

WHITE PAPER

**A REEVALUATION OF THE CURRENT DRINKING WATER REFERENCE DOSE
FOR PERCHLORATE**

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I Purpose

In 2011, EPA announced its decision (76 FR 7762- 7767) to regulate perchlorate under the Safe Drinking Water Act (SDWA, §1412.b.4.B). EPA is now developing a maximum contaminant level goal (MCLG) and National Primary Drinking Water Regulation (NPDWR) for perchlorate based a reference dose (RfD) of 0.7 µg/kg/day. The NRC derived this Reference Dose (RfD) on the basis of a precursor, non-adverse effect (i.e., inhibition of iodide uptake).

The NRC approach, and EPA's reliance on it, are both problematic. This is because the approach does not follow the EPA (2002) RfD method in part. Moreover, the approach depends on information in adults, rather than more recent data in perchlorate's critical effect in pregnant women and their offspring.

EPA's RfD method is to use the critical effect,¹ and not a distant precursor to the critical effect as the basis of the RfD. The NAS panel definition of perchlorate's first adverse effect,

¹ A continuum of effects is potentially associated with any exposure to xenobiotics and reflects a sequence of effects of differing severity. From least to most severe this continuum includes:

–Adaptive effects, –Compensatory effects, –Critical effect, –Adverse effects, and –Frank effects.

This continuum starts at low dose with upstream indicators of change, or adaptive effects, where the organism's ability to withstand a challenge is enhanced. Doses associated with such effects are often referred to as No Observed Adverse Effect Levels ([NOAELs](#)). The concept of hormesis may also be relevant here.

As dose increases, compensatory effects occur, which enable the organism to maintain overall function without further enhancement or significant cost. Doses associated with such effects are also often NOAELs. Some of these effects might be judged to be the critical effect.

As dose further increases, the [critical effect](#) is reached. This is the first [adverse effect](#), or its known precursor, that occurs to the most [relevant or] sensitive species as the dose rate of an agent increases. Note that the bracketed phrase "relevant or" is important since the most relevant species is always preferred over the most sensitive species (e.g., if data shows that the rat is more sensitive than the human, the human data are still preferred), but when such information is not available, data from the most sensitive species are chosen. Also the term "precursor" in this definition is singular, meaning the immediate precursor, not just any prior effect. This restriction is important both because it ties the concept of critical effect into common medical practice and because the resulting dose response---such as an RfD---is more meaningful, since without the restriction any RfD can be estimated. Doses associated with such effects are Lowest Observed Adverse Effect Levels ([LOAELs](#)). The highest NOAEL below this LOAEL is generally used in the dose response, and the focus is on determining this NOAEL in a sensitive population.

As dose further increases, the critical effect is exceeded, and [adverse effects](#) are manifested as biochemical changes, functional impairments, or pathologic lesions. These progressively more severe effects impair the performance of the organism, and/or reduce its ability to respond to additional challenges. At some point these adverse effects become manifestly overt and irreversible, and [frank effects](#) or disease ensues.

hypothyroidism, allows EPA and others to define the critical effect as either this endpoint, or its immediate precursor, in the NAS definition, this would be thyroid hypertrophy and hyperplasia.

NAS' unconventional, non-critical effect, approach, if taken for other chemicals, suggests that the development of RfDs for other chemicals would entirely depend on which precursor effect was chosen, or whether any precursor effects were even monitored. Thus, the purpose of this white paper is to provide guidance to the Science Advisory Board (SAB) regarding the current perchlorate RfD and recommend that EPA update its RfD prior to publishing a Health Advisory.

II Background

The EPA's current Reference Dose (RfD) for perchlorate is $0.7 \mu\text{g}/\text{kg}/\text{day}^2$ and is one basis for the EPA's 2011 determination to regulate perchlorate under the Safe Drinking Water Act (SDWA),³. EPA is now developing a maximum contaminant level goal (MCLG) and National Primary Drinking Water Regulation (NPDWR) for perchlorate. The Safe Drinking Water Act requires the EPA to request comments from the Science Advisory Board (SAB) prior to proposal of a MCLG. Although the MCLG is a non-enforceable goal defined under the SDWA (§1412.b.4.B), the NPDWR will likely specify an enforceable Maximum Contaminant Level (MCL) and monitoring and reporting requirements for public water systems. The SDWA that the enforceable MCL be set as close to the MCLG as feasible, therefore it is critical that the RfD, upon which the MCLG is based, be appropriately derived using the best data available. The EPA derived the RfD for perchlorate based on a No Observed Effect Level (NOEL) for radioactive iodide uptake (RAIU) inhibition of 1.8 percent following administration of perchlorate to 37 healthy men and women for 14 days (Greer *et al.*, 2002)⁴, and application of an intraspecies uncertainty factor (UF) of 10 to account for differences in sensitivity between the healthy adults used in the Greer *et al.* study and the most sensitive population, fetuses of pregnant women who might have hypothyroidism or iodide deficiency. This study was chosen as the critical study by the NRC because it was viewed as the first step in the MOA for perchlorate leading to all subsequent events (NRC 2005). It was proposed that a continuum of events in the mode of action following inhibition of iodine uptake would include possible changes in serum thyroid hormone levels, which have been linked with neurodevelopmental changes in iodine-deficient individuals during early life stages (NRC 2005).

It is widely accepted that maternal hypothyroidism during pregnancy, especially when occurring during early gestation, can be associated with an impairment of normal brain development and intelligence in offspring^{5, 6, 7, 8, 9}. Perchlorate inhibits iodine uptake by the thyroid gland and is

² Health Implications of Perchlorate Ingestion. Washington, DC: National Academies Press.

³ U.S. EPA 2011a. Drinking Water: Perchlorate Supplemental Request for Comments. <http://www.gpo.gov/fdsys/pkg/FR-2009-08-19/pdf/E9-19507.pdf>

⁴ Greer M, Goodman G, Pleus R, Greer S. Health effects assessment for environmental perchlorate contamination: The dose response assessment for inhibition of thyroidal radioiodine uptake in humans. *Environ Health Perspect.* 2002;110:927-37.

⁵ Vermiglio F, Lo Presti VP, Castagna MG, Violi MA, Moleti M, Finocchiaro MD, Mattina F, Artemisia A, Trimarchi F. Increased risk of maternal thyroid failure with pregnancy progression in an iodine deficient area with major iodine deficiency disorders. *Thyroid.* 1999 Jan;9(1):19-24.

thought to pose a risk for hypothyroidism, particularly in sensitive human populations that include pregnant women, neonates and individuals with iodine deficiency. However, in order to cause an adverse neurodevelopmental effect in the offspring, perchlorate would need to be present at levels sufficient to cause hypothyroidism and cause a measurable decrease in maternal T4 or increase in TSH. Despite existence of numerous epidemiological studies there is no direct human evidence linking perchlorate exposure to neurodevelopmental impacts. Although a risk to low-birth weight or preterm newborns, offspring of mothers who had iodide deficiency during gestation, and offspring of hypothyroid mothers due to perchlorate exposure can be inferred from its mode of action. Strawson et al.¹⁰ contend that inhibition of iodine uptake generally correlates poorly with thyroid function except when uptake is inhibited to a significant extent for prolonged periods, in which case intra-thyroid iodine deficiency results in decreased synthesis of key thyroid hormones (triiodothyronine, T3 and thyroxine, T4) and increased release of thyroid stimulating hormone (TSH). Thus, the RfD is inappropriate because it is based on the “unconventional” use of a non-adverse distant precursor to the critical effect, rather than the critical effect itself (hypothyroidism), or an immediate precursor. Consequently, the use of NOEL for iodine uptake results in an overly conservative safe dose and opens the door to potentially enormous cleanups that provide little or no extra health benefits.

In its 2005 recommendation, the NRC acknowledged that the RfD may need to be adjusted upward or downward on the basis of future research (NAS, 2005)¹¹. Since the development of the EPA’s 2005 Reference Dose (RfD) ten epidemiologic studies have been published on perchlorate and thyroid function in adults, pregnant women or newborns. The availability of this information now necessitates a reconsideration of the existing RfD value. Furthermore, the NAS recognized that new, useful data were under development including data from Chile that “could be considered in the evaluation of the U.S. experience with perchlorate in drinking water.” (NAS, 2005, page 69). The excellent relative source contribution evaluation, proposed in the EPA’s white paper is based on well supported and clearly described work of the FDA. However, the current RfD necessitates reconsideration before using it for the basis of calculating a life stage-specific MGCL or physiologically based pharmacokinetic analysis.

The practice of risk assessment, which is based on decades of experience in the U.S., Canada, and Europe, allows us to draw conclusions about public health in the absence of observable data

⁶ Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Ganon J, O’Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med.* 1999;341:549-55.

⁷ Smit BJ, Kok JH, Vulmsa T, Briet JM, Boer K, Wiersinga WM. Neurologic development of the newborn and young child in relation to maternal thyroid function. *Acta Paediatr.* 2000;89(3):291-5.

⁸ Pop VJ, Brouwers EP, Vader HL, Vulmsa T, van Baar AL, de Vijlder JJ. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. *Clin Endocrinol.* 2003;59(3):282-8.

⁹ Kooistra L, Crawford S, van Baar AL, Brouwers EP, Pop VJ. Neonatal effects of maternal hypothyroxinemia during early pregnancy. *Pediatrics.* 2006 Jan;117(1):161-7.

¹⁰ Strawson, J; Dourson, M; Zhao, Q. (2005) [The NAS Perchlorate Review: Is the RfD Acceptable?](#) 2005. *Env. Health Perspect* 113(11):A729-30; Nov. Author reply A730-2.

¹¹ NRC (National Research Council). Health implications of perchlorate ingestion. NAS Press, Washington, DC; 2005.

and in the presence of scientific uncertainty. The accepted process for developing RfDs¹² suggests two possible approaches to developing an RfD from the perchlorate data. The first would be to use the NOAEL of the critical effect from an adult population and apply uncertainty factors to account for sensitive populations and for lack of precision in defining this NOAEL. The second approach would be to use a NOAEL from a sensitive population. Following this second approach, a standard RfD of 0.002 mg/kg-day has been described that is adequately health-protective¹³.

III. Studies supporting a revised RfD

There are two studies that provide information useful for setting a more current RfD: Blount, et al (2006)¹⁴ and Tellez et al. (2005)¹⁵. Together, these two studies give us definitive information on perchlorate's likely critical effect, or absence of effect, in pregnant women and newborns.

Tellez et al. (2005)

Tellez et al. (2005) performed a prospective longitudinal epidemiologic study to test the hypothesis that long-term exposure to perchlorate may cause iodine deficiency in either the mother during gestation or the baby at birth. The study followed pregnant women starting prior to 24 weeks gestation through 12 weeks postpartum who resided in three cities located in northern Chile: Taltal with 114 $\mu\text{g/L}$, Chañaral with 6 $\mu\text{g/L}$, and Antofagasta with 0.5 $\mu\text{g/L}$ perchlorate in the public drinking water. Consistent with previous studies of the same populations, no changes in thyroid-related hormones were found as a consequence of perchlorate in drinking water^{16, 17}. Birth measurements, such as weight, length, and head circumference were not different among the three cities and were consistent with current U.S. norms. Urinary iodine among the entire cohort was intermediate between values in pregnant women in the United States from the National Health and Nutrition Examination Survey (NHANES) I and at NHANES III, and was consistent with current World Health Organization recommendations. Moreover, breast milk iodine was not decreased in the cities with detectable perchlorate. Because this study measured perchlorate levels and potential effects in individual subjects in a prospective manner, it can be reliably concluded that perchlorate in drinking water up to the

¹² D.G. Barnes, M.L. Dourson. *Regul Toxicol Pharmacol.* **8**: 471-486(1988).

¹³ J.Strawson, et al., *Reg. Toxicol. Pharmacol.* **39** 44 (2004).

¹⁴ Blount, B.C., J.L. Pirkle, J.D. Osterloh, L.Valentin-Blasini and K.L. Caldwell. 2006. Urinary Perchlorate and Thyroid Hormone Levels in Adolescent and Adult Men and Women Living in the United Environ Health Perspect. 2006;114(12):1865-71.

¹⁵ Tellez, RT, Michaud P, Reyes C, Blount BC, Van Landingham, CB, Crump KS, et al. 2005. Long-term environmental exposure to perchlorate through drinking water and thyroid function during pregnancy and the neonatal period. *Thyroid* 15(9):963-975.

¹⁶ Crump C., Michaud P., Tellez R., Reyes C., Gonzalez G., Montgomery E.L., Crump K.S., Lobo G., Becerra C., Gibbs J.P., (2000). Does perchlorate in drinking water affect thyroid function in newborns or school-aged children? *J. Occ. Environ. Med.* 42: 603-612

¹⁷ Tellez, R.T., Chacon, P.M., Gibbs, J., Crump, C., Abarca, C.R., 2003. Chronic environmental exposure to perchlorate and thyroid function during pregnancy and the neonatal period. Protocol and preliminary results available from

highest levels studied of 114 micrograms per liter — many times higher than several U.S. state standards and over four times higher than EPA’s reference dose — does not change human maternal thyroid function nor important birth parameters in their babies.

The lack of thyroid changes reported by Tellez et al., (2005) echoes those of Crump et al. (2000) that reported perchlorate in drinking water, at doses up to 120 g/L had caused no decrease in FT4, increase in TSH, or goiter. Among first-grade school children mean TSH, T4, and T3, were similar among the three cities although free T4 was significantly increased in children living in Taltal and Chanaral relative to Antofagasta, a change in the direction opposite that hypothesized for perchlorate. Crump et al. (2000) also studied newborns screened for hypothyroidism by a heel-stick blood sample between February 1996 and January 1999 in the same three Chilean cities. TSH levels were lower in Taltal than in the other two cities, again, a trend opposite to that hypothesized for perchlorate. Based on the results of Tellez et al (2005), Crump (2000),

The point of departure for an RfD is set at the No Observed Adverse Effect Level (NOAEL), which is the highest experimental dose that is without adverse effect. However, since no human study reported exposures high enough to cause a decrease in T4, all human studies can be said to have identified “freestanding NOAELs” for the hypothyroidism. The lowest exposure observed by Crump et al. (2000) yields a NOAEL of 0.006 mg/kg-day, based on an average of 0.112 mg/L measured in school-age children exposed *in utero* and for their entire lifetime (about 7 years). Because, these children were exposed *in utero* and as neonates, the NOAEL from this study is a freestanding NOAEL in a sensitive population. Similar to Crump Tellez et al., 2005 reported a perchlorate level of 114 (72–139) g/L in Taltal, which is in agreement with previous measurements. Thus, a NOAEL should be set based on the drinking water exposure level reported by Crump et al (2000) and Teleze (2003, 2005).

In terms of iodine uptake, a NOAEL 0.006 mg/kg-day has minimal risk of Hypothyroidism. Greer estimated that a dose of 0.0064 mg/kg-day would result in no inhibition of iodine uptake with a 95% upper confidence limit on iodine uptake inhibition of 8.3%. Furthermore, Greer concluded that an iodine uptake inhibition less than 10% would not be biologically significant. This conclusion is consistent with the National Research Council¹⁸ estimation indicating that iodine uptake greater than 75% would be necessary before adverse effects on thyroid hormones would be likely. The fact that iodine uptake inhibition is not an adverse event together with the estimation that a 75% inhibition of iodine uptake would require a serum perchlorate concentration of approximately 4 $\mu\text{mol/L}$ ¹⁹.

There are important uncertainties associated with the use of a freestanding NOAEL and are considered in detail by Strawson et al. (2004).

- A freestanding NOAEL does not provide an estimate of the true threshold or true NOAEL Since no hypothyroid effect was found in the children studied by Crump et al. (2000), pregnant women and neonates (Tellez et al., 2003 and 2005) or the adults in the

¹⁸ National Academy of Sciences 2005 Health Implications of Perchlorate Ingestion. National Academy Press, Washington D.C.

¹⁹ Tonacchera M, Pinchera A, Dimida A, Ferrarini E, Agretti P, Vitti P, Santini F, Crump K, Gibbs J 2004 Relative potencies and additivity of perchlorate, thiocyanate, nitrate, and iodide on the inhibition of radioactive iodide uptake by the human sodium iodide symporter. *Thyroid* **14**:1012–1019

Greer et al. (2002), the NOAELs could actually be higher than the ones used as the basis of our proposed RfD. The effect of this uncertainty is to make the proposed RfD lower than the actual threshold for perchlorate, increasing the margin of safety. This uncertainty is balanced, by characteristics of the study population in Crump et al. (2000) that could either lowering or raise the NOAEL.

- The children investigated by Crump et al. (2000) had an apparent iodine excess relative to other populations including U.S. This elevated iodine intake could have the effect of protecting the children from the effects of perchlorate. However, since the year 2000 iodine excretion levels have dropped markedly.
- Strawson et al. (2004) previously suggested that uncertainty factor of 3, rather than 1, is appropriate to use with the point of departure for setting the NOAEL because there are no data to suggest how the other sensitive subpopulation, pregnant women, might respond. However, the Tellez et al. (2005) addresses this issue directly and shows that pregnant women are not sensitive to the hypothyroid effect of perchlorate in drinking water during early pregnancy, late pregnancy or the neonates at birth. Furthermore, no effect on effect on breast milk iodine levels was detected.

Blount et al. (2006)

Blount et al. (2006) has been cited as evidence that people in the US are suffering health consequences at doses lower than the current EPA RfD (0.0007 mg/kg-day). Although Blount et al. (2006) provides valuable information about perchlorate in the US population, as an environmental epidemiologic study it only makes non-causal associations between urinary levels of perchlorate and thyroid related hormones (TSH and T4). The study was conducted in 2299 men and women, aged 12 and older, participating in the National Health and Nutrition Examination Survey (NHANES) during 2001-2002. However, the cross-sectional design of the study is not directly useful for evaluating dose-response relationships in risk assessment. After an initial multiple regression analysis showing that there was no relationship between urinary perchlorate and serum TSH or T4 in men, the remainder of the paper focused on women. There were 1318 women aged 12 or older. After eliminating samples for which perchlorate, TSH, or T4 data were missing, women with a reported history of thyroid disease or thyroid medication, and samples with extreme values of TSH or T4, a total of 1111 samples were included in the analysis. Since women who are iodine deficient are considered to be a sensitive population, the women were categorized into low- and normal- dietary iodine groups, based on a cut-point of 100 µg/L urinary iodine. The study also used multiple regression models that included perchlorate and covariates known or likely to be associated with these thyroid related hormones. Perchlorate was a significant predictor of two thyroid related hormones in women with urinary iodine < 100 µg/L. For women with urinary iodine ≥ 100 µg/L, perchlorate was a significant predictor for only one. The authors concluded that associations of perchlorate with thyroid hormones were coherent in direction known to affect thyroid function and independent of other variables, but were at perchlorate exposure levels unanticipated based on previous studies. The individually measured exposure (urinary perchlorate as the independent variable) and response (serum total T4 or serum TSH) provides a strong evidence of a statistical relationship, which is consistent with the known biology of perchlorate as an agent that affects thyroid physiology.

Blount et al. (2006) does not demonstrate that the urinary perchlorate levels measured in the sample population are associated with any adverse effects – effects that will harm public health, even in the sensitive populations. Rather, the associations in this study are useful for generating hypotheses for causal epidemiology studies but because it is a cross-sectional study, the positive relationship between urinary perchlorate and serum TSH and T4 only suggests a significant association. The study does not show that perchlorate caused the increase in TSH or decrease in T4. The study also showed statistically significant relationships between increased TSH and decreased T4 with several other independent variables. Since the same argument applies to these variables, they must also be considered “real”, hence the study suggests that thyroid function is complex. The key point is that since these other factors also play a role, there may be a constellation of important factors that can alter the dose-response curve, and for this reason the quantitative use of the data should be interpreted very cautiously. Additional work is needed to determine whether some unknown factor associated with perchlorate exposure, but not the factors examined in this study, might be the cause of the observed changes in TSH and T4.

Blount et al. (2006) does not suggest that people in the US are suffering health consequences at doses lower than the current EPA RfD (0.0007 mg/kg-day). Rather, based on the data and regression curves in Blount et al. (2006), doses up to 1000 times higher than the RfD (0.45-0.68 mg/kg-day) will be required, even in iodine deficient women, to raise serum TSH values to the upper limit of the normal range. This is based on regression of the perchlorate levels that cause serum TSH to increase to 4.5 IU/L – the upper limit of normal of the population. To result in an average population serum TSH value at 4.5 IU/L or greater, a urinary perchlorate level of 47,700 µg/L is required, and to result in 1% of the population at that abnormal level or higher, a urinary perchlorate level of 31,420 µg/L is required. These urinary perchlorate levels can be seen to be roughly equivalent to doses of 0.68 mg/kg-day and 0.45 mg/kg-day, respectively (assuming 100% of urinary perchlorate is attributable to oral exposure, urine is excreted at 1L/day (a lower end of daily adult urine excretion and a 70 kg body weight). These doses are consistent with other human studies which demonstrate that doses of 0.5 mg/kg-day have no effect on thyroid hormone levels of normal, healthy adults, and are well above EPA’s current RfD of 0.0007 mg/kg-day.

Measurement of total T4 might be influenced by serum protein variations; although in this study, there was not a significant relationship between serum albumin and serum T4 and TSH. Taking into account the changes in serum hormone levels predicted in the paper, the maximum urinary perchlorate levels measured in the sample population will not cause the serum hormone levels to move beyond the normal limits. However, as mentioned in the Blount et al. paper, serum albumin only accounts for 15-20% of T4 binding. Nonetheless, measurement of free T4, as was done by Tellez et al. (2005), is a better metric for assessing thyroid effects. Also, serum TSH levels are known to vary widely depending on the time of day the blood sample was collected^{20, 21}. This Blount et al. study, while good for generating hypotheses, did not appear to control for this factor.

²⁰ Weeke, J and HJ Gundersen . 1978. Circadian and 30 minutes variations in serum TSH and thyroid hormones in normal subjects. *Acta Endocrinol (Copenh)*. 89: 659-72

²¹ Fisher, DA. 1996. Physiological variations in thyroid hormones: physiological and pathophysiological considerations. *Clinical Chemistry*. 42:135-139

IV. Summary

Strawson et al. (2004) have evaluated the noncancer oral toxicity data for perchlorate. They have derived a high-confidence reference dose (RfD) of 0.002 mg/kg-day based on a free-standing NOAEL of 0.006 mg/kg-day for decreased thyroxine (T4) enzyme levels due to iodine uptake inhibition observed in children (Crump et al., 2000). Since that time, Tellez et al. (2005) have published the results of their investigation that corroborates these earlier findings. Furthermore, while Strawson et al. used an uncertainty factor of 3 (for intraspecies variability) to account for uncertainty relating to the effect of perchlorate on thyroid function in pregnant women. The 2005 study by Tellez et al. directly addresses this uncertainty making a reconsideration of this uncertainty factor necessary.

EPA should reconsider its RfD on the basis of this new epidemiology information in pregnant women and their offspring.