

## Perchlorate consumption, iodine status, and thyroid function

Paula R Trumbo

*Perchlorate inhibits the uptake of iodide into the thyroid gland, thereby possibly affecting the synthesis of thyroid hormones. Pregnant women and their fetuses and newborns have the greatest potential for risk of adverse health effects following exposure to perchlorate. Perchlorate is present in some foods and in drinking water in certain areas of the United States. Based on the available information, the United States Food and Drug Administration (FDA) is not recommending that consumers of any age alter their diet or eating habits due to perchlorate exposure. If one eats a healthy diet that is consistent with the Dietary Guidelines for Americans, taking iodine supplements is not necessary for protection against health effects associated with perchlorate at the levels present in water and foods.*

© 2009 International Life Sciences Institute

### INTRODUCTION

Perchlorate is primarily used as an oxidizer in propellants and rocket fuels (e.g., ammonium perchlorate)<sup>1</sup>; it is also used in blasting formulations, pyrotechnics, and explosives. There is evidence that perchlorate is formed naturally and that a natural perchlorate background exists.<sup>2</sup> Perchlorate competitively inhibits the uptake of iodide into the thyroid gland, where iodine is essential for the synthesis of thyroid hormones (triiodothyronine [T<sub>3</sub>] and thyroxine [T<sub>4</sub>]). Perchlorate was used in the past to treat thyrotoxicosis, particularly in Europe,<sup>3</sup> and it is still used to treat iodine-induced hyperthyroidism.<sup>4</sup> Inhibition of thyroid hormone synthesis can result in hypothyroidism, which is indicative of an elevated serum thyroid stimulation hormone (TSH) concentration. In fetuses and infants, thyroid hormones are critical for normal growth and development of the central nervous system. Cretinism is a condition of severely stunted physical and mental growth due to a congenital deficiency of thyroid hormone. Therefore, pregnant women and their fetuses and newborns have the greatest potential for risk of adverse health effects following exposure to perchlorate. The National Research Council's (NRC) Board on Environmental Studies and Toxicology evaluated the health

implications of perchlorate ingestion.<sup>5</sup> The NRC report acknowledged that while iodine deficiency is believed to be rare in the United States, pregnant women may have a low iodine intake and further research is needed to evaluate the risk factors of iodine deficiency in these women and their offspring. The report also advised a reference dose (RfD) for perchlorate of 0.0007 mg/kg/day (0.7 µg/kg/day), the daily oral exposure that is likely to be without appreciable risk of deleterious effects during a lifetime. The United States Environmental Protection Agency (EPA) accepted the NRC RfD recommendation.<sup>6</sup> Recently, the EPA released a notice of a preliminary determination for perchlorate in accordance with the Safe Drinking Water Act.<sup>5</sup> The EPA determined that a national primary drinking water regulation for perchlorate would not present a meaningful opportunity for health risk reduction for persons served by public water systems. This decision was based, in part, on some of the scientific evidence on perchlorate discussed below. In the EPA notice, a health reference level of 15 µg/L was determined for pregnant women; this represents the estimate of the maximum concentration of perchlorate that can be in the drinking water of a pregnant woman without her total (food and water) exposure exceeding EPA's RfD for perchlorate.<sup>7</sup>

Affiliation: *PR Trumbo* is with the Division of Nutrition Programs and Labeling, United States Food and Drug Administration, College Park, Maryland, USA.

Correspondence: *PR Trumbo*, HFS-830, 5100 Paint Branch Parkway, College Park, MD 20740, USA. E-mail: paula.trumbo@FDA.HHS.gov, Phone: +1-301-436-2579, Fax: +1-301-436-1191.

Key words: *iodide, iodine, perchlorate, reference dose, safety, thyroid*

## PERCHLORATE IN WATER, FOOD, AND DIETARY SUPPLEMENTS

Perchlorate has been detected in drinking water in a number of US states, with the highest concentrations detected in southern California, west central Texas, Massachusetts, and along the east coast between New Jersey and Long Island.<sup>8</sup> Between 2001 and 2005, the EPA conducted a national sampling of drinking water in 26 states and two territories and determined that approximately 4% of public water systems had at least one analytical detection of perchlorate at a level greater than or equal to the method detection limit of 4 µg/L.<sup>5</sup> Only 0.8% of public water systems had a perchlorate concentration of 15 µg/L or higher. In 2004–2005, the FDA surveyed bottled water and found very low levels of perchlorate in only 2 of 51 samples tested.<sup>9</sup>

Perchlorate consumption from foods was recently assessed as part of the FDA's Total Diet Study (TDS) (2005–2006).<sup>10</sup> Detectable levels of perchlorate were found in 59% of foods sampled, with 21% of foods sampled containing trace amounts. Dairy products were the major contributor (29–51%) of perchlorate in the diet of children (2, 6, 10, and 14–16 years of age). For adults, vegetables were the major contributor (26–38%) of perchlorate in the diet, with dairy products being the second major contributor (17–23%). The estimated lower and upper range of perchlorate intakes for the age-gender groups measured was 0.08 (men aged 25–30 years) to 0.39 (2 years for both genders) µg/kg/day.

For infants, baby food (49%) and dairy foods (32%) were the major sources of perchlorate.<sup>10</sup> Perchlorate intake from baby food ranged from 1.1 to 1.3 µg/day. The average perchlorate concentration in breast milk was 10.5 µg/L (1.4–92) and 33 µg/L (1.3–411) in samples collected in Texas and Massachusetts, respectively.<sup>11,12</sup>

Perchlorate has also been detected in dietary (vitamin and mineral) supplements. Snyder et al.<sup>13</sup> reported that 65% of the supplements sampled contained perchlorate. Based on the number of tablets recommended, a daily oral dose of perchlorate would range from 0.03 to 18 µg/day.

### IODINE FROM FOOD AND DIETARY SUPPLEMENTS

Based on the findings of the FDA TDS (2003–2004), iodine was found in the majority (59%) of foods sampled.<sup>10</sup> For children 2 years of age and older, dairy products were the major contributor of dietary iodine (45–73%), while grains were the second major contributor (10–23%). Similar to perchlorate, the major contributors of dietary iodine in infants and young children are baby foods and dairy products (collectively 90%). Cuprous and potassium iodide are considered by the

FDA to be generally recognized as safe (GRAS) for addition to table salt at a level up to 0.01%. Thus, iodized salt is another source of dietary iodine.

Data from the 1999–2002 National Health and Nutrition Examination Survey (NHANES) showed that 12% of infants and 38% of children 1–3 years of age took dietary supplements.<sup>14</sup> Use of iodine-containing supplements by adults and children (9–6 years) was approximately 28% and 17%, respectively (NHANES 2003–2004). Over-the-counter iodine-containing multivitamin supplements are available for children and pregnant women; iodine-containing prenatal multivitamin supplements requiring a prescription are also available. A recent study reported that 31% of non-prescription and 72% of prescription prenatal vitamins do not contain iodine.<sup>15</sup>

### IODINE INTAKE, STATUS, AND THYROID FUNCTION IN THE US POPULATION

#### Iodine intake

Based on the FDA TDS (2003–2004), the average iodine intake for women of reproductive age (25–45 years) was 145–197 µg/day.<sup>10</sup> Despite the fact that this intake range does not represent iodine from dietary supplements or from iodized salt added by the consumer, this intake range exceeds the estimated average requirement (EAR) of 95 µg/day. Because the distribution of iodine intake was not determined, it is not possible to estimate the percentage of women who consumed less than the EAR. Based on NHANES 1999–2004 data, the average daily amount of iodine adults obtained from supplements was 128 µg/day.

Based on the FDA TDS (2003–2004), the average iodine intake for infants ranged from 144 to 155 µg/day.<sup>10</sup> This intake level is greater than the adequate intake (AI) of 130 µg/day for infants 6–11 months of age.<sup>16</sup> The AI for infants was based on the average iodine intake by exclusively breastfed infants. This approach to setting the AI for infants was used because breast milk was considered by the Institute of Medicine panel to provide a sufficient amount of iodine to the infant. An intake level of 25–35 µg/day is a level below which there is an increase in neonatal serum TSH concentrations indicating subclinical hypothyroidism.<sup>17</sup> The average daily amount of iodine consumed by children who took an iodine-containing supplement was approximately 105 µg/day (NHANES 1999–2004).

#### Iodine status

Urinary iodine concentration is the most common measure of iodine status. The World Health Organization

(WHO) proposed a desirable urinary iodine concentration of 100–200 µg/L for non-pregnant populations and 150–249 µg/L during pregnancy.<sup>15</sup> The goal for iodine sufficiency in a population is to have less than 50% of a population with a urinary iodine concentration below 100 µg/L and less than 20% of a population with a urinary iodine concentration below 50 µg/L.<sup>18</sup> A desired urinary iodine concentration of 100 µg/L was identified because this concentration represents an iodine intake of approximately 150 µg/day, which is a reference intake level that has been identified by various organizations, such as the recommended dietary allowance (RDA) by the Institute of Medicine.<sup>13</sup> The RDA, however, is an intake level for individuals to achieve and for assessing the intake of individuals rather than populations.

The most recent available evidence for urinary iodine concentrations in the United States comes from NHANES 2003–2004.<sup>19</sup> Approximately 29%, 11%, and 2% of the general US population had a urinary iodine concentration below 100, 50, and 20 µg/L, respectively, which meets the WHO criteria for an iodine-sufficient population. NHANES 2003–2004 did not measure urinary iodine concentrations in infants and young children. For women of reproductive age, approximately 38% of non-pregnant women had a urinary iodine concentration below 100 µg/L and approximately 39% of pregnant women had a urinary iodine concentration below 150 µg/L.

### Thyroid status

Evidence from NHANES 1999–2002 showed the prevalence of hypothyroidism (TSH > 4.5 IU/L) in the general population was approximately 3.7%.<sup>20</sup> Among women of reproductive age, the prevalence of hypothyroidism was 3.1%. There are several causes of hypothyroidism (e.g., thyroiditis, surgical removal, Graves' disease, drug therapy), including inadequate and too much iodine intake.<sup>21</sup> In the United States, congenital hypothyroidism screening is performed on all infants born at healthcare facilities. Congenital hypothyroidism occurs in 1 in 4000–3000 newborns in the United States with the most common cause being some form of thyroid dysgenesis.<sup>22</sup> A common cause of hypothyroidism in other parts of the world, where endemic cretinism is common, is iodine deficiency.

### PERCHLORATE EXPOSURE, IODINE METABOLISM, AND THYROID FUNCTION

A number of intervention and observational studies have evaluated the relationship between perchlorate exposure and iodine metabolism and/or thyroid function. In one intervention study, conducted in the US state of Oregon,

37 male and female volunteers were given perchlorate in drinking water at 0.007, 0.02, 0.1, or 0.5 mg/kg/day for 14 days.<sup>23</sup> There was a dose-response inhibition of thyroidal radiolabeled iodine uptake by 17%, 44%, or 67% when 0.02, 0.1, or 0.5 mg/kg/day of perchlorate, respectively, was consumed. There was, however, no significant effect of perchlorate intake at any level on thyroid hormone levels (total T<sub>4</sub>, free T<sub>4</sub>, total T<sub>3</sub>, and TSH). While iodine intake or status was not reported, the authors of this study suggested that with sufficient iodine intake, an average reduction of thyroid iodine concentration to one-third may still allow for sufficient iodine uptake to produce thyroid hormones at a normal rate. The lowest dose of 0.007 mg/kg/day (7 µg/kg/day) from this study was used as a no-observed-effect-level (a non-adverse endpoint) for inhibition of iodine uptake for setting the NRC RfD of 0.0007 mg/kg/day (0.7 µg/kg/day), which included an uncertainty factor of 10 as an inter-species factor for protecting fetuses of pregnant women.<sup>5</sup>

Similar to the observation of Greer et al.,<sup>23</sup> another study found that consuming a higher dose (10 mg/day) of perchlorate for 14 days resulted in a 38% reduction in thyroidal radiolabeled iodine uptake, without any effect on T<sub>3</sub>, T<sub>4</sub>, and TSH levels in men.<sup>24</sup> This article stated that because the thyroid has large stores of iodine, T<sub>4</sub>, and T<sub>3</sub>, the observed decrease in thyroid uptake would not be expected to result in changes in circulating levels of thyroid hormones and TSH over a 2-week period.

Braverman et al.<sup>25</sup> conducted a randomized trial in which 13 men and women consumed a placebo, 0.5, or 3 mg/day of potassium perchlorate for 6 months. There was no significant change in thyroidal radiolabeled iodine uptake or thyroid hormone levels for either doses of perchlorate.

Intermittent, high exposure to perchlorate for many years in male workers at an ammonium perchlorate production plant did not result in any evidence of hypothyroidism, even though thyroidal iodine uptake was decreased during the work shift by 38% compared to off-shift workers.<sup>26</sup> These workers had urinary perchlorate concentrations that were much higher (mean, 43 mg/g creatinine) than those observed in the off-shift workers (mean, 0.16 mg/g creatinine) and the study controls (mean, 0 mg/g creatinine).

A cross-sectional study using NHANES 2001–2002 data reported that while perchlorate exposure was not associated with T<sub>4</sub> or TSH levels in men, in women with a urinary iodine concentration lower than 100 µg/L, perchlorate exposure (urinary perchlorate) was negatively associated with T<sub>4</sub> concentration and positively associated with TSH concentration.<sup>27</sup> For women with a urinary iodine concentration greater than 100 µg/L, urinary perchlorate concentration was negatively associated with T<sub>4</sub> concentrations, while there was no significant association

with TSH. TSH concentrations were considered to be normal in all subjects, regardless of the level of perchlorate exposure (1.31–1.42 IU/L).

No association was observed between perchlorate exposure and thyroid function in pregnant women in three cities in northern Chile, where average perchlorate concentrations in drinking water were 0.5, 6, and 114 µg/L.<sup>28</sup> An ecological analysis of seven counties in the US states of California and Nevada evaluated the association between perchlorate exposure at levels ranging from 4 to 16 µg/L in drinking water and the incidence of congenital hypothyroidism.<sup>29</sup> The number of cases reported for these counties (243 of approximately 700,000) suggested that the risk of congenital hypothyroidism was not higher in these counties than the number of cases that were expected by considering the state incidence rates.

Several cross-sectional studies have evaluated the relationship between perchlorate exposure in drinking water supplies and thyroid function in newborns. No relationship was observed between perchlorate levels ranging from 0.5 to 340 µg/L and thyroid function (T<sub>4</sub>, TSH).<sup>28,30–33</sup>

## CONCLUSION

Based on the FDA TDS, perchlorate exposure in the estimated total mean population (all persons aged 2 years and above) from the foods and beverages measured was more than 10-fold lower than the RfD of 0.7 µg/kg/day. A small percentage (4%) of public water systems had at least one analytical detection of perchlorate at levels greater than or equal to the method reporting limit of 4 µg/L. While perchlorate exposure has been shown to inhibit uptake of iodine into the thyroid gland, the levels provided (up to 10 mg/day) did not have a significant effect on thyroid function in adults. According to WHO criteria for urinary iodine, the iodine status for the US population as a whole and women of reproductive age is sufficient. Although pregnant women and their fetuses and newborns have the greatest potential for risk of adverse health effects following exposure to perchlorate, data are lacking to demonstrate a causal association between perchlorate consumption and adverse health effects in these high-risk populations.

To address concerns about perchlorate exposure from foods, the FDA has provided questions and answers about this topic on its website.<sup>34</sup> Based on the available information, the FDA is not recommending that consumers of any age alter their diet or eating habits to reduce perchlorate exposure. If one eats a healthy diet that is consistent with the Dietary Guidelines for Americans,<sup>35</sup> taking iodine supplements is not necessary for protection against the health effects associated with perchlorate at the levels present in water and food. However, the

American Thyroid Association recommends that women take iodine supplements containing 150 µg daily during pregnancy and lactation.<sup>36</sup>

## Acknowledgments

*Declaration of interest.* The author has no relevant interests to declare.

## REFERENCES

1. Mendiratta SK, Dotson RL, Brooker RT. *Perchloric Acid and Perchlorates*. New York: John Wiley and Sons; 1996.
2. Dasgupta PK, Martinelinho PK, Jackson WA, et al. The origin of naturally occurring perchlorate: the role of atmospheric processes. *Environ Sci Technol*. 2005;39:1569–1575.
3. Wolff J. Perchlorate and the thyroid gland. *Pharmacol Rev*. 1998;50:89–105.
4. Martino E, Aghini-Lombardi F, Mariotti S, et al. Treatment of amiodarone associated thyrotoxicosis by simultaneous administration of potassium perchlorate and methimazole. *J Endocrinol Invest*. 1986;9:201–207.
5. National Research Council. *Health Implications of Perchlorate Ingestion*. Washington, DC: National Academies Press; 2005.
6. United States Environmental Protection Agency. *Perchlorate and Perchlorate Salts*. Washington, DC: United States Environmental Protection Agency; 2005. Available at [www.epa.gov/iris/subst/1007.htm](http://www.epa.gov/iris/subst/1007.htm). Accessed April 8, 2009.
7. United States Environmental Protection Agency. Drinking water: preliminary regulatory determination on perchlorate. *Federal Register*. 2008;73:60262–60282.
8. Brandhuber P, Clark S. *Perchlorate Occurrence Mapping*. Washington, DC: American Water Works Association; 2005.
9. United States Food and Drug Administration. 2004–2005 exploratory survey data on perchlorate in food. 2007. Available at [www.fda.gov/Food/FoodSafety/FoodContaminantsAdulteration/ChemicalContaminants/Perchlorate/default.htm](http://www.fda.gov/Food/FoodSafety/FoodContaminantsAdulteration/ChemicalContaminants/Perchlorate/default.htm). Accessed June 8, 2009.
10. Murray CM, Egan SK, Kim H, Beru N, Bolger PM. US Food and Drug Administration's Total Diet Study: Dietary intake of perchlorate and iodine. *J Exp Sci Environ Epi*. 2008;18:571–580.
11. Kirk AB, Martinelango PK, Tian K, Dutta A, Smith EE, Dasgupta PK. Perchlorate and iodine in dairy and breast milk. *Environ Sci Technol*. 2005;39:2011–2017.
12. Pearce EN, Leung AM, Blount BC, et al. Breast milk iodine and perchlorate concentrations in lactating Boston-area women. *J Clin Endocrinol Metab*. 2007;92:1673–1677.
13. Snyder SA, Pleus RC, Vanderford BJ, Holady JC. Perchlorate and chlorate in dietary supplements and flavor enhancing ingredients. *Analytica Chimica Acta*. 2006;567:26–32.
14. Picciano MF, Dwyer JT, Radimer KL, et al. Dietary supplement use among infants, children, and adolescents in the United States, 1999–2002. *Arch Pediatr Adolesc Med*. 2007;161:978–985.
15. Leung A, Pearce EN, Braverman LE. Iodine content of prenatal multivitamins in the United States. *N Engl J Med*. 2009;360:939–940.
16. Institute of Medicine. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: National Academy Press; 2001.

17. Delange F. *Iodine Nutrition and Congenital Hypothyroidism*. New York: Plenum Press Publication; 1989.
18. World Health Organization. *Assessment of Iodine Deficiency Disorders and Monitoring Their Elimination*. Geneva: World Health Organization; 2007.
19. Caldwell KL, Miller GA, Wang RY, Jain RB, Jones RL. Iodine status of the U.S. population, National Health and Nutrition Examination Survey 2003–2004. *Thyroid*. 2008;18:1207–1214.
20. Akoi Y, Belin RM, Clickner R, Jefferies R, Phillips L, Mahaffey KR. Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999–2002). *Thyroid*. 2007;17:1211–1223.
21. Hueston WJ. *Women's Health in Primary Care*. Baltimore, Maryland: Williams and Wilkins; 1997.
22. Kaye CI and the Committee on Genetics. Newborn screening fact sheets. *Pediatrics*. 2006;118:e934–e963.
23. Greer MA, Goodman G, Pleus RC, Greer SE. Health effects assessment for environmental perchlorate contamination: the dose-response for inhibition of thyroidal radioiodine uptake in humans. *Environ Health Perspect*. 2002;110:927–937.
24. Lawrence JE, Lamm SH, Pino S, Richman K, Braverman LE. The effect of short-term low-dose perchlorate on various aspects of thyroid function. *Thyroid*. 2000;10:659–663.
25. Braverman LE, Pearce EN, He X, et al. Effects of six months of daily low-dose perchlorate exposure on thyroid function in healthy volunteers. *J Clin Endocrinol*. 2006;91:2721–2724.
26. Braverman LE, He X, Pino S, et al. The effect of perchlorate, thiocyanate, and nitrate on thyroid function in workers exposed to perchlorate long-term. *J Clin Endocrinol*. 2005;90:700–706.
27. Blount BC, Pirkle JL, Osterloh JD, Valentin-Blasini L, Caldwell KL. Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women in the United States. *Environ Health Perspect*. 2006;114:1865–1871.
28. Tellez RT, Chacon PM, Barca CR, et al. Long-term environmental exposure to perchlorate through drinking water and thyroid function during pregnancy and the neonatal period. *Thyroid*. 2005;15:963–975.
29. Lamm S, Doemland M. Has perchlorate in drinking water increased the rate of congenital hypothyroidism? *J Occup Environ Med*. 1999;41:409–411.
30. Buffler PA, Kelsh MA, Lau EC, et al. Thyroid function and perchlorate in drinking water: An evaluation among California newborns, 1988. *Environ Health Perspect*. 2006;114:798–804.
31. Li FX, Byrd DM, Deyhle GM, et al. Neonatal thyroid-stimulating hormone level and perchlorate in drinking water. *Teratology*. 2000;62:429–431.
32. Crump C, Michaud P, Tellez R, et al. Does perchlorate in drinking water affect thyroid function in newborns and school-age children? *J Occup Environ Med*. 2000;42:603–612.
33. Amitai Y, Winston G, Sack J, et al. Gestational exposure of high perchlorate concentrations in drinking water and neonatal thyroxine levels. *Thyroid*. 2007;17:843–850.
34. United States Food and Drug Administration. For Consumers: Information about Perchlorate. Questions and Answers. 2009. Available at [www.fda.gov/Food/FoodSafety/FoodContaminantsAdulteration/ChemicalContaminants/Perchlorate/ucm077572.htm](http://www.fda.gov/Food/FoodSafety/FoodContaminantsAdulteration/ChemicalContaminants/Perchlorate/ucm077572.htm). Accessed June 9, 2009.
35. United States Department of Health & Human Services. Dietary Guidelines for Americans. 2005. Available at [www.health.gov/dietaryguidelines/dga2005/document/](http://www.health.gov/dietaryguidelines/dga2005/document/). Accessed June 9, 2009.
36. The Public Health Committee of the American Thyroid Association. Iodine supplementation for pregnancy and lactation – United States and Canada: Recommendations of the American Thyroid Association. *Thyroid*. 2006;16:949–951.