Issue III – Epidemiological Evidence
How should EPA consider the post-NRC epidemiology data in deriving an MCLG?
July 19, 2012

Overall comments:
After reviewing the post-NRC epidemiology data, we determine that the studies are insufficient to guide casual inference with regard to perchlorate exposure and thyroid dysfunction.

However, these data do provide evidence that the iodine insufficiency rates in the U.S. (based on NHANES) are higher than previously appreciated.

We determine that no studies are useful as validation of a safe level of perchlorate in drinking water.

Explanation:
- New studies: exposure assessment (albeit with small sample sizes) studies provide information regarding:
    - breastfed infants as among the most highly exposed and studies suggest that intake via breast may exceed the RfD
        - 16% of infants had at least 1 dose exceeding RfD (Valentin-Blasini 2011)
        - 9/13 breast fed children ingested perchlorate at levels exceeding the RfD (Dasgupta 2008)
    - relative source contribution indicating that only ~20% of exposure occurs through drinking water (Huber 2011)

- New studies: inference from epidemiologic (association) studies are limited (large studies are powered but ecologic; small studies are underpowered)
    - ecologic studies: exposure misclassification could be extensive, given that ~80% of perchlorate exposure comes from food (Huber 2011); also misclassification due to seasonality (e.g., So. CA/Colorado River (Buffler 2006))
    - temporality: cross-sectional
    - limited power to detect associations

- NHANES studies: good for prevalence of susceptible populations (e.g., perchlorate, iodine insufficiency (Caldwell 2011); thyroid antibodies (Hallowell 2002)

- Transient hypothyroxinemia is an important adverse effect, which could result in irreversible neurodevelopmental effects if occurring during the first trimester of pregnancy.
    - difficulty defining transient hypothyroxinemia: how long/how low

- Co-exposures to goitrogens (including tobacco exposure): should be modeled as cumulative exposure (figure from Pleus)

- Model misspecification: examples
  - Mendez: over-adjustment (e.g., TSH)
  - Pearce: thyroid autoantibodies modeled as confounders (should be effect modifiers); iodine modeled as confounders (should not be included in models because it is on the causal pathway)
  - Others??
  - Most studies used linear regression (assume a linear relationship, which may not be accurate: low dose effects, plateau, inverted U, etc)

- Other co-exposures (e.g., Pb)

<u>Recommendation for future studies:</u>
- Improved understanding of perchlorate exposure assessment
  - need repeated measures of perchlorate (need to know ½ life in urine);
  - improved understanding of variability over time (e.g., diurnal, etc.)
  - the validity of using a single sample to represent exposure (e.g., low ICC among infants: Valentin-Blasini 2011)
- Studies in other sensitive subpopulations, including preterm
- Longitudinal

<u>Other issues:</u>
- Bounding estimates based on extremes of body weight estimates
- Unknowns: are preterm babies treated with thyroid hormones? What about the effect of obesity and susceptibility?
- Iodine variability: have studies been done?

Primary References
[1-16]

NHANES prevalences
Iodine: [17]
Thyroid antibodies: [18]

Primary References:

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NHANES prevalences

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