Human Cancer Studies

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Human Cancer Studies and Antimony Trioxide

Outline

- **Lung cancer** – occupational smelter worker cohorts
  - Background
  - Utility of lung cancer studies
  - Assessment of findings

- **Stomach cancer** – occupational cohort and case-control studies
  - Background
  - Utility of stomach cancer studies
  - Assessment of findings

- **Preliminary level of evidence conclusion**
Background

- Lung cancer mortality is an adequate measure of lung cancer incidence
  - Low survival: 18.1% survival five years after diagnosis

- Potential confounders among lung cancer risk factors
  - Occupational: arsenic, lead, polycyclic aromatic hydrocarbons (PAHs), asbestos
  - Non-occupational: current and past smoking

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## Overview of selected studies

<table>
<thead>
<tr>
<th>Occupational cohort study</th>
<th>Study design</th>
<th>Exposure assessment</th>
<th>Likely antimony species</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimony smelter workers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jones 1994, United Kingdom</td>
<td>Historical mortality cohort [SMR]</td>
<td>Company records</td>
<td>Antimony trioxide, other antimony oxides, antimony sulfides</td>
</tr>
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<td>Schnorr et al. 1995, United States</td>
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<tr>
<td>Jones et al. 2007, United Kingdom</td>
<td>Modeled cumulative inhalation and lung cancer mortality</td>
<td>Area and personal air sampling, job-exposure matrix</td>
<td>Antimony trioxide</td>
</tr>
</tbody>
</table>
Study Quality and Utility Assessment

Domain level judgments
- Low/minimal concern (+++)
- Some concern (++)
- Major concern (+)
- Critical concern (0)
- No information

RoC Handbook:
Study Quality and Utility Assessment

Study utility

Domain level judgments
- Low/minimal concern (+++)
- Some concern (++)
- Major concern (+)
- Critical concern (0)
- No information

Overall study utility level
- High utility (+++)
- Moderate utility (++)
- Low utility (+)
- Inadequate utility (0)

RoC Handbook:
Studies were “high/moderate” or “moderate” utility to inform a cancer hazard evaluation.

Most studies had some or major concerns of selection bias, exposure misclassification, and study sensitivity.

Most studies had some or major concerns of confounding by occupational co-exposures and smoking.
- Small number of studies (n=3) examined antimony-exposed lung cancer deaths.
- Two antimony smelter cohort studies used ever-exposure to antimony and conducted an external analysis.
- Concurrent exposure to other metals during smelting process and high prevalence of smoking among workers may confound the results.

* NTP calculated estimate based on Jones et al. (2007), Table 3 (weighted Sb exposure, β =1.18, p-trend: 0.013)
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• Preliminary level of evidence conclusion
Stomach Cancer

Background

• Stomach cancer mortality is an adequate measure of stomach cancer incidence
  – Low survival five years after diagnosis

• Potential confounders among stomach cancer risk factors
  – Occupational: lead, asbestos
  – Non-occupational: current and past smoking

Overview of selected studies

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<tr>
<td><strong>Wingren and Axelson 1993, Sweden</strong></td>
<td>Case-control study, art-glass producing area</td>
<td>Occupation on death records and regional use patterns</td>
<td>Antimony trioxide</td>
</tr>
</tbody>
</table>
## Quality and Utility of Stomach Cancer Studies

### Two “high/moderate” and one “low” utility studies

<table>
<thead>
<tr>
<th>Study type, citation</th>
<th>Consideration for potential bias</th>
<th>Quality</th>
<th>Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Selection</td>
<td>Exposure</td>
<td>Outcome</td>
</tr>
<tr>
<td>Antimony smelter workers (cohort studies)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Jones 1994</td>
<td>++</td>
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- Antimony smelter studies had high/moderate utility, and case-control had low study utility.
- For case control study, major concerns for potential exposure misclassification, confounding bias from occupational co-exposures, and major concerns for study sensitivity.
Utility of Stomach Cancer Studies

Inconsistent associations across studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Exposed cases</th>
<th>Exposure level</th>
<th>Risk estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones 1994 (UK)</td>
<td>2</td>
<td>Ever exposure</td>
<td>SMR: 0.42 (0.05–1.51)</td>
</tr>
<tr>
<td>Schnorr et al. 1995 (US)</td>
<td>10</td>
<td>Ever exposure</td>
<td>SMR: 1.49 (0.71–2.74)</td>
</tr>
<tr>
<td>Wingren and Axelson 1993 (Sweden)</td>
<td>NR</td>
<td>Low antimony use</td>
<td>OR: 1.60 (0.90–2.60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High antimony use</td>
<td>OR: 0.80 (0.30–2.00)</td>
</tr>
</tbody>
</table>

- Limited by small number of studies (n=3) and small number of exposed cases.
- Although two studies found positive associations with stomach cancer, there were inconsistent findings within and across studies.
- Likely unmeasured confounding from smoking and occupational lead.
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• Preliminary level of evidence conclusion
NTP preliminary conclusion:

“The data available from studies in humans are **inadequate** to evaluate the relationship between human cancer and exposure specifically to antimony trioxide or other antimony compounds.”

- Limited by:
  - Number of studies with small sample sizes for stomach and lung cancers.
  - Potential confounding due to smoking and occupational co-exposures.
Questions?
Reviewer Questions

Human Cancer Studies

• Comment on whether the scientific information from the cancer studies in humans for antimony trioxide is clear, technically correct, and objectively presented.
  – Identify any information that should be added or deleted.

• Comment on whether the approach (described in the Protocol) and assessment of the utility of the human cancer studies (risk of bias and sensitivity to detect an effect) for informing the cancer evaluation (Appendix C, Sections 4.2) is systematic, transparent, objective, and clearly presented.

• Provide any scientific criticisms of NTP’s cancer assessment of the epidemiologic studies of exposure to antimony trioxide, including how the findings from the individual studies were interpreted and the evidence across studies was synthesized.