November 19, 2017

Samuel Hernandez
U.S. EPA, Office of Ground Water and Drinking Water
Standards and Risk Management Division, (Mail Code 4607M), 1200
Pennsylvania Avenue NW.
Washington, DC 20460;

RE: Comments on EPA's Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water at Docket No. EPA-HQ-OW-2016-0438

Dear Mr. Hernandez:

The Environmental Defense Fund (EDF) and the Natural Resources Defense Council (NRDC) appreciate the opportunity to comment on the Environmental Protection Agency's (EPA) draft report on proposed approaches to inform the derivation of a maximum contaminant level goal (MCLG) for perchlorate in drinking water at Docket No. EPA-HQ-OW-2016-0438-0019.[1] EPA requested comments on the draft report in the September 15, 2017 *Federal Register* and extended the comment period to November 20, 2017 in the October 12, 2017 *Federal Register*.

With this latest analysis, EPA scientists address the central question raised by EPA's Science Advisory Board (SAB) in 2013, commenters (including NRDC and EDF), and the agency's peer review panel: what is the relationship between perchlorate exposure in the first trimester of pregnancy on a child's neurodevelopmental outcomes when the mother gets insufficient iodine in the diet. The issue is critical because almost half of US pregnant women get insufficient iodine, especially in the first trimester when they may not be yet aware they are pregnant and under a doctor's care. The SAB specifically requested that EPA consider the effects of low levels of free thyroxine (fT4), referred to as hypothyroxinemia, that had not resulted in an increase in thyroid stimulating hormone (TSH), rather than hypothyroidism where the low T4 had already triggered an increase in TSH levels.

From their review of literature, EPA scientists stated that:

> [E]arly in brain development, fT4 deficiency can affect neuronal cell proliferation and cell migration in the hippocampus (essential for learning and memory, cognitive function), cerebral cortex (essential for executive function, cognitive function), and the medial ganglionic eminence (transitory development structure responsible for guiding axonal migration) (G. Williams, 2008). Maternal hypothyroidism or hypothyroxinemia at these early stages may result in problems with gross motor skills and visual attention and processing (Zoeller & Rovet, 2004). As the first trimester progresses, increases in hCG [Human chorionic gonadotropin] result in a higher production of T4 and reduced TSH and TBG (Morreale de Escobar et al., 2007). In the fetus this period also corresponds to

[1] EPA Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water, September 2017. See https://www.regulations.gov/document?D=EPA-HQ-OW-2016-0438-0019.

> neurogenesis in the midbrain and cortex, neuronal migration into the cortex, deiodinase activity for conversion of T4 to T3, and presence of nuclear thyroid receptors in the brain (Morreale de Escobar et al., 2004).[2]
>
> Higher levels of maternal fT4 throughout pregnancy allow for normal neuron and glial cell migration and differentiation, axonal growth, dendritic branching, neurogenesis, and synaptogenesis to occur (G. Williams, 2008). The complex interconnectedness of brain regions required for normal function could be impaired by effects on all of these processes simultaneously or in sequence, and across multiple brain regions. Maternal thyroid deficiencies during these processes further affect visual processing, development of fine motor skills, IQ, and selective learning problems (Zoeller & Rovet, 2004; Zoeller et al., 2007).[3]

EPA scientists concluded that:

> Evaluating these results as a whole demonstrates that in different populations, at different ages for neurodevelopmental assessment, and at various cut points for fT4, there is a significant difference in performance on global cognitive tests when comparing the offspring of hypothyroxinemic women to those of non-hypothyroxinemic women (Costeira et al., 2011; Ghassabian et al., 2014; Júlvez et al., 2013; Korevaar et al., 2016; Li et al., 2010; Pop et al., 1999; Pop et al., 2003; Suárez-Rodríguez, Julián, and Aguilar, 2012).[4]

EPA's scientists also highlight that neurodevelopmental adverse outcomes other than cognition have also been found:

> Additionally, studies identified in the literature review . . . also associated maternal hypothyroxinemia with an offspring's increased risk of schizophrenia (Gyllenberg et al., 2016), ADHD (Modesto et al., 2015), expressive language delay (Henrichs et al., 2010) and other outcomes (Finken et al., 2013; Kooistra et al., 2006; Noten et al., 2015; Päkkilä et al., 2015; Román et al., 2013; van Mil et al., 2012).[5]

Based on the targeted literature search, EPA's scientists identified 55 studies assessing thyroid hormone levels and neurodevelopmental outcomes.[6] They narrowed the list to 29 studies, referred to as Group 2, which considered the relevant exposure window and were compatible with the Biologically Based Dose Response (BBDR) developed by the Food and Drug Administration (FDA) and refined by EPA. They further narrowed the list to 15 studies, designated as Group 1, which evaluated fT4 as a continuous or categorical measure. EPA concluded that:

[2] EPA Draft Report, Section 2.6, pp. 2-8 to 2-9.
[3] EPA Draft Report, Section 2.6, pp. 2-9.
[4] EPA Draft Report, Section 5.4, page 5-56.
[5] EPA Draft Report, Section 5.4, page 5-56.
[6] EPA Draft Report, Section 5.4, page 5-56.

> Taken as a whole, the majority of the Group 1 studies imply that **neurodevelopmental impacts due to altered maternal fT4 levels or presence of maternal hypothyroxinemia occur.** In addition, the Group 2 studies (along with several Group 1 studies) also demonstrate adverse impact of maternal hypothyroxinemia on neurodevelopmental outcomes of the offspring. **Overall, the results of this literature review lend support to the concept that maternal fT4, especially in the hypothyroxinemic range, is critical to the offspring's proper neurodevelopment**. Across different age ranges and neurodevelopment indices, **the impact of altered fT4 is seen even with small incremental changes in fT4 (and in populations with fT4 across the "normal" range)**.[7] [Emphasis added]

EPA scientists developed two approaches to developing a reference dose.

- Quantified relationship between perchlorate exposure and maternal fT4 levels in early pregnancy and neurodevelopmental outcomes in children; and
- Estimated amount of perchlorate needed to increase the proportion of low-iodine individuals that will fall below a hypothetical hypothyroxinemic cut point by a define percentage.

Quantified relationship between perchlorate exposure and maternal fT4 levels in early pregnancy and neurodevelopmental outcomes in children.

EPA scientists characterized the relationship between perchlorate exposure and fT4 levels in mothers with low dietary iodine intake and how that exposure changes neurodevelopmental outcomes. Of the 15 studies in Group 1, EPA scientists identified five studies and four neurodevelopmental endpoints that were quantitatively connected to changes in fT4 levels in the first trimester for pregnant women with iodine intake of less than 75 micrograms per day (µg/day). The four endpoints were:

- **Psychomotor Development Index (PDI):** Assessment of fine and gross motor skills such as body control, coordination, and manipulation. It is the other main indices in BSID.
- **Mental Development Index (MDI):** Assessment of cognitive and language development using items related to sensory perception, knowledge, memory, problem solving, and early language. It is one of two main indices for assessing neurodevelopment in children in the Bayley Scales of Infant Development (BSID).
- **Standard Deviation of Reaction Time:** Assessment using the Amsterdam Neuropsychological Test computerized assessment program.
- **Intelligence Quotient (IQ).**

EPA scientists calculated the dose of perchlorate needed to result in a unit change in each of these neurodevelopmental endpoints. They predicted that:

- **PDI:** A dose of 1.7 micrograms of perchlorate per kilogram of body weight per day (µg/kg/day) was needed to decrease the index by one point using data from week 12 of pregnancy;
- **MDI:** A perchlorate dose of 2.2 µg/kg/day was needed to decrease the index by one point using data from week 12 of pregnancy;

[7] EPA Draft Report, Section 5.5, page 5-61.

- **Reaction Time:** A dose of 3.0 µg/kg/day was associated with a one standard deviation decrease in reaction time using data from week 13 of pregnancy;
- **IQ:** Doses from 6.5 to 45 µg/kg/day were associated with a one point drop in IQ based on two studies with data from gestation week 16 and 13.[8]

Based on this method, the most sensitive endpoint appears to be PDI with IQ being the least sensitive one. It is worth noting that the estimates are based on a limited number of endpoints and health effects. In Section 8 of the report, EPA noted that there are additional potential adverse health effects that were not captured in the analysis to inform the derivation of a perchlorate MCLG.

Estimated amount of perchlorate needed to increase the proportion of low-iodine individuals that will fall below a hypothetical hypothyroxinemic cut point by a define percentage.

Recognizing the risks to a child's neurodevelopment from hypothyroxinemia, EPA scientists evaluated how much perchlorate exposure is needed to shift the proportion of the population that will fall below a hypothetical hypothyroxinemic cut point by 1% or 5%. In other words, how many thousands pregnant women will become hypothyroxinemic in the presence of perchlorate. They acknowledged that:

> This approach does not directly connect the BBDR output to neurodevelopment. However, for pregnant mothers in early pregnancy, this shift could be related to avoiding an increase in the offspring population's risk of adverse neurodevelopmental impacts given the preponderance of evidence located in EPA's literature review that finds an association between hypothyroxinemia and adverse neurodevelopmental outcomes . . .[9]

EPA's scientists defined hypothyroxinemia as the 10th percentile of fT4 of median-iodine intake population of 170 µg/day. The estimated fT4 values at the 10th percentile of a normal iodine intake population corresponded to about 50th percentile of a low-iodine intake population. In other words, approximately 50% of pregnant women with iodine intake less than 75 µg/day would already be hypothyroxinemic.

They predicted that a dose of:

- 0.3-0.4 µg perchlorate/kg/day is associated with a 1% increase in pregnant women with hypothyroxinemia; and
- 2.1-2.2 µg perchorate/kg/day is associated with a 5% increase in pregnant women with hypothyroxinemia.[10]

While these percentages appear small, they represent a significant number of potentially affected children since neurodevelopmental harm is likely irreversible. EPA did not estimate the number of pregnant women or children potentially affected. We did. Based on four million children born

[8] EPA Draft Report, Section 9, Table 39.
[9] EPA Draft Report, Section 7, page 7-1.
[10] EPA Draft Report, Section 7.1, Table 35 and Section 9, Table 40.

in the US each year,[11] an estimated 400,000 were born to women with hypothyroxinemia (10th percentile). A 1% shift in the population of women with hypothyroxinemia associated with perchlorate exposure would correspond to an increase of 4,000 impacted children; if there is a 5% shift, the number of children born to hypothyroxinemic mothers would increase to 20,000 impacted children. EPA also considered other percentiles to define hypothyroxinemia and came up with similar perchlorate doses of concern.

Exposure to additional goitrogenic chemicals should be considered.
We understand that EPA's analysis concerns perchlorate exposures. However, as clearly noted in its report, pregnant women are likely exposed to additional chemicals negatively affecting the thyroid gland's function. EPA stated that "[w]hile the BBDR model does not explicitly consider other goitrogens (e.g., thiocyanate, nitrate), simulating results for a mother with low iodine intake and low baseline fT4 may help to address the sensitivity of individuals with high exposures to other goitrogens."[12] We encourage the agency, and its partners at FDA, to continue improving the BBDR model to make it compatible with iodine levels below < 75µg/day to better represent these other exposures that affect the thyroid. Approximately 16% of American women have an iodine intake of 50 µg/day.[13] Until those refinements are made, EPA needs recognize the uncertainty through safety factors.

Safety factors are needed.
EPA clearly recognized the variability in fT4 as an important uncertainty factor in estimating perchlorate exposure associated with low fT4. Specifically, it stated that "…different populations vary widely in their distribution of fT4 levels;" there also are "intra-individual variance in fT4."

These intraspecies and intra-individual variation could be based on physiological fluctuations or due to the presence of other goitrogenic chemicals affecting the thyroid function. For these reasons, we recommend EPA apply at a minimum a safety factor of 10 to the most sensitive endpoints. For the first approach, EPA should use PDI as the most sensitive endpoint to provide a reference dose that would be 0.17 µg/kg/day. For second approach, the reference dose would be the 0.21 µg/kg/day to protect all but an estimated 20,000 affected children and 0.03 µg/kg/day to protect all but an estimated 4,000 affected children.

General observations on the process.
EPA scientists have risen to the challenge presented by the SAB, the previous review panel, and the public comments. They have conducted a rigorous analysis of the science and presented its findings in a coherent and clear manner. Having watched this process over the years, we wanted to take the opportunity to provide some general observations:

1. **EPA's scientists provide an essential service:** Academic researchers laid a solid foundation for the analysis. Without their work, typically funded by government grants, we would not have the evidence necessary to recognize the harm from perchlorate at the levels under consideration. But it took the independent scientists at EPA, building on a

[11] Centers for Disease Control and Prevention, National Vital Statistics System, Birth Data accessed on November 4, 201 at https://www.cdc.gov/nchs/nvss/births.htm.
[12] EPA Draft Report, Section 3.5, page 3-15.
[13] Caldwell KL, et al. (2013) Iodine Status in Pregnant Women in the National Children's Study and in U.S. Women (15-44 years), National Health and Nutrition Examination Survey 2005-2010. Thyroid 23:927-937

model developed by FDA, to provide the objective rigorous review of the evidence and adapt the model.

2. **Peer-review process works:** The agency rose to the challenge of two previous peer-review panels, one established by EPA's SAB and the other by EPA's Office of Water. The panels operated in a transparent process and provided independent and objective review of the analysis by EPA. We anticipate that this third and final panel will do the same. The integrity of the process depends on credibility of the experts on the panel. Screening out these experts because they receive government funding as EPA is now doing[14] is irresponsible and unlawful. It undermines the quality of the review and the credibility of the process.
3. **Incremental changes in free T4 (fT4) are fundamental:** Critical neurodevelopmental adverse effects could be missed by measuring full range maternal fT4. Windows of susceptibility are common in all organs during development. Hormonal control of brain development is no exception. Therefore, adverse neurodevelopmental outcomes will vary based on the time and duration of decreases in fT4 levels. We appreciate seeing the agency building a model based on this fundamental principle of developmental biology.

For questions, please contact us at tneltner@edf.org or 202-572-3263 for Tom Neltner, eolson@nrdc.org for Erik Olson, or drmvma@gmail.com for Maricel Maffini.

Sincerely,

Tom Neltner
Environmental Defense Fund
1875 Connecticut Ave., NW, Suite 600
Washington, DC 20009
Phone: 202-572-3263

Erik Olson
Natural Resources Defense Council
1152 15th Street NW, Suite 300
Washington, D.C. 20005

Maricel V. Maffini
Independent Consultant
Germantown, MD 20874

[14] EPA Administrator, Strengthening and Improving Membership on EPA Federal Advisory Committees, October 31, 2017. See https://www.epa.gov/faca/strengthening-and-improving-membership-epa-federal-advisory-committees.