“Potential Utility” of Epidemiologic Studies of Arsenic in Drinking Water and Cancer

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Overview of Main Points

- **EPA's summary of the epidemiologic literature was inadequate and did not follow the SAB's recommendations**
- **Nondifferential exposure misclassification ≠ bias toward the null**
- **Issues of statistical power were overstated**
  - Direction, precision and consistency of RR estimates should be considered
- **Recent meta-analyses and individual epidemiologic studies should be included**

Charge 1 to the SAB Arsenic Review Panel

- Please comment on EPA's response to the recommendations and the conclusions of the SAB (2007) Arsenic panel regarding the evaluation of the epidemiological literature

What did the SAB ask EPA to do?

- **June 28, 2007**
  - Describe the considerable limitations (quantitatively or qualitatively) of the Taiwanese database "to help inform risk managers about the strength of the conclusions"
    - Limitations of the SW Taiwan data have not been adequately described in the 2010 draft IRIS Toxicological Summary

What did the SAB ask EPA to do?
(continued)

- **June 28, 2007**
  - Critically evaluate the published epidemiology studies of US and other populations chronically exposed from 0.5 to 160 µg/L inorganic arsenic in drinking water, using a uniform set of criteria and transparently document the results
    - The review of epidemiology studies in the 2010 draft IRIS Toxicological Summary does not use a uniform set of criteria nor is there a transparent documentation of results

Nondifferential Misclassification Does Not Always Produce Bias in the Direction of the Null

- **"If the exposure is not dichotomous, there may be bias toward the null value; but there may also be bias away from the null value…" (Rothmann, 2002; p.101)**
- **Arsenic levels in drinking water is NOT a binary (dichotomous) exposure variable**
- **Even in the case of a binary exposure variable, there is no guarantee that bias will be in the direction of the null**
  - "Even in the best-designed studies, the estimated odds ratio will not equal the true odds ratio, and the inaccuracies can go in either direction, because of sampling variation" (Weinberg, Umbach and Greenland 1995; p. 784)

Issues of Statistical Power Were Overstated

- ***A priori* criteria for evaluation of study size and statistical power were not defined**
  - "Strengths" and "weaknesses" were identified inconsistently across studies
- **Criteria for consideration of sample size needs to take into account study design**
- **Direction, precision, and consistency of relative risk estimates should be considered**

Recent Studies Should Be Included:

- **Two meta-analyses:**
  - Chu and Crawford-Brown (2006; 2007)
  - Mink et al. (2008)
- **Individual epidemiologic studies:**
  - Chen et al. (2009)
  - Chen et al. (2010)
  - Heck et al. (2009)
  - Meliker et al. (2010)

Same NE Taiwan cohort as Chiou et al. 2001. Improved cancer case ascertainment; additional 10 years of follow-up time. Since prospective design, recall bias is not an issue (exposure is assessed prior to onset of disease)

Updated Meta-Analysis of Low Level Exposure to Arsenic in Drinking Water and Bladder Cancer (Mink et al.)

- **Updated results for never-smokers were more precise and remained well below the relative risks predicted by NRC (2001) based on high dose exposure in Southwest Taiwan**

Analysis	SRRE	95% CI	P-value for Heterogeneity
Never smokers	0.83	0.65–1.06	0.894
Ever smokers	1.19	0.97–1.45	0.038
All subjects	1.12	0.95–1.32	0.026

SRREs from published meta-analysis were 0.81 (0.60-1.08), 1.24 (0.99-1.56), and 1.11 (0.95-1.30) for Never smokers, Ever smokers, and All subjects, respectively.

Final Points

- **EPA has dismissed an entire body of literature as not having "potential utility" in assessing cancer risk**
  - One exception: SW Taiwan, mainly high dose data
- **Transparent scientific rationale and justification have not been provided**
  - SW Taiwan studies: Strengths outweigh weaknesses
  - Every other epidemiologic study: Weaknesses outweigh strengths
  - WHY?

Final Points *(continued)*

- **The utility of the epidemiologic studies is that they may be used to compare to the estimates derived from the SW Taiwan data, as recommended by the SAB (2007):**
  - "If, after this evaluation, one or more of these studies are shown to be of potential utility, the low-level studies and Taiwan data may be compared for concordance" (SAB 2007; p. 7)

Extra Slides

- Additional comments re: Charge 1 to the current SAB

The SAB Made Specific Recommendations:

- **June 28, 2007**
- **When reviewing the "low-level" epidemiologic studies (and the "high level" studies as well), EPA should consider at least the following issues:**
  - Level of exposure misclassification
  - Temporal variability in assigning past iAs levels from recent measurements
  - Reliance on imputed exposure levels
  - The number of persons exposed at various levels of arsenic in H2O
  - Study response/participation rates
  - Estimates of exposure variability
  - Control selection methods in case-control studies
  - Influence of these factors on the magnitude and statistical stability of risk estimates

Comments from Others also Characterize EPA Response to SAB as Inadequate

- **Comments on 2010 draft IRIS Toxicological Review submitted to EPA by 5 Members of the SAB Arsenic Review Panel (2007)**
  - "While the February 2010 USEPA draft document did review a large number, but not all, of these studies and presented tabled results (Appendix B) as suggested by SAB (2007), the draft did not present a review of each study conducted by systematic consistent application of the uniform performance criteria called out in the 2007 SAB Arsenic Review Panel report (SAB, 2007, p 39)." [Comments submitted to EPA by Barchowsky et al., March 25, 2010]

Comments from Others also Characterize EPA Response to SAB as Inadequate *(continued)*

- **Interagency comments to EPA from OMB (posted to http://www.regulations.gov/search/Regs/home.html#doc0123ketDetail?R=EPA-HQ-ORD-2010-, 2/25/10)**
- "Appendix B: it is helpful that EPA added front matter discussion to Appendix B describing the factors SAB asked to have considered. However, as EPA mentions, **all of this information is not in the table, and when we look to section 4.1 we can not uniformly find how this information was considered. In particular, for many studies we are unable to locate: a) estimates of the level of exposure misclassification; b) temporal variability in assigning past arsenic levels from recent measurements; c) the extent of reliance on imputed exposure levels; d) the number of persons exposed at various estimated levels of waterborne arsenic; e) study response/participation rates; f) estimates of exposure variability; g) control selection methods in case-control studies; and, h) the resulting influence of these factors on the magnitude and statistical stability of cancer risk estimates. As these are the issues that SAB suggested EPA consider, is there a way to more clearly present this information either in the table or text of section 4.1?** We note that SAB suggested a tabular format; thus, perhaps adding this information to the table may meet SAB's concern. **SAB also suggested that the strengths and weaknesses be described in relation to each of the criterion above and suggested that the caveats and assumptions "be presented so that they are apparent to anyone who uses these data." Is there a way to better present this evaluation? "** [IRIS STEP 6 INTERAGENCY COMMENTS (OMB)]