Preliminary Draft Language for Discussion for the 11/9/12 Draft Panel Report
12/7/1212 Teleconference Call
Science Advisory Board (SAB) Perchlorate Advisory Panel

Purpose: Preliminary draft language for discussion by the Members of the Panel during the December 7, 2012 SAB Panel teleconference call related to the Panel's review of the Panel's November 9, 2012 draft report entitled *SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate.* The draft report ia available on the SAB's website at:
http://yosemite.epa.gov/sab/sabproduct.nsf/a84bfee16cc358ad85256ccd006b0b4b/ceceaa071cc61da985257a9300620f2f!OpenDocument&Date=2012-12-05

Description of Hypothyroxinemia and Current Literature

Insert this at Page 10 line 16 striking current language

~~Although evidence is lacking that directly links perchlorate intake to altered brain development in humans, animal evidence is suggestive of perchlorate intake having an impact on mammalian brain development (Gilbert and Sui 2008). Likewise, studies of children born to women with mild to moderate reductions in TH during pregnancy (hypothyroxinemia) (Man et al. 1991; Pop et al. 1999; Pop et al. 2003; Kooistra et al. 2006) and children born to women with clinical (Smit et al. 2000, Mirabella et al. 2000) or subclinical hypothyroidism (Haddow et al. 1999) show reduced intelligence quotients (IQ), selective cognitive deficits, as well as behavioral abnormalities. Similar observations have been made in offspring of women with iodide deficiency during pregnancy (Pharoah et al. 1984; Vermiglio et al. 2004).~~

~~It is important to note that changes in brain development caused by perchlorate exposure and observed at any level of biological organization, including the molecular, cellular, or whole organism behavioral levels, could be considered adverse due to the difficulty in associating changes in brain development (e.g., altered expression patterns of TH-regulated brain genes) with later functional effects (e.g., specific intellectual abilities, sociobehavioral effects). In addition, molecular effects during development can be irreversible, although they may be later modified via various enrichment and intervention approaches.~~

Although the critical evidence is lacking to directly link perchlorate to altered brain development in humans, animal studies show that perchlorate in pregnancy is associated with compromised mammalian brain development in the progeny (Gilbert & Sui 2008). In humans, studies of children born to mothers with either iodide or thyroid hormone insufficiencies provide complementary evidence. Offspring of women who were iodide deficient during pregnancy show cognitive and behavioral impairments (Pharoah et al. 1984; Vermiglio et al. 2004). These impairments could be ameliorated by giving mothers iodide supplementation from the first trimester (Berbel et al. 2009; Velasco et al. 2009; see also Glinoer & Rovet 2009) but not later

trimesters, suggesting a critical and early window of iodide sufficiency for fetal brain development. Similarly, children born to women with clinical (Smit et al. 2000; Mirabella et al. 2000) or subclinical hypothyroidism (Haddow et al. 1999) show reduced IQ, selective cognitive deficits, and behavioral abnormalities compared with children whose mothers had normal pregnancy TSH levels. Since the Haddow study also showed better outcome in the subgroup of children whose mothers reportedly took thyroid hormones exogenously in pregnancy, this signifies the need to prevent any degree of hypothyroidism, regardless of its cause, in pregnancy.

Finally, and perhaps most critically, are the findings from studies examining the effects of isolated maternal hypothyroxinemia, defined as a fT4 value in the lower end of the normal range. This research has involved a variety of cutoffs to signify maternal hypothyroxinemia ranging from fT4 below the 10th or 5th percentiles to below the 2.5th percentile (Moleti et al. 2011), with the former being used to investigate neurodevelopmental outcome and the latter, the incidence and effects on pregnancy (e.g., Casey et al. 2007). Children exposed gestationally to maternal hypothyroxinemia show reduced levels of global and specific cognitive abilities, as well as increased rates of behavior problems including greater dysregulation in early infancy and attentional disorders in childhood (Man et al. 1991; Pop et al. 1999; Pop et al. 2003; Kooistra et al. 2006), and these effects are correlated with both degree (Pop et al. 1999; Henrichs et al. 2010) and duration (Pop et al, 2003) of maternal hypothroxinemia. The Henrichs study (2010), which stratified children into severe (<5th percentile) and mild (5-10th percentile) maternal hypothyroxinemia subgroups, showed that while effects were stronger and broader in the severe subgroup, the mild subgroup still showed delayed language development, thus suggesting any factor that lowers maternal fT4, even slightly, can affect her child.

Consistent Definition for Sensitive populations and Life Stages.

Insert this at Page 10 line 25 replacing the recommendation.

~~"The SAB recommends that the EPA consider the sensitive life stages of the pregnant and lactating woman and her fetus and infant in modeling levels of perchlorate exposure and effects."~~

The SAB recommends that the EPA consider sensitive life stages in developing an MCLG for perchlorate. The SAB finds that the sensitive life stages are the fetus, neonates and infants because this when thyroid dependent brain development occurs. The sensitive populations for perchlorate exposure are hypothyroxinemic pregnant and lactating women and bottle-fed infants exposed to perchlorate through formula. This would replace "the fetuses of pregnant women who might have hypothyroidism or iodide deficiency" as defined by the NRC (2005).

Diversity of Markers for Developmental Changes from Low thyroid hormones
Insert this additional language on page 12 at line 4

There is diversity in markers in the developing brain that are sensitive to alterations in thyroid hormone concentrations during development (Bernal 2005; Ahmed et al. 2008; Gilbert et al.

2012). The molecular basis of thyroid hormone action is the regulation of gene transcription. Target genes can be regulated directly through receptors bound to gene regulatory regions, or indirectly through thyroid hormone-dependent changes in regulatory gene expression. Alterations in the expression of target genes in the brain may also be associated with downstream changes in, for example, brain cytoarchitecture, cellular function, morphology, physiology, and function. Some panel members thought that associated downstream changes could be used as markers of thyroid hormone insufficiency during development provided they are validated as directly or indirectly regulated by thyroid hormone. Changes in any of these markers could be considered evidence of a precursor event to an adverse effect when assessing the potential impact of perchlorate on iodide uptake inhibition and altered thyroid hormone economy, during brain development.

Gilbert, M.E., Rovet, J., Chen, Z., and Koibuchi, N. 2012 Developmental thyroid hormone disruption: prevalence, environmental contaminants and neurodevelopmental consequences. *Neurotoxicology* 33:842-852.
http://www.sciencedirect.com/science/article/pii/S0161813X11002051

Ahmed, O.M., El-Gareib, A.W., El-Bakry, A.M., Abd El-Tawab, S.M., and Ahmed, R.G. 2008. Thyroid hormones states and brain development interactions. *Int J Dev Neurosci* 26:147-209.

Bernal, J. 2005. Thyroid hormones and brain development. *Vitam Horm* 71:95-122
http://www.ncbi.nlm.nih.gov/pubmed/16112266

Changes to Section 3.3.1 – Thyroid Antibodies

Replace Paragraph on Page 20 Line 39 through Page 21 line 9

The thyroid antibodies –thyroglobulin antibody (TgAb), thyroid stimulating hormone receptor antibody (TSH-RAb) and thyroid peroxidase antibody (TPOAb) –can interfere with TH synthesis via humoral and cell-mediated mechanisms (Sinclair 2006). Those with elevated levels of thyroid antibodies are at increased risk for hypothyroxinemia and for progression from hypothyroxinemia to overt hypothyroidism (De Groot 2012; Krassas 2010). However, only a small proportion of hypothyroxinemia is likely related to elevated thyroid antibodies (Moleti 2011). Individuals with these conditions may be more susceptible to additional thyroid disruption, such as that occurring when exposed to perchlorate. Hollowell et al. (2002) estimated the prevalence of thyroid antibodies in the NHANES 1988-1994 sample (2002). In the overall study population, 13.0% and 11.5% had detectable TPOAb and TgAb, respectively. Among the disease-free population, 11.3% (TPOAb) and 10.4% (TgAB) were antibody-positive. Antibody-positive participants were more likely to be female and among females, antibody prevalence increased significantly with age. Using NHANES data, it would be possible to estimate the proportion of women of childbearing age and the proportion of pregnant women (with imprecision due to the small number of pregnant women typically represented in NHANES) that are thyroid antibody-positive and therefore at increased risk for hypothyroxinemia.

De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, Eastman CJ, Lazarus JH, Luton D, Mandel SJ, Mestman J, Rovet J, Sullivan S. 2012 **Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline.** J Clin Endocrinol Metab. 2012 Aug;97(8):2543-65. doi: 10.1210/jc.2011-2803. Accessed December 6, 2012 http://www.ncbi.nlm.nih.gov/pubmed?term=22869843

Krassas GE, Poppe K, Glinoer D. 2010. **Thyroid function and human reproductive health.** Endocr Rev. 2010 Oct;31(5):702-55. Epub 2010 Jun 23. Accessed December 6, 2012 **http://www.ncbi.nlm.nih.gov/pubmed?term=20573783**

Moleti 2011 (PMID 21765991)
http://www.ncbi.nlm.nih.gov/pubmed?term=21765991