Appendix A

Review of EPA's Assessment of Human Data

Comments on EPA's Draft Perchlorate Risk Assessment

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General Comments

In Chapter 4, Human Health Effects Data, the EPA's review of the epidemiology studies reflects some misunderstanding of the biological basis of the neonatal thyroid-screening program, leading to misinterpretation of epidemiologic and statistical data. The EPA's review includes unsupported speculations regarding sources of potential confounding that leads to minimal use of important data.

The conclusion that the epidemiology studies support an established effect of perchlorate on thyroid function at these exposure levels (4 -28, line 30) has a questionable basis. The EPA gives little weight to the results of several reasonable negative studies, in part based on unsupported speculations regarding bias and confounding, and fails to recognize limitations of studies that they consider positive. In the two studies considered positive, the exposed populations had levels of T_4 and TSH that are routinely found in normal infants, levels that create no need for treatment or follow-up. These studies each have important limitations that are disregarded in EPA's review. In Brecher et al, (2001) possible confounding by high TSH levels from earlier age of testing in the exposed population is difficult to control adequately by statistical analysis, and this detracts from the reliability of the results. The EPA presumes that the detailed exposure assessment in Schwartz (2001) is an improvement on other ecological studies, and leads to less exposure misclassification, whereas it is merely an accommodation to mixed water sources. Because the populations studied by Schwartz had the most heterogeneous water sources, more, not less misclassification is likely to occur.

These misinterpretations have lead to the dismissal of valuable data on humans, the species of interest in this assessment. The other epidemiologic studies that do not report positive associations contribute human data that, although not without limitations, provide information regarding the sensitive population. The studies of a large population in Nevada found no increase in congenital hypothyroidism in counties with contamination, or exposure related changes in T_4 or TSH (Lamm et al, 1999; Li et al 2000a, b, 2001). The advantages of the study in Chile are that it examines a sensitive endpoint, studied a population that has had long-term exposure, evaluated other health endpoints in the schoolchildren, and evaluated urinary iodine to control for possible reduced iodine intake (Crump et al, 2000). These studies are basically ignored or dismissed in the EPA's summary (Section 4.3) and in the risk assessment, based on questionable biological assumptions.

Recommendations

The chapter should be revised in several ways. Speculation about potential confounders for which there is no supporting data should be removed, and the merits of negative studies should be considered, alone with limitations, in the weight of the evidence. The multivariate analyses in Schwartz (2001) should be reassessed. For any study with reasonable data, the discussion should distinguish between statistically significant differences and clinically significant data.

The epidemiological data could contribute valuable information that seems to be particularly necessary in light of the multiple uncertainty factors that EPA has used to extrapolate from animal data. The epidemiologic data should be considered for use as the basis for the RfD, and at the very least for providing a test, or "reality check" of the proposed RfD based on animal LOAEL.

EPA might consider consulting an experienced specialist in neonatal thyroid disorders, or a pediatric endocrinologist, to ensure that the revised document properly addresses the clinical significance of any exposure –related differences in levels of T_4 or TSH detected in neonates. Biological issues are also important in assessing the basis for and appropriateness of statistical models such as those used in Schwartz (2001).

Specific Comments

4-2 Section 4.1 is a tutorial on risk assessment that is unnecessary in an EPA document.

Lines 19- 31. The EPA analysis refers to an unpublished report, a review by Park (2001) that provides no new data. Park (2001) is essentially the basis of EPA's chapter and interpretation, and reference to it for support for EPA's opinion is misleading and inappropriate.

4-3 Lines1-9 The draft provides no references other than Park for the list of variables that may affect human health. Unless support can be provided, delete (line 6) "possibly social class" and line 9 'possibly environmental temperature' as speculative. Add references, e.g. Lorey and Cunningham, 1992. Waller et al, 2000.

4-5 Lines 20-21. Delete the phrase that only one study is convincing. Statements like this should be in the summary. The Park reference is not a supporting reference; as stated above, this chapter *is* the Park reference.

4-6 Lines 8-11. Re: Li et al, 2001. The phrase "quite large" overstates the differences among (not between) the comparison groups. The assumption that these differences were due to uncontrolled confounding is speculative, as random variation is equally likely.

4-7 Line 11. The idea of confounding is valid, but 'overwhelming' overstates the case given that the draft provides no data to show the magnitude of uncontrolled risk factors.

4-7 The discussion of Crump et al (2000) should be revised. As written it includes unsupported speculations about potential confounders and errors in interpretation. These speculations introduce a critical tone in areas in which it is unwarranted. The issues that EPA has raised regarding the interpretation of this study are not substantive.

Line 21-23. The statement that all cities had elevated goiter prevalence disregards the role of the control city, Antofagasta, which had no perchlorate exposure. Table 6 shows no increase in goiter in the cities with perchlorate in the water compared to Antofagasta. In the analysis of the 127 children that were lifelong residents, no increase occurred in the city with intermediate levels. The revision should state that basically, the data on goiter provide no evidence of any increase related to perchlorate exposure.

Line 24-27. Delete the sentence regarding boiling the drinking water, as speculative, or explain the presumed basis in more detail. The following sentences are speculative and should be omitted: if socioeconomic status was not thought to differ there is no reason to control for it. Socioeconomic status has not been identified as a risk factor for thyroid function; if the EPA has evidence to the contrary, the supporting references should be included.

Line 27-31. Delete the sentence speculating about the effects of ambient indoor and outdoor temperatures. It is unsubstantiated, and questionable for babies born in hospitals. If the EPA has evidence that ambient temperatures play a role in thyroid status after the birth itself, the supporting references should be included. The following sentence is thus unsupported and should be deleted.

Line 31. to page 4-8 Line 2. The comment about iodine deficiency differences across the three cities is questionable, because "no evidence was found that urinary iodine levels were associated with city of residence or thyroid function status" (Crump et al, p 609). Urinary iodine concentration was measured, and analyses for T_4 and TSH were statistically adjusted for urinary iodine. Also, if goiter prevalence had been increased because of low iodine intake, the population would be more, not less, sensitive to an effect of perchlorate exposure.

Page 4-8

Line 3. After noting that the "paradoxical trend' in T_4 remain unexplained, the summary should note that none of the observed differences in T_4 was clinically significant, and no differences in TSH levels were reported among school children.

Line 6-11. Regarding Crump et al (2000) results in neonates:
This discussion of the systematic error disrupts the flow of the review, and is unnecessary.

Line 13-14. The analysis was adjusted for gender and age at testing, and these were predictors of TSH. Most of these lists of covariates that are allegedly lacking are not important to the accuracy of the analysis: iodine intake may have been low in one city, but likely corrected in 1982; ethnicity was similar across the three cities.

Line 16-17 The sentence "other important environmental variables…" should be deleted as speculative because there is no evidence that these are in any way important.

Line 18-19 The ending should be revised to clarify that the observed differences among the cities have no known link to perchlorate exposure, and no known clinical significance.

4-9 through 4-10 Li et al, 2000a, 2000b

The review does not acknowledge that the study focuses on a restricted birth weight range, and excluded day 1, in order to reduce instability.

Line 25-26 The comment that this restriction "would be inappropriate" is highly speculative; since no evidence is given that birth weight is an intervening variable. The EPA report later acknowledges the value of these restrictions, given the usual method for screening T_4 data for further testing (Page 4-11 lines 21-23), that "Both summary and age specific TSH comparisons would be unbiased … only if the same age at screen distributions were obtained in both the …populations." Page 4-11 lines 26-28. This approach is an attempt to reach that goal.

4-10 through 4-11 Regarding review of Brechner et al, 2000

Although median TSH levels were statistically significantly higher in Yuma, the city with perchlorate exposure, Yuma had many more samples taken at day 0 than did Flagstaff. Early sampling gives higher values, and earlier sampling occurred more often in the Yuma/exposed population, thus the potential for confounding is high. The differences remained after attempting to control for time at sampling. However, EPA raises the valid question of whether statistical methods can control for the sampling differences, (Line 13-14), although the discussion is awkward (line 15-16) and unclear. These differences would be one possible explanation for higher levels in Yuma, rather than an effect of exposure. No adverse outcomes are associated with the reported levels. The study offers minimal and questionable support, rather than positive support (4-11, line 17) for an association between increased TSH and perchlorate exposure.

4-12 line 10 through 4-13 line 12. Regarding review of Schwartz, 2001

EPA's assumption that the 'elaborate' level of detail in assessing perchlorate exposure actually leads to a better exposure classification than other studies is inaccurate. Given the complexity of water distribution systems and the mixing of sources within these pipes, the postal code method may be needed to identify which geographic areas provide an exposure source. However, this does not mean that postal codes lead to less misclassification than a comparison between towns with contamination in the public water supply and towns without contamination (e.g. Las Vegas compared to Reno, Yuma compared to Flagstaff, towns in Chile having different levels of contamination). The latter situation was specifically studied to minimize exposure misclassification and the related dilution of effect. The postal code analysis assesses only exposure at home, whereas contamination of the public water supply would mean that exposure may occur at other locations as well – the workplace, or restaurants for example.

The statistical results displayed in the Schwartz study are at times difficult to interpret, for example, percentages in the table do not correspond to table headings, and verbal summaries are not always consistent with the results in the tables. EPA's summary of the statistical analysis of the Schwartz study emphasizes the results of the ANCOVA analysis and neglects the logistic regression. The former shows trends in T_4 and TSH related to dose in presumptive positives, whereas the logistic regression shows that presumptive positive status is strongly related to low birth weight, low but not high perchlorate, some of the 20 ethnic groups, and blood sampled at times before 18 hours. . Given the number of variables and the large effect of birth weight, and the essentially null results of the logistic regression, EPA's conclusion that this study found positive results in newborns (4-29, line 6) should be reassessed after a critical and thorough review of the statistical analyses. Other inconsistencies in the results in the study are not adequately reflected in the summaries. Again, the clinical relevance of the data should also be considered, and speculation about the role of temperature (4-29 lines 21-26) should be avoided.