Reference

Subject: Re: [CPEO-MEF] perchlorate
Date: Wed, 19 Jun 2002 11:07:57 -0700
From: Lenny Siegel <lsiegel@cpeo.org>
Organization: Center for Public Environmental Oversight
To: Military Environmental Forum <cpeo-military@igc.topica.com>

[I forwarded Bob McNally's query about perchlorate to Tom Zoeller, a biologist at the University of Massachusetts. Here is his reply. It's fairly technical and detailed, but I didn't feel comfortable editing it down. - Lenny]

Hi Lenny,

You caught me as I am finishing my review of the ATSDR tox profile for perchlorate, so this stuff is pretty fresh. I think the main issue in ecosystems is whether aquatic animals, who require thyroid hormone for metamorphosis (frogs/toads/salamanders), for par/smolt transformation (anadromous fishes), as well as for general health are being affected by levels of perchlorate that are often much higher than what humans are exposed to at the tap. I think there is little work focused on perchlorate in plants, microbes, etc. I kind of think that it won't be that important, but I could be wrong. A recent paper that Ron Kendall's group published from Lubbock Tx is:

Smith PN, Theodorakis CW, Anderson TA, Kendall RJ (2001) Preliminary assessment of perchlorate in ecological receptors at the Longhorn Army Ammunition Plant (LHAAP), Karnack, Texas. Ecotoxicology 10:305-313. ABSTRACT: There have been increasing human health and ecological concerns about ionic perchlorate (ClO4-) since it was detected in drinking water sources in 1997. Perchlorate is known to affect thyroid function, causing subsequent hormone disruption and potential perturbations of metabolic activities. According to current estimates, perchlorate is found in the surface of groundwater of 14 states, including Texas. Longhorn Army Ammunition Plant, located in east central Texas, was a facility historically associated with perchlorate-containing propellants and rocket motors. Subsequently, perchlorate contamination in ground and surface waters at the facility has been reported. Soil, sediment, water, vegetation, and animal tissue samples were collected from several locations within the plant for a preliminary site assessment of perchlorate contamination. Perchlorate concentrations ranged from 555-5,557,000 ppb in vegetation, 811-2038 ppb in aquatic insects, below detection limits (ND) to 207 ppb in fish, ND-580 ppb in frogs, and ND-2328 ppb in mammals. Consistent with our hypothesis, aquatic organisms inhabiting perchlorate-contaminated surface water bodies contained detectable concentrations of perchlorate. Additionally, terrestrial organisms were exposed through pathways not necessarily related to contaminated surface waters. Therefore, these data demonstrate that aquatic and terrestrial species are exposed to perchlorate in the environment. To our knowledge, this represents the first incidence of perchlorate exposure among wild animals reported in the scientific literature.

In terms of humans (I realize that this isn't part of the question), but here are my comments to the ATSDR that I think generally capture the logical errors that general toxicologists have in thinking about population exposures to a compound that affects thyroid function. This is probably more than you asked for, but here it is:

A. INTERACTIONS WITHIN THE HYPOTHALAMIC-PITUITARY-THYROID AXIS.

First, the description and interpretation of the negative feedback system of thyroid hormone regulation is inaccurate in some of its

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details. Specifically, the negative feedback system of the HPT axis limits the degree to which circulating levels of thyroid hormone can change within a specific range. However, it is not accurate to assume, as the ATSDR document states explicitly at times and implicitly at other times, that the negative feedback system prevents adverse effects of small changes in circulating levels of thyroid hormone. As described in the ATSDR document, when circulating T4 declines, the secretion of TSH from the pituitary gland increases. Increased circulating TSH will have the effect of stimulating the thyroid gland to increase synthesis and secretion of T4 and T3. This system maintains circulating levels of T4 within narrow individual limits under normal conditions (Andersenet al., 2002). The aspect of the ATSDR review that is not logical is that this negative feedback system prevents T4 levels from declining under conditions of perchlorate exposure (e.g., in the studies by Greer et al.). By definition, circulating TSH will increase only when the hypothalamic-pituitary system detects a reduction, slight as it may be, in circulating levels of thyroid hormone. Therefore, if TSH levels are increased, despite measuring "normal" levels of T4, it demonstrate that T4 levels are in fact reduced. An important question is whether subtle reduction in circulating T4 that trigger an increase in TSH release is detected as thyroid hormone insufficiency in other tissues including the fetal brain. The ATSDR document does not appear to consider these aspects of the HPT axis, especially as it relates to the developing brain. Therefore, the implicit assumption made in the ATSDR document is that the HPT axis is more sensitive to small changes in circulating levels of thyroid hormone than any other tissue. The ATSDR has no formal evidence to support this hypothesis. Two recent human studies support the interpretation that modest changes in circulating levels of T4 can produce adverse effects in adults. First, Andersen et al. (Andersenet al., 2002) demonstrated in humans that individual variation in T4 levels are much more narrow than the population variance in T4 which is the basis for the normal reference range. Second, long-term follow-up studies of patients given T4 replacement therapy following thyroid ablation for thyroid cancer or Grave's disease (Osman et al., 2002). These patients exhibit a much higher incidence of cardiovascular disease. The interpretation is that chronic, sustained elevations in circulating levels of T4 can produce adverse effects on the cardiovascular system.

B. INTERPRETATION OF PERCHLORATE EFFECTS IN THE STUDY BY GREER et al.

The second issue relates to the logic used to interpret perchlorate effects on circulating levels of thyroid hormone in the Greer study and its relationship to the oral MRL. It is logical to conclude that, within a 14 day period, the critical event upon which predicted health effects of perchlorate in adults should be based is a change in circulating levels of thyroid hormones. The logic is that, if perchlorate affects only the thyroid gland (and there is a great deal of evidence to support this view), adverse consequences of perchlorate exposure can only be presumed when the dose is high enough to cause a reduction in circulating levels of thyroid hormone. However, as the ATSDR document points out, the human adult thyroid gland contains perhaps several months worth of T4 stored in the colloid. Therefore, it appears arbitrary to choose the 0.5 mg/kg/day dose level for the NOAEL. Clearly, if the Greer study had used 1.0 mg/kg/day, this would have been the NOAEL (or 5 mg/kg/day). In fact, the question is whether there is a dose of perchlorate that would affect circulating levels of thyroid hormone in normal, euthyroid individuals within a 14 day period. Considering this, it is important to question the applicability of the Greer study to pregnant and lactating women, and their offspring, within the 2-week period. The ATSDR document indicates that perchlorate may be transported by the NIS instead of iodide. Therefore, because the NIS is induced in lactating breast tissue by prolactin (Perron et al., 2001; Rillema and Rowady, 1997; Rillema et al., 2000; Spitzweg et al., 1998), it is possible that perchlorate is concentrated in milk (Howard et al., 1996;

Mountford et al., 1986). In addition, it is clear that perchlorate will reduce iodide uptake into milk, thus reducing the sole source of iodine to the infant. A 14 day exposure of a lactating woman to 14 grams of perchlorate per day (200 µg/kg/day x ~70kg) may expose the infant to considerably more perchlorate than 200 µg/kg. There are two reasons this should be considered (and discussed) in the ATSDR document. First, the dose response relationship between serum perchlorate and RAIU inhibition in infants is unknown, or not considered. If it is unknown, this should be explicitly stated in the document. The ATSDR document described how the fetal thyroid gland does not begin to function until the second trimester, but for the 2nd and 3rd trimesters, the fetus may be damaged by RAIU inhibition even if the mother is not so affected. For example, Haddow et al. (Haddow et al., 1999) showed that maternal hypothyroxinemia (not hypothyroidism) was associated with measurable neurological deficits in their offspring, despite the fact that their children were euthyroid. Moreover, the duration of NIS inhibition required to produce significant decrements in circulating levels of T4 is unknown for the fetus and neonate. However, it is known that a 14 day period of thyroid hormone insufficiency is long enough to produce measurable neurological deficits in newborns (van Vliet, 1999). Moreover, Vulsma et al. (Vulsma et al., 1989) estimated that the neonatal thyroid gland contains thyroid hormones equivalent to only a single day secretion. This estimate was revised by van den Hove et al. (van den Hove et al., 1999) who empirically measured intrathyroidal stores of thyroid hormones in human fetuses and neonates and found that the amount of hormone stored in the colloid is less than that required for a single day. Thus, fetuses, neonates and infants represent a sizable population at risk of permanent damage caused by thyroid hormone insufficiency. In addition, they exhibit known differences in iodine requirements and fluid consumption compared to adults, and the duration they can withstand reduced thyroid hormone synthesis before sustaining a decreased circulating level of thyroid hormone is considerably less than that of a normal adult. However, the ATSDR document does not consider these known issues. However, considering this information, the MDL for acute exposure calculated by the ATSDR can reasonably be predicted to cause harm to a significant proportion of our population (fetuses, neonates and infants).

Note: This is perhaps my error, but the term "sensitive subpopulation" upon which the uncertainty factor of 3 is applied, connotes an unknown population such as those with thyroid disease or other illness for which there is little or no information. Fetuses, neonates and infants would not fall into this category, in my opinion. They are normal. They are in a normal life-stage. There is sufficient information to make reasonable predictions. Therefore, they should be considered explicitly in the document, and should not be considered an unknown sensitive subpopulation for which an uncertainty factor is determined.

C. THE RELATIONSHIP BETWEEN PERCHLORATE EXPOSURE, CIRCULATING LEVELS OF THYROID HORMONE, AND THYROID HORMONE-RESPONSIVE ENDPOINTS IS NOT WELL ARTICULATED IN THE ATSDR DOCUMENT.

If the adverse effects of perchlorate are mediated by its action on thyroidal iodide uptake leading to reduced circulating levels of thyroid hormone, then thyroid hormone-responsive endpoints should be evaluated in experimental studies. This logic is especially important to interpret the ARGUS 2001 study (York, 2001). Specifically, there is no evidence that the linear measures taken of specific brain areas are responsive to changes in circulating levels of thyroid hormone. However, when effects are observed, it is important to consider these potential thyroid hormone responsive since there is no known mechanism by which perchlorate could induce effects on brain structures in the absence of changes in circulating levels of thyroid hormone. Minimally, the relationship between perchlorate, thyroid hormone, and thyroid hormone responsive endpoints needs to be better developed in the ATSDR document.

REFERENCES

Andersen S, Pedersen KM, Bruun NH, Laurberg P (2002) Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab 87:1068-1072.
Howard BJ, Voigt G, Segal MG, Ward GM (1996) A review of countermeasures to reduce radioiodine in milk of dairy animals. Health Physics 71:661-673
Ladenson PW (2000) Diagnosis of hypothyroidism. In: Braverman LE, Utiger RD, ed, Werner and Ingbar's The Thyroid: A fundamental and Clinical Text. Lippincott Williams and Wilkins, Philadelphia, 848-852.
Mountford PJ, Coakley AJ, Fleet IR, Hamon M, Heap RB (1986) Transfer of radioiodide to milk and its inhibition. Nature 322:600
Osman F, Gammage MD, Sheppard MC, Franklyn JA (2002) Clinical review 142: cardiac dysrhythmias and thyroid dysfunction: the hidden menace? J Clin Endocrinol Metab 87:963-967.
Perron B, Rodriguez AM, Leblanc G, Pourcher T (2001) Cloning of the mouse sodium iodide symporter and its expression in the mammary gland and other tissues. J Endocrinol 170:185-196.
Rillema JA, Rowady DL (1997) Characteristics of the prolactin stimulation of iodide uptake into mouse mammary gland explants. Proc Soc Exp Biol Med 215:366-369
Rillema JA, Yu TX, Jhiang SM (2000) Effect of prolactin on sodium iodide symporter expression in mouse mammary gland explants. Am J Physiol Endocrinol Metab 279:E769-772.
Spitzweg C, Joba W, Eisenmenger W, Heufelder AE (1998) Analysis of human sodium iodide symporter gene expression in extrathyroidal tissues and cloning of its complementary deoxyribonucleic acids from salivary gland, mammary gland, and gastric mucosa. J Clin Endocrinol Metab 83:1746-1751
van den Hove MF, Beckers C, Devlieger H, de Zegher F, De Nayer P (1999) Hormone synthesis and storage in the thyroid of human preterm and term newborns: effect of thyroxine treatment. Biochimie 81:563-570.
van Vliet G (1999) Neonatal hypothyroidism: Treatment and Outcome. Thyroid 9:79-84
Vulsma T, Gons MH, deVijlder J (1989) Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect of thyroid agenesis. N Engl J Med 321:13-16

>Tom,
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>I don't know whether you're on CPEO's listserver, so I'm forwarding this
>query to you. If you have time, could you reply to me so I can send it
>out to our list.
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>As I recall from your presentation in Oakland the other day, the best
>studies of perchlorate are animal studies, but they have been lab
>studies. Do you have any sense of the impact of perchlorate on ecosystems?
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>Lenny
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>ramcnally@nasw.org wrote:
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>> In all the discussion of perchlorate in the Aberdeen water supply, I'm
>> wondering if any study has been done of how perchlorate affects the

>> water supply for species other than humans and what effect the chemical
>> has on microbial and animal life. Any hell would be appreciated.
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>> Bob McNally
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