based Guideline	1 ug/L – Public Health Goal	15 ug/L	56 ug/L – Proposed Maximum Contaminant Level Goal (MCLG)
Enforceable Drinking Water Standard	MCL - 5 ug/L (recommended by DWQI; proposed but not adopted by NJDEP)	MCL - 2 ug/L (set higher than health-based value due to concerns about perchlorate in hypochlorite disinfectant used by public water systems)	MCL – 6 ug/L (based on older Public Health Goal of 6 ug/L that was revised to 1 ug/L in 2015)	Not applicable	56 ug/L – proposed MCL
Comments	Calculation for bottle-fed infant (5.7 kg; 0.8 L/day, RSC = 100%) - also 5 ug/L	Alternative calculation for bottle-fed infant (4 kg; 0.64 L/day, RSC = 100%) – 0.44 ug/L	Analytical reporting level is 4 ug/L; currently determining if it can be decreased so that MCL can be lowered.	Stated to be a <u>Subchronic</u> Health Advisory	Three additional options: MCLGs for decrease of 1 IQ point - 18 µg/L and 3 IQ points - 90 µg/L; withdraw proposed MCL (e.g. do not regulate perchlorate in drinking water)

APPENDIX 2 - CHRONOLOGY OF FEDERAL AND STATE DOCUMENTS AND PUBLICATIONS RELATED TO RISK ASSESSMENT OF PERCHLORATE IN DRINKING WATER

Prepared by Gloria Post, NJDEP, for the NJDEP SAB Public Health Standing Committee
Perchlorate MCL Review

DOCUMENTS RELATED TO EPA PERCHLORATE EVALUATIONS:

Earlier EPA and National Research Council (NRC) Perchlorate Risk Assessment Documents (1998-2008)

These documents (except Research Triangle Institute, 1999 and EPA, 2008) are posted under “Downloads” at <https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=24002> or <https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=72117> .

- EPA (1998). Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization Based on Emerging Information. Review Draft.
http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=4606
This draft document develops a Reference Dose of 0.9 ug/kg/day based on thyroid follicular cell hypertrophy in rat pups following gestational exposure. The Reference Dose includes a total uncertainty factor of 100.
- Research Triangle Institute. (1999). Perchlorate peer review workshop report. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response; contract no. 68-W98-085.
Peer review of EPA (1998). *This document could not be located online and does not appear to be posted online.*
- EPA (2002). Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization. External Review Draft.
http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=36247
This draft assessment considered additional studies not available when the earlier draft (EPA, 1998) was written. The proposed Reference Dose of 0.03 ug/kg/day was based on several effects in rats including effects on brain morphometry, thyroid histopathology, hormone changes in offspring after gestational exposure, and decreased maternal T4 and increased TSH in the dams in the same study; thyroid histopathology and hormone changes at 14- and 90-days in a subchronic rat study, and indications of immunotoxicity (dermal contact hypersensitivity). Physiologically-based pharmacokinetic modeling was used for rat-to-human dose extrapolation, and the total uncertainty factor was 300.

- Report on the Peer Review of EPA (2002).
 - Main document:
http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=523397
 - Appendices:
http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=523398

- EPA's Disposition of Comments and Recommendations for Revisions to EPA (2002).
http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=442305
This document states that the EPA (2002) draft risk assessment is superseded by the NRC (2005) perchlorate report (below).

- National Research Council (2005). Health Implications of Perchlorate Ingestion. This report can be downloaded at <https://www.nap.edu/catalog/11202/health-implications-of-perchlorate-ingestion>
This document recommends a Reference Dose of 0.7 ug/kg/day based on inhibition of uptake of radioactive iodide into the thyroid in healthy adult volunteers who ingested perchlorate for 14 days (Greer et al., 2002). The lowest dose was considered to be the NOEL and an uncertainty factor of 10 for intra-human variation was used.

- EPA (2005) IRIS assessment
https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1007
EPA IRIS adopted the Reference Dose recommended by NRC (2005).

- EPA (2008) Interim Drinking Water Health Advisory
<https://nepis.epa.gov/Exe/ZyPDF.cgi/P1004X7Q.PDF?Dockey=P1004X7Q.PDF>).
The Interim Health Advisory of 15 ug/L is based on the EPA IRIS/NRC Reference Dose of 0.7 ug/kg/day, default adult drinking water ingestion assumptions (70 kg body wt., 2 L/day), and a Relative Source Contribution factor of 62% (62 percent of exposure assumed to come from drinking water) based on an analysis presented in the document.

EPA Regulatory Determination to develop a perchlorate MCL

- EPA (2008) Preliminary Regulatory Determination Notice not to regulate perchlorate in drinking water. <http://www.gpo.gov/fdsys/pkg/FR-2008-10-10/html/E8-24042.htm>

- EPA (2011) Final Regulatory Determination to develop an MCL for perchlorate.
<http://www.gpo.gov/fdsys/pkg/FR-2011-02-11/html/2011-2603.htm>

In 2011, EPA made a regulatory determination that a National Primary Drinking Water Regulation (e.g. MCL) should be developed for perchlorate, based on the criteria specified in the Safe Drinking Water Act.

- Additional supporting documents are posted at <https://www.epa.gov/dwstandardsregulations/perchlorate-drinking-water>

EPA (2008-2017) Perchlorate Risk Assessment Documents Related to Development of the Proposed (2019) MCLG/MCL

- EPA (2008). Inhibition of the Sodium-Iodide Symporter by Perchlorate: An Evaluation of Life Stage Sensitivity Using Physiologically-Based Pharmacokinetic (PBPK) Modeling. EPA/600/R-08/106A.

<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=212508>

EPA evaluated the NRC (2005) PBPK models for the effects of perchlorate on iodide uptake into the thyroid in the average adult, pregnant woman and fetus, lactating woman and neonate, and young child. EPA identified the near-term fetus as the most sensitive subgroup for inhibition of iodide uptake at the perchlorate dose (7 µg/kg/day) used as the point of departure for the Reference Dose; breastfed and bottle-fed infant were also predicted to be more sensitive than the average adult. EPA stated that: *“The lack of biological information and data ... particularly for early fetal development, limits EPA’s confidence on predictions for fetal endpoints. Therefore, EPA simply chose not to use model predictions for the early- or midterm fetus. However, because many of the physiological and iodide- and perchlorate-specific parameters in the late-term fetus are expected to be quite close to those of the newborn and there are many more data available for validation of the model in the newborn, the higher confidence in model predictions for the newborn is then partially extended to the late-term fetus....”*

- Peer Review Comments and EPA Responses for EPA (2008).
 - EPA (2009). Summary of External Peer Review Comments and Disposition for the 2008 External Review of the Report “Inhibition of the Sodium-Iodide Symporter by Perchlorate: An Evaluation of Lifestage Sensitivity Using Physiologically-Based Pharmacokinetic (PBPK) Modeling (External Review Draft). <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=199347#Download>
 - Detailed peer review comments on EPA (2008) http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=484251

- EPA (2009). Drinking Water: Perchlorate Supplemental Request for Comments. Fed. Reg. 74 (159): 41883. August 19, 2009. <https://www.govinfo.gov/content/pkg/FR-2009-08-19/pdf/E9-19507.pdf>

EPA requested comments on additional approaches to analyzing scientific data related to its perchlorate regulatory determination. Specifically, comments were requested on interpretation of physiologically based pharmacokinetic (PBPK) modeling, alternative Health Reference Levels based upon body weight and water consumption of other life stages, and consideration of studies published since EPA Adopted the NRC (2005) Reference Dose for perchlorate.
- EPA (2012). White Paper: Life Stage Considerations and Interpretation of Recent Epidemiological Evidence to Develop a Maximum Contaminant Level Goal for Perchlorate (*provided to EPA SAB for their review of “Approaches to Derive an MCLG for Perchlorate”*).

[https://yosemite.epa.gov/sab/sabproduct.nsf/0/d3bb75d4297ca4698525794300522ace/\\$file/final+perchlorate+white+paper+05.29.12.pdf](https://yosemite.epa.gov/sab/sabproduct.nsf/0/d3bb75d4297ca4698525794300522ace/$file/final+perchlorate+white+paper+05.29.12.pdf)

This white paper presents scientific information published subsequent to the NRC (2005) perchlorate report and explains how EPA derived a range of MCLGs for life stages of concern. The NRC/IRIS Reference Dose of 0.7 ug/kg/day was used to develop a range of MCLGs from 2 ug/L for bottle-fed infants (7-60 days old) to 18 ug/L for non-pregnant females, 13-49 years old. The purpose of this white paper was to seek guidance from EPA SAB on how best to consider and interpret the life stage information, the epidemiologic and biomonitoring data since the NRC Report, physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive an MCLG for perchlorate.
- EPA Science Advisory Board (2013) review of “Approaches to Derive an MCLG for Perchlorate”

(<https://nepis.epa.gov/Exe/ZyPDF.cgi/P100J7WK.PDF?Dockey=P100J7WK.PDF>)

EPA requested that its SAB provide advice on how to consider the recent information summarized in EPA (2012) on sensitive life stages, physiologically-based pharmacokinetic modeling, epidemiological and biomonitoring studies, and approaches to use and integrate this information in deriving an MCLG. The SAB recommended that EPA derive a perchlorate MCLG that addresses sensitive life stages (fetus, infant, pregnant and lactating woman) through physiologically-based pharmacokinetic/pharmacodynamic modeling, rather than the default approach based on the NRC/IRIS RfD. Specifically, the SAB suggested that the model link data on the degree of iodide uptake inhibition that causes hypothyroxinemia (low levels of thyroid hormone) in a pregnant woman with data on the relationship between perchlorate exposure and decreased iodine uptake into the thyroid.

- EPA (2016). Biologically Based Dose Response 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. https://cfpub.epa.gov/si/si_public_file_download.cfm?p_download_id=537621&Lab=OGWDW

In response to the SAB (2013) recommendations, EPA in collaboration with FDA developed a Biologically Based Dose Response model (BBDR; also called a Physiologically Based Pharmacokinetic/Pharmacodynamic (PBPK/PD model) for late pregnancy (gestation week 40), formula-fed and breast-fed infants, and lactating women.

- Peer Review of EPA (2016) - External Peer Review for EPA’s Draft Biologically Based Dose-Response (BBDR) Model and Draft BBDR Model Report for Perchlorate in Drinking Water (2017) <https://www.regulations.gov/document?D=EPA-HQ-OW-2016-0439-0006>

The peer review of the EPA (2016) model recommended that it be extended to early pregnancy and made other technical recommendations.

- EPA (2017). Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water.
 - Main Report - Volume I. <https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OW-2016-0438-0019&contentType=pdf>
 - Volume II – Appendix A. <https://www.regulations.gov/document?D=EPA-HQ-OW-2016-0438-0020>
 - Volume III – Appendices B-G. <https://www.regulations.gov/document?D=EPA-HQ-OW-2016-0438-0021>

In response to the peer review comments on the EPA (2016) model, EPA (2017) developed a draft report presenting a revised model that focuses on early pregnancy instead of the life stages (late pregnancy, infants, and lactating women) evaluated in the earlier model; other technical recommendations are also incorporated. The report states that early pregnancy was the focus because the epidemiology data for the relationship between decreased maternal thyroid hormone levels and subsequent neurodevelopmental outcomes is stronger for the first trimester than for later pregnancy. Additionally, a model based on early pregnancy is simpler than a model for later pregnancy because the fetal thyroid gland does not function at this time and it (as well as some other compartments from the late pregnancy model) do not need to be modeled. The EPA (2017) model links predictions of perchlorate’s effect on thyroid hormone

production in early-pregnancy women who have low/adequate iodide intake with epidemiology data for effects of decreased early pregnancy thyroid hormone levels on neurodevelopment. The draft report presents perchlorate doses ($\mu\text{g}/\text{kg}/\text{day}$) predicted to cause specified quantitative changes in neurodevelopmental parameters, and perchlorate doses predicted to cause specified increased percentages of low thyroid early pregnancy women. EPA also added an alternative approach that would estimate the perchlorate level that would increase the percentage of hypothyroxinemic (low thyroid function) pregnant women in the population.

- External Peer Review for EPA's Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water (2018).

<https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OW-2016-0439-0012&contentType=pdf>

Peer review comments on EPA (2017) report and model. The peer reviewers generally supported the BBDR model approach. However, they recommended that other sensitive life-stages (later pregnancy, breast-fed infant, and formula-fed infant) also continue to be addressed along with early pregnancy that was added to the model at the suggestion of the earlier peer reviewers. It should be noted that the peer reviewers were not asked which of several potential studies, endpoints, and models should be used as the basis for the dose-response relationship between decreased thyroid hormone (fT4) in early pregnancy and neurodevelopmental effects in the offspring. Finally, it should be noted that the peer reviewers did not review the uncertainty factors or exposure assumptions (ingestion rate; Relative Source Contribution factor) used to develop the proposed MCLG.

Proposed EPA MCLG/MCL (2019)

- Federal Register Notice - National Primary Drinking Water Regulations: Proposed Perchlorate Rule (6/26/19).

<https://www.federalregister.gov/documents/2019/06/26/2019-12773/national-primary-drinking-water-regulations-perchlorate>.

An MCLG and MCLG of 56 $\mu\text{g}/\text{L}$, based on a predicted decrease of 2 IQ points in offspring of a subpopulation of pregnant women who are more susceptible to perchlorate's effects and who were exposed during the 1st trimester of pregnancy. Alternative MCLGs/MCLs of 18 $\mu\text{g}/\text{L}$ and 90 $\mu\text{g}/\text{L}$, based on decreases of 1 or 3 IQ points, and an option not to adopt a perchlorate MCL, are also presented.

- EPA (2019). Technical Support Document: Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water.

<https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OW-2018-0780-0123&contentType=pdf>

This document provides the detailed basis for the proposed MCLG and MCL. The Reference Dose is based on the two linked models mentioned above. It is based on one of several studies (Korevaar et al., 2016, “independent analysis” for dose-response; see table III-2, pgs. 30533-34 of FR notice) linking decreased fT4 (free thyroxine) in early pregnancy to neurodevelopmental effects in the offspring. It is also based on one of three different modeling approaches presented in the draft EPA (2017) document (Tables 25, 27, and 28 on pp. 6-5 to 6-9).

- Supporting documents for the proposed MCL are posted at <https://www.regulations.gov/docketBrowser?rpp=25&so=DESC&sb=commentDueDate&po=0&dct=SR%2BO&D=EPA-HQ-OW-2018-0780>

Comments submitted to EPA on 2019 Perchlorate MCL Proposal

- A total of 109 comments were submitted to EPA on the proposed perchlorate MCL. They are posted at <https://www.regulations.gov/docketBrowser?rpp=50&so=DESC&sb=commentDueDate&po=0&dct=PS&D=EPA-HQ-OW-2018-0780>
 - NJDEP comments <https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OW-2018-0780-0266&attachmentNumber=1&contentType=pdf>
 - Massachusetts DEP comments <https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OW-2018-0780-0236&attachmentNumber=1&contentType=pdf>
 - NY State DOH comments <https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OW-2018-0780-0253&attachmentNumber=1&contentType=pdf>

Final EPA Decision Not to Regulate Perchlorate in Drinking Water

- EPA (2019). Perchlorate Occurrence and Monitoring Report. Office of Water. EPA 816-R-19-003. May 2019. <https://www.regulations.gov/document?D=EPA-HQ-OW-2018-0780-0127>

EPA conducted an updated analysis of the data on occurrence of perchlorate in public water systems in Unregulated Contaminant Monitoring Rule 1 including occurrence above the Reporting Level (4 ug/L) and the proposed and alternative proposed MCLs of 18, 56, and 90 ug/L.

- EPA (2020). EPA Issues Final Action for Perchlorate in Drinking Water. News Release. June 18, 2020. <https://www.epa.gov/newsreleases/epa-issues-final-action-perchlorate-drinking-water> and
- EPA (2020). Drinking Water: Final Action on Perchlorate. Fed. Reg. 85 (140): 43990. July 21, 2020. <https://www.govinfo.gov/content/pkg/FR-2020-07-21/pdf/2020-13462.pdf>
EPA announced that it was withdrawing the 2011 regulatory determination and made a final determination not to regulate perchlorate in drinking water. Specifically, EPA stated that perchlorate is not found in drinking water with a frequency and at levels of public health concern to support a meaningful opportunity for health risk reduction through a national perchlorate drinking water regulation. EPA stated that the occurrence of perchlorate in drinking water had decreased because Massachusetts and California are now regulating it, it has been addressed at some contaminated sites, and procedures for storage and handling of hypochlorite solutions used as drinking water disinfectants had improved. EPA also stated that it had determined that the concentrations at which perchlorate may present a public health concern are higher than the concentrations considered in the 2011 regulatory determination.

STATE RISK ASSESSMENTS FOR PERCHLORATE IN DRINKING WATER

California and Massachusetts both have adopted MCLs for perchlorate, and New Jersey proposed an MCL in 2005 but it was not adopted.

- California EPA (2015). Public Health Goal – Perchlorate in Drinking Water. <https://oehha.ca.gov/media/downloads/water/public-health-goal/perchloratephgfeb2015.pdf>
Cal EPA updated its perchlorate Public Health Goal (the California term for an MCLG) from 6 ug/L to 1 ug/L in 2015. The enforceable MCL remains at 6 ug/L due to analytical Reporting Level limitations. The basis of the CalEPA Reference Dose (0.37 ug/kg/day) is similar to the NRC/IRIS Reference Dose (0.7 ug/kg/day). Both are based on the Greer et al. (2002) study with an uncertainty factor of 10 for sensitive subpopulations, but CalEPA used Benchmark Dose modeling instead of the NOAEL (the lowest dose in the study - 7 ug/kg/day). The Cal EPA Public Health Goal of 1 ug/L is based on infant exposure assumptions (95th percentile for infant fluid intake) and a Relative Source Contribution of 73% (based on data on perchlorate in the food supply). Links to other Cal EPA perchlorate risk assessment documents are found at <https://oehha.ca.gov/water/press-release/press-release-water/oehha-adopts-updated-public-health-goal-perchlorate-0>
- Massachusetts DEP - Zewdie T, Smith CM, Hutcheson M, West CR. (2010). Basis of the Massachusetts reference dose and drinking water standard for perchlorate. Environ Health Perspect. 118(1):42-8. Open access at: <https://ehp.niehs.nih.gov/doi/pdf/10.1289/ehp.0900635>

The Massachusetts Reference Dose of 0.07 ug/kg/day is 10-fold lower than the NRC/IRIS Reference Dose because it includes an additional uncertainty factor of 10 for a total uncertainty factor of 100 instead of 10. This uncertainty factor was used because the lowest dose was considered to be a "minimal LOAEL" (for reasons described in Zewdie et al.) rather than a NOAEL, and because of database uncertainties (no chronic studies, uncertainties about transport into breast milk, mode of action, immunotoxicity and possible carcinogenicity). The health-based drinking water values are 0.49 ug/L for adults and 0.44 ug/L for formula-fed infants. The final MCL of 2 ug/L is higher than the health-based values. It was set based on practical considerations that are not related to the human health risk assessment.

- NJDEP. New Jersey Drinking Water Quality Institute (2005). MCL Recommendation for Perchlorate.

https://www.state.nj.us/dep/watersupply/pdf/perchlorate_mcl_10_7_05.pdf

NJDEP proposed a perchlorate MCL of 5 ug/L in 2008. However, it was not adopted within the one year period allowed for in NJ law, and the proposal therefore lapsed. The proposed MCL was based on a NJ Drinking Water Quality Institute (DWQI) recommendation of a Health-based MCL (equivalent to MCLG) of 5 ug/L. It was based on the NRC/IRIS Reference Dose of 0.7 ug/kg/day, and default adult exposure assumptions (70 kg body wt., 2 L/day drinking water consumption, 20% (default) Relative Source Contribution). Exposures to formula-fed infants were also considered.