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Iodine supplementation and drinking-water perchlorate mitigation

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ABSTRACT

Ensuring adequate iodine intake is important, particularly among women of reproductive age, because iodine is necessary for early life development. Biologically based dose–response modeling of the relationships among iodide status, perchlorate dose, and thyroid hormone production in pregnant women has indicated that iodide intake has a profound effect on the likelihood that exposure to goitrogens will produce hypothyroxinemia. We evaluated the possibility of increasing iodine intake to offset potential risks from perchlorate exposure. We also explored the effect of dietary exposures to nitrate and thiocyanate on iodine uptake and thyroid hormone production. Our modeling indicates that the level of thyroid hormone perturbation associated with perchlorate exposures in the range of current regulatory limits is extremely small and would be overwhelmed by other goitrogen exposures. Our analysis also shows that microgram levels of iodine supplementation would be sufficient to prevent the goitrogenic effects of perchlorate exposure at current regulatory limits among at risk individuals. The human health risks from supplementing drinking water with iodine are negligible; therefore, this approach is worthy of regulatory consideration.

1. Introduction

High dietary salt is considered to be the cause of about 30% of hypertension cases among US adults (NAS, 2010). Globally, approximately one quarter of the adult population has hypertension, a leading risk factor for premature death. High salt intake is also linked to other diseases, including gastric cancer, obesity, kidney stones, and osteoporosis. A number of scientific bodies and professional health organizations, including the World Health Organization (WHO), American Heart Association, American Medical Association, and American Public Health Association, support reducing dietary salt intake (NAS, 2010, Campbell et al., 2012a). At the same time, dietary salt is one of the most important sources of iodine, which is critical to thyroid function and thus to fetal and childhood development (NAS, 2005).

Dietary iodine deficiency is a well known problem that occurs in areas worldwide, particularly in inland areas with limited access to seafood (Ahad and Ganie, 2010; Dunn, 1993). The implications of severe iodine deficiency are also well known, particularly for developing children because iodine (*via* thyroid hormone) is necessary for proper neurological development (NAS, 2005). It is well recognized that severe fetal iodine deficiency, left untreated, can result in significant brain impairment (*i.e.*, cretinism) (Zimmermann, 2009; NAS, 2005). The extent to which mild maternal iodine deficiency during pregnancy (hypothyroxinemia) can impact child cognitive development remains controversial (Negro et al., 2011) but has been cited as a source of concern for low level exposures to agents which could impact maternal iodine metabolism (NAS, 2005).

International efforts to correct iodine deficiency through universal salt iodization are considered a major global public health triumph (Campbell et al., 2012a). In the US, however, salt iodization is not mandatory, and mean iodine intake has declined from about 320 μg/day in the 1970s to about 150 μg/day more recently (Caldwell et al., 2005; Hollowell et al., 1998). Iodine is also not a mandatory component of prenatal vitamins and according to National Health and Nutrition Examination Survey (NHANES) data, up to 15% of women of childbearing age in the US are considered iodine deficient, with average urinary iodine levels below 100 μg/L (Caldwell et al., 2013). Caldwell et al. (2013) also reported that more than 50% of women of childbearing age have iodine levels below that considered adequate by WHO (150 μg/day). The Salt Institute estimates that only about 70% of the table salt sold in the US is iodized

Abbreviations: DWEL, Drinking Water Equivalent Level; EPA, US Environmental Protection Agency; FDA, US Food and Drug Administration; fT4, free thyroxine levels; HPT, hypothalamic pituitary thyroid; NHANES, National Health and Nutrition Examination Survey; NIS, sodium iodide symporter; PBPK, physiologically based pharmacokinetic; PEC, perchlorate equivalent concentration; RAIU, relative amount of iodine uptake; RDA, recommended daily allowance; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; WHO, World Health Organization.

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and notes that the salt used in processed foods is not iodized (Salt Institute, 2013). Thus, only about 20% of US salt intake involves iodized salt (Dasgupta et al., 2008). In fact, WHO has recommended universal salt iodization in all countries where there is a concern for iodine deficiency; *i.e.*, iodization of all human and livestock salt, including salt used in the food industry (WHO, 2007; Campbell et al., 2012b).

Exposure to goitrogens such as nitrate and perchlorate is of regulatory concern because they can competitively inhibit iodide accumulation by the thyroid gland, potentially leading to changes in thyroid hormone levels (NAS, 1995, 2005; Eskandari et al., 1997; EPA, 2011a). Pregnant and lactating women and infants who are hypothyroxinemic due to iodide deficiency are considered most sensitive to these potential effects. Although the potential effects of nitrate exposure on the thyroid have long been known (Bloomfield et al., 1961), perchlorate has recently been under greater regulatory scrutiny due to studies indicating a much greater environmental distribution of perchlorate (in drinking water, food, and biological tissues) than was previously known (Kucharzyk et al., 2009).

Ensuring adequate iodine intake is the most direct approach to reducing risks from exposure to goitrogens, especially for women of reproductive age (WHO, 2007, 2013; Brent, 2010). Recent biologically based dose–response modeling of the relationships among iodide status, perchlorate dose, and thyroid hormone production in pregnant women and the fetus shows that iodide intake has a profound effect on the likelihood that exposure to goitrogenic chemicals will produce hypothyroxinemia (Lumen et al., 2013). For example, iodine supplementation has been shown to counteract perchlorate's developmental effects experimentally (Clarkson et al., 2006; Sparling et al., 2003). Ensuring adequate iodine intake is thus not only essential for healthy fetal and neonatal development in general, but prevents the potential effects of goitrogens such as perchlorate (Blount et al., 2006; EPA, 2010).

This paper evaluates the biological basis for the possibility of increasing iodine intake to offset potential risks from perchlorate exposure. It is worth noting that the US Food and Drug Administration (FDA) mandates infant formula iodine concentrations of 100 to 233 μg/L to prevent iodine deficiency (FDA, 2012) and that, historically, adding iodine to drinking water supplies has been successful at alleviating iodine deficiency in communities in Malaysia, Italy, and the Central African Republic (Foo et al., 1996; Squatrito et al., 1986; Yazipo et al., 1995). We also explore the potential impact of dietary exposures to nitrate and thiocyanate on iodine uptake and thyroid hormone production. Although there are other natural goitrogens consumed in food (*e.g.*, flavones and isoflavones), we have limited our analyses to nitrate and thiocyanate because they act *via* a similar pathway (inhibition of iodide uptake at the sodium iodide symporter) and there are studies readily available that have evaluated the relative inhibition potency of these three compounds.

2. Materials and methods

2.1. Model features

To conduct our analysis, we used the physiologically based pharmacokinetic (PBPK) model published by Lumen et al. (2013) to estimate the effect of different intakes of perchlorate, nitrate, thiocyanate, and iodide on free thyroxine (fT4) levels as well as thyroidal iodide uptake at the sodium iodide symporter (NIS). The Lumen et al. model represents a synthesis of several earlier models developed to estimate perchlorate and iodide metabolism (Clewell et al., 2003a, 2003b, 2007; Merrill et al., 2005). As reported by the authors, the purpose of the PBPK model is to evaluate the interactions of dietary iodide and perchlorate exposure on the hypothalamic pituitary thyroid (HPT) axis in the pregnant woman and fetus. The pregnant woman and fetus are the most sensitive receptors for HPT perturbation by goitrogens because the maternal thyroid experiences a greatly increased demand for thyroid hormone synthesis, and thus iodide, during pregnancy. The PBPK model includes maternal compartments for plasma, thyroid, placenta, and lumped richly and slowly perfused tissues and fetal compartments for plasma, thyroid, and the remaining fetal tissues. The model provides as outputs serum concentrations of thyroid hormones (triiodothyronine [T3], thyroxine [T4], and fT4) as well as maternal and fetal thyroidal NIS activity. Additional details about the model can be found in Lumen et al. (2013).

The PBPK model has been extensively validated against human data. Model predictions of serum T4 for varying iodide intake rates in pregnant women were compared to values reported in the study of Silva and Silva (1981), which investigated the effects of varying iodide intake on serum thyroid hormone levels in 250 pregnant women from an iodine-deficient area of Santiago, Chile. To evaluate the model-predicted levels for maternal fT4 and T3, data from several published studies were used representing populations of pregnant women in several countries (Costeira et al., 2010; Moleti et al., 2011; Soldin et al., 2007; Vermiglio et al., 1999). The iodide intake rates in these studies generally ranged from 60 to 200 μg/day, although one population (Vermiglio et al., 1999) included moderately iodine-deficient women (mean urinary iodide excrete rates of 46.1 μg/day).

Biomonitoring data (Téllez-Téllez et al., 2005) were used to calibrate the model in terms of the effects of perchlorate on thyroid hormone production. Data obtained from pregnant women and newborns from the Chilean city of Taltal, with fairly high levels of perchlorate in the drinking water (114 μg/L), were used to calibrate the perchlorate portion of the model. The average iodide intake level for pregnant women in the city of Taltal was estimated to be 337.1 μg/day. It should be noted that it is not possible to validate the model predictions during the fetal period since sampling of fetal blood would pose some risk and would therefore be considered unethical. Model validation is thus limited to measurements collected in the mother and neonate.

The model requires as inputs urinary iodide levels (in μg/L) and daily perchlorate intakes (in μg/kg/day). The urinary iodide levels are then used to calculate daily iodine intakes based on a near-term urinary output volume and a 97% daily clearance rate (described in more detail in Lumen et al., 2013). Intakes of perchlorate and iodine are modeled using a PULSE function, intended to mimic the periodic intakes of these chemicals during waking hours. Note that because the model was validated against data that already include a background level of non-drinking water perchlorate (and other goitrogen) exposure (*i.e.*, from vegetables and other foods), there is a baseline perchlorate exposure implicit in the model. That is, the model provides predictions of the effect of dietary perchlorate exposures that are in excess of normal goitrogen levels in the diet and in drinking water.[1] Goitrogen levels in these media can vary substantially across populations, but there are studies that have attempted to quantify those exposures in the US (Blount et al., 2010; Murray et al., 2008; Sanchez et al., 2007). FDA's Total Diet Study estimates a background level of perchlorate exposure of 0.0054 to 0.0073 mg/day for women between 25 and 45 years of age (Murray et al., 2008). Median exposure to nitrates in US women of childbearing age was estimated to be 40.48 mg/day in one study (Griesenbeck et al., 2010). Blount et al. (2010) evaluated exposure to perchlorate and nitrate in drinking water based on data from NHANES. The authors concluded that urinary concentrations of these anions corresponded to median doses of 0.009 μg/kg/day for perchlorate and 11.3 μg/kg/day for nitrate. We did not identify any studies that attempted to quantify baseline thiocyanate intake, likely due to the difficulty in reporting/quantifying both thiocyanate and the many thiocyanate precursors that exist in dietary items. It is possible to back calculate a surrogate thiocyanate dose using the NHANES urinary data, but the interpretation of this dose would be complicated by the uncertainty in metabolism of the thiocyanate precursors, as well as the difficulty in accounting for smoking exposure. However, just one 80-g serving of broccoli can contain 1.4 mg of thiocyanate (Sanchez et al., 2007).

2.2. Model simulations

We first ensured we could reproduce the results reported by Lumen et al. (2013). Using perchlorate intakes of 0 to 1000 μg/kg/day and iodine intakes ranging from 75 to 250 μg/day, we were able to reproduce the maternal and fetal fT4 results reported by Lumen et al. in their table 7. In this exercise, we used Lumen et al.'s approach of running the model at zero perchlorate until 4100 hours to allow serum iodide levels to reach steady state. After this point, perchlorate exposure was initiated as a repeated and identical daily dose. It is interesting that under this scenario, the model does not reach steady state conditions for 10,000 to 40,000 hours, depending on perchlorate dose. This is in contrast to the nine-month (6840 hours) period of a normal pregnancy. A more variable perchlorate exposure pattern might never reach steady state conditions.

Having established that the model was performing as intended, we then ran simulations with a perchlorate dose equivalent to consuming water with a perchlorate concentration of 20 μg/L (0.86 μg/kg/day for a 68-kg pregnant woman with a water consumption of 0.043 L/kg/day; California EPA, 2012). We conducted this analysis with an iodine intake of 75 μg/day – the lowest value considered by Lumen et al. An iodine intake of 75 μg/day is also representative of the transition point between

[1] It should be noted that the model is calibrated using data from Téllez-Téllez et al. (2005). This study evaluated perchlorate exposure in three Chilean populations and looked at only changes in perchlorate. Other goitrogens were not measured in these populations, and thus it was assumed that overall goitrogen exposure was similar in all three populations.