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

Amy Wang, PhD
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
# Peer Review Panel Members

<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>
</tr>
<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>
</tr>
<tr>
<td>Michael Waalkes, PhD</td>
<td>NIEHS (retired)</td>
</tr>
<tr>
<td>Richard Peterson II, DVM, PhD</td>
<td>AbbVie</td>
</tr>
</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• Public comments, including published and unpublished information, were received in several phases of the process.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.
Electrophilicity
- Affinity to vicinal thiol groups

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

Increase oxidative stress
- 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

Supporting mechanistic information

= direct evidence from Sb\(_2\)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: Report on Carcinogens Monograph on Antimony Trioxide

August 15, 2018

Office of the Report on Carcinogens
National Toxicology Program
National Institute of Environmental Health Sciences
U.S. Department of Health and Human Services

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.

Antimony Trioxide
CAS No. 1289-84-44
Reversibly antagonized to be a human carcinogen²

Carcinogenicity
Antimony trioxide is reversibly antagonized to be a human carcinogen based on sufficient evidence of carcinogenicity. The data available from studies in laboratory animals and supporting evidence from mechanistic studies. The data available from studies in laboratory animals are inadequate to evaluate the relationship between human cancer and exposure specifically to antimony trioxide or antimony in general.

Carcinogenicity in Experimental Animals
Antimony trioxide administered by subcutaneous or intravenous injections to rats and mice in several other species at dose levels and in doses of both sexes. As a result of these studies in experimental animals with exposure to antimony trioxide by other routes were identified. This conclusion of carcinogenicity was based on data from studies in three different strains of mice with exposure to antimony trioxide by the subcutaneous route, and in both sexes of Wistar rats and B6C3F1 mice. Antimony trioxide was administered by subcutaneous injection to rats and mice in several other species at dose levels and in doses of both sexes. However, the NTP studies were more informative based on the study design and detailed reports, while other studies were also conducted in a more carcinogenic after chronic exposure to potential hazards.

In the long, exposure of female rats to antimony trioxide significantly increased the incidence of benign long tumors (acinar/breast lobular adenoma) (Enna et al. 1986, NTP 1977), which can progress to malignant tumors, and incidences of malignant long tumors (malignant carcinomas of the breast) were also increased. Antimony trioxide administered subcutaneously to mice did not significantly increase the incidence of benign long tumors (acinar/breast lobular adenoma and malignant long tumors (malignant carcinomas of the breast) and of the mammary gland). The benzo-a-pyrene (BaP) control group for the female rats and the biliary system control group for the male rats were exposed to antimony trioxide (NTP 1977). The incidence of malignant long tumors increased significantly in the mammary gland control group for the female rats exposed to antimony trioxide (NTP 1977). Another study in male and female rats (Enna et al. 1986) found no increase in the incidence of long tumors, possibly because the higher oral dose of antimony trioxide was too low to induce a statistically significant increase in tumors. Exposure of mice to antimony trioxide caused a statistically significant decrease in the incidence of benign long tumors (acinar/breast lobular adenoma) in females, malignant long tumors

² NTP preliminary testing recommendation for the RoC.

+ 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>
</tr>
</thead>
<tbody>
<tr>
<td>+++</td>
<td>The study duration was 2 years, with 12 months++</td>
</tr>
<tr>
<td>+++</td>
<td>The study duration was 2 years, with 1 year++</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Confounding bias rating</th>
<th>Confounding bias rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>+++</td>
<td>Material of high purity. Animal husbandry++</td>
</tr>
<tr>
<td>+++</td>
<td>Animals in high dose group were heavier++</td>
</tr>
</tbody>
</table>

### 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>
</tr>
</thead>
<tbody>
<tr>
<td>Lung were examined after 12 months and after 24 months.</td>
<td>12 Month results:</td>
<td>0</td>
<td>65</td>
<td>1/52</td>
</tr>
<tr>
<td>Lung were examined after 12 months and after 24 months.</td>
<td>12 Month results:</td>
<td>0.06</td>
<td>65</td>
<td>0/52</td>
</tr>
<tr>
<td>Lung were examined after 12 months and after 24 months.</td>
<td>12 Month results:</td>
<td>0.51</td>
<td>65</td>
<td>0/53</td>
</tr>
<tr>
<td>Lung were examined after 12 months and after 24 months.</td>
<td>12 Month results:</td>
<td>4.5</td>
<td>65</td>
<td>1/52</td>
</tr>
<tr>
<td>Lung were examined after 12 months and after 24 months.</td>
<td>12 Month results:</td>
<td>0</td>
<td>50</td>
<td>0/49</td>
</tr>
<tr>
<td>Lung were examined after 12 months and after 24 months.</td>
<td>12 Month results:</td>
<td>0.06</td>
<td>50</td>
<td>0/52</td>
</tr>
<tr>
<td>Lung were examined after 12 months and after 24 months.</td>
<td>12 Month results:</td>
<td>0.51</td>
<td>50</td>
<td>1/54</td>
</tr>
<tr>
<td>Lung were examined after 12 months and after 24 months.</td>
<td>12 Month results:</td>
<td>4.5</td>
<td>50</td>
<td>0/50</td>
</tr>
<tr>
<td>Lungs from exposed animals grossly appeared mottled – with Only the incidence</td>
<td>0</td>
<td>0/13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lungs from exposed animals grossly appeared mottled – with Only the incidence</td>
<td>1.6</td>
<td>0/17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lungs from exposed animals grossly appeared mottled – with Only the incidence</td>
<td>4.2</td>
<td>9/18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lungs from exposed animals grossly appeared mottled – with Only the incidence</td>
<td>0</td>
<td>0/13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lungs from exposed animals grossly appeared mottled – with Only the incidence</td>
<td>1.6</td>
<td>0/17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Immediate next steps after BSC meeting

- Present to NTP director
- Finalize RoC monograph
Acknowledgements

Collaborators

Ruth M. Lunn NIEHS, DNTP*
Sanford C. Garner ILS
Joanne Trgovcich ICF
Suril S. Mehta NIEHS, DNTP*
Andrew D. Ewens ILS
Alton F. Peters ILS
Kristine L. Witt NIEHS, DNTP

Contributors

Gloria D. Jahnke NIEHS, DNTP*
Jui-Hua Hsieh NIEHS, DNTP
Melanie C. Buser ATSDR
Kristina M. Hatlelid CPSC
Linda M. Sargent CDC
Yin-tak Woo EPA
Whitney D. Arroyave ILS
Stephen S. Ferguson NIEHS, DNTP
Gordon P. Flake† NIEHS, DNTP
Michelle J. Hooth NIEHS, DNTP
B. Alex Merrick NIEHS, DNTP
Daniel L. Morgan NIEHS, DNTP
Arun K.R. Pandiri NIEHS, DNTP
Matthew D. Stout NIEHS, DNTP
Kyla W. Taylor NIEHS, DNTP

Acknowledgements

Michael A. Babich CPSC
Alison H. Harrill NIEHS, DNTP
Sharon L. Oxendine EPA
Nisha S. Sipes NIEHS, DNTP
Stanley T. Atwood ILS
Mary S. Wolfe NIEHS, DNTP
Andy J. Shapiro, MS NIEHS, DNTP (formerly)

Susan Dakin Independent consultant
Jessica A. Geter ILS (formerly)
Lara Handler ILS
Ella J. Darden ILS
Tracy L. Saunders ILS
F. Louise Assem ICF
Susan Blaine ICF
Cannden N. Byrd ICF
Anna N. Stamatogiannakis ICF

*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