Report on the Peer Review of the Report on Carcinogens (RoC) Draft Monograph on Antimony Trioxide

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Office of the Report on Carcinogens, Division of National Toxicology Program
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
October 9, 2018
Antimony trioxide

- Antimony is a metalloid found in nature

- Antimony(III) trioxide is the most commercially significant form of processed antimony
Uses of Antimony(III) Trioxide

Formulation
- flame retardant synergist
- polyethylene terephthalate (PET) catalyst
- special glass manufacture additive
- pigments, paints, ceramics

Processing

Consumer products

= Sb$_2$O$_3$  = no longer Sb$_2$O$_3$  = depends on circumstance

Slide courtesy of Sandy Garner, ILS
<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebecca Fry, PhD</td>
<td>University of North Carolina at Chapel Hill</td>
</tr>
<tr>
<td>Hao Zhu, PhD</td>
<td>Rutgers University-Camden</td>
</tr>
<tr>
<td>Elaine Symanski, PhD</td>
<td>The University of Texas Health Science Center at Houston</td>
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<tr>
<td>Elizabeth Ward, PhD</td>
<td>American Cancer Society (retired)</td>
</tr>
<tr>
<td>John Wise, Sr., PhD</td>
<td>University of Louisville</td>
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<tr>
<td>Michael Waalkes, PhD</td>
<td>NIEHS (retired)</td>
</tr>
<tr>
<td>Richard Peterson II, DVM, PhD, DACVP</td>
<td>AbbVie</td>
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</tbody>
</table>

**NTP BSC liaison**

Kenneth McMartin, PhD  Louisiana State University
Public comments

- Public comments, including published and unpublished information, were received in several phases of the process
- ORoC staff considered technical and scientific issues at all phases
- Public comments on draft monograph were provided to the peer review panel
A significant number of people in the United States are exposed to antimony(III) trioxide

- Highest levels of exposure occur in the workplace
- The general population is exposed
  - Primary releases (i.e., pollutant is antimony(III) trioxide) from industrial uses to air: Estimated 11,365 lb to air in year 2010
  - Secondary (i.e., pollutant is transformed from other antimony species into antimony(III) trioxide) releases to the environment
  - House dust from some consumer products
  - Antimony detected in urine (The National Health and Nutrition Examination Survey, or NHANES)

Panel: Concurred
Inadequate human evidence for determining carcinogenicity

- Limited by:
  - Few studies with small sample sizes for stomach and lung cancers
  - Potential confounding due to smoking and occupational co-exposures

Panel: Agreed unanimously
Key issues discussed at the peer review panel meeting

- **Male rat lung tumors**
  - Overload alone does not explain the observed carcinogenicity in rats
    - Increased lung tumors in mice at Sb$_2$O$_3$ concentrations below overload threshold
    - Genotoxicity in exposed mice, indicating Sb$_2$O$_3$ has intrinsic toxicity
  - Incidences of alveolar/bronchiolar adenoma exceed current and historical controls
  - Adenoma can progress to carcinoma

→ **Rat lung tumors are evidence of carcinogenicity (i.e., agree with NTP 2017)**
**Sufficient animal evidence for antimony trioxide carcinogenicity**

Increased incidences of malignant tumors and combined incidences of malignant and benign tumors at multiple tissue sites in multiple species

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Species</th>
<th>Tissue Site</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung tumors</td>
<td>Mice</td>
<td>Alveolar/bronchiolar adenoma (F)</td>
<td>NTP 2017</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alveolar/bronchiolar carcinoma (M and F)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alveolar/bronchiolar adenoma or carcinoma (F)</td>
<td></td>
</tr>
<tr>
<td>Skin tumors</td>
<td>Mice</td>
<td>Fibrous histiocytoma (M)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibrous histiocytoma or fibrosarcoma (M)</td>
<td></td>
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<tr>
<td>Lymphoma</td>
<td>Mice</td>
<td>Malignant</td>
<td>Newton et al. 1994</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lymphoma (F)</td>
<td>reported no increase in tumors.</td>
</tr>
</tbody>
</table>

Panel: Agreed unanimously
Electrophilicity
- Affinity to vicinal thiol groups

Interact with
- Peptides (e.g., GSH)
- Proteins/ enzymes (including zinc finger)

Increase oxidative stress
- \( \cdot O_2^- \)

Decrease DNA damage repair capacity

Cause receptor-mediated effects
- e.g., Prevent cell differentiation → Preserve proliferation potential

Genotoxicity
- DNA damage
- Chromosomal aberrations
- Sister chromatid exchange

Decrease DNA damage repair capacity
- e.g., Prevent cell differentiation

Supporting mechanistic information

= direct evidence from \( \text{Sb}_2\text{O}_3 \)

= direct evidence from compounds containing Sb(III)
Antimony trioxide should be listed in the RoC as *reasonably anticipated to be a human carcinogen* based on sufficient evidence from studies in experimental animals and supporting mechanistic data.

Panel: Agreed unanimously
Revised Draft RoC Monograph

Revised Draft: Report on Carcinogens Monograph on Antimony Trioxide
August 15, 2018

This revised Report on Carcinogens monograph has not been formally distributed by the National Toxicology Program. It does not represent and should not be construed to represent any final NTP determination or policy.

+ appendices
+ supplemental material
## New: Supplemental Material

### Detailed risk of bias information on animal studies

<table>
<thead>
<tr>
<th>Adequacy of study duration bias rating</th>
<th>Adequacy of study duration rationale</th>
<th>Confounding bias rating</th>
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<th>Reporting and statistics bias rating</th>
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<tbody>
<tr>
<td>+++</td>
<td>The study duration was 2 years, with 12 months</td>
<td>+++</td>
<td>Material of high purity. Animal husbandry</td>
<td>+++</td>
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<tr>
<td>+++</td>
<td>The study duration was 2 years, with 1 year</td>
<td>+++</td>
<td>Animals in high dose group were heavier</td>
<td>+++</td>
</tr>
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### Animal cancer study results ready for further analysis

<table>
<thead>
<tr>
<th>Non-neoplastic findings</th>
<th>Other comments</th>
<th>Dose</th>
<th>N at start</th>
<th>Incidence</th>
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<tr>
<td>Lung were examined after 12 months and after 24 months.</td>
<td>12 Month results: 0</td>
<td>65</td>
<td>1/52</td>
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<td>Lung were examined after 12 months and after 24 months.</td>
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<td>Only the incidence</td>
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<td>0/17</td>
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<td>18</td>
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Immediate next steps after BSC meeting

- Present to NTP director
- Finalize RoC monograph
Acknowledgements

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*Members of the Office of the Report on Carcinogens (ORoC)
†Deceased July 30, 2018
CPSC = Consumer Product Safety Commission
DNTP = Division of National Toxicology Program
ICF = ICF Incorporated, LLC (Support provided through NIEHS Contract Number GS00Q14OADU417/HHSN273201600015U)
ILS = Integrated Laboratory Systems, Inc. (Support provided through subcontract number 16EDBO0078 with ICF)
NIEHS = National Institute of Environmental Health Sciences