Using Epidemiologic Data to Evaluate Cancer Risk:

A Review and Meta-Analysis of Low-Level Arsenic Exposure in Drinking Water and Bladder Cancer

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Overview

• Charge C2 to SAB: “Does the SAB agree that the Taiwanese dataset remains the most appropriate choice for estimating cancer risk in humans?”

• Relevant epidemiologic literature has been incompletely evaluated and considered

• Meta-analysis of bladder cancer and low-level arsenic exposure in drinking water, primarily from the U.S.
  – No significant association observed
  – Models based on SW Taiwanese data tended to overestimate the meta-relative risks observed in our analyses, particularly for nonsmokers
Background

• NRC and EPA risk analyses and dose-response models rely on data from SW Taiwan
  – Lack of systematic discussion of studies from US and similar populations
  – Exclusion criteria applied to other epidemiologic studies not applied to SW Taiwan data
  – Limitations of SW Taiwan dataset largely ignored
    • Ecologic design
    • Bias and confounding
    • Generalizability to populations with low exposure

• Uniform criteria should be applied to the review of all relevant epidemiologic studies

• Epidemiologic data from populations with low exposure to iAs are informative
Objectives of Meta-Analysis

- **Meta-analysis of epidemiologic studies of low-level arsenic exposure in drinking water and bladder cancer**
  - Clarify association
  - Improve precision
  - Assess accuracy of models based on SW Taiwan data

- **Two questions:**
  - Is there a significant association between exposure to low levels of arsenic in drinking water and bladder cancer?
  - Are the relative risks (and meta-RR) from these epidemiologic studies within the range of **1.2 to 2.5** as would be predicted by the dose-response curves based on data from the Taiwan studies (NRC 2001, Table 5-3)?
Methods and Data Analysis

• Inclusion/exclusion criteria for meta-analysis

• Eight studies eligible for meta-analysis
  – Case-control or cohort studies of low-level exposure to iAs in drinking water and bladder cancer incidence (mortality)

• Episheet used to calculate mRRs, confidence intervals, tests for heterogeneity

• Smoking status: Combined and stratified analyses

• Exposure category models:
  – Collapsed exposure categories
  – All exposure categories

• Additional analyses
  – Sources of heterogeneity
  – Influence analyses
Results

• See Table 2 and Figures 1–3 for summary of main results
• Appendices B, C for full results
### Results (all studies)

<table>
<thead>
<tr>
<th></th>
<th>Smokers and Never Smokers Combined</th>
<th>Smokers and Never Smokers Combined</th>
<th>Never Smokers All Exposure Categories</th>
<th>Never Smokers All Exposure Categories</th>
<th>Ever Smokers Collapsed Exposure Categories</th>
<th>Ever Smokers All Exposure Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRR 95% CI</td>
<td>1.08 0.82–1.43</td>
<td>1.11 0.95–1.30</td>
<td>0.76 0.52–1.12</td>
<td>0.81 0.60–1.08</td>
<td>1.21 0.88–1.66</td>
<td>1.24 0.99–1.56</td>
</tr>
<tr>
<td>P–Heterogeneity</td>
<td>0.056</td>
<td>0.207</td>
<td>0.724</td>
<td>0.937</td>
<td>0.162</td>
<td><strong>0.032</strong></td>
</tr>
<tr>
<td>Number of Studies</td>
<td>7</td>
<td>8</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

Source: Table 2, “Epidemiologic Studies of Low-level Arsenic Exposure in Drinking Water and Bladder Cancer: A Review and Meta-analysis"
Arsenic Exposure and Risk of Bladder Cancer: Collapsed Exposure Categories

Source: Figure 1., “Epidemiologic Studies of Low-level Arsenic Exposure in Drinking Water and Bladder Cancer: A Review and Meta-analysis”
Arsenic Exposure and Risk of Bladder Cancer Among NEVER Smokers: Collapsed Exposure Categories

Source: Figure 2., “Epidemiologic Studies of Low-level Arsenic Exposure in Drinking Water and Bladder Cancer: A Review and Meta-analysis”
Arsenic Exposure and Risk of Bladder Cancer Among EVER Smokers: Collapsed Exposure Categories

Source: Figure 3., “Epidemiologic Studies of Low-level Arsenic Exposure in Drinking Water and Bladder Cancer: A Review and Meta-analysis”
### Statistical Power

<table>
<thead>
<tr>
<th></th>
<th>Meta-Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Ever + Never Smokers (n=7 studies)</strong></td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Never Smokers (n=5 studies)</strong></td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Ever Smokers (n=5 studies)</strong></td>
<td>0.78</td>
</tr>
</tbody>
</table>

Source: One-sided test of significance (Hedges and Pigott, 2001)
Table 3, “Epidemiologic Studies of Low-level Arsenic Exposure in Drinking Water and Bladder Cancer: A Review and Meta-analysis”
Summary

• Question 1: Bladder cancer was not significantly associated with low-level exposure to arsenic in drinking water
  – Never smokers: mRRs were consistent, robust, and < 1.0
  – Ever smokers: Results were heterogeneous; no consistent evidence of increased risk or effect modification

• Question 2: Main results of meta-analysis were not consistent with, and were below the range of RRs predicted by NRC (1.2 to 2.5)
  – Majority of mRRs were less than 1.2
  – Results for smokers were variable
Conclusion

- Thus, the SW Taiwan dataset is inadequate for estimating cancer risk in U.S. populations exposed to iAs in drinking water.
Thank You