THE CHLORINE INSTITUTE
1300 Wilson Boulevard, Suite 525, Arlington, VA 22209
Phone: 703-894-4140 Fax: 703-894-4130
www.chlorineinstitute.org

November 20, 2017

U.S. Environmental Protection Agency
Office of Ground Water and Drinking Water
1200 Pennsylvania Ave., NW
Washington, D.C. 20460

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

Dear Sir or Madam:

The Chlorine Institute ("CI" or the "Institute") is a 190 member, not-for-profit trade association of chlor-alkali producers worldwide, as well as packagers, distributors, users, and suppliers. The Institute's mission chemicals, namely chlorine, sodium and potassium hydroxides, sodium hypochlorite, the distribution of vinyl chloride monomer (VCM), and the distribution and use of hydrogen chloride, are used throughout the U.S. economy and are paramount to the protection of public health.

The Chlorine Institute would like to submit the following comments to the United States Environmental Protection Agency's (EPA's) recent request for public comment on the "Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water'' (draft MCLG Approaches Report) Volumes I, II, and III as noted in the September 15, 2017, Federal Register notice (FRN, 2017).

Epidemiology Data Used in the Model: The data used to establish parameters for the model, calibrate the model, and validate the model relies heavily on epidemiology data in early pregnancy. While we agree that an extension of the model to include early pregnancy would be

beneficial to capture a vulnerable time of brain development and the impact of perchlorate on thyroid hormones, the quality of the available data should be highly considered and evaluated. Epidemiology, focused on human populations, is heavily biased with confounding factors that can impact the effects of perchlorate on thyroid hormone levels, as noted throughout the current draft document. Confounding factors that are difficult to control in human epidemiology studies include identification of smokers, diet, previous disease status, dietary supplement intake etc., all of which can impact levels of thyroid hormones and perchlorate exposure. EPA does not provide justification for excluding pertinent animal studies such as that by Mahle et al., (2003) in which pregnant rats were administered perchlorate in drinking water from gestation day 2 and thyroid hormone levels were measured. Animal studies may provide useful data that have been conducted in well controlled environments with less genetic variability. In fact, Clewell et. al., (2003) developed and published a PBPK model in rat modeling fetal perchlorate dose and inhibition of iodide kinetics during gestation.

Literature Review - Group 1 Study Selection. It is unclear why EPA chose to not include studies with results that were not statistically significant in the association between fT4 and neurodevelopment outcome. These studies would add value in determining hormone levels during pregnancy and neurodevelopment outcome (Ghassabian et.al., 2014; Modesto et.al., 2015; Moleti et. al., 2016; Noten et.al., 2015; Oken et.al., 2009; Velasco et. al., 2009) EPA's reason, for example, for not including the data form the Noten et. al. (2015) paper states that "statistical significance was lost after controlling for confounders" (EPA, 2017, Section 6.0, Table 22). Without taking into consideration studies in which no neurodevelopmental effects were found, creates a bias within the model and therefore the model lacks robustness in informing derivation of an MCLG.

Failure to address other goitrogens in the model. The lack of consideration of other goitrogens such as thiocyanate, which has been shown to compete with perchlorate to inhibit NIS and also is a competitive substrate for thyroid peroxidase, the enzyme required to form T3 and T4 from thyroglobulin and iodine (Steinmaus et al., 2007; 2013), can lead to uncertainty in the model results. It is not enough to justify the lack of consideration and effect of other goitrogens by saying that the model simulates mothers with low iodine intake and low baseline fT4 which addresses the sensitivity to high exposure of other goitrogens (EPA, 2017, Section 3.5, page 3-

15). Additional data should be considered in the model of how other goitrogens can alter availability of thyroid hormones as well as iodide's interaction with the NIS.

Further, the model assumes that exposures to perchlorate and other goitrogens vary independently in the population and that the effects are additive (EPA, 2017, Section 3-5, p.3.17). The assumption that the effects are "additive" should be further evaluated and clarified. As noted above, other goitrogens can have additional effects on the thyroid hormones that are not consistent with the perchlorate mode of action. Making the wrong assumption on this point can greatly impact the predictions of the effects of perchlorate on neurodevelopment.

Therefore, EPA cannot ignore the effects of other goitrogens on the transport of iodine into the thyroid. Pursuant to Section 1412(b)(4) of the Safe Drinking Water Act (SDWA), the Maximum Contaminant Level Goal (MCLG) "shall be set at the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety." In order to meet this obligation, all goitrogens should be considered in the PBPK model rather than focusing solely on one goitrogen.

Variable expression of the NIS gene. As EPA states, "The degree to which there is inter-individual variation in NIS structure and/or regulation contributing to variance across the population in the impact of perchlorate exposure on thyroid function is currently unknown" (EPA, 2017, Section 3.5, p. 3.16). As supporting data that variation in the NIS gene exisits, EPA sites a paper by Al-Rasheed et al. (2015) who identified variations in the NIS gene that could lead to development of differentiated thyroid cancer. This data indicates that variability in the expression of the NIS gene could render some individuals more or less sensitive to exposure to all goitrogens. This variability, while it has been recognized as an uncertainty within the model, should be considered within the parameters of the mode.

Limited data on toxicokinetics and toxicodynamics of perchlorate. EPA does acknowledge there is limited data on the effects of perchlorate on circulating hormone levels needed for the model (EPA, 2017, Section 3.5, p.3-16). It is noted that clinical toxicology and occupational studies show minimal changes in the thyroid hormone levels (Braverman, et. al., 2007). Epidemiology studies with low exposures, however, show associations between urinary

perchlorate, increases in TSH and decrease in T4 (fT4) (Blout et al., 2006, Braverman et. al., 2007, Steinmaus et. al., 2016). The lack of toxicodynamic and toxicokinetic data, especially during pregnancy, could impact the prediction of fT4 on neurodevelopmental outcomes. This puts the validity of the model at question. Additional studies should be conducted to increase the validity of the model if using the model to influence and set regulatory standards.

Incorporation of the TSH feedback loop. TSH levels do not have a consistently predictable impact on T4 levels according to Fitzgerald et. al., (2016), due to interindividual variations including genetics, subclinical thyroid disease, age, and gender. The model does account for some of the variability and does make an association between weak responders and strong responders however, not within a fixed set-point. It is important to point out that the whole HPT feedback loop is tightly controlled and that homeostatic set points will vary among individuals. Within this discussion EPA points out that "any exposure to perchlorate is predicted to reduce fT4" (EPA, 2017, Section 3.4, p.3-17). However, a no observed adverse effect level (NOAEL) was established in humans at 7 µg/kg/day in which perchlorate inhibition of radioiodine uptake by the thyroid (Greer et. al., 2002) (EPA, 2017, Section 3.4, p. 3-14). In fact, EPA incorrectly cites this level as the NOAEL but Greer et al, 2002, cite this level as the No Observed Effect Level (NOEL), the level at which no statistically or biologically significant increases in the frequency or severity of any effect is observed. This clearly indicates there is a dose at which perchlorate does not impact iodide uptake by the thyroid and therefore fT4. This statement should be changed to reflect the dose-response of perchlorate on fT4 levels. In additional, perchlorate acts on the NIS to alter iodine levels, not directly fT4 levels. The model's only output being considered is the effect of perchlorate on free thyroxine (fT4) and no other measures of thyroid function. To understand the complex feedback and homeostatic mechanisms in the hypothalamic-pituitary-thyroid axis, several measures of thyroid function should be modeled, including, T3, T4, TSH, thyroglobulin, and thyrotropin releasing hormone.

Determining Distribution of fF4. The literature review suggests that gestational weeks 12, 13 and 16 were best to focus on and further that the fT4 is best to assess in order to calibrate the model for the median-iodine intake. However, the data is very limited at these time points during gestation. Specifically, Li et. al., 2014), Männistö et. al., 2011), and Zhang et. al., 2016) were evaluated for weeks 12 and 13. Only Männistö et. al., 2011) and Zhang et. al., 2016) were

evaluated for week 16. Only one study evaluated week 13 (Männistö et al., 2011). Further it is difficult to determine whether the lognormal distribution can be applied versus a normal distribution with such limited data. Additional data should be considered at additional gestational timepoints in the first trimester (EPA, 2017, Section 4.1, p. 4-1). Perhaps the studies that measured levels of fT4 at various gestational time points in Group 1 of the literature reviewed but were disregards by EPA as not having statistical significance could be helpful here.

Failure to address compensation and adaptation. Critical assumption for concern in the model is that there is no compensation or adaptation of thyroid hormones, levels of iodide, or changes in expression of the NIS considered. As noted already, homeostatic control of the HPT axis, iodide intake and gene expression of NIS are all variable and as such compensatory mechanisms or mechanism of adaptation to varying levels of thyroid hormones, iodide and NIS expression should be included in the model to more accurately reflect the effects of perchlorate on neurodevelopmental outcomes.

Neurodevelopmental endpoint selection. It is unclear why EPA selected ADHD and autism in their literature search as neurodevelopmental endpoints to assess the effects of iodine on thyroid hormone levels (EPA, 2017, Section 5, page 5-1). These are not appropriate endpoints given the spectrum of both diseases. The literature review should focus on studies in which measurable and clearly defined endpoints in the study are reflective of neurodevelopment outcomes.

In addition, neurodevelopment can be affected by many different types of exposure scenarios. A single measurement of thyroid hormone in the first trimester of pregnancy cannot predict neurodevelopment in offspring at one year after birth and up to 10 years after birth. During this period, there are many factors that could affect brain development.

Alternative Approach (Section 7.0). EPA cites that an "alternative option to inform future decisions on the derivation of an MCLG using the BBDR model is to evaluate a shift in the proportion of the population that will fall below a hypothyroxinemic cut point, given exposure to perchlorate" (EPA, 2017, Section 7, page 7-1). However, EPA indicates this approach does not directly connect the BBDR output to neurodevelopment. It appears the approach is to be preventative in that the shift could prevent an increase in "risk" to the neurodevelopmental impacts of low thyroid hormone levels based on EPA's literature review of hypothyroxinemia

and adverse neurodevelopmental outcomes. However, the data used in the model should link to neurodevelopmental outcome; otherwise the model will not meet the goal of assessing the effects of perchlorate on neurodevelopment.

In addition, it seems that this approach would increase uncertainty in individual fT4 measurements within a presumed smaller population size. A single fT4 measurement may represent hypothyroxinemia for one individual at a certain time point, but not for the same individual at a different time point or for another individual (EPA, 2017, Section 7.0, page 7-5). There is an assumption that neurodevelopment deficits would occur however, the data does not measure neurodevelopmental outcomes. Again, without the proper data being input into the model, the validity of the model is questionable, rendering the model not useful.

Appendix C: Comparison of the BBDR model with the Steinmaus et al. Data - Change in IQ: In Appendix C of Volume III, EPA makes a comparison between the Steinmaus et. al., (2016) data of urinary perchlorate and fT4 levels in women in urine at 7 weeks of gestation and in blood at 15-20 weeks of gestation to the results of the BBDR model and states that the results of the model indicate it would take 2.91 µg/kg/day to cause a 1 point change in IQ. However, the results of the Steinmaus et. al., (2016) study are only based on one collection time point for each pregnant woman and it appears to be a big assumption that 1 point change in IQ can be determined by one time point in one study.

Independent Review Recommended Prior to Completion. As the model nears completion, it is essential that an independent, third party evaluation and validation of the model be conducted to understand the completed models' strengths, weaknesses and what further improvements may be required of the model before using the model to inform a MLCG for perchlorate.

In conclusion, EPA has made great strides in improving the draft PBPK model to inform a MCLG for perchlorate. However, there are still many limitations of the draft PBPK model that need to be addressed, including the lack of data to calibrate and validate the model specific to sensitive life-stages. We encourage EPA to select peer reviewers with the expertise to evaluate all facets of this model with the understanding that it will be used to inform MCLG which, in turn, will influence global regulatory standards.

Thank you for the opportunity to comment and your consideration of our requests.

Sincerely,

Erica Bernstein
Director - Outreach
The Chlorine Institute
703.894.4114
ebernstein@CL2.com

REFERENCES:

Al-Rasheed, M. M., Alzahrani, A. S., Macadam, A., Overall, A., Gard, P., & Dzimiri, N. (2015). The potential role of the sodium iodide symporter gene polymorphism in the development of differentiated thyroid cancer. Gene, 572(2), 163-168.

Blount, B. C., Pirkle, J. L., Osterloh, J. D., Valentin-Blasini, L., & Caldwell, K. L. (2006). Urinary Perchlorate and Thyroid Hormone Levels in Adolescent and Adult Men and Women Living in the United States. Environ Health Perspect, 114(12), 1865-1871.

Braverman, L. (2007). Clinical studies of exposure to perchlorate in the United States. Thyroid, 17(9), 819-822.

Braverman, L., Pearce, E. N., He, X., Pino, S., Seeley, M., Beck, B., Magnani, B., Bleunt, B. C., & Firek, A. (2006). Effects of six months of daily low-dose perchlorate exposure on thyroid function in healthy volunteers. J. Clin. Endocrinol. Metab, 91(7), 2721-2794.

Clewell R.A., Merrill E.A., Yu K.O., Mahle D.A., Sterner T.R., Mattie D.R., Robinson P.J., Fisher J.W., Gearhart J.M. (2003) Predicting fetal perchlorate dose and inhibition of iodide kinetics during gestation: a physiologically-based pharmacokinetic analysis of perchlorate and iodide kinetics in the rat. Toxicol Sci. 73(2):235-55.

Environmental Protection Agency (EPA). (2005). Integrated Risk Information System Chemical Assessment Summary: Perchlorate and Perchlorate Salts.

Environmental Protection Agency (EPA). (2005) News Release by EPA: EPA Sets Reference Dose for Perchlorate.
https://yosemite.epa.gov/opa/admpress.nsf/0/c1a57d2077c4bfda85256fac005b8b32?OpenDocument

Environmental Protection Agency (EPA). (2017). Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water. https://www.epa.gov/dwstandardsregulations/perchlorate

Federal Register Notification (FRN): 82 Federal Register 43355, September 2017.

Ghassabian, A., Marroun, H. E., Peeters, R. P., Jaddoe, V. W., Hofman, A., Verhulst, F. C., Tiemeier, H., & White, T. (2014). Downstream effects of maternal hypothyroxinemia in early pregnancy: nonverbal IQ and brain morphology in school-age children. Journal of Clinical Endocrinology and Metabolism, 99(7), 2383-2390. doi: 10.1210/jc.2013-4281

Greer, M. A., Goodman, G., Pleus, R. C., & Greer, S. E. (2002). Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans. Environmental Health Perspectives, 110(9), 927.

Li, C., Shan, Z., Mao, J., Wang, W., Xie, X., Zhou, W., Li, C., Xu, B., Bi, L., Meng, T., Du, J., Zhang, S., Gao, Z., Zhang, X., Yang, L., Fan, C., & Teng, W. (2014). Assessment of thyroid function during first-trimester pregnancy: What is the rational upper limit of serum TSH during the first trimester in Chinese pregnant women? Journal of Clinical Endocrinology and Metabolism, 99(1), 73-79.

Mahle D.A., Yu K.O., Narayanan L., Mattie D.R., Fisher J.W. (2003) Changes in cross-fostered Sprague-Dawley rat litters exposed to perchlorate. Int J Toxicol. 22(2):87-94.

Männistö, T., Surcel, H. M., Ruokonen, A., Vääräsmäki, M., Pouta, A., Bloigu, A., Järvelin, M. R., Hartikainen, A. L., & Suvanto, E. (2011). Early pregnancy reference intervals of thyroid hormone concentrations in a thyroid antibody-negative pregnant population. Thyroid, 21(3), 291-298.

Modesto, T., Tiemeier, H., Peeters, R. P., Jaddoe, V. W., Hofman, A., Verhulst, F. C., & Ghassabian, A. (2015). Maternal Mild Thyroid Hormone Insufficiency in Early Pregnancy and Attention-Deficit/Hyperactivity Disorder Symptoms in Children. JAMA Pediatr, 169(9), 838-845.

Moleti, M., Trimarchi, F., Tortorella, G., Candia Longo, A., Giorgianni, G., Sturniolo, G., Alibrandi, A., & Vermiglio, F. (2016). Effects of Maternal Iodine Nutrition and Thyroid Status on Cognitive Development in Offspring: A Pilot Study. Thyroid, 26(2), 296-305.

National Research Council (NRC). 2005. Health Implications of Perchlorate Ingestion. Washington, DC: National Academies Press.

Noten, A. M., Loomans, E. M., Vrijkotte, T. G., van de Ven, P. M., van Trotsenburg, A. S., Rotteveel, J., van Eijsden, M., & Finken, M. J. (2015). Maternal hypothyroxinaemia in early pregnancy and school performance in 5-year-old offspring. Eur J Endocrinol, 173(5), 563-571.

Oken, E., Braverman, L., Platek, D., Mitchell, M. L., Lee, S. L., & Pearce, E. N. (2009). Neonatal thyroxine, maternal thyroid function, and child cognition. Journal of Clinical Endocrinology and Metabolism, 94(2), 497-503.

Steinmaus, C., Miller, M. D., & Howd, R. (2007). Impact of smoking and thiocyanate on perchlorate and thyroid hormone associations in the 2001-2002 national health and nutrition examination survey. Environmental Health Perspectives, 1333-1338.

Steinmaus, C., Miller, M. D., Cushing, L., Blount, B. C., & Smith, A. H. (2013). Combined effects of perchlorate, thiocyanate, and iodine on thyroid function in the National Health and Nutrition Examination Survey 2007-08. Environ Res, 123, 17-24.

Steinmaus, C., Pearl, M., Kharrazi, M., Blount, B., Miller, M., Pearce, E., Valentin-Blasini, L., G, D., Hoofnagle, A., & J, L. (2016). Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in Southern California. Environ Health Perspect, 124, 861-867.

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

Tran, N., Valentin-Blasini, L., Blount, B. C., McCuistion, C. G., Fenton, M. S., Gin, E., Salem, A., & Hershman, J. M. (2008). Thyroid-stimulating hormone increases active transport of perchlorate into thyroid cells. Am J Physiol Endocrinol Metab, 294(4), E802-806.

Velasco, I., Carreira, M., Santiago, P., Muela, J. A., García-Fuentes, E., Sánchez-Muñoz, B., Garriga, M. J., González-Fernández, M. C., Rodríguez, A., Caballero, F. F., Machado, A., González-Romero, S., Anarte, M. T., & Soriguer, F. (2009). Effect of iodine prophylaxis during pregnancy on neurocognitive development of children during the first two years of life. Journal of Clinical Endocrinology and Metabolism, 94(9), 3234-3231.

Zhang, X., Yao, B., Li, C., Mao, J., Wang, W., Xie, X., Teng, X., Han, C., Zhou, W., Li, C., Xu, B., Bi, L., Meng, T., Du, J., Zhang, S., Gao, Z., Yang, L., Fan, C., Teng, W., & Shan, Z. (2016). Reference Intervals of Thyroid Function During Pregnancy: Self-Sequential Longitudinal Study Versus Cross-Sectional Study. Thyroid, 26(12), 1786-1793.