Foreword

The National Toxicology Program (NTP) is an interagency program within the Public Health Service (PHS) of the Department of Health and Human Services (HHS) and is headquartered at the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH). Three agencies contribute resources to the program: NIEHS/NIH, the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC), and the National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA). Established in 1978, the NTP is charged with coordinating toxicological testing activities, strengthening the science base in toxicology, developing and validating improved testing methods, and providing information about potentially toxic substances to health regulatory and research agencies, scientific and medical communities, and the public.

The Report on Carcinogens (RoC) is prepared in response to Section 301 of the Public Health Service Act as amended. The RoC contains a list of identified substances (i) that either are known to be human carcinogens or are reasonably anticipated to be human carcinogens and (ii) to which a significant number of persons residing in the United States are exposed. The NTP, with assistance from other Federal health and regulatory agencies and nongovernmental institutions, prepares the report for the Secretary, Department of HHS. The most recent RoC, the 13th Edition (2014), is available at http://ntp.niehs.nih.gov/go/roc.

Nominations for (1) listing a new substance, (2) reclassifying the listing status for a substance already listed, or (3) removing a substance already listed in the RoC are evaluated in a scientific review process (http://ntp.niehs.nih.gov/go/rocprocess) with multiple opportunities for scientific and public input and using established listing criteria (http://ntp.niehs.nih.gov/go/15209). A list of candidate substances under consideration for listing in (or delisting from) the RoC can be obtained by accessing http://ntp.niehs.nih.gov/go/37893.
**Objectives and Methods**

**Objective and scope**

Antimony is a metalloid found in nature in over 100 mineral species; it can exist in four oxidation states, $-3, 0, +3, \text{ and } +5$, of which the Sb(III) (trivalent) and Sb(V) (pentavalent) forms are the most common in nature. Elemental antimony is a silver-white metal used primarily to make alloys. The trivalent compound antimony(III) trioxide is the most commercially significant form of processed antimony, used primarily as a synergist for halogenated flame retardants in plastics, rubber, and textiles.

The objective of this monograph is to conduct a cancer hazard evaluation of antimony(III) trioxide for possible listing in the Report on Carcinogens (RoC). Antimony species can be interconverted in the environment and *in vivo*. The monograph evaluation focuses on antimony(III) trioxide and also provides scientific and exposure information on elemental antimony and other antimony compounds, because (1) people can be exposed to antimony(III) trioxide resulting from transformation from other forms of antimony, and (2) studies of biological effects and other relevant information may inform understanding of antimony(III) trioxide’s mechanistic basis for potential carcinogenicity. The table below summarizes the evidence streams, exposures of interest, and outcomes. This is somewhat analogous to a “population, exposure, comparator, outcome” statement (Whaley *et al.* 2016) except that population has been replaced by evidence stream (e.g., humans, experimental animals, *in vitro* studies). The comparator (no or low exposure to antimony compounds) is the same for all outcomes.

<table>
<thead>
<tr>
<th>Scientific evidence stream</th>
<th>Exposure</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Primary evidence</td>
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<tr>
<td>Experimental animal studies</td>
<td>Antimony trioxide</td>
<td>All reported neoplasms</td>
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<tr>
<td>Human studies</td>
<td>Antimony trioxide (primarily)</td>
<td>Lung and stomach cancer</td>
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<td></td>
<td>and other antimony compounds</td>
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<tr>
<td>Supporting evidence</td>
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<tr>
<td>Human studies</td>
<td>Antimony(III) compounds</td>
<td>Biological effects related to</td>
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<td><em>In vitro</em> studies</td>
<td>Antimony(III) compounds</td>
<td>Biological effects related to</td>
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<td>carcinogenicity or toxicity</td>
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The monograph also assesses exposure information (summarized in the table below) to determine whether a significant number of people residing in the United States are currently exposed or were exposed in the past to antimony(III) trioxide.
Information | Antimony compounds
--- | ---
Uses, consumption, and production | Antimony(III) trioxide and other commercially important antimony compounds
Occupational exposure | Primarily antimony(III) trioxide
Consumer products | Products containing antimony(III) trioxide
Environmental exposure | Antimony (species mostly undefined)

**Methods for developing the RoC monograph**

**Process leading to the selection of antimony(III) trioxide for review**

As per the process for preparation of the RoC, the Office of the Report on Carcinogens (ORoC) released a draft concept document, “Antimony Trioxide,” which outlined the rationale and proposed the approach for the review, for public comment. The ORoC also presented the draft to the NTP Board of Scientific Counselors (BSC) at its meeting on December 14–15, 2016, which provided opportunity for written and oral public comments. After the meeting, the concept was finalized, and antimony was approved by the NTP Director as a candidate substance for review. The concept document is available on the RoC website ([https://ntp.niehs.nih.gov/go/809361](https://ntp.niehs.nih.gov/go/809361)).

Public comments on scientific issues were requested at several time points prior to the development of the RoC monograph, and they include the request for information on the nomination and the request for comment on the draft concept document, which outlined the rationale and approach for conducting the scientific review. In addition, the NTP posted its protocol for preparing the draft RoC monograph on antimony trioxide for public input on the RoC webpage at ([https://ntp.niehs.nih.gov/go/809361](https://ntp.niehs.nih.gov/go/809361)) prior to the release of the draft monograph.

**Monograph development**

This monograph evaluates the available, relevant scientific information and assesses its quality, applies the RoC listing criteria to the scientific information, and recommends a RoC listing status. The monograph also includes a draft substance profile containing the NTP’s preliminary listing recommendation for antimony(III) trioxide, a summary of the scientific evidence considered key to reaching that recommendation, and data on antimony(III) trioxide’s properties, use, production, and exposure, along with federal regulations and guidelines to reduce exposure.

The process of applying the RoC listing criteria to the body of evidence includes assessing the level of evidence from cancer studies of antimony(III) trioxide in humans and experimental animals. In addition, the available mechanistic and other relevant data (such as disposition and toxicokinetics) are assessed, and the final listing recommendation is based on an integration of all the relevant information (as summarized in the table above). This information is captured in the following sections of the monograph:

- Physical and Chemical Properties (Section 1)
- Human Exposure (Section 2)
- Disposition and Toxicokinetics (Section 3)
- Human Cancer Studies (Section 4)
- Studies of Cancer in Experimental Animals (Section 5)
- Mechanistic and Other Relevant Data (Section 6)
- Evidence Integration and Preliminary Listing Recommendation (Section 7).

The overall cancer hazard evaluation in Section 7 is informed by the information and assessments of the data reported in the earlier sections. The information must come from publicly available sources. The appendices in the RoC Monograph contain important supplementary information, including the literature search strategy, disposition data tables, study-quality tables for cancer studies in experimental animals, and findings from studies of mechanistic and other relevant studies.

**Key scientific questions for each type of evidence stream**

The monograph provides information relevant to the following questions for each type of evidence stream or section topic.

**Questions related to the evaluation of properties and human exposure information**

- What are the physicochemical properties of antimony(III) trioxide and other relevant antimony compounds?
- What are the sources of exposure? How are people exposed to antimony(III) trioxide?
- Are a significant number of people residing in the United States exposed to antimony(III) trioxide?
- To what chemical forms of antimony are humans exposed? Can the current analytical methods and available monitoring studies address this question?

**Questions related to the evaluation of disposition and toxicokinetics**

- How are antimony compounds absorbed, distributed, metabolized, and excreted (i.e., ADME information)?
  - What evidence do we have regarding antimony metabolism in mammals and potential effects from antimony metabolites?
  - To what extent does transformation between Sb(III) and Sb(V) occur *in vivo*? Is Sb(III) the ultimate carcinogenic species?
- How can toxicokinetics models (if any) inform biological plausibility, interspecies extrapolation, or other questions about potential mechanisms of carcinogenicity?

**Questions related to the evaluation of human cancer studies**

- What are the methodological strengths and limitations of these studies?
- What are the potential confounding factors for cancer risk at the tumor sites of interest?
- Is there a credible association between exposure to antimony and cancer?
  - If so, can the relationship between cancer end points and exposure to antimony be explained by chance, bias, or confounding?
Questions related to the evaluation of cancer studies in experimental animals

- What is the level of evidence (sufficient, limited, or inadequate) for the carcinogenicity of antimony(III) trioxide in animal studies?
- What are the methodological strengths and limitations of the studies?
- At what tissue sites was cancer observed?
- If lung tumors are seen in rats after inhalation exposure to antimony(III) trioxide, what role does lung overload play in causing observed rat lung tumors?

Questions related to the evaluation of mechanistic data and other relevant data

- What are the genotoxic effects of antimony(III) trioxide exposure?
- What are the major biological effects contributing to the potential carcinogenicity of antimony(III) trioxide?
  - For biological effects contributing to potential carcinogenicity that have not been tested in studies with exposure to antimony(III) trioxide, could data from other antimony compounds be used to infer likely results for antimony(III) trioxide?

Methods for preparing the monograph

The methods for preparing the RoC monograph on antimony(III) trioxide are described in the RoC Protocol for preparing the draft monograph on antimony(III) trioxide, which incorporated a systematic review approach for identification and selection of the literature (see Appendix A), using inclusion/exclusion criteria, extraction of data and evaluation of study quality according to specific guidelines, and assessment of the level of evidence for carcinogenicity according to established criteria. Links are provided to the appendices within the document, and specific tables or sections can be selected from the table of contents (see below).

General procedures. See the Handbook for Preparing RoC Monographs (hereinafter referred to as RoC Handbook) for a detailed description of methods.

Selection of the literature. Preparation of the monograph began with development of a literature search strategy to obtain information relevant to the topics listed above for Sections 1 through 6 using search terms outlined in the Protocol. Approximately 5,500 citations were identified from these searches and uploaded to web-based systematic review software for separate evaluation by two reviewers applying the inclusion/exclusion criteria. Based on these criteria, 256 references were selected for final inclusion in the monograph. Literature searches are updated on a monthly basis.

Data extraction and quality assurance procedures. Information for the relevant cancer and mechanistic studies was systematically extracted in tabular format and/or summarized in the text from studies selected for inclusion in the monograph. All sections of the monograph underwent scientific review and quality assurance (i.e., assuring that all the relevant data and factual information extracted from the publications had been reported accurately) by a separate reviewer. Any discrepancies were resolved by the writer and the reviewer through discussion and reference to the original data source.
Evaluation of human cancer studies. The available epidemiological studies are not specific for exposure to antimony(III) trioxide. Based on the studies’ descriptions, it is likely that the workers were exposed to other forms of antimony in addition to the trioxide. Two reviewers evaluated the quality of each study using a series of questions (and guidelines for answering the questions) related to risk of bias and to study sensitivity (as described in the Protocol). Any disagreements between the two reviewers were resolved through discussion or by consultation with a third reviewer and reference to the original data source. The approach to synthesizing the evidence across studies and reaching a conclusion on the level of evidence for carcinogenicity is also outlined in the Protocol. Level-of-evidence conclusions (inadequate, limited, or sufficient) were made by applying the RoC criteria (see below) to the body of evidence.

RoC Listing Criteria

**Known To Be Human Carcinogen:**
There is sufficient evidence of carcinogenicity from studies in humans*, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

**Reasonably Anticipated To Be Human Carcinogen:**
There is limited evidence of carcinogenicity from studies in humans*, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded, OR

there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset, OR

there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

Evaluation of cancer studies in experimental animals. Two reviewers evaluated the quality of each study using methods described in the Protocol. Any disagreements between the two reviewers were resolved through discussion or by consultation with a third reviewer and reference to the original data source. The level-of-evidence conclusions (sufficient, not sufficient) were made by applying the RoC criteria (see below) to the body of evidence. These conclusions were made after the evaluation of the mechanistic data and are reported in the overall cancer hazard evaluation.

Evaluation of mechanistic and other relevant data. As mentioned in the protocol, the mechanistic data were organized by characteristics of carcinogens (such as genotoxicity,
oxidative stress, epigenetic alterations, and promotion of cell proliferation) to help inform understanding of the relevant biological effects potentially contributing to carcingenesis. Mechanistic data, toxicokinetics data, and other relevant data (such as non-cancer health outcomes and carcinogenicity studies of other antimony compounds) are discussed for all antimony compounds, to help inform the cancer evaluation of antimony(III) trioxide and whether there is sufficient information to identify the antimony species ultimately responsible for carcingenicity.

**Overall evaluation and preliminary listing recommendation.** The evidence from the cancer studies in human and experimental animals was integrated with the assessment of the mechanistic and other relevant data. The RoC listing criteria were then applied to the body of knowledge to reach a listing recommendation regarding antimony(III) trioxide.
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1 Chemical identification and properties

This section provides information on the physical and chemical properties of antimony(III) trioxide (Sb(III)₂O₃) and on antimony compounds with toxicological and other relevant information (Sections 3, 4, 5, and 6). As mentioned in the Objectives and Methods, toxicological information (Section 6) and information on properties for other antimony compounds (see below) may inform the cancer hazard evaluation of antimony(III) trioxide.

1.1 Properties of antimony(III) trioxide and other antimony compounds

Antimony(III) trioxide exists as an odorless white powder or polymorphic crystals (HSDB 2013). It is slightly soluble in water, dilute sulfuric acid, dilute nitric acid, or dilute hydrochloric acid. It is soluble in solutions of alkali hydroxides or sulfides and in warm solutions of tartaric acid or of bitartrates. Figure 1-1 shows the chemical structure for antimony(III) trioxide and Table 1-1 presents its physical and chemical properties.

![Figure 1-1. Structure for antimony(III) trioxide](image)

<table>
<thead>
<tr>
<th>Property</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>Sb(III)₂O₃⁹</td>
</tr>
<tr>
<td>CAS No.</td>
<td>1309-64-4⁸</td>
</tr>
<tr>
<td>InChi key</td>
<td>ADCOVFLJGNWNNZ-UHFFFAOYSA-N⁰</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>291.5⁸</td>
</tr>
<tr>
<td>% Antimony by weight</td>
<td>83.6⁸</td>
</tr>
<tr>
<td>Antimony charge</td>
<td>+3⁸</td>
</tr>
<tr>
<td>Specific gravity, at 24°C</td>
<td>5.9⁶</td>
</tr>
<tr>
<td>Melting point</td>
<td>655°C⁶</td>
</tr>
<tr>
<td>Boiling point</td>
<td>1425°C⁶</td>
</tr>
<tr>
<td>Water solubility, at 22.2°C [3.3 x 10⁻⁴] g/100 mL</td>
<td>d,e</td>
</tr>
<tr>
<td>Vapor pressure, at 574°C</td>
<td>1 mm Hg⁹</td>
</tr>
</tbody>
</table>

Table 1-1. Physical and chemical properties for antimony(III) trioxide

<table>
<thead>
<tr>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>e Reported as 0.0033 g/L; brackets denote conversion of units.</td>
</tr>
</tbody>
</table>

Physical and chemical properties for other antimony compounds discussed in this monograph are listed in Table 1-2 together with their structures; the compounds listed are those with carcinogenicity (Section 4 and 5), mechanistic (Section 6), or disposition (Section 3) data. In addition to elemental antimony (valence = 0), most antimony compounds have valences of either +3 (11 compounds) or +5 (5 compounds) although one compound with valence -3 is also included in the table. Compounds with +3 valence are likely to share more similarity with antimony(III) oxide but as discussed in Sections 2 and 3, interconversion between antimony(III) and antimony(V) occurs during manufacturing processes, in the environment, and in vivo. Both the +3 and +5 valence states include both inorganic antimony compounds, e.g., antimony(III)
trisulfide and antimony(V) pentasulfide, and organic antimony compounds, primarily those used as anti-leishmanial drugs, such as sodium antimony 2,3-mesodimercaptosuccinate (the active ingredient in Astiban) and sodium stibogluconate(III) (the active ingredient in Pentostam).

Solubilization of some water-insoluble compounds may be enhanced in biological fluids at low pH and in the presence of binding proteins (IARC 2006), and this information may provide better understanding of potential absorption of an antimony compound than solubility in water. Because in vivo bioavailability testing can be cost prohibitive and time consuming, solubility of compounds in artificial fluids (i.e., bioaccessibility) can be estimated using synthetic equivalents of gastric fluid (for ingestion exposure), interstitial and lysosomal fluids (for inhalation exposure), perspiration fluids (for dermal exposure), and human blood serum (for transport within the body). The solubility of antimony(III) trioxide and other antimony compounds in these different fluids, which have pH ranging from 1.6 for gastric fluid to 7.4 for lung interstitial fluid and human blood serum are listed in Table 1-3. European Union Registration, Evaluation and Authorisation of ChEmicals (REACH) data for bioaccessibility for antimony(III) trioxide, antimony(V) pentoxide, and antimony(III) sulfide in simulated human fluids is expressed as percent solubility in simulated human fluids at various pH values (ECHA 2017). For these three antimony compounds, in fluids simulating physiologic pH, bioaccessibility after 24 hours of exposure was highest for antimony(III) trioxide and lowest for antimony sulfide, with antimony pentoxide occupying an intermediate position. Antimony(III) trioxide had the highest percent solubility in artificial alveolar lysosomal fluid (pH = 4.5), which may be representative of the lung tissue contacted by inhaled antimony(III) trioxide (see Section 2) (ECHA 2017). Intermediate values were reported for artificial sweat (pH = 6.5), interstitial fluid within the deep lung (pH = 7.4), and human blood serum (pH = 7.4). The lowest value reported was for artificial gastric fluid (pH = 1.6).

### Table 1-3. Bioaccessibility of antimony(III) trioxide and other antimony compounds

<table>
<thead>
<tr>
<th>Antimony</th>
<th>Percent (%) solubility in simulated human fluid after 24 hours of exposure</th>
<th>GMB&lt;sup&gt;a&lt;/sup&gt; (pH = 7.4)</th>
<th>PBS&lt;sup&gt;b&lt;/sup&gt; (pH = 7.4)</th>
<th>ASW&lt;sup&gt;c&lt;/sup&gt; (pH = 6.5)</th>
<th>ALF&lt;sup&gt;d&lt;/sup&gt; (pH = 4.5)</th>
<th>GST&lt;sup&gt;e&lt;/sup&gt; (pH = 1.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimony(III)</td>
<td></td>
<td>56.7</td>
<td>41.5</td>
<td>60.8</td>
<td>81.7</td>
<td>13.6</td>
</tr>
<tr>
<td>trioxide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimony(V)</td>
<td></td>
<td>32.5</td>
<td>29.2</td>
<td>60.8</td>
<td>71.4</td>
<td>94.3</td>
</tr>
<tr>
<td>pentoxide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimony(III)</td>
<td></td>
<td>3.9</td>
<td>8.5</td>
<td>3.6</td>
<td>5.1</td>
<td>4</td>
</tr>
<tr>
<td>sulfide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: ECHA 2017.

<sup>a</sup>GMB = Gamble’s solution. GMB mimics interstitial fluid within the deep lung under normal health conditions.

<sup>b</sup>PBS = Phosphate-buffered saline. PBS mimics the ionic strength of human blood serum.

<sup>c</sup>ASW = Artificial sweat. ASW mimics hypomolar fluid excreted upon sweating.

<sup>d</sup>ALF = Artificial lysosomal fluid. ALF mimics intracellular conditions in lung cells during phagocytosis.

<sup>e</sup>GST = Artificial gastric fluid. GST mimics stomach acid.
Table 1-2. Physical and chemical properties for metallic (elemental) antimony and other antimony compounds with carcinogenicity or mechanistic data

<table>
<thead>
<tr>
<th>Name</th>
<th>CAS No. (InChI Key)</th>
<th>Formula</th>
<th>Chemical structure</th>
<th>Molecular weight (% Sb by weight)</th>
<th>Density or specific gravity</th>
<th>Solubility in water (g/100 mL), descriptive level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Valence = 0</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimony (elemental)</td>
<td>7440-36-0&lt;sup&gt;a&lt;/sup&gt; (WATWJUSRGPENY-UHFFFAOYSA-N&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>Sb&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Sb</td>
<td>121.8&lt;sup&gt;a&lt;/sup&gt; (100.0&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>6.68&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Insoluble&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Valence = -3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stibine</td>
<td>7803-52-3&lt;sup&gt;a&lt;/sup&gt; (OUULRIDGPHMNQ-UHFFFAOYSA-N&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>SbH&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>124.8&lt;sup&gt;a&lt;/sup&gt; (97.6&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>2.26&lt;sup&gt;a,d&lt;/sup&gt;</td>
<td>[4.1 × 10&lt;sup&gt;-1&lt;/sup&gt;]&lt;sup&gt;a,c&lt;/sup&gt; Slightly soluble</td>
</tr>
<tr>
<td><strong>Valence = +3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimony acetate; acetic acid antimony (+3) salt</td>
<td>6923-52-0&lt;sup&gt;a&lt;/sup&gt; (JVLRYPRBKSMEBF-UHFFFAOYSA-K&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;O&lt;sub&gt;6&lt;/sub&gt;Sb&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>298.9&lt;sup&gt;a&lt;/sup&gt; (40.7&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Antimony hydroxide</td>
<td>39349-74-1&lt;sup&gt;1&lt;/sup&gt; (SZOADBKOANDULT-UHFFFAOYSA-K&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;Sb&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>172.8&lt;sup&gt;a&lt;/sup&gt; (70.5&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Name</td>
<td>CAS No. (InChI Key)</td>
<td>Formula</td>
<td>Molecular weight (% Sb by weight)</td>
<td>Density or specific gravity</td>
<td>Solubility in water (g/100 mL), descriptive level</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>----------------------</td>
<td>----------------------------------</td>
<td>-----------------------------</td>
<td>--------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Antimony potassium tartrate</td>
<td>28300-74-5 (WBTCZEPSIFSIFAN-MSFWTACDSA-J)</td>
<td>C₈H₄K₂O₁₂Sb₂</td>
<td>667.8 [36.5]</td>
<td>2.6</td>
<td>[8.3 x 10⁰] S₃, h</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Soluble</td>
<td></td>
</tr>
<tr>
<td>Antimony tartrate</td>
<td>12544-35-3 (JFVMOLRNQCNLCHI-WZZCOQPSA-J)</td>
<td>C₈H₄O₁₂Sb₂</td>
<td>535.6 [45.5]</td>
<td></td>
<td>[2.8 x 10³] j</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very soluble</td>
<td></td>
</tr>
<tr>
<td>Antimony trichloride</td>
<td>10025-91-9 (FAPDDOBMIUGHIN-UHFFFAOYSA-K)</td>
<td>SbCl₃</td>
<td>228.1 [53.4]</td>
<td>3.14 [k]</td>
<td>10 x 10⁰ S₄, l</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Soluble</td>
<td></td>
</tr>
<tr>
<td>Sodium antimony(III) gluconate (antimony(III) sodium gluconate)</td>
<td>12550-17-3 (JEKOQEIHGHQVEI-ZBHRUSISSA-M)</td>
<td>C₆H₈NaO₇Sb</td>
<td>336.9 [36.2]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Name</th>
<th>CAS No. (InChI Key)</th>
<th>Formula</th>
<th>Chemical structure</th>
<th>Molecular weight (% Sb by weight)</th>
<th>Density or specific gravity</th>
<th>Solubility in water (g/100 mL), descriptive level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium antimony 2,3-mesodimercaptosuccinate (active ingredient in Astiban)</td>
<td>1986-66-9(^a) (AOGOCZMBIYQOF E-UHFFFAOYSAYA-B(^b))</td>
<td>C(_{12})H(_6)Na(<em>6)O(</em>{15})Sb(_2)(^a)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>916.0(^a)</td>
<td>(26.6(^a))</td>
<td>-</td>
</tr>
<tr>
<td>Sodium stibogluconate (active ingredient in Pentostam)</td>
<td>16037-91-5(^f) (CUEDNFKBFQCOVF -UZVLBLASSA-L(^f))</td>
<td>C(<em>{12})H(</em>{20})O(_{17})Sb(_2) 3Na(^+) 9H(_2)O(^f)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>908.9(^f)</td>
<td>(26.8(^f))</td>
<td>-</td>
</tr>
<tr>
<td>Stibophen(^m)</td>
<td>15489-16-4(^f) (ZDDUXABBATYFS-UHFFFAOYSA-F(^f))</td>
<td>C(<em>{12})H(</em>{12})Sb(_7)H(_2)O(_5)Na(^+)(^f)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>895.2(^f)</td>
<td>(13.6(^f))</td>
<td>-</td>
</tr>
<tr>
<td>Trimethylstibine</td>
<td>594-10-5(^a) (PORFVJURJKREIL-UHFFFAOYSA-N(^a))</td>
<td>C(_{3})H(_9)Sb(^a)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>166.9(^a)</td>
<td>(73.0(^a))</td>
<td>-</td>
</tr>
<tr>
<td>Triphenylstibine</td>
<td>603-36-1(^a) (HVYVMSPUJWUNA-UHFFFAOYSA-N(^a))</td>
<td>C(<em>{18})H(</em>{15})Sb(^a)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>353.1(^a)</td>
<td>(34.5(^a))</td>
<td><img src="image" alt="Insoluble" /></td>
</tr>
</tbody>
</table>

*Valence = +5*
<table>
<thead>
<tr>
<th>Name</th>
<th>CAS No. (InChI Key)</th>
<th>Formula</th>
<th>Chemical structure</th>
<th>Molecular weight (% Sb by weight)</th>
<th>Density or specific gravity</th>
<th>Solubility in water (g/100 mL), descriptive level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimony pentachloride</td>
<td>7647-18-9&lt;sup&gt;a&lt;/sup&gt; (VMPVEPPPRYRXYN P-UHFFFAOYSA-1&lt;sup&gt;f&lt;/sup&gt;)</td>
<td>SbCl&lt;sub&gt;5&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="https://example.com/structure.png" alt="Chemical structure" /></td>
<td>299.0&lt;sup&gt;a&lt;/sup&gt; (40.7&lt;sup&gt;f&lt;/sup&gt;)</td>
<td>2.35&lt;sup&gt;a,k&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>Antimony pentasulfide</td>
<td>1315-04-4&lt;sup&gt;a&lt;/sup&gt; (PPKVKREKQVREQ D-UHFFFAOYSA-N&lt;sup&gt;f&lt;/sup&gt;)</td>
<td>S&lt;sub&gt;2&lt;/sub&gt;Sb&lt;sub&gt;2&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="https://example.com/structure.png" alt="Chemical structure" /></td>
<td>403.8&lt;sup&gt;a&lt;/sup&gt; (60.3&lt;sup&gt;f&lt;/sup&gt;)</td>
<td>-</td>
<td>[9.9 × 10&lt;sup&gt;-6&lt;/sup&gt;]&lt;sup&gt;p&lt;/sup&gt; Insoluble</td>
</tr>
<tr>
<td>Antimony pentoxide</td>
<td>1314-60-9&lt;sup&gt;f&lt;/sup&gt; (LJCOYOSGPHIOO UHFFFAOYSA-N&lt;sup&gt;f&lt;/sup&gt;)</td>
<td>Sb&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;5&lt;/sub&gt;&lt;sup&gt;f&lt;/sup&gt;</td>
<td><img src="https://example.com/structure.png" alt="Chemical structure" /></td>
<td>323.5&lt;sup&gt;f&lt;/sup&gt; (75.3&lt;sup&gt;f&lt;/sup&gt;)</td>
<td>-</td>
<td>[4.3 × 10&lt;sup&gt;-6&lt;/sup&gt;]&lt;sup&gt;p&lt;/sup&gt; Insoluble</td>
</tr>
<tr>
<td>Meglumine antimoniate</td>
<td>133-51-7&lt;sup&gt;a&lt;/sup&gt; (XOGYVDXYPAAQ -SESJOKTNSA-M&lt;sup&gt;f&lt;/sup&gt;)</td>
<td>C&lt;sub&gt;7&lt;/sub&gt;H&lt;sub&gt;18&lt;/sub&gt;NO&lt;sub&gt;8&lt;/sub&gt;Sb&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="https://example.com/structure.png" alt="Chemical structure" /></td>
<td>366.0&lt;sup&gt;a&lt;/sup&gt; (33.3&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Potassium hexahydroxy antimonate</td>
<td>12208-13-8&lt;sup&gt;i&lt;/sup&gt; (IAYJQRROUBIPRX-UHFFFAOYSA-H&lt;sup&gt;f&lt;/sup&gt;)</td>
<td>H&lt;sub&gt;6&lt;/sub&gt;KO&lt;sub&gt;6&lt;/sub&gt;Sb&lt;sup&gt;i&lt;/sup&gt;</td>
<td><img src="https://example.com/structure.png" alt="Chemical structure" /></td>
<td>262.9&lt;sup&gt;i&lt;/sup&gt; (46.3&lt;sup&gt;i&lt;/sup&gt;)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

---

<sup>a</sup> = No data found, CAS = Chemical Abstracts Service, InChI = IUPAC International Chemical Identifier.

<sup>b</sup> = PubChem 2017.

<sup>c</sup> = Descriptive levels are converted from solubility in water based on [www.SolubilityofThings.com/levels-of-solubility](http://www.SolubilityofThings.com/levels-of-solubility).

<sup>d</sup> = At -25°C.

<sup>e</sup> = Reported as 4.1 g/L at 0°C in water. Brackets denote unit conversion.

<sup>f</sup> = ChemIDplus 2017.

<sup>g</sup> = Formula and structure shown are for anhydrous form of antimony potassium tartrate.

<sup>h</sup> = Reported as 83,000 mg/L at 20°C. Brackets denote unit conversion.

<sup>i</sup> = Antimony tartrate ion. Felicetti et al. (1974) reported starting solution as <sup>124</sup>Sb-tartrate complex.


<sup>k</sup> = At 68°F.

<sup>l</sup> = At 25°C.

<sup>m</sup> = The anhydrous form of Stibophen is C<sub>12</sub>H<sub>4</sub>Na<sub>5</sub>O<sub>16</sub>S<sub>4</sub>Sb (CAS number = 23940-36-5, molecular weight = 769.1 g/mol).
Reported as 0.043 mg/L at 25°C. Brackets denote unit conversion. Accessed 11/29/2017.


1.2 Antimony speciation and variability of valence

The form of antimony (i.e., its speciation) affects its toxicity, mobility, and transformation in the environment, and antimony speciation depends on pH and redox potential (Herath et al. 2017). Similar to many other metallic elements, antimony toxicity is thought to be exerted through its ions (EU 2008), and ions of antimony are capable of performing redox reactions in biological systems (Beyersmann and Hartwig 2008). In general, antimony(III) species have been reported to be more toxic than antimony(V) species (Filella et al. 2002b, Herath et al. 2017); however, the European Union (2008) noted that there is no evidence to support a firm conclusion on toxicity differences for the two valences, and NTP was also unable to identify data showing a clear difference in toxicity based on valence.

Elemental antimony exists in four primary oxidation states; -3, 0, +3, and +5; Sb(III) (trivalent form) and Sb(V) (pentavalent form) are the most common in environmental, biological, and geochemical systems. Thermodynamic equilibrium calculations indicate that antimony(V) predominates in oxic systems, and antimony(III) predominates in anoxic systems. However, antimony(III) concentrations at higher than calculation-predicted values have been detected in oxic systems; similarly, higher than calculation-predicted antimony(V) concentrations have been detected in anoxic systems (Filella et al. 2002b). Both trivalent (III) and pentavalent (V) antimony ions hydrolyze readily. When any form of antimony dissolves in water, it exists as the hydroxide forms, Sb(OH)$_3$ (uncharged) or Sb(OH)$_6^{−}$ (charged) (Herath et al. 2017).

Antimony(III) is present as the neutral species Sb(OH)$_3$ (or H$_3$SbO$_3$) for pH values from 2 to approximately 10 (Krupka and Serne 2002) and antimony(V) is present as the anion Sb(OH)$_6^{−}$ (or H$_2$SbO$_4^{−}$) for pH values from 2.7 to 10.4 (EU 2008, Herath et al. 2017). As shown in Figure 1-2, these forms are the major ones at physiologic pH around 7.4. Figure 1-2 also illustrates antimony speciation for antimony(III) and antimony(V) species over a pH range of 0 to 12.

The evidence for formation of these hydroxide forms in cellular or extracellular fluids is limited; however, the presence of Sb(III) in oxic water at higher than predicted levels has been proposed to be related to the presence of organic matter, particularly organic acids that also occur in plasma, such as citric acid, pyruvic acid, and fumaric acid (Filella et al. 2002a,b).

![Figure 1-2. Antimony speciation for antimony(III) and antimony(V) species over a range of pH values](source: Herath et al. 2017. Sb(OH)$_2^{+}$ = dihydroxoantimony (III); Sb(OH)$_3$/H$_2$SbO$_3$ = trihydroxy antimony (III)/Antimonious acid (III); H$_2$SbO$_4^{−}$ = dissociated form of SbO$_4^{2−}$ (III); Sb(OH)$_6^{−}$ = tetrahydroxoantimony (III), dissociated form of SbO$_4^{2−}$; SbO$_2^{2+}$ = cation (V); H$_2$SbO$_4$ = antimonic acid (V); H$_2$SbO$_4^{−}$ = dihydrogen antimonate (V); Sb(OH)$_6^{−}$ = antimonate ion (V), hexahydroxoantimonate.)
Inorganic forms generally are found more often than organic forms in many environmental systems (EU 2008, Herath et al. 2017). However, antimony can form organic compounds via biological methylation (i.e., the chemical combination of methyl groups with metals or metalloids through the action of a living organism such as bacteria, fungi, or plants) (Filella et al. 2007). Evidence for in vivo methylation of antimony in mammals is limited (see Section 3).

1.3 Detection of antimony and antimonial species

Measurements in both environmental and biological samples (Table 1-4) can include total antimony, the oxidation state of antimony, and methylated species (Belzile et al. 2011).

Table 1-4. Methods for detection of antimony and antimonial species in environmental and biological samples

<table>
<thead>
<tr>
<th>Method</th>
<th>Antimony (Sb) forms measured: environmental</th>
<th>Antimony forms measured: biological</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomic absorption spectrometry (AAS) with either flame or graphite furnace</td>
<td>Total Sb</td>
<td>–</td>
<td>ATSDR 2017</td>
</tr>
<tr>
<td>Inductively coupled plasma-atomic emission spectroscopy (ICP-AES)</td>
<td>Total Sb</td>
<td>Total Sb in blood, tissue, hair, and others</td>
<td>ATSDR 2017</td>
</tr>
<tr>
<td>Hydride generation-atomic absorption spectrometry (HG-AAS)</td>
<td>Sb(III) and Sb(V) species in river water</td>
<td>–</td>
<td>Zheng et al. 2006, ATSDR 2017</td>
</tr>
<tr>
<td>Liquid chromatography-hydride generation-atomic fluorescence spectrometry (LC-HG-AFS)</td>
<td>Sb(III) and Sb(V) in tap water and river water</td>
<td>–</td>
<td>Vinas et al. 2006, ATSDR 2017</td>
</tr>
<tr>
<td>Ion chromatography with inductively coupled plasma atomic emission spectrometry (IC-ICP-AES) and mass spectrometry (ICP-MS)</td>
<td>Sb(III) and Sb(V) and in surface water samples and soil extracts</td>
<td>Total Sb in urine, serum, blood, liver, and lung tissue; Sb(III) and Sb(V) in plant tissues (with HPLC separation)</td>
<td>Ulrich 1998, Müller et al. 2009</td>
</tr>
<tr>
<td>High performance liquid chromatography-hydride generation-atomic fluorescence spectrometry (HPLC-HG-AFS)</td>
<td>Sb(III), Sb(V) and total antimony in road dust and airborne particulate matter</td>
<td>Sb(III) and Sb(V) in human urine, marine algae and mollusks</td>
<td>Quiroz et al. 2011, ATSDR 2017</td>
</tr>
<tr>
<td>High-performance liquid chromatography-ultraviolet-hydride generation-atomic fluorescence spectrometry (HPLC-UV-HG-AFS)</td>
<td>–</td>
<td>Sb(III) and Sb(V) in marine algae and mollusks</td>
<td>De Gregori et al. 2007, ATSDR 2017</td>
</tr>
</tbody>
</table>

1.4 Summary

Elemental antimony is a metalloid that exists in four primary oxidation states: −3, 0, +3, and +5. The most common forms in environmental, biological, and geochemical systems are Sb(III) (the trivalent form) and Sb(V) (the pentavalent form). Antimony speciation can affect its toxicity, mobility, and transformation in the environment. Detection of antimony species depends on chromatographic separation of Sb(III) from Sb(V) followed by determination of elemental antimony by methods such as atomic absorption spectrometry after destruction of the chemical compound at high temperatures or conversion to the hydride.
Antimony(III) trioxide is the oxide of trivalent (+3) antimony that exists as an odorless white powder or polymorphic crystals (HSDB 2013). It is only slightly soluble in water, but it is bioaccessible in artificial body fluids, especially lysosomal fluid of lung cells where more than 80% dissolves in 24 hours. In solution, antimony(III) trioxide exists primarily as the uncharged hydroxide form, Sb(OH)_3.
2 Human Exposure

In the United States, antimony(III) trioxide (Sb\text{III}_2O_3) is the most commercially significant form of processed antimony. In nature, Sb\text{III}_2O_3 exists in minerals such as valentinite and senarmontite (Roper et al. 2012, ATSDR 2017). Antimony is found in nature in these and other mineral species, often in association with arsenic compounds due to their similar geochemical properties.

Exposure to this compound is the focus of the RoC monograph. However, evaluating exposure data specific to antimony(III) trioxide is complicated by the fact that antimony species can be interconverted in the environment and in vivo; thus, people can be exposed to antimony(III) trioxide from sources releasing other forms of antimony and to other forms of antimony from sources releasing antimony(III) trioxide. In addition, environmental and biomonitoring studies generally use methods that measure total elemental antimony (Sb) and not specific species of antimony. (Data on exposure for specific antimony compounds are consequently limited.) This section discusses exposure specifically to antimony(III) trioxide and also briefly reviews exposure to other forms of inorganic antimony that might lead to exposure to antimony(III) trioxide.

Exposure to antimony(III) trioxide primarily results from its production, industrial and consumer uses (Section 2.1), recycling, and release into the environment. In industrial processes, antimony(III) trioxide often changes its chemical form during production processes of formulation and processing, which will be discussed in more detail for manufacturing process (Section 2.2.). Primary and secondary exposure from those uses is discussed in Sections 2.3 (occupational exposure), 2.4.1 (consumer products), and 2.4.2 (environmental exposure).

2.1 Uses, manufacturing processes, and production-related information

2.1.1 Uses

Antimony(III) trioxide

The major industrial use of antimony(III) trioxide (EPA 2014, NTP 2016c) is as a synergist for halogenated flame retardants in plastics, rubber, and textiles, all of which are used in a wide variety of consumer products. Other uses include as a catalyst for polyethylene terephthalate (PET) production, an additive in art and specialized glasses, and an additive in pigments, paints and ceramics (See Figure 2-1 for downstream products associated with each of these four uses).

Flame retardant synergist: The bromine- or chlorine-containing flame retardants work by quenching free radicals in the gas phase of combustion. Hydrogen halides (HCl and HBr) released from the halogenated flame retardants react with antimony(III) trioxide to form antimony halides, which are more effective as flame retardants than the hydrogen-containing molecules. The final concentration of antimony(III) trioxide as a flame-retardant synergist is 4% to 6% of the treated textile, but back-coating for textiles may contain up to 24% (EU 2008).

PET production: The use of antimony(III) trioxide (EU 2008, EPA 2014) as a catalyst for PET plastics results in final concentrations of 180 to 550 ppm antimony in the plastic. While the major current use for PET plastic is in bottles for water and other beverages, often intended for
single use and then disposal, the major use for recycled PET is as PET fibers for fleece fabrics for clothing, in soft toys, rugs, carpets, and upholstery, including in automobiles. Antimony is not generally removed from the PET to recycle antimony (Grund et al. 2006).

**Specialty glass:** Antimony(III) trioxide is also used in art and other specialty glasses as a fining agent to remove gaseous inclusions that could leave bubbles in the glass product. Approximately 0.8% antimony is found in finished glass.

**Paints and pigments:** Antimony is also used in paints and pigments as a white pigment and an opacifier. The resulting pigments are used in a broad range of industries and consumer products such as plastics, coatings, enamels, ceramics, and building materials.

An additional minor use of antimony(III) trioxide is in cement to reduce chromium(VI) to chromium(III). However, only those individuals working with cement as a powder would likely be exposed to antimony(III) trioxide because of the intended chemical reaction, which will change its chemical form (without changing antimony’s trivalent oxidation status) from \( \text{Sb}^{\text{III}}_2\text{O}_3 \) to the \( \text{Sb}^{\text{III}}\text{O}_3^{3-} \) ion (antimonite) in the finished concrete (Mapei Group 2017).

Future uses of antimony(III) trioxide are predicted to grow globally for use as a synergist with flame retardants (2% per year) and in PET production (8% per year) (EU 2008). No prediction for the uses in the U.S. market was found. Antimony(III) trioxide was introduced as a fining agent in glass manufacture to replace the more toxic arsenic, but the form of antimony used is shifting to sodium antimoniate(V) so that use of antimony(III) trioxide will likely decrease in the future.

### 2.1.2 Other notable uses for major antimony forms

Major uses of elemental antimony, i.e., the metal, are to make metal alloys, such as lead-based alloys used in lead-acid batteries, lead pipe, cable sheathing, and ammunition; other alloys are used in electrical equipment, and plumbing. Antimony compounds (e.g., antimony pentoxide and sodium antimonite) are used as synergists for flame retardant additives in plastics (EU 2008, ATSDR 2017). Other antimony compounds (e.g., lead stibnite and antimony sulfides) are also used as primers for ammunition, and in production of fireworks, pesticides, synthetic rubber, and automobile brake pads and linings. Antimony diamyldithiocarbamate is used in lubricating compositions, such as grease, to provide extreme pressure protection (Hiza et al. 2006).

Medical uses of antimony compounds include as emetics (e.g., potassium antimonyl(III) tartrate or tartar emetic) (NTP 2016c) and to treat leishmaniasis (pentavalent antimonials, such as sodium stibogluconate(V)). However, the use of these drugs in the United States has declined. Pentavalent antimonials are no longer licensed for U.S. commercial use to treat leishmaniasis (CDC 2016a), but sodium stibogluconate(V) can be made available to U.S.-licensed physicians through the Centers for Disease Control and Prevention (CDC) Drug Service under an Investigational New Drug protocol approved by the U.S. Food and Drug Administration (FDA) and by CDC’s Institutional Review Board. In many other countries, the pentavalent antimonials administered by intravenous (i.v.) injection are still widely used.
2.2 Manufacturing processes

Antimony(III) trioxide for manufacturing processes may either be imported in that form (second box by the number 1 in Figure 2-1) or produced in the United States by oxidation of imported antimony metal (box 2 in Figure 2-1). The lifecycle for antimony and antimony(III) trioxide often ends at disposal as waste during either production processes or in the final consumer product.

Antimony(III) trioxide is produced primarily by re-volatilization of crude antimony(III) trioxide or by oxidation of antimony metal (EU 2008). The only domestic producer of primary antimony metal and oxide identified is a company in Montana that uses imported feedstock (USGS 2017), as no marketable antimony has been mined in the United States since 2015 (USGS 2017). The most recent U.S. mine production was in Nevada in 2013 and 2014, when about 800 tons of stibnite (Sb\text{III}_2S_3), the principal antimony ore, was extracted. That mine has been on care-and-maintenance status (i.e., production has ceased but management for public health and safety continues) since 2015 (USGS 2017).

Antimony trioxide changes its chemical form during the formulation and processing stages for many products. For example, antimony(III) trioxide may be chemically transformed to antimony(V) pentoxide by oxidation during the production process, and the resulting antimony(V) form may either be chemically bonded in a crystal matrix in pigments or present as antimony(V) pentoxide in glass. Antimony(III) trioxide used as a catalyst for polyethylene terephthalate (PET) production in Japan and China has been shown to be present in the finished plastic as antimony glycolate (Takahashi et al. 2008). An exception to transformation during production is the use of antimony(III) trioxide as a synergist for flame retardants, in which Sb\text{III}_2O_3 retains the trioxide form in finished consumer products. However, transformation of antimony(III) trioxide does occur if the product is burned. The changes in chemical form for antimony are illustrated in Figure 2-1 by the grey shading in the boxes, which indicates the likelihood that antimony(III) trioxide is present at that stage of the process as described in the figure legend.

2.2.1 Production, consumption, and trade of antimony and antimony(III) trioxide in the United States

Antimony(III) trioxide, elemental antimony, and several other antimony compounds (e.g., antimony(V) pentoxide, and antimony diamyldithiocarbamate) are high-production-volume chemicals, based on their production in, or import into, the United States in quantities of 1 million pounds or more per year (see Table 2-1 for U.S. antimony(III) trioxide and antimony compound production volumes for 2015 and Table 2-2 for import and export information. Elemental (i.e., metallic) antimony may be converted to antimony(III) trioxide by oxidation, and various forms of antimony, such as antimony(III) trisulfide in brake lubricants oxidize to antimony(III) trioxide at the high temperature achieved during the use of vehicle brakes. Other forms do not generally give rise to the trioxide form except through incineration. The EU (2008) risk assessment report noted that combustion or incineration processes produce antimony(III) trioxide from all forms of pre-incinerated antimony.
Antimony(III) trioxide accounts for 80% of total antimony use in the United States (EPA 2014, NTP 2016c). Reports under the U.S. Environmental Protection Agency’s (EPA’s) Chemical Data Reporting rule indicate that approximately 1 million to 10 million pounds of antimony(III) trioxide is produced in the United States (see Table 2-1); however, the actual consumption of antimony(III) trioxide is likely much higher. EPA (2014) reported that most (approximately 87%) of the roughly 70 million pounds of antimony(III) trioxide consumed in the United States each year between 2007 and 2011 was imported (EPA 2014). The majority of total antimony (83%) used in the United States is also imported, mostly from China, and the remainder (17%) is recovered from antimony-lead batteries (USGS 2017). In 2012, the U.S. EPA identified three companies manufacturing and ten companies importing antimony(III) trioxide (EPA 2012).
Table 2-1. U.S. antimony(III) trioxide and antimony compound production volumes for 2015 exceeding 1,000,000 pounds per year ranked by quantity

<table>
<thead>
<tr>
<th>CAS Number</th>
<th>Antimony compound</th>
<th>Quantity (lb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>68937-20-2</td>
<td>1,2-Ethanediol, reaction products with antimony(III) trioxide</td>
<td>28,926,800</td>
</tr>
<tr>
<td>7440-36-0</td>
<td>Antimony (elemental)</td>
<td>10,000,000–50,000,000</td>
</tr>
<tr>
<td>1309-64-4</td>
<td>Antimony(III) trioxide</td>
<td>1,000,000–10,000,000</td>
</tr>
<tr>
<td>1314-60-9</td>
<td>Antimony(V) pentoxide</td>
<td>1,000,000–10,000,000</td>
</tr>
<tr>
<td>15890-25-2</td>
<td>Antimony diamyldithiocarbamate</td>
<td>1,000,000–10,000,000</td>
</tr>
</tbody>
</table>

aEPA 2017a. bAntimony diamyldithiocarbamate is a form of antimony dialkyldithiocarbamate with 5-carbon alkyl chains.

Table 2-2. U.S. imports and exports of antimony metal and compounds for 2016

<table>
<thead>
<tr>
<th>Antimony compound/category</th>
<th>Imports (lb)</th>
<th>Exports (lb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimony and articles thereof, not elsewhere specified or included</td>
<td>1,940,267</td>
<td>612,439</td>
</tr>
<tr>
<td>Antimony ores and concentrates</td>
<td>383,137</td>
<td>25,428</td>
</tr>
<tr>
<td>Antimony oxides</td>
<td>42,921,232</td>
<td>3,524,784</td>
</tr>
<tr>
<td>Antimony waste and scrap</td>
<td>91,085</td>
<td>389,788</td>
</tr>
<tr>
<td>Unwrought antimony (powders)</td>
<td>13,581,996</td>
<td>393,526</td>
</tr>
</tbody>
</table>

Source: USITC 2017. aQuantities converted from kilograms by NTP. bUSITC harmonized tariff schedule (HTS) code 28258000 does not distinguish between antimony(III) trioxide and antimony(V) pentoxide.

2.3 Occupational exposure

The highest exposures to antimony(III) trioxide and total antimony occur in the workplace. Historic data for the number of workers exposed to antimony were reported for the National Occupational Exposure Survey (NOES) conducted by the National Institute for Occupational Safety and Health (NIOSH) from 1981 to 1983, during which an estimated 209,773 male and female workers were potentially exposed to antimony(III) trioxide (CDC 2017b). Although these data are over 30 years old, cancer has a long latency and thus this exposure information is still relevant. In 2010, 273 U.S. facilities likely produced or used antimony(III) trioxide (in flame retardants), based on information from EPA’s Toxics Release Inventory Program (EPA 2014). Fire fighters may be exposed to antimony in smoke particulates released from combustion of retardant-treated textiles during fires (Fabian et al. 2010).

U.S. monitoring data from the Occupational Safety and Health Administration (OSHA) Chemical Exposure Health Dataset during a period of more than 30 years (1984 to 2017) reported data from 2,126 personal breathing zone samples collected from companies producing or using “antimony and compounds (as Sb)” (forms of antimony not specified) (OSHA 2017). The antimony air levels (breathing zone), as total antimony, ranged from 0.2 µg/m³ to 54,500 µg/m³ across all facilities. Facilities with the highest antimony air concentrations were in the following industries: standard industrial classification (SIC) Code 2899, chemicals and chemical preparations, not elsewhere classified (e.g., antimony-containing flame retardants) (3.3 µg/m³ to
54,500 µg/m³); SIC Code 3341, secondary smelting and refining of nonferrous metals (e.g., antimonial lead refining) (1.8 µg/m³ to 47,700 µg/m³), and SIC Code 3339, primary smelting and refining of nonferrous metals (including antimony) (5 µg/m³ to 18,500 µg/m³). All of these industries are likely to involve exposure to antimony(III) trioxide as either a primary product or through oxidation of elemental antimony during smelting and refining processes.

Workers in the United States producing or using antimony(III) trioxide, as well as workers in occupations exposed to other antimony compounds, can be exposed to antimony(III) trioxide through inhalation of airborne solid dust or by skin contact. Among industries using or producing antimony(III) trioxide, the highest levels (up to 5,000 to 6,000 µg/m³, levels 10 times higher than the threshold limit value [TLV]), are found among smelters or antimony manufacturing industries (see Table 2-3). The European Union (EU) (2008) risk assessment report (RAR) for antimony trioxide (Sb\textsubscript{III}O\textsubscript{3}) considered metal smelting and refining to be one of the major anthropogenic sources of antimony release to the atmosphere. U.S. air monitoring data specific for antimony(III) trioxide industries come primarily from NIOSH walk-through surveys of a few smelters or antimony(III) trioxide companies conducted largely in the 1970s, which usually were conducted as part of health hazard evaluations (CDC 2016b) or industrial hygiene surveys, the results for two of which were also reported in an epidemiological study (Schnorr et al. 1995) (see Table 2-3). Workers using or producing other types of antimony, such as elemental antimony used in the battery industry, can also be exposed to antimony(III) trioxide because metallic antimony oxidizes to antimony(III) trioxide in the air (EU 2008).

Urinary excretion of antimony by exposed workers generally increases with the level of exposure, although relatively few studies have reported both exposure and urinary excretion for the same workers. A few studies that reported both parameters are summarized in Table 2-3 together with studies that reported air levels only. The current TLV for elemental antimony and antimony compounds in air is 500 µg/m³ (ACGIH 2017) and levels above as well as below this value have been reported. Bailly et al. (1991) measured urine and air concentrations of total antimony for workers manufacturing pentavalent antimony compounds (antimony(V) pentoxide and sodium antimoniate(V)) and reported a significant correlation ($r = 0.83$, $P < 0.0001$) between airborne antimony concentrations (log value) and both post-shift urinary antimony concentrations (log value) and an increase in urinary antimony concentrations during the work shift ($r = 0.86$, $P < 0.0001$). Air concentrations and pre-shift and post-shift urinary antimony levels are also reported in Table 2-3.

### Table 2-3. Air levels and urine levels of total antimony in U.S. workers occupationally exposed to various antimony compounds in the air

<table>
<thead>
<tr>
<th>Exposure scenario (N)</th>
<th>Form of Sb used</th>
<th>Air Sb levels (as total Sb) (µg/m³)</th>
<th>Urine Sb levels (as total Sb), µg/g creatinine unless specified</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Industries that produce or use producing antimony(III) trioxide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimony(III) trioxide production</td>
<td>Sb\textsubscript{III}O\textsubscript{3}</td>
<td></td>
<td></td>
<td>Donaldson and Gentry 1975\textsuperscript{a}</td>
</tr>
<tr>
<td>Personal samples (2)</td>
<td></td>
<td></td>
<td>2,700–5,000</td>
<td>NR</td>
</tr>
<tr>
<td>General area samples (2)</td>
<td></td>
<td></td>
<td>1,800–5,600</td>
<td>NR</td>
</tr>
<tr>
<td>Exposure scenario (N)</td>
<td>Form of Sb used</td>
<td>Air Sb levels (as total Sb) (µg/m³)</td>
<td>Urine Sb levels (as total Sb), µg/g creatinine unless specified</td>
<td>Reference</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------</td>
<td>-------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Antimony &amp; antimony(III) trioxide production (smelting and refining)</td>
<td>Sb³⁺S₃ &amp; Sb³⁺2O₃</td>
<td>50–6,210 140–2,120</td>
<td>NR</td>
<td>Donaldson 1976⁴</td>
</tr>
<tr>
<td>Breathing zone (55)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area samples (NR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimony oxide production (5)</td>
<td>Sb³⁺S₃ &amp; Sb³⁺2O₃</td>
<td>210–3,200</td>
<td>NR</td>
<td>Cassady and Etchison 1976</td>
</tr>
<tr>
<td>Antimony(III) trioxide production (12)</td>
<td>Sb³⁺2O₃</td>
<td>766</td>
<td>419.8 µg/L</td>
<td>Kim et al. 1999</td>
</tr>
<tr>
<td>Flame retardant industry (NR)</td>
<td></td>
<td></td>
<td></td>
<td>ATSDR 1992</td>
</tr>
<tr>
<td>Glass production facility (NR)</td>
<td></td>
<td></td>
<td></td>
<td>Burroughs and Horan 1981</td>
</tr>
<tr>
<td>Glass industry- batch bunker</td>
<td>Sb³⁺2O₃</td>
<td></td>
<td></td>
<td>Lüdersdorf et al. 1987</td>
</tr>
<tr>
<td>Personal air (3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stationary air (4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batch Mixer (45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubber company Compounding area</td>
<td>Antimony oxide</td>
<td>10–150</td>
<td>NR</td>
<td>Salisbury 1980</td>
</tr>
</tbody>
</table>

**Other exposures**

<table>
<thead>
<tr>
<th>Exposure scenario (N)</th>
<th>Form of Sb used</th>
<th>Air Sb levels (as total Sb) (µg/m³)</th>
<th>Urine Sb levels (as total Sb), µg/g creatinine unless specified</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead battery production</td>
<td>Sb³⁺2O₃ Sb³⁺H₃</td>
<td>4.5–12.4</td>
<td>3.9–15.2</td>
<td>Kentner et al. 1995</td>
</tr>
<tr>
<td>Lead-acid battery plant (NR)</td>
<td>Sb³⁺H₃</td>
<td>ND–2,500</td>
<td>NR</td>
<td>Jones and Gamble 1984, Young 1979a, b</td>
</tr>
<tr>
<td>Secondary lead smelter (reclaiming scrap batteries) Breathing zone (2 of 21 TWAs)</td>
<td></td>
<td></td>
<td></td>
<td>Craig et al. 1981</td>
</tr>
<tr>
<td>Manufacture of pentavalent antimony compounds Wet process (26)</td>
<td>Sb⁵⁺₂O₅ Na₃Sb⁵⁺O₄</td>
<td>86 ± 3.9 927 ± 985</td>
<td>812.3 ± 5.0 110 ± 76</td>
<td>Bailly et al. 1991</td>
</tr>
<tr>
<td>Dry process (14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refinery workers</td>
<td></td>
<td></td>
<td></td>
<td>Smith et al. 1995</td>
</tr>
<tr>
<td>Chemical manufacturers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Battery manufacturers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resinoid grinding wheel manufacture (NR)</td>
<td>Sb³⁺S₃</td>
<td>~3,000</td>
<td>800–9,600 µg/L</td>
<td>Brieger et al. 1954</td>
</tr>
<tr>
<td>Iron foundry (NR)</td>
<td></td>
<td>0.15</td>
<td>NR</td>
<td>Zhang et al. 1985</td>
</tr>
<tr>
<td>Exposure scenario (N)</td>
<td>Form of Sb used</td>
<td>Air Sb levels (as total Sb) (µg/m³)</td>
<td>Urine Sb levels (as total Sb), µg/g creatinine unless specified</td>
<td>Reference</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------------</td>
<td>----------------</td>
<td>------------------------------------</td>
<td>-----------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Injection molding of ignition resistant polystyrene (NR)</td>
<td>NR</td>
<td>0.03–200</td>
<td>NR</td>
<td>Willets et al. 1982</td>
</tr>
</tbody>
</table>

*a* Also reported by Schnorr et al. 1995 (see Section 5).

*b* BDL = below detection limit; level of detection reported as 0.3 µg/m³, NR = not reported.

*c* ND = not detectable. No detection limit reported in ATSDR 1992.

Extensive and systematic occupational monitoring data specific to antimony(III) trioxide, or exposures converted to antimony(III) trioxide equivalents, were reported by the EU risk assessment report (EU 2008) (Table 2-4). The industrial processes used in Europe are likely similar to those used in the United States, so data from the EU can help inform potential U.S. exposure. In general, the levels reported in the EU risk assessment report fall within similar ranges to those reported for the most recent U.S. data in Table 2-3 although considerable variability exists for reported values. In addition, the EU risk assessment report data are reported as antimony(III) trioxide; however, this represents only about a 20% difference from the estimates based on total antimony due to the adjustment for the atomic weight of oxygen. Also, the data for the United States are older and, thus, in general, U.S. exposure levels for some industries were higher than the European data. Both U.S. and European data indicate the highest exposures are for antimony(III) trioxide production, followed by the flame retardant industries. Lower exposures are reported for production of crystal glass and pigment industries.

Inhalation exposure can also occur when antimony(III) trioxide powder is used in cement mixing (or cement powder-based product blending) applications (see Section 2.3) (Mapei Group 2017).
### Table 2-4. Antimony(III) trioxide occupational exposure level estimates (as antimony(III) trioxide)

<table>
<thead>
<tr>
<th>Exposure scenario</th>
<th>Exposure level(^a) (worst case(^b)), µg/m(^3)</th>
<th>Dermal, typical(^a) (worst case(^c)), mg/kg/day(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimony(III) trioxide production(^e)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conversion</td>
<td>27 (540)</td>
<td>0.23 (0.72)</td>
</tr>
<tr>
<td>Refining (refuming)</td>
<td>12 (230)</td>
<td>0.54 (0.99)</td>
</tr>
<tr>
<td>Final product handling</td>
<td>40 (790)</td>
<td>0.81 (1.4)</td>
</tr>
<tr>
<td>Flame retardants in plastics(^f)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw material handling</td>
<td>130 (570)</td>
<td>0.19 (0.34)</td>
</tr>
<tr>
<td>Flame retardants in textiles(^f)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formulation</td>
<td>130 (570)</td>
<td>0.13 (0.22)</td>
</tr>
<tr>
<td>Flame retardants in rubber production(^f)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formulation</td>
<td>51 (220)</td>
<td>0.066 (0.11)</td>
</tr>
<tr>
<td>Processing</td>
<td>64 (140)</td>
<td>0.051 (0.089)</td>
</tr>
<tr>
<td>Catalyst in PET production(^f)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powder handling(^g)</td>
<td>2 (26)</td>
<td>0.10 (0.17)</td>
</tr>
<tr>
<td>Production of crystal glass(^f)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutting</td>
<td>3 (15)</td>
<td>0.086 (0.31)</td>
</tr>
<tr>
<td>Use in paints, coatings, and ceramics(^f)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loading and mixing</td>
<td>36 (160)</td>
<td>0.066 (0.11)</td>
</tr>
</tbody>
</table>

Source: EU 2008.

\(^a\) All values are reported as antimony(III) trioxide. EU 2008 explained that results reported as total antimony were converted to an equivalent mass of antimony(III) trioxide by applying a correction factor of 1.197.

\(^b\) Job-specific typical exposure is equal to the median (50\(^{th}\) percentile) exposure level.

\(^c\) Job-specific (reasonable) worst-case exposure is equal to the 90\(^{th}\) percentile exposure level.

\(^d\) The body weight of the worker is 70 kg and the exposed dermal area is 2000 cm\(^2\).

\(^e\) Exposure levels for inhalation and dermal exposure during antimony(III) trioxide production were measured as Sb\(^{III}\)\(_2\)O\(_3\) (inhalation) or as total Sb (dermal) with conversion to equivalent concentration of Sb\(^{III}\)\(_2\)O\(_3\).

\(^f\) EU reported that analogous or surrogate data (e.g., read-across from antimony(III) trioxide production or extrapolation from related exposures) were used to estimate exposures by inhalation and dermal routes for these processes when collected data was not considered to be sufficient.

\(^g\) Exposures for processing and final product manufacturing in use of antimony(III) trioxide as a catalyst in PET production were considered negligible.

### 2.4 General population exposure

Evidence for exposure of the U.S. general population to antimony is provided by biomonitoring data showing its presence in urine, whole blood, and saliva. Data from the National Health and Nutrition Examination Survey (NHANES) indicate low exposure to antimony, with geometric means of 0.132 µg/L urine for years 1999 to 2000 and 0.043 µg/L urine for years 2013 to 2014 (Table 2-5). Although the most recent data suggest that levels might be decreasing over time, this could reflect the use of more sensitive analytical methods in recent years, rather than actual decreasing exposure, an explanation supported by reports of values close to the lower detection limits for the methods used (Filella et al. 2013a). Older publications tended to report higher
concentrations of total antimony in urine. Based on analysis of NHANES data, higher urinary antimony levels were found in individuals with lower socioeconomic status, defined as either low income or living in economically deprived neighborhoods (Belova et al. 2013, Tyrrell et al. 2013, Gonzales et al. 2016). Slightly higher urinary antimony levels were reported for smokers than non-smokers in 2013 to 2014 data. Total antimony measured in urine as the elemental form can be from various forms of antimony, not just antimony(III) trioxide (see Table 2-6).

Several studies have reported an association between biomonitoring data in the general population (e.g., urinary antimony, cord blood antimony) and adverse biological effects (Scinicariello and Buser 2016) or non-cancer endpoints, such as cardiovascular-related diseases (e.g., Shiue and Hristova 2014, Guo et al. 2016) and adverse pregnancy outcomes (Zheng et al. 2014), suggesting that chronic exposure to low levels of antimony may be a potential public health concern.

### Table 2-5. Ranges of geometric mean total antimony levels in urine, blood, and saliva samples of U.S. populations

<table>
<thead>
<tr>
<th>Sample</th>
<th>No. of individuals</th>
<th>Concentration (µg Sb/L)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine of general U.S. population in 1999–2000</td>
<td>2,276</td>
<td>0.132</td>
<td>NHANES (CDC 2017c)</td>
</tr>
<tr>
<td>Urine of general U.S. population in 2013–2014</td>
<td>2,664</td>
<td>0.043</td>
<td>NHANES (CDC 2017c)</td>
</tr>
<tr>
<td>Urine of adult (&gt; 18 years) U.S. population in 2013–2014</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smokers</td>
<td>822</td>
<td>0.042</td>
<td>Filella et al. 2013a, 2013b</td>
</tr>
<tr>
<td>Smokers</td>
<td>977</td>
<td>0.051</td>
<td>Filella et al. 2013a, 2013b</td>
</tr>
<tr>
<td>Urine</td>
<td>15</td>
<td>0.061–0.74</td>
<td>Filella et al. 2013a, 2013b</td>
</tr>
<tr>
<td>Whole blood</td>
<td>9</td>
<td>2.53–4.07</td>
<td>Filella et al. 2013a, 2013b</td>
</tr>
<tr>
<td>Saliva of healthy volunteers</td>
<td>4</td>
<td>BDL to 3</td>
<td>Olmez et al. 1998</td>
</tr>
<tr>
<td>Saliva of 3 patients with hypogeusia, 6 with hyposmia, and 3 with both hypogeusia and hyposmia</td>
<td>12</td>
<td>BDL to 9</td>
<td>Olmez et al. 1998</td>
</tr>
</tbody>
</table>

BDL = below detection limit; hypogeusia = decreased taste acuity; hyposmia = decreased smell acuity.

*a Filella et al. 2013a,b also reported a single arithmetic (rather than geometric) mean that falls outside this range- 1.3 ug/L in urine.

*b A mean ± SD of 110 ± 90 (N = 6) was reported for hyposmia, but this value was at least 10 times higher than the other data and is not included in the range above.

No U.S. data on total antimony concentrations in breast milk were found, but concentrations (arithmetic means) measured outside the United States ranged from below the detection limit to 13 ng/g [13 µg/L] (Filella et al. 2013a).

The general population is potentially exposed to antimony directly from consumer products (Section 2.4.1) or indirectly from the environment by inhaling contaminated air (Section 2.4.2) or by consuming contaminated food or drinking water (Section 2.4.3). Because antimony can
change its form in the environment, the form of antimony to which people are exposed may not be the same form initially released into the environment.

Table 2-6 and Figure 2-1 summarize exposure sources to antimony compounds from exposure to products manufactured with antimony(III) trioxide and the final forms of antimony to which people are exposed.

### Table 2-6. Sources of antimony(III) trioxide and the final forms of antimony (Sb\textsubscript{III}O\textsubscript{3} and others) to which people are exposed

<table>
<thead>
<tr>
<th>Source</th>
<th>Exposure route</th>
<th>Expected form of antimony exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimony(III) trioxide (Sb\textsubscript{III}O\textsubscript{3}) (e.g., industrial facility releases)</td>
<td>Inhalation of Sb\textsubscript{III}O\textsubscript{3}</td>
<td>Sb\textsubscript{III}O\textsubscript{3}</td>
</tr>
<tr>
<td></td>
<td>Ingestion (from consuming contaminated soil)</td>
<td>Sb ions</td>
</tr>
<tr>
<td></td>
<td>Ingestion (from drinking contaminated water)</td>
<td>Sb(V) ion in oxic environments, and Sb(III) ion in anoxic environments</td>
</tr>
<tr>
<td>Sb\textsubscript{III}O\textsubscript{3} in flame retardant</td>
<td>Inhalation (from breathing indoor air containing house dust)</td>
<td>Mainly Sb\textsubscript{III}O\textsubscript{3} from flame-retardant-treated fabric wear and tear, but also Sb(V) and Sb(III) from outside soil</td>
</tr>
<tr>
<td></td>
<td>Dermal (from sitting on flame-retardant-treated upholstery)</td>
<td>Sb ions</td>
</tr>
<tr>
<td></td>
<td>Ingestion (from mouthing flame-retardant-treated toys)</td>
<td>Sb ions</td>
</tr>
<tr>
<td>Sb\textsubscript{III}O\textsubscript{3} in PET</td>
<td>Ingestion (from drinking liquid in PET bottles)</td>
<td>Sb ions</td>
</tr>
</tbody>
</table>


#### 2.4.1 Consumer products

Consumers are potentially exposed to antimony from consumer products as a result of the use of antimony(III) trioxide as a synergist with flame retardants or in PET containers. Exposure of the general population from consumer products is generally to antimony(III) trioxide by inhalation of dust from these products although some exposure could also occur orally to antimony(III) trioxide or other forms of antimony. Exposure is likely higher for children, especially infants, because of their direct skin contact with carpet material containing antimony(III) trioxide as a flame-retardant synergist while crawling, their mouthing of other fabrics containing flame retardants or toys with antimony-containing paint or plastic, and their potential to inhale more dust containing antimony from carpets because they are closer to the floor than adults (see Table 2-7). A 1998 study (Jenkins \textit{et al.} 1998) reported that antimony could be detected in infant cot mattress covers containing polyvinyl chloride (PVC), and antimony was present in the leachate (extraction fluids) from mattress material.

Because antimony(III) trioxide can change its form during the manufacture of many products, exposure may be to other forms of antimony. For instance, if antimony is released in liquid (e.g., water, sweat, or saliva) at near-neutral pH, it will exist as hydrolyzed forms in solution (see Figure 1-1 in Section 1), Sb(III) as Sb\textsuperscript{(III)}(OH)\textsubscript{3} or H\textsubscript{3}Sb\textsuperscript{(III)}O\textsubscript{3} and Sb(V) as Sb\textsuperscript{(V)}(OH)\textsubscript{6}⁻ or
H$_2$Sb$^{(V)}$O$_4$ rather than as antimony cations (ATSDR 1992). The antimony in house dust is mainly antimony(III) trioxide (from wear and tear of flame-retardant-treated fabric) (EU 2008). Table 2-7 shows exposure levels for consumer products evaluated in the EU antimony trioxide (i.e., antimony(III) trioxide) risk assessment report, which converted all exposure levels to the equivalent mass of antimony(III) trioxide (i.e., converting measured antimony to corresponding antimony(III) trioxide based on molecular weight).

### Table 2-7. Estimated consumer exposure to antimony (as antimony(III) trioxide) directly and indirectly from products containing antimony(III) trioxide

<table>
<thead>
<tr>
<th>Exposure scenario (exposure route)</th>
<th>Form of antimony in exposure</th>
<th>Weight of exposed subject (kg)</th>
<th>Typical level (Sb$^{III}$O$_3$ µg/kg b.w./day)$^a$</th>
<th>Reasonably worst-case level (µg Sb$^{III}$O$_3$ /kg b.w./day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting on flame-retardant-treated upholstery fabric (dermal)</td>
<td>in hydro-complexed form</td>
<td>60</td>
<td>ND$^b$</td>
<td>1.8</td>
</tr>
<tr>
<td>Ingesting house dust via hand-to-mouth behavior (oral)</td>
<td>largely antimony(III) trioxide</td>
<td>10</td>
<td>0.156</td>
<td>0.600</td>
</tr>
<tr>
<td>Sucking on toys (oral)</td>
<td>ions</td>
<td>10</td>
<td>ND$^b$</td>
<td>0.25</td>
</tr>
<tr>
<td>Drinking from a PET bottle (oral)</td>
<td>ions</td>
<td>60</td>
<td>0.014</td>
<td>0.035</td>
</tr>
<tr>
<td>Inhaling house dust; corresponds to indoor air level</td>
<td>largely antimony(III) trioxide</td>
<td>–</td>
<td>15.6 µg Sb$^{III}$O$_3$/g dust; 0.00082 µg Sb$^{III}$O$_3$/m$^3$ air$^c$</td>
<td>60 µg Sb$^{III}$O$_3$/g dust; 0.0032 µg Sb$^{III}$O$_3$/m$^3$ air$^d$</td>
</tr>
</tbody>
</table>

Source: EU 2008.

$^a$All values are reported as antimony(III) trioxide. EU 2008 explained that results reported as total antimony were converted to an equivalent mass of antimony(III) trioxide by applying a factor of 1.197.

$^b$ND = not determined.

$^c$Reported as $0.82 \times 10^{-6}$ mg/m$^3$.

$^d$Reported as $3.2 \times 10^{-6}$ mg/m$^3$.

The only U.S. data on indoor air antimony levels are from an elementary school in Arizona (Majestic et al. 2012), where the particles less than 1 µm in diameter (PM$_{1}$) fraction of air samples averaged 0.017 µg antimony/m$^3$. Antimony in air was most likely resuspended from flame-retardant-treated carpet by foot traffic.

A study in the United Kingdom measured antimony in 750 consumer products (rubber, textile, and foamed materials) (Turner and Filella 2017), and detected antimony in 18% of over 800 measurements of those products at approximately 60 µg/g to 60,000 µg/g. Antimony was also detected in another study in the United Kingdom that measured antimony and other toxic metals in paints on public playground structure surfaces; levels ranged from 273 µg/g to 16,000 µg/g (Turner et al. 2016). Similar products in the United States would likely have similar levels.

### 2.4.2 Environmental exposure

Antimony enters the environment through releases from industries producing, using, or recycling antimony and from natural sources (e.g., volcanic activity or erosion). An estimate for antimony emissions to the air from natural sources in the 1980s indicated that 41% could be accounted for...
from wind-borne soil particles, volcanoes, sea salt spray, forest fires, and biogenic sources (ATSDR 2017). Anthropogenic activities such as mining, fossil fuel combustion (coal or petroleum), smelting, waste incineration, and other human activities increase antimony concentrations in the local environment, which may be carried by air or water beyond the immediate area of those activities.

Toxics Release Inventory (TRI) data indicate that production- and use-related releases of antimony and antimony compounds to the environment have occurred at numerous U.S. industrial facilities. In 2014, 542 U.S. facilities that manufactured, processed, and used antimony reported releasing 8.6 million pounds of antimony and antimony compounds into the environment (land, water, and air) (TRI 2016). An EPA Toxic Substances Control Act (TSCA) Work Plan Chemical Risk Assessment for Antimony Trioxide (EPA 2014) sorted 2010 TRI data by industry codes using the North American Industry Classification System (NAICS) codes to identify a subset of 273 U.S. facilities that likely produced, processed, or used antimony(III) trioxide-containing flame retardants. In addition, 11,635 pounds of antimony per year were released into the air from antimony(III) trioxide plants.

Air

Releases into air are the most relevant source of exposure specifically to antimony(III) trioxide. Increases above background levels result from releases by companies producing or using antimony(III) trioxide and from geogenic emissions by oxidation of antimony as noted above (EU 2008, ATSDR 2017). Individuals living near industrial facilities may be exposed to much higher levels of antimony in the air; a study in the 1970s reported that antimony air levels downstream of a copper smelter in the United States exceeded 300 ppm [300,000 µg/m^3] (HSDB 2013). U.S. antimony air particulate matter levels ranged from not detectable (the lower limit of detection was not reported) to 1.21 µg/m^3, which was reported for a site close to a lead smelter (Ragaini et al. 1977). Elevated mean air levels of 0.146 µg/m^3 were reported in areas near operating mines producing various ores in Kellogg, Idaho in 1970 (an area that includes one of six companies producing antimony in the United States in 1992) and 0.040 µg/m^3 in an industrial area in England (ATSDR 2017).

Antimony can change oxidation state in the environment and during industrial use. Aerosolized elemental antimony oxidizes to antimony(III) trioxide through reactions with atmospheric oxidants (ATSDR 1992, EU 2008, ATSDR 2017). During coal combustion, antimony forms antimony oxides, regardless of the form of antimony present in the coal (Health Canada 2010); Pavageau et al. (2004) also reported formation of antimony(V) pentoxide from coal combustion. Similarly, antimony(III) trioxide is the primary species released to the atmosphere from other high-temperature industrial processes, such as smelting, combustion of petroleum and petroleum products, and incineration of products that contain antimony (Health Canada 2010, NTP 2016c). Recycling of antimony as part of antimonal lead in automobile batteries, where antimony has historically made up to 2% of the total weight, generally involves oxidation of both metals, with production of antimony(III) trioxide (Grund et al. 2006, Dupont et al. 2016). Antimony(III) trisulfide (used as automobile brake lubricant) and antimony(III) trisulfate (used as automobile brake filler) have been reported to oxidize to antimony(III) trioxide at temperatures reached in the braking process (above 300°C) (EU 2008). Port workers in Valparaiso, Chile were exposed to elevated air concentrations of antimony from heavy vehicular traffic due to oxidation of antimony sulfide or sulfate in brake pads to antimony(III) trioxide at temperatures achieved
during braking (Quiroz et al. 2009). People thus can inhale antimony(III) trioxide transformed from other antimony compounds.

Antimony is present almost entirely in the particulate matter in air. ATSDR summarized these data from various U.S. cities for 2014, reporting daily mean concentrations as total antimony ranging from 0.00037 to 0.002 µg/m³ for total suspended particulate, 0.0013 to 0.0206 µg/m³ for particles less than 10 µm in diameter (PM₁₀), and 0.0019 to 0.022 µg/m³ for particles less than 2.5 µm in diameter (PM₂.₅) (see Table 6-4 in ATSDR 2017.) Antimony levels in areas unpolluted by anthropogenic activity are low (approximately 0.001 µg/m³) (ATSDR 2017). The EU (2008) estimated that the reasonable worst-case background concentration of antimony in outdoor air is 0.0026 µg/m³.

**Water, rain, and soil**

Antimony(III) trioxide most likely oxidizes to antimony(V) following contact with moisture and oxygen in air (EU 2008, Health Canada 2010) and exposure to antimony in aqueous media like water, rain, and snow are most likely to other forms of antimony. Thermodynamic equilibrium calculations indicate that antimony(V) predominates in oxic systems and antimony(III) in anoxic systems; however, antimony(III) has been detected at higher concentrations than predicted in oxic systems, and antimony(V) has been detected at higher concentrations than predicted in anoxic systems (Filella et al. 2002b).

According to the National Water-Quality Assessment (NAWQA) program, which surveyed groundwater between 1992 and 2003, U.S. groundwater had generally low concentrations of antimony, with a median concentration of less than 1 µg/L (ATSDR 2017). Mining activities have been shown to increase antimony levels in nearby water systems. For example, waste from antimony mining and smelting activities in the Kellogg district of northern Idaho were dumped into the South Fork River, which had a mean antimony level of 4.3 µg/L while the nearby North Fork River was considered unpolluted with a mean level of 0.9 µg/L (ATSDR 2017). Increased levels of antimony in rainwater likely depend on release of antimony from industrial sites. The mean total antimony concentration in rainwater collected downwind from a copper smelter in Tacoma, Washington was 1.3 ppb while that collected upwind during the same storms was only 0.03 ppb (ATSDR 1992).

Exposure to antimony in the soil is expected to be minimal because of low solubility and mobility of antimony (EPA 2014, Li et al. 2014). However, both trivalent and pentavalent antimony compounds are present in dust and soil carried into houses (EU 2008). Although the levels of antimony in the earth’s crust average 0.2 µg/g to 0.3 µg/g, levels in soil vary more widely when samples are taken at different locations within the United States. A survey of soils by the United States Geological Survey (USGS) found levels from less than 1 µg/g to 8.8 µg/g with an average concentration of 0.48 ppm (µg/g), (Shacklette and Boerngen 1984). Proximity to motor vehicle traffic can also result in higher levels of antimony in soil. Levels of antimony in soil 0 cm to 5 cm below the surface at three locations in Austria indicated that the location with very little vehicular traffic had much lower antimony levels (0.64 µg/g) than the other sites with more traffic (6.30 µg/g and 2.74 µg/g) (Amereih et al. 2005).
2.4.3 Food and drinking water

Levels of antimony (form not specified) in food in the United States range from not detectable (limit of detection not reported) to 1.7 µg/g of dry weight (Belzile et al. 2011). Antimony(V) is the most prevalent antimony species in drinking water, as the result of oxidative treatments (chlorination or ozonation) used in water disinfection processes. Antimony levels in U.S. drinking water range from 0.02 µg/L to 9.6 µg/L. The value of 9.6 µg/L was reported for bottled water heated in PET bottles at 80°C for 48 hours.

Exposure to antimony can result from consumption of contaminated food or drinking water (see Table 2-8). However, the EU risk assessment report (EU 2008) noted that antimony(III) trioxide in solution will produce the antimony(III) ion, which hydrolyzes to either the trivalent form as neutral Sb(III)(OH)$_3$, or the pentavalent form as charged Sb(OH)$_6$ (see Section 1.2).

Table 2-8. Antimony (as antimony(III) trioxide equivalents) typical and worst-case exposure levels from food, breast milk, and drinking water based on data measured in Europe

<table>
<thead>
<tr>
<th>Exposure category</th>
<th>Typical (µg Sb$_{III}$O$_3$/kg b.w./day)$^b$</th>
<th>Worst case (µg Sb$_{III}$O$_3$/kg b.w./day)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food</td>
<td>0.074</td>
<td>0.096</td>
</tr>
<tr>
<td>Breast milk (children 0–3 months)</td>
<td>0.023</td>
<td>0.087</td>
</tr>
<tr>
<td>Drinking water$^c$</td>
<td>ND$^d$</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Source: EU 2008.

$^a$EU (2008) reported exposures as either “typical,” based on the median value for levels or “worst case,” based on the 90th percentile for the levels. Levels were based on measured values where possible but extrapolation and estimation from similar exposures were also used.

$^b$All values are reported as antimony(III) trioxide. EU 2008 explained that results reported as total antimony were converted to an equivalent mass of antimony(III) trioxide by applying a factor of 1.197.

$^c$EU (2008) noted that antimony concentrations in water can also be influenced by the local collection area’s mineral composition and sources of antimony other than antimony(III) trioxide emissions.

$^d$ND = not determined.

2.5 Summary and synthesis

A significant number of people in the United States are exposed to antimony(III) trioxide (Sb$_{III}$O$_3$), as evidenced by occupational exposure data and supporting data on production, consumption, and releases into the environment and exposures from consumer products. In addition to exposure to antimony(III) trioxide in the workplace from its use as a synergist with flame retardant chemicals, as a catalyst in production of PET plastic, as a pigment and fining agent in glass production, and as a colorant and opacifier in pigments for paints and ceramic glazes, people are potentially exposed from using consumer products containing antimony(III) trioxide, and by breathing contaminated air, or a combination of these sources. The chemical form of antimony changes during manufacturing, in the environment, and in vivo, and detection methods typically measure total antimony rather than specific forms of antimony, so identifying exposure specifically to antimony(III) trioxide is presently difficult.

The highest occupational exposure to antimony(III) trioxide occurs in workplaces that produce or use antimony(III) trioxide (e.g., smelting and refining operations and production of antimony(III) trioxide). During the 1970s, reported levels ranged from 50 to 5,000 µg/m$^3$, compared with the current threshold limit value (TLV) of 500 µg/m$^3$. In the United States, roughly 70 million pounds of antimony(III) trioxide are used annually as a synergist for halogenated flame
retardants in plastics, rubber, and textiles, as a catalyst in PET production, and as an additive in optical and art glass, pigments, paints, and ceramics. Workers at an estimated 273 U.S. facilities (based on information from EPA’s Toxics Release Inventory) were exposed to antimony(III) trioxide in 2010. More than 200,000 workers were exposed to antimony(III) trioxide in the 1981 to 1983 U.S. National Occupational Exposure Survey, indicating extensive past exposure to antimony(III) trioxide.

The highest occupational exposure to antimony(III) trioxide in the United States, exceeding current regulatory levels by at least 10-fold, occurred during smelting and refining operations and production of antimony(III) trioxide in the 1970s and 1980s. Antimony is no longer mined in the United States and smelting and refining of metallic antimony and production of antimony(III) trioxide was limited to one company in the United States in 2017. More recent European data suggest that the highest exposure to antimony(III) trioxide occurs during production of antimony(III) trioxide, followed by the flame retardant industry. Lower levels of exposures occur during the use of $\text{Sb}^{\text{III}}_2\text{O}_3$ in the glass and PET industries.

Biomonitoring for antimony in urine and environmental data provide evidence of widespread exposure to antimony; however, the proportion that results from exposure to antimony(III) trioxide is usually not known. Antimony in air is expected to be mainly in the form of antimony(III) trioxide with the highest concentrations near facilities, such as mines and smelting operations, that release antimony(III) trioxide into the air. People can also be exposed to antimony(III) trioxide in the air from oxidation of various forms of antimony, such as antimony(III) trisulfide in brake lubricants which is heated to a high temperature during the use of vehicle brakes, various antimony compounds in burning of coal and petroleum, and various forms of antimony in waste that is burned or incinerated. Household products that contain antimony(III) trioxide, particularly flame-retardant-treated textiles, plastics, and rubber, can release particles containing antimony(III) trioxide to the air or dust and antimony ions in liquids leading to dermal or oral exposures, e.g., through mouthing of these products by infants or small children.
3 Disposition and Toxicokinetics

Disposition and toxicokinetics refer to how a chemical enters and leaves the body, what happens to it within the body, and the rates of these processes. Disposition includes absorption, distribution, metabolism, and excretion (ADME), all of which can affect a chemical’s toxicity. This monograph focuses on antimony(III) trioxide (Section 3.1); however, exposure also occurs to other forms of antimony (Section 3.2), such as antimony salts or organic molecules used to treat leishmaniasis or schistosomiasis. Separate subsections discuss absorption and distribution (Sections 3.1.1 [trioxide] and 3.2.1 [other forms]) and excretion (Sections 3.1.2 [trioxide] and 3.2.2 [other forms]) of antimony. Similar to metals in general, antimony is metabolized by changing its valence state, which generally varies between +3, i.e., antimony(III) (trivalent), and +5, i.e., antimony(V) (pentavalent), in vivo, and data for these conversions are discussed in Section 3.3. Toxicokinetic studies are discussed in Section 3.4 and an overall synthesis and summary is provided in Section 3.5. The mechanistic implications of these data are discussed in Section 6.

3.1 Antimony(III) trioxide

Absorption of antimony via the lung or gastrointestinal (GI) tract in humans and experimental animals is indicated through measurement of elemental antimony in blood, urine, or body tissues. Antimony is initially distributed to the blood, where it tends to accumulate mainly in red blood cells. Tissue distribution is generally to spleen, liver, and bone marrow, all of which are rich in reticuloendothelial cells, although the thyroid may also accumulate antimony in some species. Antimony(III) accumulates in tissues with repeated oral administration (Stemmer 1976).

3.1.1 Absorption and distribution

The main sources for information on absorption and distribution of antimony(III) trioxide are authoritative reports from governmental and international agencies (MAK 2007, EU 2008) and recent reviews summarizing many older publications (Belzile et al. 2011, Tylenda and Fowler 2015). The quality of the data was critically assessed in Belzile et al. and in the EU (2008) risk assessment report for antimony(III) trioxide. Only two recent studies with exposure to antimony(III) trioxide comply with current research standards: TNO Quality of Life (2005), conducted according to OECD Guidelines and Good Laboratory Practice (GLP), and NTP (2016c), conducted according to U.S. Food and Drug Administration GLP.

Human studies

The bioavailability of antimony is generally low because of its limited water solubility, but absorption does occur from various routes, including inhalation and oral ingestion (Belzile et al. 2011). (See Section 1.1 and Table 1-3 for a discussion of the bioaccessibility of several antimony compounds.)

Inhalation. The highest exposures of people to antimony by inhalation are from occupational exposure. Antimony has been detected in the lungs, blood, and urine of workers who had inhaled antimony identified as antimony(III) trioxide or likely to be antimony(III) trioxide; inhaled antimony compounds are retained long term in the lung (HSDB 2013, NTP 2016c). Elevated urinary excretion of antimony has been reported for workers exposed to antimony(III) trioxide in
lead battery production (Kentner et al. 1995) (see Table 2-3) and for port workers in Valparaiso, Chile exposed to elevated air concentrations of antimony from heavy vehicular traffic when antimony sulfide or sulfate in brake pads is oxidized to antimony(III) trioxide at temperatures achieved during braking (see Sections 2.1 and 2.3.2) (Quiroz et al. 2009). Accumulation of antimony in the lung was demonstrated for seven workers accidentally exposed to radioactive antimony ($^{125}$Sb, described as antimony oxides, but likely including antimony(III) trioxide). Biomonitoring of whole-body radioactivity found the antimony to be almost entirely confined to the lungs (Garg et al. 2003). However, workers occupationally exposed to antimony(III) trioxide had detectable antimony in urine as well as lungs even after their exposure ceased (HSDB 2013).

The EU (2008) risk assessment report used data from humans to predict absorption from inhalation exposure based on the Multiple Path Particle Deposition (MPPD) model prediction using particle size and density from collected antimony(III) trioxide samples and gastrointestinal tract absorption in humans. Absorption was predicted to be 6.82% resulting from deposition in the alveolar region (6.0%) and the upper airways (0.82%, based on transportation via mucociliary transport of 81.6% of the inhaled amount to the gastrointestinal tract, where 1% is assumed to be absorbed).

Oral exposure. Antimony(III) trioxide is generally considered to be poorly absorbed from the GI tract (Stemmer 1976). No data for oral exposure to antimony(III) trioxide in humans was identified, but absorption is likely low. The EU (2008) calculated a rate of 0.3% for oral absorption from antimony(III) trioxide; however, concerns were expressed because the absorption was based on one study of oral exposure of rats to antimony(III) trioxide, with antimony levels 2 to 3 orders of magnitude higher than human exposures and on human studies using protocols that do not meet current standards.

Experimental animal studies

Inhalation. Animals exposed to antimony(III) trioxide by inhalation showed increased concentrations of antimony in blood in the studies by Newton et al. (1994) and NTP (2016c). In Fischer F344 rats of both sexes exposed by inhalation to antimony(III) trioxide at 0.055, 0.51, or 4.50 mg/m$^3$ for 12 months followed by 12 months of observation, antimony levels in red blood cells (the authors reported that essentially no antimony was detected in plasma) increased proportionally with exposure level but did not increase with exposure duration (Newton et al. 1994) (Table B-1).

The NTP (2016c) exposed rats and mice of both sexes to antimony(III) trioxide by inhalation with either short-term inhalation exposure (2 weeks plus a 4-week recovery period) to 0, 3.75, 7.5, 15, 30, or 60 mg/m$^3$ for 6 hours plus T90 (12 minutes) per day, 5 days per week, or long-term exposure for 2 years at concentrations of 0, 3, 10, or 30 mg/m$^3$ with the same 5 days per week exposure. Blood levels (see Appendix B, Table B-2 and Figure 3-1) increased with exposure concentration in rats and mice for both exposure periods. Blood concentrations increased with exposure duration for rats but not as clearly for mice in the 2-year study. Blood concentrations normalized to exposure concentrations decreased with increasing exposure concentration, particularly at higher concentrations. Lung burdens also increased with exposure concentrations during the 2-year study (see Table 3-1 in Section 3.4, Toxicokinetics).
Another difference observed for the short-term exposure was a continued increase in blood antimony concentrations relative to the concentrations in lung. During the 4-week recovery period in rats the percentage in blood relative to lung concentrations increased from 0.8% in both sexes at the end of exposure to 2% in female rats at 4 weeks post exposure [only females were examined post exposure]). In contrast, the blood concentrations in mice were only 0.004% of lung concentrations in the same animals for males and 0.005% for females at both time points. In the 2-year study, blood concentration was 7% of lung concentration in rats, but only 0.002% in mice.
Intratracheal instillation (i.t.). Leffler et al. (1984) exposed adult male Syrian golden hamsters to 19.5-µm or 7-µm particles of antimony(III) trioxide by i.t. instillation. In addition to a large percentage in the lung, antimony was detected in the liver (12.6% of 19.5-µm particles and 7.2% of 7-µm particles), with lesser amounts in the kidney, stomach, and trachea (the only other tissues examined). Based on this study, the EU (2008) risk assessment concluded that absorption following i.t. instillation was greater than 12.6%.

Oral exposure. Absorption from the GI tract is generally slow (Stemmer 1976). In Sprague-Dawley Crl:CD rats exposed orally (by daily gavage) to antimony(III) trioxide, it took 24 hours to reach the maximum concentration (C_{max}) in blood for either a 100 mg/kg or a 1,000 mg/kg dose (TNO Quality of Life 2005). However, the C_{max} reached after exposure to 1,000 mg/kg for that time period was only about twice that observed at 100 mg/kg. Bioavailability calculated from the area under the curve was 0.3% for the low dose and 0.05% for the high dose.

In a study of oral exposure to antimony(III) trioxide (TNO Quality of Life 2005), rats exposed to a single dose of 100 mg/kg showed little increase in tissue concentrations above control levels (data not shown), but at a dose of 1,000 mg/kg for 1 day or repeated for 14 days, tissue levels increased several fold in bone marrow and in thyroid, and blood levels increased in males and females (see Appendix B, Table B-3). In other studies, oral exposure of rats to antimony(III) trioxide in the diet for 49 days (Westrick 1953) resulted in a general increase in tissue antimony levels over rats with 14 days of exposure (EU 2008), but the difference between tissue levels at 49 days and 8 months (Gross et al. 1955) were relatively small (Table 3-2). Exposure levels were very similar across all three studies.

Excretion

Antimony is eliminated mainly in the urine, regardless of the exposure route, but it can also appear in the feces when some ingested antimony passes through the GI tract without being absorbed or is absorbed and then excreted in the bile where it fails to form a complex with glutathione (GSH) and is not reabsorbed via enterohpatic circulation (EU 2008). Clearance of antimony from the lung follows a biphasic pattern in both humans and experimental animals, with a rapid early phase likely mediated by mucociliary transport and a slower second phase due to dissolution and absorption. Antimony cleared from the lung by mucociliary action can be swallowed and excreted in the feces. In general, antimony(III) has a greater affinity for red blood cells than antimony(V) and antimony(III) is preferentially excreted in the feces compared with antimony(V), which is more likely to be excreted in the urine (Tylenda and Fowler 2015).

Human studies (occupational exposures)

Urinary levels of antimony resulting from exposure to antimony(III) trioxide by inhalation have been reported for a few occupational uses of antimony(III) trioxide. Urinary excretion of antimony by exposed workers generally increases with the exposure level. Three studies were identified that reported both exposure to antimony(III) trioxide in air and urinary excretion for the same workers (see Section 2.2 and Table 2-3). The geometric mean or median air levels reported in these studies were mostly below the current threshold limit value for antimony and antimony compounds in air of 500 µg/m³ (ACGIH 2017), but one study (Kim et al. 1999) reported a geometric mean air level of 766 µg/m³, which was associated with a urinary excretion level of ~420 µg/L. This level was much higher than the 15.2 µg/g creatine excretion reported by
Kentner et al. (1995) for a mean air level of 12.4 µg/m³ in a starter battery factory using antimony(III) trioxide. The half-life for elimination of antimony in the urine following inhalation of antimony(III) trioxide was estimated as 95.1 hours for these 14 employees (Kentner et al. 1995).

**Laboratory animal studies**

*Inhalation and intratracheal instillation.* In laboratory animals, elimination of inhaled antimony(III) trioxide is generally slow. As in humans, animals eliminate antimony in a relatively rapid phase, likely mediated by mucociliary transport, followed by a slower phase. In hamsters instilled i.t. with antimony(III) trioxide, biological half-lives were 40 hours for the rapid phase and 20 to 40 days for the slower phase of clearance from the lung (EU 2008).

### 3.2 Other antimony compounds

The absorption, distribution, and excretion of other antimony compounds are discussed here because they may provide useful information for discussion of potential mechanisms in Section 6.

#### 3.2.1 Absorption and distribution

As for antimony(III) trioxide, absorption of other or unspecified forms of antimony via the lung or gastrointestinal (GI) tract in humans and experimental animals is indicated through measurement of antimony in body tissues or urine.

**Human studies**

When humans are exposed to antimony, usually by occupational exposure, the initial retention of antimony(V) in blood is primarily in the plasma rather than in red blood cells in contrast with antimony(III), but equilibration of antimony between plasma and cells occurs over a period of hours, and intracellular antimony concentrations increase (see Section 3.3). Repeated administration results in both higher plasma levels and increased urinary excretion. Antimony(III) concentration is generally highest in liver, while antimony(V) concentration is higher than that of antimony(III) in the spleen. A high concentration in spleen is considered a necessary condition for cure of leishmaniasis and thus may be related to therapeutic effects of antimony.

For people without known exposure to antimony, potential reference ranges for blood or serum levels of total antimony and either whole-body burden or levels in individual organs include a mean body burden of 0.7 mg, with the highest levels in skin and hair for a Japanese autopsy study (Sumino et al. 1975), the presence of 28% of the body’s antimony content in the skeleton in Chinese men (Zhu et al. 2010), and serum antimony levels of 0.09 to 0.25 µg/L in Irish infants less than a year old (Cullen et al. 1998).

**Inhalation.** Occupational and environmental exposure to antimony is mainly via inhalation. Elevated urinary excretion of antimony was reported in workers exposed to antimony trisulfide in the production of resinoid grinding wheels (Brieger et al. 1954) or to stibine (Sb(III)H₃) in lead battery production (Kentner et al. 1995). (Exposure to antimony(III) trioxide in this facility was discussed in Section 3.1.2.) Pregnant or lactating women in an antimony plant were exposed occupationally to unspecified amounts of antimony(III) trioxide, metallic antimony, or
antimony(V) pentasulfide as aerosols, and antimony was detected in breast milk (3.3 ± 2.2 mg/L), placenta (3.2 to 12.6 mg% [units as reported in EU 2008 and HSDB 2013]), amniotic fluid (0.62 ± 0.28 mg/L), and umbilical cord blood, indicating absorption and potential exposure to fetuses and breast-fed infants (Belyaeva 1967). Mean levels in blood and urine were generally higher for workers in areas with high dust levels.

Evidence also indicates that long-term retention of inhaled antimony compounds occurred in seven workers accidentally exposed to radioactive antimony (\(^{125}\)Sb); biomonitoring of whole-body radioactivity found the antimony to be almost entirely confined to the lungs (Garg et al. 2003). In addition, concentrations of antimony in lung tissue were 12 times as high in 40 retired and deceased smelter plant workers (315 µg/kg) as in 11 controls (26 µg/kg) (Gerhardsson et al. 1982).

Accumulation of antimony in lung tissue correlated with age for deceased individuals in Belgium (Vanoeteren et al. 1986a, Vanoeteren et al. 1986b, Vanoeteren et al. 1986c), and lung tissue from 15 deceased individuals in Scotland (Molokhia and Smith 1967) had concentrations in the apex of the lung (0.084 ppm wet weight) that were more than twice as high as those at the base (0.033 ppm wet weight). The work and living environment, and smoking habits of individuals were investigated by Vanoeteren and co-workers, but no information was reported by Molokhia and Smith. In both studies, the authors concluded that the source of the accumulated antimony was from inhalation of atmospheric contaminants, likely airborne dust.

**Oral exposure.** Belzile et al. (2011) reported poisoning from either accidental or intentional consumption of antimony compounds, indicating absorption sufficient to cause toxicity (Dunn 1928, Lauwers et al. 1990, Bailly et al. 1991 as cited by Belzile et al. 2011). One of four exposed adults died after consuming a cake made with 6 g of tartar emetic (antimony potassium tartrate, APT) instead of cream of tartar and was found to have 15 to 20 mg (~5% of the amount ingested) as a total body pool of antimony, compared with an estimated body burden of 7.9 mg in antimony-exposed workers (ATSDR 1992). In a woman who attempted suicide by ingesting an unknown amount of antimony trisulfide, blood and urine levels of antimony remained elevated a week after ingestion (Bailly et al. 1991).

ICRP (2012) recommended a single fractional absorption value of 0.05 for situations where no specific information is available. ICRP’s conclusions were based on studies reporting fractional absorption rates ranging from greater than 0.01 to approximately 0.2. Human GI absorption of antimony compounds in general has been estimated in older literature as 5% to 15%; however, neither Belzile et al. (2011) nor the NTP could identify any quantitative data to support this estimate.

**Injection.** After intravenous (i.v.) injections of radiolabeled sodium antimony dimercaptosuccinate to male volunteers, body scans found the highest levels in liver, thyroid, and heart (ICRP 1981, 2012).

**Experimental animal studies**

A few publications have reported levels of antimony in blood and tissues of control animals that had not been experimentally exposed to antimony. In rats, the levels in thyroid, bone marrow, liver, spleen, and whole blood ranged from 0.028 (2.8 ngSb/g in whole blood) to 0.195 µg/g (195
Numerous studies have reported that antimony binds to red blood cells and that tissue concentrations are generally highest in spleen, liver, bone marrow, and thyroid; however, the order varies among studies, which used various species, routes of exposure, and forms of antimony. For example, in mice exposed to antimony (as antimony tartrate) by inhalation, i.p. injection (tartar emetic [antimony(III) potassium tartrate] or Astiban [sodium antimony(III) 2,3-mesodimercaptosuccinate]), or oral administration (tartar emetic), up to half of antimony that entered the systemic circulation was deposited in the liver, but the fraction was smaller in rats, hamsters, and dogs (ICRP 1981). In dogs, inhaled antimony also accumulated in the thyroid.

**Inhalation and intratracheal instillation.** In general, aerosols of antimony oxides with small particle sizes and low water solubility (Newton et al. 1994) were retained in the lungs longer than larger particles with high water solubility (antimony tartrates) (Felicetti et al. 1974b). Large differences in blood levels of antimony following i.t. instillation have been reported for different species. For example, following exposure to antimony(III) trichloride, blood levels in rabbits and dogs were less than 1% of those in rats (Tylenda and Fowler 2015).

**Oral exposure or injection.** Tylenda and Fowler (2015) reported that at least 15% of a single oral dose of labeled antimony(III) as the soluble compound antimony potassium tartrate was absorbed (i.e., recovered in urine and tissues) compared with the estimated oral absorption of 1% for antimony(III) trioxide. Antimony(V) administered orally as meglumine antimoniate(V) or complexed with N-alkyl-N-methylglucamide surfactant was rapidly absorbed by mice and accumulated in liver (Fernandes et al. 2013). Pregnant rats exposed to antimony(V) (meglumine antimoniate) by subcutaneous (s.c.) injections transferred antimony to fetuses via the placenta (Miranda et al. 2006, Coelho et al. 2014), and exposure during lactation resulted in transfer of antimony(V) in milk to suckling pups (Coelho et al. 2014).

Blood levels of antimony in rats exposed to antimony(III) potassium tartrate by oral exposure (in drinking water) or by intraperitoneal (i.p.) injection were compared in the NTP (1992) study. Blood levels following administration in drinking water (14 days) were only about twice those observed after repeated daily i.p. injections (12 injections over 16 days) even though the oral exposure was 10 times higher, suggesting limits on absorption from the GI tract (NTP 1992). No blood levels were detected in mice exposed via drinking water or i.p. injection following the same protocol as for rats, but antimony was detected in liver (24 µg/g with 273 mg/kg antimony(III) potassium tartrate in drinking water or with 50 mg/kg by i.p. injection) and spleen (5 µg/g with 50 mg/kg by i.p. injection).

3.2.2 Excretion

**Human studies**

Excretion of inhaled antimony via urine and feces and in breast milk in humans (HSDB 2013) has been reported. The background level of urinary antimony excretion in the general population without occupational exposure has been estimated by Filella et al. (2013a) as ≤ 0.1 µg/L, based on their compilation and critical review of recent studies using sensitive detection methods and
large numbers of individuals. Filella et al. considered that many older publications likely overestimated urinary antimony levels because of higher detection limits if values below the limit of detection were excluded from their calculations (see Section 2). Urinary levels of antimony have most commonly come from studies of occupational exposure or therapeutic use of antimony-containing drugs for leishmaniasis or schistosomiasis.

**Occupational exposure.** The highest levels of urinary excretion identified for occupational exposure to antimony was for workers in a resinoid grinding wheel manufacturing plant using antimony(III) trisulfide (Brieger et al. 1954). Urine levels of 800 to 9,600 µg/L were associated with air levels that the authors reported as mostly exceeding 3,000 µg/m³, far above the current threshold limit value for antimony and antimony compounds in air of 500 µg/m³ (ACGIH 2017).

In seven workers exposed to radioactive antimony (reported as 124Sb antimony oxides, but specific form not identified) (Garg et al. 2003, HSDB 2013), biphasic clearance from the lung was reported, with a rapid initial phase of 7 days and a slower second phase (individual half-lives of 600 to 1,100 days calculated for non-smokers and 1,700 to 3,700 days for smokers), which would be consistent with long-term retention of antimony in lung tissue.

**Antimony-containing drugs.** Excretion of injected antimony, usually therapeutic anti-leishmanial drugs, is primarily via urine and feces, but the predominant route depends largely on the valence state of the antimony injected (CDC 1978, Tylenda and Fowler 2015).

**Laboratory animal studies**

Both urinary and fecal elimination have been reported for laboratory animals exposed to antimony with variations for different routes of exposure.

**Inhalation and intratracheal instillation.** Following exposure by inhalation or intratracheal instillation, larger and more soluble particles were generally cleared most quickly from the lungs (EU 2008). A study in 20 hamsters compared two soluble radioactive (124Sb) antimony aerosols, one Sb(III) and one Sb(V), each with median aerodynamic diameters of 1.6 µm (CDC 1978). Whole-body clearance of both aerosols was biphasic with a rapid phase during the first 24 hours and a slower clearance with a half-life of 16 days; excretion of the two forms did not differ significantly. Two hours after exposure, < 1% of body burden remained in the lungs, but a high antimony content was reported in the GI tract shortly after the first exposure. By day 7, 90% of the body burden on day 1 had been cleared.

**Other routes.** Oral ingestion of radiolabeled antimony(III) potassium tartrate by rats resulted in slow excretion, primarily in the feces but also in the urine (NTP 1992). In rats, i.v. injection of antimony(III) trichloride (Sb(III)Cl₃) resulted in excretion of 30% of total antimony in feces and 12% in urine during the first 24 hours, indicating that biliary excretion exceeded urinary excretion (TNO Quality of Life 2005). Enterohepatic cycling occurs due to binding of antimony(III) to GSH; in adult rats, depletion of GSH decreased fecal excretion and increased urinary excretion after i.v. or i.p. injection of antimony(III) trichloride (Bailly et al. 1991).

### 3.3 Metabolism and valence states

Mammalian metabolism of antimony consists primarily of interconversion of the valence state between +3 and +5. Methylation is a well-known pathway for metabolism of arsenic in vivo, but
evidence for methylation of antimony in vivo is limited to one study of two workers occupationally exposed to antimony during lead battery production (Krachler and Emons 2001). However, other studies in humans (Miekeley et al. 2002, Quiroz et al. 2011) and animals (Bailly et al. 1991) were negative for formation of methylated antimony.

Major forms of antimony under physiological conditions are an uncharged form of antimony(III) as Sb(OH)$_3$ and an electrically charged form of antimony(V) as Sb(OH)$_6$$^-$ (MAK 2007) (see Section 1). The uncharged antimony(III) form should pass more easily through cell membranes than the charged form of antimony(V), which would remain in the plasma and be subject to excretion, consistent with the shorter half-life of antimony(V) in vivo.

The relative distribution of antimony between red blood cells and plasma differed with valence state. Quiroz and coworkers (Quiroz et al. 2013, Barrera et al. 2016) separated antimony(III) and antimony(V) chromatographically and demonstrated that antimony(V) can enter human erythrocytes in vitro via protein channels through the membrane, where antimony(V) is reduced intracellularly, at least in part, to antimony(III) through interaction with glutathione (GSH) via its redox couple with glutathione disulfide (GSSG). This could explain the equilibration over time of the distribution of antimony(V) between red blood cells and plasma. In rats administered antimony(III) and antimony(V) by i.p. injection, uptake by red blood cells was more rapid for antimony(III) than antimony(V). At 2 hours post-injection, over 95% of the antimony(III) in blood was incorporated into red blood cells, but 90% of antimony(V) was in the plasma (Edel et al. 1983). By 24 hours after inhalation exposure in hamsters, the ratios of antimony in red blood cells to serum were similar regardless of the valence (Felicetti et al. 1974a).

Reduction of antimony(V) to antimony(III) occurs in vitro, and perhaps also in cell cytoplasm or in lysosomes, by reaction with GSH, cysteine, or cysteinyl-glycine. Evidence for reduction of antimony(V) to antimony(III) in humans is based on detection of both antimony(III) and antimony(V) in the urine of people injected with meglumine antimoniate(V) (Glucantime) (Petit de Peña et al. 1990, Miekeley et al. 2002), consistent with release of anionic antimony(V) from the drug and possible reduction to antimony(III) in vivo. The kinetics of reduction of antimony(V) from the antileishmanial drug meglumine antimoniate to antimony(III) by L-cysteine in vitro indicate a peak rate constant at pH 4.7, which is consistent with the pH range of 4.5 to 5.0 within lysosomes, where the drug is believed to act (De Oliveira et al. 2006). Reduction of antimony(V) to antimony(III) in various types of human cells in vitro is consistent with this finding. Antimony(V) from sodium stibogluconate (Pentostam) was reduced to antimony(III) in the human macrophage cell line Mono Mac 6 (Hansen et al. 2011). Antimony(V) incubated with human blood in vitro was reduced to antimony(III) in the plasma and red-cell cytoplasm in the presence of GSH; however, antimony(III) could be re-oxidized to antimony(V) in the plasma (López et al. 2015). No conversion was detected when cultured human keratinocytes were incubated with antimony(V) as potassium hexahydroxy antimonate (Patterson et al. 2003).

Data for interconversion between antimony(III) and antimony(V) in experimental animals are generally limited, but one study in dogs injected s.c. with a single dose of meglumine antimoniate(V) reported systemic conversion of 23.62% of antimony(V) to antimony(III) in blood in 24 hours (de Ricciardi et al. 2008). In rhesus monkeys injected i.m. with meglumine antimoniate(V) daily for 21 days, the proportion of antimony(V) remained in the range of 11% to
20% of total antimony, while that of antimony(III) increased from 5% on day 1 to 50% on day 9, which could indicate reduction of antimony(V) to antimony(III) within cells (Friedrich et al. 2012). The authors did not report what form of antimony made up the balance of the total concentration.

The valence state also affects the distribution of antimony in tissues. Felicetti et al. (1974a) reported that hamsters exposed to radioactive antimony ($^{124}$Sb) aerosols, one antimony(III) and one antimony(V), both with median aerodynamic diameters of 1.6 µm, had similar average body burdens on the day after exposure. However, slightly more antimony(III) than antimony(V) accumulated in the liver while more antimony(V) accumulated in the skeleton; reduction of antimony(V) to antimony(III) was not extensive. Antimony(III) tartrate inhaled as aerosols by mice (Thomas et al. 1973) or beagle dogs (Felicetti et al. 1974b) was distributed primarily to the lung, bone, pelt, and thyroid gland.

Several recent studies have determined blood and tissue levels resulting from exposure to antimony(V) from drugs used to treat leishmaniasis, primarily meglumine antimoniate(V) (Glucantime) in rats (Coelho et al. 2014), mice (Borborema et al. 2013), and dogs (de Ricciardi et al. 2008, Ribeiro et al. 2010). In rats injected s.c., the highest levels of antimony were in the spleen, bone, thyroid, and kidney (Coelho et al. 2014) and a biphasic clearance was reported. Biphasic clearance was also reported for mice injected i.p. (Borborema et al. 2013). Dogs injected s.c. converted 23.62% of antimony(V) to antimony(III) by 24 hours after injection, and clearance of antimony(III) was not biphasic (de Ricciardi et al. 2008, Ribeiro et al. 2010). In hamsters (Al Jaser et al. 2006) injected intramuscularly (i.m.) with antimony(III) as sodium stibogluconate, antimony concentrations were highest in kidney and lowest in spleen, and clearance was linear from blood but biphasic from individual tissues.

The valence of antimony also affects the route and rate of excretion, which vary among species. Following injection of organic antimonials with different valences, antimony from the antimony(V) drug was excreted mainly in the urine, and that from the antimony(III) drug mainly in the feces (Otto et al. 1947, Tylenda and Fowler 2015). In mice injected s.c., i.p., or i.m. with either stibophen with antimony(III) or sodium antimony(V) gluconate, total urinary excretion after 48 hours was ~70%. Although the initial excretion rate was slower for antimony(III), the difference decreased over 48 hours. In hamsters, i.p. injection resulted in urinary excretion of 15% for antimony(III) and 65% for antimony(V), while fecal excretion was 50% for antimony(III) and < 10% for antimony(V).

The quantification of antimony(III) and antimony(V) in human erythrocytes (Quiroz et al. 2013), in rhesus monkey plasma (Friedrich et al. 2012), and in urine (Miekeley et al. 2002) described above was based on ion chromatography for separation of antimony(III) and antimony(V). Miekeley et al. also determined the different valence states in human blood and hair, and Friedrich et al. examined thyroid, liver, spleen, kidneys, and other tissues from rhesus monkeys. However, no studies reporting additional data based on these methods were identified.

### 3.4 Toxicokinetics

The available information on the toxicokinetics of antimony is from Newton et al. (1994) and a recent NTP (2016c) report on lung accumulation and clearance in rats and mice exposed to...
antimony(III) trioxide via inhalation. No studies on the toxicokinetics of antimony in humans were identified.

Newton et al. (1994) exposed F344 male and female rats to antimony(III) trioxide for either 13 weeks followed by 27 weeks of observation (0.0, 0.25, 1.08, 4.92, or 23.46 mg/m$^3$) or 1-year exposure followed by 1-year observation (0.0, 0.055, 0.51, or 4.5 mg/m$^3$) with intermediate sample collection at 6 months for each period. The authors reported near steady-state lung burdens by 6 months of exposure for the 12-month exposure period (see Table 3-3). Semilogarithmic plots of clearance data (µg antimony(III) trioxide concentration per g of tissue plotted against time) indicated a lung-burden-dependent effect on the clearance rate. At a lung burden of ~2 mg antimony(III) trioxide per lung, the rate of lung clearance decreased by approximately 80% with a resulting increase in the clearance half-time from 2 months to 10 months.

Table 3-1. Antimony(III) trioxide levels* (µg/g) in lung tissue during a 1-year chronic exposure (6 mo and 12 mo samples) and a 1-year observation period (6 mo and 12 mo samples) in Fischer 344 male and female rats

<table>
<thead>
<tr>
<th>Group</th>
<th>6 mo</th>
<th>12 mo</th>
<th>18 mo (6 mo obs)</th>
<th>24 mo (12 mo obs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I- Control</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>II- 0.055 mg/m$^3$</td>
<td>19.6 ± 4.9</td>
<td>11.5 ± 1.6</td>
<td>1.4 ± 1.3</td>
<td>0.4 ± 0.6</td>
</tr>
<tr>
<td>III- 0.51 mg/m$^3$</td>
<td>75.4 ± 10.1</td>
<td>132.0 ± 35.1</td>
<td>28.9 ± 5.1</td>
<td>8.1 ± 3.2</td>
</tr>
<tr>
<td>IV- 4.5 mg/m$^3$</td>
<td>1190 ± 167</td>
<td>1420 ± 238</td>
<td>991 ± 194</td>
<td>554 ± 189</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I- Control</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>II- 0.055 mg/m$^3$</td>
<td>15.1 ± 4.0</td>
<td>9.6 ± 1.1</td>
<td>2.2 ± 0.6</td>
<td>0.2 ± 0.5</td>
</tr>
<tr>
<td>III- 0.51 mg/m$^3$</td>
<td>76.9 ± 10.6</td>
<td>107.0 ± 28.3</td>
<td>33.2 ± 9.9</td>
<td>14.7 ± 8.2</td>
</tr>
<tr>
<td>IV- 4.5 mg/m$^3$</td>
<td>1100 ± 332</td>
<td>1500 ± 183</td>
<td>757 ± 59</td>
<td>663 ± 54</td>
</tr>
</tbody>
</table>

Source: Newton et al. (1994). mo = months.

*Total antimony in lung tissue was reported as total antimony(III) trioxide.

Kinetic parameters were determined for inhaled antimony(III) trioxide in female rats and mice exposed at 0.0, 3.75, 7.5, 15, 30, or 60 mg/m$^3$ for 2 weeks followed by recovery for 4 weeks (NTP 2016c). Clearance half-lives in lung ranged from 73 to 122 days in rats and 47 to 62 days in mice. The shortest half-life was for the lowest exposure concentration, but no clear concentration-response trend was seen. Deposition rates (micrograms of antimony(III) trioxide per day) were approximately proportional or slightly less than proportional to exposure concentrations; deposition rates increased 15-fold in rats and 13-fold in mice when exposure increased 16-fold. Steady-state lung burdens were not reached during the 2-week exposure, but half-lives to steady state were estimated to be 365 to 610 days in rats and 235 to 310 days in mice.

Lung burdens were expressed as mass rather than concentration because lung weights increased in exposed animals. NTP also reported that normalized antimony(III) trioxide lung burdens
increased in approximate proportion to exposure concentration and with exposure duration during the two-year bioassay in rats and mice. The lung burden in female rats increased steadily over time. The 3 mg/m$^3$ and 10 mg/m$^3$ exposure groups nearly reached steady state, but the 30 mg/m$^3$ exposure group did not. The results in rats were consistent with the clearance rates from the lungs progressively decreasing.

NTP (2016c) also attempted to fit a lung-burden model to data for rats and mice based on assumptions of a zero-order (constant) deposition rate and a first-order (with respect to lung burden) clearance rate. Model-predicted values are shown in Table 3-2 and lung burdens are shown in Figures 3-2 and 3-3. In rats, the predicted deposition rates were consistent with the measured lung-burden data. In mice, the data showed a poor fit, and meaningful deposition and clearance parameters could not be calculated for any of the exposure concentrations. In rats, approximately five half-lives would be required to reach steady state, and the durations for the two higher concentrations would exceed the normal life span of this rat strain.

Table 3-2. Model-predicted values for Wistar Han rats exposed to antimony(III) trioxide via inhalation for 2 years

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Exposure level (mg/m$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Deposition rates (µg Sb$_2$O$_3$ per total lung per day)</td>
<td>17</td>
</tr>
<tr>
<td>Percent deposition efficiency (%)</td>
<td>3.3</td>
</tr>
<tr>
<td>Clearance half-life (days)</td>
<td>136</td>
</tr>
<tr>
<td>Time to steady state (days)</td>
<td>680</td>
</tr>
</tbody>
</table>

Source: NTP 2016c.

Based on relatively longer clearance half-lives at the higher doses and an unexpectedly high lung burden in mice after 551 days of exposure, NTP (2016c) concluded that the reduced pulmonary clearance was associated with lung overload at 10 mg/m$^3$ and 30 mg/m$^3$, but not 3 mg/m$^3$. Two theories to explain overload in relation to inhalation exposure to particulates have been proposed, one based on particle volume and the second on particle surface area. Volumetric overload is initiated when individual alveolar macrophages accumulate a particulate volume exceeding 60 µm$^3$ per macrophage (Morrow 1988, 1992). When the particulate volume per macrophage exceeds 600 µm$^3$, all macrophage-mediated clearance ceases, and the dust accumulates linearly with continued inhalation. Tran et al. (2000) proposed a second hypothesis for clearance impairment based on the total particle surface area of ultrafine particulates. This particle surface area hypothesis proposes that ultrafine particles with high surface area will cause macrophages to release proinflammatory mediators (chemokines), such as tumor necrosis factor, that attract macrophages and could prevent their migration. The NTP concluded that volume-based overload occurred at 10 mg/m$^3$ by day 418 in rats and day 369 in mice and at 30 mg/m$^3$ by day 94 in rats and day 124 in mice.
This information is distributed solely for the purpose of pre-dissemination peer review under applicable information quality guidelines. It has not been formally distributed by the National Toxicology Program. It does not represent and should not be construed to represent any NTP determination or policy.
forms tend to accumulate mainly in red blood cells, although antimony(V) is initially present in plasma during the first few hours after exposure. The highest levels of antimony are generally in organs rich in reticuloendothelial cells, such as the spleen, liver, and bone marrow. In rats, dogs, and some studies in humans, high levels have also been reported in the thyroid. However, the relative accumulation of inhaled antimony in liver and skeleton differs by valence; antimony(III) is distributed more rapidly than antimony(V) to the liver, while antimony(V) is delivered more rapidly than antimony(III) to the skeleton. Both forms were also found in the kidneys and other organs. In humans exposed to radioactive antimony, it was still detected in tissues, particularly the liver, weeks or months after exposure ended. During pregnancy and lactation, both humans and rats passed antimony to the fetus via the placenta and to infants via milk.

3.5.2 Metabolism

Mammalian metabolism of antimony consists of interconversion of the valence state between +3 and +5. The valence state and electrical charge affect the distribution of antimony between blood and cells and its excretion. Reduction of antimony(V) to antimony(III) has been shown to occur in the presence of glutathione, cysteine, or cysteinyl glycine in vitro. Although methylated forms of antimony have been reported in the environment, no convincing evidence was found for methylation in mammals.

3.5.3 Excretion

Studies of workers exposed to antimony by inhalation showed generally higher urinary excretion with higher levels of exposure in air. Both antimony(III) and antimony(V) are excreted mainly in the urine, but excretion occurs over a relatively long period after exposure, and the pattern of excretion can vary with exposure route and species. The data generally support slower excretion of antimony(III) than antimony(V). Some studies have reported greater excretion of antimony(III) than antimony(V) in feces, but generally at lower levels for both compared with their excretion in urine. Antimony excreted in bile undergoes enterohepatic recycling, which likely depends on binding to GSH.

3.5.4 Toxicokinetics

Toxicokinetics data for antimony are mainly from the NTP (2016c) report on studies in rats and mice exposed to antimony(III) trioxide by inhalation for 2 weeks plus 4 weeks’ recovery or for 2 years. Clearance half-lives from lung were calculated from 2-week exposure data as 73 to 122 days for rats and 47 to 62 days for mice. The models that NTP used fit the data for rats relatively well, but not those for mice. Model-estimated clearance half-lives ($t_{1/2}$) for 2-year exposure data in rats increased with exposure concentration with durations of 136 for 3 mg/m$^3$, 203 days for 10 mg/m$^3$, and 262 days for 30 mg/m$^3$. (Data for mice could not be modeled.) The NTP also considered the question of lung overload during the 2-year exposure, concluding that lung overload was not reached at the lowest concentration tested (3 mg/m$^3$), but was reached in both rats and mice at the middle (10 mg/m$^3$) and high concentrations (30 mg/m$^3$).
4 Human Cancer Studies

The objective of the cancer hazard evaluation of antimony(III) trioxide is to reach a level of evidence conclusion (sufficient, limited, or inadequate) for the carcinogenicity of antimony(III) trioxide from studies in humans by applying the RoC listing criteria to the body of evidence.

In general, the available human studies do not provide specific information on the antimony species to which occupational study populations were exposed; however, workers in antimony smelting and in art glass production were reportedly exposed to antimony(III) trioxide, as well as other antimony oxides and antimony sulfides. It is less clear what specific antimony species tin smelting workers were exposed to. Because specific antimony species or antimony groups are not available in human cancer studies, the generic term “antimony” is used in this section.

The cancer hazard evaluation of antimony primarily focuses on lung and stomach cancers because these were evaluated in multiple studies. (For rationale, see Antimony Protocol [NTP 2017c] and Table 4-1).

The steps in the cancer hazard evaluation are presented in this section as below.

1. Selection and overview of the human cancer studies (Section 4.1 and Antimony Protocol [NTP 2017c]).
2. Evaluation of risk of bias and study sensitivity (Section 4.2, and Appendix C, Tables C-1 to C-6).
3. Cancer hazard assessment: lung cancer (Section 4.3.1), stomach (Section 4.3.2), and other cancers (Section 4.3.3).
4. NTP preliminary level-of-evidence conclusion for carcinogenicity (sufficient, limited, or inadequate) of antimony from human studies (Section 4.4).

4.1 Selection of the relevant literature and overview of the study characteristics

Procedures to identify and select the primary studies and supporting literature for the human cancer evaluation are detailed in Section 3 of the Antimony Protocol (NTP 2017c).

Briefly, primary epidemiological studies were considered for the cancer evaluation if the study (1) was peer reviewed; (2) provided risk estimates (or sufficient information to calculate risk estimates) for antimony and human cancer; and (3) provided exposure-specific analyses for antimony at an individual level or, based on the authors’ report, antimony exposure was probable or predominant in the population, job, or occupation under study. Both cohort and case-control studies, but not ecological or other types of epidemiological studies, of antimony were found to fit these criteria and therefore were included for evaluation.

A U.S. population-based cohort study on urinary antimony concentrations and cancer (Guo et al. 2016) and a Turkish geospatial study on antimony exposure from drinking water and cancer incidence (Colak et al. 2015) were excluded from the cancer evaluation because only all malignant neoplasms, not site-specific cancers, were reported. Two Swedish post-mortem studies comparing antimony concentrations in various tissue types in deceased metal smelter workers...
and deceased controls (Gerhardsson et al. 1982, Gerhardsson and Nordberg 1993) were excluded because no point estimates were reported and exposure measurements did not precede cancer outcomes.

The available epidemiological studies that satisfy the criteria for consideration in the cancer evaluations are three occupational cohort studies (Wingren and Axelson 1993, Jones 1994, Schnorr et al. 1995, Jones et al. 2007) and one case-control study (Wingren and Axelson 1993) conducted in four independent populations. These were two antimony smelting cohorts in the United Kingdom and the United States, a tin smelting cohort in the United Kingdom, and a case-control study from an art glass region in Sweden. Detailed data on study design, methods, and findings for each of the available studies are provided in Table 4-3 in Section 4.3.

In both cohort and case-control studies, participants were occupationally exposed to antimony via metal smelting (Jones 1994, Schnorr et al. 1995, Jones et al. 2007) or art glass manufacturing (Wingren and Axelson 1993). Ever-exposure to antimony was characterized by occupational status based on company records (Jones 1994, Schnorr et al. 1995) or listed occupation on mortality records (Wingren and Axelson 1993). Only Jones et al. (2007) established a job-exposure matrix (JEM) based on personnel work histories and both area and personal air sampling measurements for antimony and four other heavy metals.

The likely antimony species to which workers were occupationally exposed were antimony(III) trioxide in art glass workers (Wingren and Axelson 1993, Jones 1994, Schnorr et al. 1995) and, with less certainty, tin smelter workers (Jones et al. 2007), as well as other antimony oxides and antimony sulfides in antimony smelter workers (Jones 1994, Schnorr et al. 1995). In three of the four studies (Wingren and Axelson 1993, Jones 1994, Schnorr et al. 1995), the levels of exposure to antimony alone were not defined in enough detail to explore exposure-response relationships. Jones et al. (2007) did model a linear exposure-response relationship between antimony air concentrations and lung cancer mortality.

All studies examined cancer mortality. All cohort studies reported lung cancer mortality (Jones 1994, Schnorr et al. 1995, Jones et al. 2007), and two cohort studies and one case-control study reported on gastric cancer mortality (Wingren and Axelson 1993, Jones 1994, Schnorr et al. 1995). All studies used the International Classification of Diseases (ICD) coding schemes based on death certificates or death registries. Jones (1994) reported mortalities from all causes, from noncancer cardiovascular, respiratory, and urinary diseases, and from accidental causes. Besides lung and stomach cancer, other malignant neoplasms in antimony smelter workers were reported without specific cancer site information. Schnorr et al. (1995) also examined mortality from all causes, all cancers, and cancers from all digestive system, all respiratory system, and specific sites (i.e., stomach; liver and gallbladder; colorectal; buccal cavity and pharynx; trachea, bronchus, and lung; urinary organs; lymphatic and hematopoietic tissues; and male genital organs). Additionally, the study reported 14 other major noncancer causes of death in the United States, including pneumoconiosis. In addition to stomach cancer mortality cases, Wingren and Axelson (1993) conducted analyses for lung and colon cancer cases using a Swedish death registry, but they only published risk estimates for colon cancer.

Given the reported cancer sites in the available studies, lung and stomach were chosen as focal cancer sites for the current evaluation. The study methods and characteristics of each study are described in Table 4-1.
Table 4-1. Antimony exposure and human cancer studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design (location, years, population)</th>
<th>Outcome, including cancer sites, data analysis</th>
<th>Exposure: antimony compounds, source of information, assessment, metrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones 1994</td>
<td>Antimony smelter worker cohort (United Kingdom) 1961–1992 (study enrollment and follow-up period) N = 1,420 male workers</td>
<td>Historical mortality cohort (standardized mortality ratio [SMR]) All cancers; lung cancer; stomach cancer; other neoplasms (ICD-8 and ICD-9 codes: NR) All-cause and 7 noncancer sites</td>
<td>Smelting of antimony ore to antimony oxides and antimony alloys Company records Exposed: ever employed in U.K. antimony smelter External referent: local population Duration of employment, years of exposure</td>
</tr>
<tr>
<td>Schnorr et al. 1995</td>
<td>Antimony smelter worker cohort (United States) 1937–1989 (employment and follow-up period) N = 1,014 male workers</td>
<td>Historical mortality cohort (SMR) Cancers in trachea, bronchus, lung (ICD-9 code: 161); stomach cancer (ICD-9 code: 151); all cancer; 9 other site-specific cancers All-cause and 14 noncancer sites</td>
<td>Antimony ore (oxide and sulfide), metal, and antimony oxides Company records Exposed: ever employed in U.S. antimony smelter External referents: national and ethnic-specific local U.S. population Duration of employment</td>
</tr>
<tr>
<td>Jones et al. 2007; methods described in Binks et al. 2005</td>
<td>Tin smelter worker cohort (United Kingdom) 1937–2001 (employment and follow-up period) N = 1,462 male workers</td>
<td>Poisson regression analysis (relative risk [RR]) Lung cancer (ICD-8 code: 162.0–162.1 and ICD-9 code: 162.0–162.9)</td>
<td>Antimony species NR Exposure sources: area and personal air sampling, JEM Quantitative cumulative inhalation exposure (mg-year/m$^3$)</td>
</tr>
<tr>
<td>Wingren and Axelsson 1993; methods described in Wingren and Axelsson 1985</td>
<td>Case-control study of men in art glass-producing area (Sweden) 1950–1982 (mortality period) N for cases and controls = NR</td>
<td>Case-control analysis (OR) Cases: stomach cancer (ICD-8 code: 151); colon cancer (code: NR) Controls: death other than cancer or cardiovascular disease</td>
<td>Antimony(III) trioxide Exposure status determined by listed occupation in death registry Intensity (based on glass works consumption patterns)</td>
</tr>
</tbody>
</table>


4.2 Study quality and utility evaluation

This section assesses the adequacy of the identified cohort and case-control studies to evaluate cancer hazard of antimony. This assessment considers factors relating to study quality (potential for selection and attrition bias, information bias regarding exposure and outcome, and concern for inadequate analytical methods, selective reporting, and inadequate methods or information to
evaluate confounding) and study sensitivity (e.g., adequate numbers of individuals exposed to substantial levels of antimony). The ratings for each of these factors are provided in Table 4-2 and the rationale for the rating is described in detail in Appendix C, Tables C-1 to C-6.

No critical concerns for the potential for any of the bias domains were identified in the available studies; thus, each study may be informative for evaluating potential cancer hazards. The occupational cohort and case-control populations had small numbers of exposed cancer deaths, and, therefore, suffered from low statistical power. Table 4-2 depicts the overall assessment of the ability to inform the cancer evaluation based on the overall utility of the studies, including potential for biases and study sensitivity.

Table 4-2. Summary of ratings for concerns for potential bias, study quality, and study utility in antimony epidemiology studies

<table>
<thead>
<tr>
<th>Study type, citation</th>
<th>Concern 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><strong>Cohort studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimony smelter workers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jones 1994</td>
<td>++</td>
<td>+++/++</td>
<td>+++</td>
</tr>
<tr>
<td>Schnorr et al. 1995</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Tin smelter workers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jones et al. 2007</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Case-control study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wingren and Axelson 1993</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

*aLevels of concern for bias and for study quality rating. Equal column width for types of bias does not imply they have equal weight (see RoC Handbook for description of terms): +++ = low/minimal concern or high quality; +++/+ = minimal/some concern or high/medium quality; ++ = some concern or medium quality; + = major concern or low quality; 0 = critical concern.

*bUtility of the study to inform the hazard evaluation (see RoC Handbook for description of terms): +++ = high utility; +++/++ = high/moderate utility; ++ = moderate utility; ++/+ = moderate/low utility; + = low utility; 0 = inadequate utility.

All three retrospective cohort studies (Jones 1994, Schnorr et al. 1995, Jones et al. 2007) had low risk of selection bias because they all had clearly defined cohorts by exposure status during specific time periods and geographic locations associated with the antimony and tin smelters. All cohort studies had minimal (3.0% to 5.7%) loss to follow-up, and relied on death certificates to trace workers’ outcome status. Bias due to healthy worker survival effect (HWSE) is possible in all studies, though unlikely. Observed all-cause mortality rates in study participants did not differ from the general population. All three cohort studies enrolled workers already employed by the smelter companies and likely already exposed to antimony before enrollment, although all three studies accounted for time-since-exposure in their analyses.
The cohort studies of metal smelter workers (Jones 1994, Schnorr et al. 1995, Jones et al. 2007) were deemed to have some concern for non-differential exposure misclassification, and the case-control study of Swedish art glass workers (Wingren and Axelson 1993) had major concerns for exposure misclassification (see Appendix C, Table C-2). Reasons for these concerns include lack of individual-level exposure data (Wingren and Axelson 1993, Jones et al. 2007), lack of exposure information prior to enrollment date, and reliance on ever-exposure to antimony. Furthermore, antimony exposure likely varied over time as changes in occupational smelting practices and different source materials were reported in studies. To better characterize exposure, reliance on job titles (Jones 1994) and worker functions (Jones et al. 2007) allowed for greater specificity. Regardless, exposure misclassification in all four studies is non-differential and would likely attenuate effect estimates.

Major concerns for confounding bias were found in studies of antimony smelter workers (Jones 1994) and the art glass worker case-control study (Wingren and Axelson 1993), and moderate concern in the studies of antimony smelter workers (Schnorr et al. 1995) and tin smelter workers (Jones et al. 2007) (see Appendix C, Table C-5). No studies controlled for lifestyle-related confounders such as smoking, or occupational co-exposures, e.g., arsenic, lead, asbestos, or polycyclic aromatic hydrocarbons (PAHs). Although smoking prevalence was not directly controlled for in the three occupational cohort studies, smoking rates were assessed. Occupational co-exposure to lead, arsenic, and PAHs were identified or concurrently examined, but were not adequately controlled for in all occupational metal-working cohorts; however, in some studies, available monitoring data on co-exposures and antimony helped inform the evaluation of confounding bias. Lead and asbestos were suspected occupational co-exposures in the case-control study involving art glass workers. Given there is either some concern (Jones et al. 2007) or major concern (Wingren and Axelson 1993, Jones 1994) for confounding bias in most studies (a noted exception is minimal concern for confounding bias in Schnorr et al. [1995]), reported estimates of antimony exposure and both lung and stomach cancer mortalities may be confounded by smoking and/or occupational co-exposures.

The available studies on antimony exposure had low, moderate, or moderate-to-high utility in informing a cancer hazard evaluation (Table 4-2).

Two studies of antimony smelter workers (Jones 1994, Schnorr et al. 1995) were judged to have moderate-to-high study utility based on potential biases and moderate concern for study sensitivity. A critical factor lowering the utility for informing a cancer hazard was potential confounding from co-exposures to known carcinogens for lung and stomach cancers.

The cohort of tin smelter workers (Jones et al. 2007) was rated as having moderate study utility, with moderate concerns for exposure misclassification and confounding, and major concerns for study sensitivity. The Swedish-based case-control study (Wingren and Axelson 1985) was rated as having low study utility due to major concerns for potential exposure misclassification, confounding bias from occupational co-exposures, and major concerns for study sensitivity.

4.3 Cancer hazard assessment

The primary cancer sites evaluated are lung (Section 4.3.1) and stomach cancers (Section 4.3.2). Other cancer sites are briefly summarized in Section 4.3.3.
4.3.1 Lung cancer

Among all cancers, lung cancer has the highest mortality rate and the third highest incidence rate in the United States. From 1975 to 2014, age-adjusted incidence rates per 100,000 people were 84.2 for men and 46.3 for women in the general U.S. population (see Table 15.6 of Howlader et al. 2017). Lung cancer mortality rates are comparable to their respective incidence rates given the low five-year survival rate (18.1%) based on 2007 to 2013 age-adjusted data (Table 15.12 of Howlader et al. 2017), suggesting incidence and mortality data may have similar ability to inform a cancer evaluation.

Potential confounders evaluated in relevant antimony exposure studies include occupational co-exposures and non-occupational exposures or lifestyle factors. Among antimony smelters or glass workers, lung carcinogens most likely to be present in the occupational setting include arsenic and lead and, to a lesser extent, PAHs and asbestos (IARC 2017a).

Evidence from individual studies

The available occupational cohort studies of antimony and lung cancer include a cohort of U.K. antimony smelter workers, a cohort of U.S. antimony smelter workers, and a cohort of U.K. tin smelter workers. Based on the study quality evaluation, these three studies were considered to be informative for inclusion in the cancer assessment. The findings from individual studies are discussed below and presented in Table 4-3.

Jones (1994) reported a significantly increased risk of lung cancer mortality in antimony smelter workers compared with local mortality rates in England and Wales (standardized mortality ratio [SMR] = 1.55, 95% CI = 1.11 to 2.11; presented in Figure 4-1). The elevated risk of lung cancer mortality was maintained only for workers who joined prior to 1961 (SMR = 2.18, 95% CI = 1.51 to 3.04), and not for workers who joined during or after 1961 (SMR = 0.54, 95% CI = 0.20 to 1.20). No trend in lung cancer mortality was seen when stratifying by years as an antimony worker; however, an increased risk of lung cancer mortality was seen in antimony workers whose first exposure was more than 20 years ago. Changes in antimony smelting practices may help explain why the increased risk of lung cancer was only observed among workers hired at earlier time periods; however, follow-up (which is thought to be at least 20 years) may not be long enough for workers hired at later time periods. Considering the study included prevalent hires before the study enrollment date, it is possible the study missed antimony workers who may have been too sick to participate (i.e., HWSE).
Table 4-3. Evidence from epidemiological cohort and case-control studies on lung and stomach cancers and exposure to antimony

<table>
<thead>
<tr>
<th>Reference, location, study-design and year</th>
<th>Population description &amp; exposure assessment method</th>
<th>Exposure category</th>
<th>Risk estimate (95% CI)</th>
<th>Exposed cases</th>
<th>Covariates</th>
<th>Comments, strengths and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones 1994 Cohort, Northeast England, United Kingdom</td>
<td>Population: Antimony smelter workers N = 1,420 men</td>
<td>Lung cancer: Ever employed antimony workers, SMR (95% CI)</td>
<td>Ever antimony worker [1.55 (1.11–2.11)]</td>
<td>37</td>
<td>Age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exposure assessment method: company records</td>
<td></td>
<td>Before 1/1/1961 [2.18 (1.49–3.07)]</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>After 12/31/1960 [0.54 (0.18–1.27)]</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stomach cancer: Ever employed antimony workers, SMR (95% CI)</td>
<td>Ever antimony worker [0.42 (0.05–1.51)]</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schnorr et al. 1995 Cohort, Southern Texas, United States</td>
<td>Population: Antimony smelter workers N = 1,014 men</td>
<td>Lung cancer: External analysis - U.S. white male mortality rates, SMR (95% CI)</td>
<td>Ever antimony worker [0.75 (0.51–1.07)]</td>
<td>30</td>
<td>Age, calendar year, latency period</td>
<td>Exposure information: Exposure level: Ever exposure to antimony defined as employment in antimony plant for 3+ months from 1937–1971. Exposure duration: &lt; 5 years to &gt; 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung cancer: External analysis - Texas ethnic-specific mortality rates, SMR (90% CI)</td>
<td>Ever antimony worker 1.39 (1.01–1.88)</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference, location, study-design and year</td>
<td>Population description &amp; exposure assessment method</td>
<td>Exposure category</td>
<td>Risk estimate (95% CI)</td>
<td>Exposed cases</td>
<td>Covariates</td>
<td>Comments, strengths and limitations</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-----------------------------------------------------</td>
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</tr>
<tr>
<td>follow-up: 1937–1989 (employment and follow-up period)</td>
<td>assessment method: company records</td>
<td>&lt; 5 years employment</td>
<td>SMR only: 0.83</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5–10 years employment</td>
<td>SMR only: 2.24</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 10 years employment</td>
<td>SMR only: 2.73</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stomach cancer: External analysis – U.S. white male mortality rates, SMR (95% CI)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Ever antimony worker</td>
<td>1.49 (0.71–2.74)</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stomach cancer: External analysis – Texas ethnic-specific mortality rates, SMR (95% CI)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Ever antimony worker</td>
<td>1.24 (0.50–2.55)</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model 1(^a) (unweighted)</td>
<td>[1.23 (0.79–1.92)]</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model 1(^a) (weighted)</td>
<td>[5.26 (1.75–43.38)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model 2(^b) (unweighted)</td>
<td>[1.13 (0.80–1.60)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model 2(^b) (weighted)</td>
<td>[3.25 (1.32–21.76)]</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Model 3(^c) (unweighted)</td>
<td>[1.12 (0.80–1.55)]</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model 3(^c) (weighted)</td>
<td>[3.32 (1.42–8.08)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung cancer: Cumulative exposure, beta coefficient ((\beta)) (90% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model 1(^a) (unweighted)</td>
<td>0.21 (0.24–0.65)</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model 1(^a) (weighted)</td>
<td>1.66 (0.56–3.77)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model 2(^b) (unweighted)</td>
<td>0.12 (0.22–0.47)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model 2(^b) (weighted)</td>
<td>1.18 (0.28–3.08)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Exposure information:**
- **Exposure level:** cumulative antimony inhalation over employment duration.
- **Confounding concern:** Highly correlated antimony, lead, and arsenic air concentrations; minimal concern for smoking, but not controlled for in analysis.
- **Strengths:** Concentration-response relationship examined; use of JEM from work histories and 20 years of air measurements; antimony exposure years based on employment.

**Confounding concern:** Minimal concern from smoking, arsenic, and lead exposure.

**Strengths:** Antimony workers primarily exposed to antimony compounds; both national and local ethnic-specific expected mortality rates were calculated; two-time air sampling of antimony and arsenic.

**Limitations:** External analysis only; small number of exposed cases for lung and stomach cancers; individual-level data on exposure not available.

**Level of evidence:** Some evidence (lung); some evidence (stomach)
<table>
<thead>
<tr>
<th>Reference, location, study-design and year</th>
<th>Population description &amp; exposure assessment method</th>
<th>Exposure category</th>
<th>Risk estimate (95% CI)</th>
<th>Exposed cases</th>
<th>Covariates</th>
<th>Comments, strengths and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No use</td>
<td>2.00 (1.30–3.10)</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low level of use</td>
<td>1.60 (0.90–2.60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>High level of use</td>
<td>0.80 (0.30–2.00)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NR = Not reported; [ ] = NTP calculated risk estimates and 95% CI.

*aModel 1: back-extrapolated missing air concentrations, holding 1972–1974 concentrations constant.*

cModel 3: back-extrapolated missing air concentrations by increasing (1937–1960) then decreasing (1960s–1970s) linear trends.
Study limitations that decrease this study’s sensitivity include a small-to-moderate number of exposed cases, no direct control of smoking or occupational co-exposures, and lack of individual-level exposure data. Occupational co-exposures to other lung cancer carcinogens at this smelter site include arsenic and arsenic compounds and possibly PAHs from blast furnaces. Given the reported variable use of arsenic and arsenic(III) trioxide in the smelting process over the study period, it is difficult to determine if arsenic exposure is confounding the relationship without more information. Jones (1994) noted smoking prevalence for all workers at the smelter site in 1961 was 72%. However, zircon sand millers in the same cohort had a lower lung cancer mortality risk than the referent population (SMR = 0.57, 95% CI = 0.18 to 1.33; 5 cases), suggesting that smoking alone may not account for all increased lung cancer mortality. Overall, the evidence for an association for exposure specific to antimony and lung cancer is inconclusive.

Schnorr et al. (1995) reported a lung cancer SMR of 1.39 (90% CI = 1.01 to 1.88) for white and Spanish-surnamed antimony smelter workers in the United States (28 exposed lung cancer cases), when compared with state ethnic-specific expected lung cancer deaths (presented in Figure 4-1). Longer employment duration increased the risk of lung cancer mortality for white and Spanish-surnamed men (test for trend = $P < 0.005$). When compared to the expected U.S. white male mortality rates, the risk of lung cancer mortality was not elevated in antimony smelter workers.

Several limitations may impact the interpretation of the risk estimates in this study (Schnorr et al. 1995), and they include the small-to-moderate number of exposed cases and lack of individual-level exposure data. Smoking and occupational co-exposures to other lung cancer carcinogens, such as arsenic and lead, were noted but not assessed in the study; however, bias from confounding was minimal. Spanish-surnamed workers were assumed to have substantially lower smoking and lung cancer mortality rates based on national trend data of Mexican-Americans at the time. Composition of antimony ore and air sampling of arsenic were assessed at the smelter site. Authors noted the sourced ore generally contained less than 1% arsenic and lead, and 32% to 60% antimony. Furthermore, arsenic air concentrations were orders of magnitude lower than antimony concentrations: in 1975, mean airborne concentrations were 2 µg/m$^3$ arsenic and 551 µg/m$^3$ for 8-hour area samples; in 1976, mean airborne concentrations were 5 µg/m$^3$ arsenic and 747 µg/m$^3$ antimony for 8-hour personal (breathing zone) samples. Therefore, arsenic exposure is unlikely to fully account for the excess lung cancer mortality seen in this population. Overall, this study provides some evidence that antimony exposure is associated with an increased risk of lung cancer mortality, despite its limited sample size and lack of individual-level exposure data.

Jones et al. (2007) reported an increased risk for lung cancer mortality for workers with both unweighted and weighted cumulative exposure to ambient antimony in three different exposure scenarios, although significant risk estimates were seen only when exposure was weighted by attained age and time since exposure. In one exposure scenario (presented in Figure 4-1) where missing antimony air concentrations were assumed to be the mean of 1972 to 1974 concentrations, the calculated relative risk of lung cancer mortality from weighted cumulative antimony exposure was 3.25 (90% CI = 1.32 to 21.76). In an alternative exposure scenario where antimony air concentrations in 1937 were assumed to have been twice the mean measurements from 1972 to 1974, the calculated relative risk of lung cancer mortality from weighted cumulative antimony exposure was 5.26 (90% CI = 1.75 to 43.38). A dose-response relationship
between cumulative exposure to antimony air concentrations and lung cancer mortality was seen for all three scenarios.

Limitations of the Jones et al. study (2007) included a small number of exposed cases and moderate concerns for potential biases (e.g., exposure misclassification and confounding). Although the study attempted to estimate missing antimony exposure measurements spanning over 30 years via data extrapolation, modeled exposure levels and timing of exposure may not represent true antimony concentrations and, thus, may not reflect true exposure for workers prior to 1972.

The reported association between antimony exposure and lung cancer is potentially due to confounding from occupational arsenic and lead exposures. Based on air monitoring data at the smelter site, median estimated cumulative air lead concentrations (1.5 mg/m³-year) were higher than either arsenic (0.28 mg/m³-year) or antimony (0.37 mg/m³-year) from 1972 to 1991. Besides reporting increased lung cancer risk from antimony exposure, Jones et al. (2007) reported an increased risk of lung cancer mortality for weighted cumulative exposure to lead and arsenic, but not cadmium or polonium-210, in three exposure scenarios. A high level of correlation between lead, arsenic, and antimony air concentrations was seen at the smelter site, suggesting concurrent exposure. It is possible that arsenic, a known and potent lung carcinogen, is driving the observed incident lung cancer in this cohort. Since all three metals are highly correlated and offer similar slopes in their exposure-response relationships, the causality of one exposure over the other cannot be separated.

Although not controlled for in the analysis, smoking was likely not confounding the effect in Jones et al. (2007) given the large effect estimate and positive dose-response relationship observed. Furthermore, mortality from other non-cancer smoking-related diseases was not elevated in this cohort (Binks et al. 2005). Overall, this study provides inconclusive evidence that antimony exposure is positively associated with lung cancer mortality.

**Integration of evidence across studies**

Figure 4-1 displays the results of the three available studies in a forest plot. Risk estimates (SMR and RR) and confidence intervals (90% or 95% CI) show the relationship between metal smelter workers occupationally exposed to antimony and risk of lung cancer mortality.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Utility</th>
<th>Risk Estimate (90% or 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones 1994 (UK)</td>
<td></td>
<td>SMR = 1.55 (95% CI = 1.11 to 2.11)</td>
</tr>
<tr>
<td>Schnorr et al. 1995 (US)</td>
<td>+++</td>
<td>SMR = 1.39 (90% CI = 1.01 to 1.88)</td>
</tr>
<tr>
<td>Jones et al. 2007 (UK)</td>
<td>++</td>
<td>RR = 3.25 (90% CI = 1.32 to 21.76)</td>
</tr>
</tbody>
</table>

![Figure 4-1](image.png)

**Figure 4-1. Forest plot of effect estimates of lung cancer mortality (SMR or RR, 90% or 95% CI) in metal smelter workers exposed to antimony in available cohort studies**

All three studies found an elevated relative risk of lung cancer mortality in workers exposed to antimony in an occupational smelter setting, with a magnitude of effect of lung cancer mortality
ranging from 1.39 to 5.23, based on both ever-exposure to antimony (Jones 1994, Schnorr et al. 1995) and a positive dose-response relationship (Jones et al. 2007). Workers from these cohorts were likely exposed to numerous antimony species, including antimony sulfides, antimony oxides, and other antimony compounds both from naturally occurring antimony ore and via the smelting process.

Human studies on antimony exposure and lung cancer were limited to three studies with a small number of antimony-exposed lung cancer cases. Unaccounted occupational co-exposures to lead and arsenic may be confounding these associations. Therefore, it is difficult to attribute lung cancer solely to occupational antimony exposure. Workers at all three smelter sites were exposed to a complex mixture of metals and other known lung cancer carcinogens. Concomitant exposure to compounds operating via mechanistic pathways lead to possible additive, more than additive, or other effects. Furthermore, limited information on smoking in each study population may have accounted for some, but not all, of the increased mortality attributed to antimony exposure.

4.3.2 Stomach cancer

In 2017, there will be approximately 28,000 cases and 10,960 deaths of stomach cancer in the United States (https://seer.cancer.gov/). For stomach cancer from 1975 to 2014, age-adjusted incidence rates for men in the United States were 12.6 per 100,000 men (see Table 24.5 of Howlader et al. 2017). Similar to lung cancer, stomach cancer has comparable low five-year survival rate (30.3%) based on 2007 to 2013 SEER age-adjusted data (see Table 24.8 of Howlader et al. 2017). Given the low survival for stomach cancer, mortality data may have similar utility as incidence data do.

Based on the study quality evaluation, two occupational cohort studies (Jones 1994, Schnorr et al. 1995) and one case-control study (Wingren and Axelson 1993) reporting on stomach cancer and antimony exposure were considered to be informative and were included in the cancer hazard assessment. The findings from individual studies are discussed below and presented in Table 4-3 and Appendix C, Tables C-1 to C-6. The two available occupational cohort studies of antimony and stomach cancer were a cohort of U.S. antimony smelter workers (Schnorr et al. 1995) and a cohort of U.K. tin smelters (Jones 1994). The available case-control study (Wingren and Axelson 1993) compared antimony exposure in cases of stomach cancer and local controls in a Sweden art glass-producing area.

**Evidence from individual studies**

The U.K. cohort of antimony smelter workers (Jones 1994) reported a non-statistically significant decrease in the risk of stomach cancer mortality in workers at an antimony smelter site compared with local mortality rates in England and Wales (SMR = 0.42, 95% CI = 0.05 to 1.51). As mentioned in Section 4.2.3, limitations of this study include a very low number of exposed cases, no direct control of smoking, and lack of individual-level exposure data. Evidence is inconclusive for the association of antimony exposure and stomach cancer mortality.

A non-statistically significant increase in the risk of stomach cancer mortality was seen in exposed workers from a U.S. antimony smelter, compared with both the national white male mortality rate (SMR = 1.49, 95% CI = 0.71 to 2.74; 10 cases) and state ethnic-specific male mortality rate (SMR = 1.24, 95% CI = 0.50 to 2.55; 7 cases) (Schnorr et al. 1995). As noted in
Section 4.2.3, limitations of this study include a small number of stomach cancer deaths and lack of individual-level exposure data. The likelihood of confounding bias from smoking and lead exposure (both stomach cancer carcinogens) was minimal. Although lead exposure was concomitantly present, lead made up < 1% of the antimony ore used at this plant. This study offers some evidence that antimony exposure increases risk of stomach cancer mortality.

A case-control study of Swedish art glass workers (Wingren and Axelson 1993) found an increased association of stomach cancer mortality in glass workers who died in parishes with low antimony consumption (odds ratio [OR] = 1.60, 90% CI = 0.90 to 2.60), but not in parishes with high antimony consumption (OR = 0.80, 90% CI = 0.30 to 2.00), when compared with the unexposed controls in these parishes. The highest risk of stomach cancer mortality was actually found in glass workers who died in parishes with no reported antimony consumption (OR = 2.00, 90% CI = 1.30 to 3.10), compared with unexposed controls in these parishes.

Major limitations in this study (Wingren and Axelson 1993) raise the potential for biased estimates and lowered study quality. The study did not report the number of cases or controls studied. Exposure to antimony was based on job title at death, which may be subject to misclassification. Furthermore, the characterization of exposure to antimony was not on an individual level, but was based on antimony consumption patterns by glassworks. These antimony consumption patterns were solely based on a survey of metal consumption in the 1960s, and exposure at other periods was unknown.

Potential confounders that were not directly controlled for in Wingren and Axelson (1993) include smoking and occupational exposure to lead and asbestos. Although smoking prevalence was unknown, a previous study (Wingren and Axelson 1985) of the same study population reported a lower lung cancer mortality in the cohort compared with the Swedish mortality rate (SMR = 0.50, 95% CI = 0.32 to 0.74), which suggests that smoking was not associated with antimony exposure. Lead consumption was highly correlated with antimony consumption in the study ($r = 0.76$), and elevated lead air concentrations and detected lead on blowpipes used in the glass-working process were reported. Furthermore, an increased risk of stomach cancer mortality was found in glass workers who died in parishes with both low lead consumption (OR = 1.70, 90% CI = 1.00 to 2.80) and high lead consumption (OR = 1.50, 90% CI = 1.00 to 2.30), compared to unexposed controls. Therefore, the increased risk in stomach cancer mortality seen in workers who died in parishes with low antimony consumption may be subject to confounding bias by lead co-exposures. Asbestos was widely used in the art glass working process until the mid-1970s to handle warm glass products and in furnaces, leading to likely asbestos exposure among participants. Asbestos, however, is unlikely to be a major confounder given the lower rates of lung cancer deaths in the study population from a previous study on the same study population (Wingren and Axelson 1985). Overall, this study provides inconclusive evidence of antimony exposure and stomach cancer mortality.

**Integration of evidence across studies**

The available studies do not indicate a consistent pattern of increased stomach cancer mortality associated with antimony exposure. In similar populations of antimony smelter workers, two studies offered conflicting results for antimony exposure and risk of stomach cancer mortality. The case-control study of a Swedish art glass region only showed nonsignificantly increased odds of stomach cancer mortality for cases who died in parishes with low antimony.
consumption, but not in parishes with high antimony consumption. Additionally, co-exposure to other stomach cancer carcinogens, including lead, and smoking, may be confounding the reported associations.

4.3.3 Other types of cancers

Available data are inadequate to evaluate other types of cancers in human studies of antimony exposure. Two cohort studies examined colon cancer mortality in relation to antimony exposure, but they reached conflicting conclusions. Schnorr et al. (1995) reported only two colon cancer cases in U.S. antimony smelter workers. The study found a significantly lower risk of colon cancer mortality in antimony-exposed workers (SMR = 0.12, 95% CI = 0.01 to 0.45) compared with U.S. white males. Wingren and Axelson (1993), on the contrary, reported an increased OR of 5.00 (90% CI = 2.60 to 9.60) for colon cancer in male glass workers who died in a parish where glassworks reported using a high level of antimony, compared with unexposed controls. Furthermore, an increasing trend of colon cancer risk was seen with greater consumption of antimony by parish. Although these trends may indicate an increased risk for colon cancer, lack of adequate individual-level exposure information and potential confounding by co-exposure to other metals limited the interpretation of these results.

Jones (1994) reported other malignant neoplasms in antimony smelter workers, but no cancer sites were specified. Schnorr et al. (1995) also reported increased risks of mortality in cancers in buccal cavity and pharynx, liver, biliary tract, and gall bladder, as well as cancers from unspecified sites in male antimony smelter workers, when compared with U.S. mortality rates and to state ethnic-specific rates. However, the available data are inadequate to evaluate these cancer sites given the lack of a priori hypotheses as noted by Schnorr et al. (1995) and no additional studies examining these specific endpoints.

Guo et al. (2016) saw an increased risk of malignant neoplasms in National Health and Nutrition Examination Survey (NHANES) participants when comparing the highest quartile of urinary antimony concentrations to the lowest quartile (fully-adjusted hazard ratio [HR] = 1.20, 95% CI = 0.70 to 2.06). However, no trend was seen across quartiles (P-value for trend test = 0.20). Furthermore, as noted in the introduction, all malignant neoplasms (i.e., all sites as one outcome) are insensitive for evaluating potential cancer hazards.

4.4 NTP preliminary level of evidence conclusion

The available human studies are inadequate to evaluate the relationship between antimony exposure and human cancer. The reported excess lung and stomach cancer deaths associated with occupational antimony exposure are potentially confounded by co-exposure to other lung and stomach cancer carcinogens.

The relevant data for evaluation of antimony exposure are two cohort studies of antimony smelter workers in the United Kingdom (Jones 1994) and the United States (Schnorr et al. 1995), a cohort study of tin smelter workers in the United Kingdom (Jones et al. 2007), and a case-control study of art glass workers in Sweden (Wingren and Axelson 1993).

For lung cancer, elevated mortality was seen in all studies of antimony-exposed smelter worker cohorts. Results may be impacted due to non-differential exposure misclassification and confounding bias due to concurrent exposure from other metals.
An increased risk of stomach cancer was found in the U.S. antimony smelter cohort study (Schnorr et al. 1995) and the Swedish case-control study (Wingren and Axelson 1993), but not in the U.K. antimony smelter cohort study (Jones 1994).
5 Studies of Cancer in Experimental Animals

This section reviews and assesses the evidence from carcinogenicity studies in experimental animals exposed to antimony(III) trioxide, applies the RoC listing criteria to reach a preliminary level of evidence conclusion of carcinogenicity.

Experimental animal carcinogenicity studies of antimony(III) trioxide were identified using methods described in the protocol and literature search strategy document (see Appendix A). Briefly, besides having a concurrent or historical control group, and reporting study design and results with sufficient detail, studies to be included need to meet one of the three following inclusion criteria (NTP 2015): (1) had an exposure duration of 12 months or greater for rats and mice and reported on the presence or absence of neoplastic and related nonneoplastic lesions (e.g., preneoplastic lesions or lesions considered part of the morphological continuum of neoplasia); (2) had a less than 12-month exposure, but showed increased neoplastic lesions; or (3) were cocarcinogen exposure studies (initiation/promotion and other cocarcinogen studies).

Among 16 papers initially identified, four papers met the inclusion criteria. Among the 12 excluded papers, nine were not carcinogenicity studies, while three were carcinogenicity studies, but they tested antimony combined with nickel (Sunderman and McCully 1983, Sunderman et al. 1984, Sunderman 1984). The effects from antimony alone cannot be identified for these papers, and thus these three papers were excluded.

Among the seven studies for antimony(III) trioxide reported in four papers (NTP 2017a, Groth et al. 1986, Watt 1983, Newton et al. 1994), five studies were used in this assessment. The study by Watt (1983) was a dissertation and not in the peer-reviewed literature, but it was cited in an IARC monograph (IARC 1989) and therefore considered peer reviewed by IARC. One of the two studies in Watt (1983) was excluded because the one-year exposure in the miniature pig study did not cover a significant portion of the animal’s life span of 15 years (Ellegaard et al. 2010). One of two studies in the Groth et al. (1986) study was excluded due to having tested antimony ore that contained only 46% antimony, along with large amounts of other metals. In short, seven carcinogenicity studies in six journal articles and one carcinogenicity study in a dissertation were evaluated (Table 5-1).

Section 5 is organized by tumor site for tumors caused by exposure to antimony(III) trioxide. Section 5.1 provides an overview of the studies reviewed. Section 5.2 reports the quality of the included studies. Section 5.3 reports neoplastic findings (lung neoplasms in Section 5.3.1; other neoplasms (adrenal gland neoplasms, skin neoplasms, and lymphoma) in Section 5.3.2). Section 5.4 synthesizes findings across studies and provides NTP preliminary level of evidence conclusion.

5.1 Overview of the studies

All five antimony trioxide carcinogenicity studies listed in Table 5-1 used inhalation exposure. Two studies exposed rats and mice for the whole duration of the study, two years, with interim sacrifice at 6 months and 12 months (NTP 2017a). Three studies exposed rats for approximately one year, followed by at least four months of post-exposure observation (Watt 1983, Groth et al. 1986, Newton et al. 1994). All studies used both sexes of rats or mice, except the Watt (1983)
study, in which only female rats were used. The studies in rats were conducted in four different strains or stocks.

Table 5-1. Experimental animal studies evaluated for carcinogenicity of antimony(III) trioxide

Studies are presented in descending order of overall utility in informing carcinogenicity (see Section 5.2 and Table 5-2). Whole-study durations are combined exposure and post-exposure follow-up durations.

<table>
<thead>
<tr>
<th>Species, strain or stock (sex)</th>
<th>Route</th>
<th>Exposure/whole-study duration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat, Wistar Han (M&amp;F)</td>
<td>Inhalation</td>
<td>105 weeks/105 weeks</td>
<td>NTP 2017a</td>
</tr>
<tr>
<td>Mouse, B6C3F1/N (M&amp;F)</td>
<td>Inhalation</td>
<td>105 weeks /105 weeks</td>
<td>NTP 2017a</td>
</tr>
<tr>
<td>Rat, F344 (M&amp;F)</td>
<td>Inhalation</td>
<td>12 months/24 months</td>
<td>Newton et al. 1994</td>
</tr>
<tr>
<td>Rat, CDF (F)</td>
<td>Inhalation</td>
<td>1 year/2 years</td>
<td>Watt 1983</td>
</tr>
<tr>
<td>Rat, Wistar (M&amp;F)</td>
<td>Inhalation</td>
<td>53 weeks /71–73 weeks</td>
<td>Groth et al. 1986</td>
</tr>
</tbody>
</table>

M = male, F = female.

5.2 Study quality assessment

Each primary carcinogenicity study was systematically evaluated for its utility in informing the cancer hazard evaluation. A series of questions related to the following study performance elements was used: study design, exposure conditions, outcome, confounding, reporting, and analysis (see Protocol for Preparing RoC Monographs at https://ntp.niehs.nih.gov/ntp/roc/handbook/roc_handbook_508.pdf). The following subsections discuss antimony(III) trioxide studies. Each study was evaluated individually and is presented in descending order of overall utility in determining carcinogenicity (Table 5-2). For details of each study assessment, see Appendix D.

All studies used concurrent negative controls, and two studies (NTP 2017a) also included historical control data. Two studies reported that animals were randomly assigned to treatment groups (Newton et al. 1994, NTP 2017a), while the older studies did not report whether randomization was performed. The study durations approached near life-span durations in all but one study, Groth et al. (1986), which was less than a year and a half. Tumors were appropriately reported in all studies. The remaining ratings for study quality factors are reported in Table 5-2.

Table 5-2. Quality assessments of antimony trioxide cancer studies in experimental animals

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</td>
<td>R</td>
<td>M</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Sex</td>
<td>MF</td>
<td>MF</td>
<td>MF</td>
<td>F</td>
<td>MF</td>
</tr>
<tr>
<td>Study design</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = not reported.
### Table: Antimony Trioxide Studies Summary

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent controls</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Animal model</td>
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<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Statistical power</td>
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<td>+++</td>
<td>+</td>
<td>+++</td>
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<tr>
<td>Exposure</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Chemical characterization</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Dosing regimen</td>
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<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Exposure duration</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Dose/response</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Outcome methodology</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>Group methodology consistency</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Adequacy of study duration</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Confounding</td>
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<tr>
<td>Consideration of confounding</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Analysis and reporting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Reporting and statistics</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Tumor combining</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>NR</td>
<td></td>
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<tr>
<td>Study judgment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall utility</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

In the row for species, R = rats, M = mice. In the row for sex, M = males, F = females. In rows for each signaling question, NR = not reported, +++ = high utility, ++ = moderate utility, + = low utility. The two most recent antimony trioxide studies (NTP 2017a) presented no concerns regarding the utility to assess the cancer hazard and were considered of high overall utility.

Two antimony(III) trioxide studies were considered of moderate overall utility for assessing cancer hazard. The Watt (1983) study used fewer than 10 CDF rats per group, limiting the statistical power of the study, and also used only females, eliminating the ability to detect cancer increases in males or differences between sexes. Furthermore, only a few organs were reported to have been examined during necropsy. The statistical methods used for tumor incidences were not reported. In the Newton et al. (1994) study, the highest exposure level caused no changes in body weight, survival, or tumor incidence, so the dose levels might not have reached the maximally tolerated dose.
One antimony(III) trioxide study (Groth et al. 1986) is considered to have a low utility for the cancer hazard evaluation due to several concerns. The antimony(III) trioxide used was only 80% pure and was contaminated with arsenic (a known human carcinogen and animal carcinogen [NTP 2016b]) and lead (a reasonably anticipated human carcinogen and animal carcinogen. [NTP 2016a]). Arsenic and lead are potential confounders depending on the tumor site. For instance, lung tumors (benign adenoma and malignant carcinoma), lymphocytic leukemia, and lymphoma were seen in animals exposed to arsenic (NTP 2016b). Lung was one of tumor sites in animals after lead exposure (NTP 2016a).

5.3 Findings from carcinogenicity studies

Increased neoplastic lesions were observed in antimony(III) trioxide studies (see Table 5-3). Four of five studies showed increased neoplasms, and all four reported increases in lung neoplasms in rats or mice (Watt 1983, Groth et al. 1986, NTP 2017a). One study did not report an increase in neoplasms, but did report an increase in preneoplastic lung lesions (Newton et al. 1994). The NTP studies (2017a) also reported increases in adrenal gland tumors in Wistar Han rats, and increases in lymphoma and skin tumors in B6C3F1/N mice. For detailed results at each tested concentration, see Table 5-8. Four studies were performed in rats; three studies were in both sexes (Groth et al. 1986, Newton et al. 1994, NTP 2017a) and one study was in just female rats (Watt 1983). One study was in mice of both sexes (NTP 2017a).
Table 5-3. Neoplasms induced in experimental animal carcinogenicity studies of inhaled antimony(III) trioxide.
Studies are presented in the order of descending overall utility.

<table>
<thead>
<tr>
<th>Species*, strain or stock</th>
<th>Site</th>
<th>Classification</th>
<th>Neoplasms (Sex of animal)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat, Wistar Han</td>
<td>Adrenal gland</td>
<td>Benign</td>
<td>Pheochromocytoma (M and F)</td>
<td>NTP 2017a</td>
</tr>
<tr>
<td></td>
<td>Adrenal gland</td>
<td>Combined</td>
<td>Pheochromocytoma (F)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>Benign</td>
<td>Alveolar/bronchiolar adenoma (M* and F)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>Combined</td>
<td>Alveolar/bronchiolar adenoma or carcinoma (M*)</td>
<td></td>
</tr>
<tr>
<td>Mouse, B6C3F1/N</td>
<td>Lung</td>
<td>Benign</td>
<td>Alveolar/bronchiolar adenoma (F)</td>
<td>NTP 2017a</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>Malignant</td>
<td>Alveolar/bronchiolar carcinoma (M and F)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>Combined</td>
<td>Alveolar/bronchiolar adenoma or carcinoma (F)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td>Benign</td>
<td>Fibrous histiocytoma (M)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td>Combined</td>
<td>Fibrous histiocytoma or fibrosarcoma (M)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Whole body</td>
<td>Malignant</td>
<td>Lymphoma (F)</td>
<td></td>
</tr>
<tr>
<td>Rat, Wistar</td>
<td>Lung</td>
<td>Benign</td>
<td>Bronchiolar/alveolar adenoma (F)</td>
<td>Groth et al. 1986</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>Malignant</td>
<td>Squamous-cell carcinoma (F)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>Malignant</td>
<td>Scirrhous carcinoma (F)</td>
<td></td>
</tr>
<tr>
<td>Rat, Fischer 344</td>
<td>None</td>
<td>None</td>
<td>None (M and F)</td>
<td>Newton et al. 1994</td>
</tr>
<tr>
<td>Rat (F only), CDF</td>
<td>Lung</td>
<td>Malignant</td>
<td>Scirrhous carcinoma (F)</td>
<td>Watt 1983</td>
</tr>
</tbody>
</table>

F = female, M = male.
*Considered evidence of antimony trioxide based on multiple factors, although the increase in incidence was not statistically significant.
*Both sexes, unless specified.
In the Classification column, combined = benign or malignant (total number of animals with tumors).
5.3.1 Lung neoplasms

Increased incidences of lung tumors were seen in three of the four rat studies and in the mouse study.

The NTP (2017a) 2-year study included a 1-year interim sacrifice in addition to the sacrifice at the end of the study. The NTP (2017) study is discussed below in an order that follows the progression of lung tumor development, i.e., from preneoplastic hyperplasia to benign adenoma and then to malignant carcinoma.

Nonneoplastic lesions of the lung relevant to the carcinogenic process were increased in treated groups compared with vehicle controls. Both sexes of B6C3F1/N mice and Wistar Han rats had increased incidences of preneoplastic hyperplasia of alveolar and/or bronchiolar epithelium (see Table 5-4), in all exposed groups (3, 10, and 30 mg/m$^3$) after two years (NTP 2017a).

Table 5-4. Lung tumors in the 2-year NTP 2017a studies

<table>
<thead>
<tr>
<th>Antimony trioxide concentration →</th>
<th>3 mg/m$^3$</th>
<th>10 mg/m$^3$</th>
<th>30 mg/m$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary overload</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Preneoplastic$^a$</td>
<td>↑ F, ↑ M</td>
<td>↑ F, ↑ M</td>
<td>↑ F, ↑ M</td>
</tr>
<tr>
<td>Benign</td>
<td>↑ F</td>
<td>↑ F</td>
<td>↑ F</td>
</tr>
<tr>
<td>Malignant</td>
<td>↑ F, ↑ M</td>
<td>↑ F, ↑ M</td>
<td>↑ F, ↑ M</td>
</tr>
<tr>
<td>Combined</td>
<td>↑ F, ↑ M</td>
<td>↑ F, ↑ M</td>
<td>↑ F, ↑ M</td>
</tr>
<tr>
<td>Rat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary overload</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Preneoplastic$^a$</td>
<td>↑ F, ↑ M</td>
<td>↑ F$^b$, ↑ M</td>
<td>↑ F$^b$, ↑ M</td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
<td></td>
<td>↑ F$^d$</td>
</tr>
<tr>
<td>Combined</td>
<td>*M</td>
<td>*M</td>
<td>*M</td>
</tr>
</tbody>
</table>

$^a$ Considered evidence of antimony(III) trioxide carcinogenicity based on multiple factors, although the increase in incidence was not statistically significant.
$^b$ F = increase in females.
$^c$ M = increase in males.
$^d$ Increased hyperplasia of both alveolar and bronchiolar epithelium.
Hyperplasia only increased in bronchiolar epithelium, not in alveolar epithelium.
$^c$ Findings include an equivocal finding of benign cystic keratinizing epithelioma and some evidence for alveolar/bronchiolar adenoma.
$^d$ Equivocal finding was seen for malignant squamous-cell carcinoma.

Male Wistar Han rats exposed to 10 or 30 mg/m$^3$ antimony(III) trioxide had higher incidences of alveolar/bronchiolar adenoma than control rats, but the difference was not statistically significant. The incidences did exceed the historical control incidences for inhalation studies. The incidence in the exposed rats might not have reached statistical significance, because the concurrent controls had exceeded the historical control incidence range for inhalation studies and studies by all routes. Furthermore, multiple alveolar/bronchiolar adenoma, not seen in controls, were observed at 3 and 30 mg/m$^3$. While alveolar/bronchiolar carcinoma was seen in only two
Wistar Han rats in the 10 mg/m$^3$ group (not significantly increased), the incidences were zero (0) in the concurrent and historical controls. The combined incidences of alveolar/bronchiolar adenoma or carcinoma were increased in all treated groups of males. The observations above together with consideration of historical data and exposure-related increases in lung neoplasms in female Wistar Han rats and male and female B6C3F1/N mice, and the higher combined incidences of adenoma or carcinoma were considered to be some evidence of lung carcinogenicity in male Wistar Han rats (NTP 2017a).

In female Wistar Han rats, incidences of alveolar/bronchiolar adenoma, which were not seen in 300 historical control female Wistar Han rats, were higher (though not statistically significant) at 3 mg/m$^3$, and were significantly increased at 10 and 30 mg/m$^3$ in the 2-year study. Additionally, at the 12-month interim evaluation, one female Wistar Han rat exposed to 30 mg/m$^3$ had alveolar/bronchiolar adenoma. Adenoma is known to progress to carcinoma, but no alveolar/bronchiolar carcinoma was seen, and the combined incidence was not increased. The incidence of lung cystic keratinizing epithelioma or squamous-cell carcinoma combined was not significantly increased, but was considered an equivocal finding (i.e., might have been related to exposure). Overall, these data were considered to be some evidence of carcinogenic activity in the lung based on benign alveolar/bronchiolar adenoma in female Wistar Han rats (NTP 2017a).

Because the RoC listing criteria requires malignant and/or combined benign and malignant tumors in experimental animal studies, the findings in female Wistar Han rat lung do not meet the RoC listing criteria.

In the NTP (2017a) studies, as discussed in Section 3 (ADME), pulmonary overload was seen at 10 and 30 mg/m$^3$, but not at 3 mg/m$^3$ for both Wistar Han rats and B6C3F1/N mice, if the same criteria for increased clearance half-life are used for B6C3F1/N mice. At 3 mg/m$^3$, benign lung tumors were increased in female B6C3F1/N mice, malignant lung tumors were increased in male and female B6C3F1/N mice, and combined benign and malignant lung neoplasms were increased in male Wistar Han rats and in male and female B6C3F1/N mice. Lung carcinogenesis occurring at 3 mg/m$^3$, in all groups except female Wistar Han rats, indicates that pulmonary overload is not required to induce carcinogenesis and is supportive of the RoC listing criteria.

For mice, females in all treated groups showed increased incidences in alveolar and bronchiolar epithelium hyperplasia, alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, and alveolar/bronchiolar adenoma or carcinoma (combined) at two years. During the 1-year interim sacrifice a low frequency of alveolar/bronchiolar adenoma were seen in female mice and prominent peribronchial lymphoid infiltrates were seen in the lung providing additional support for antimony(III) trioxide-induced tumorigenesis. Males showed increased alveolar and bronchiolar epithelium hyperplasia in all treated groups, slightly (not significantly) higher incidence of alveolar/bronchiolar adenoma in the 3 and 30 mg/m$^3$ groups, increased incidences of alveolar/bronchiolar carcinoma in all treated groups, and increased combined incidence of alveolar/bronchiolar adenoma or carcinoma in all treated groups after two years. After just one year males had a low frequency of alveolar/bronchiolar adenoma and alveolar/bronchiolar carcinoma. Males treated for one year also had prominent peribronchial lymphoid infiltrates. These early findings indicate lung carcinogenesis related to antimony exposure (NTP 2017a). Tumors were observed at exposure concentration as low as 3 mg/m$^3$. 
In the Groth et al. (1986) study, incidences of alveolar hyperplasia and cuboidal and columnar-cell metaplasia were increased (statistical significance not reported) in female and male Wistar rats, and incidences of benign alveolar/bronchiolar adenoma as well as incidence of malignant lung neoplasms (squamous-cell carcinoma and scirrhous carcinoma) were increased significantly in female rats. Tumor incidences were not increased in male rats. Neoplasms occasionally developed from metaplastic foci, suggesting that metaplastic foci are preneoplastic. As mentioned above, the antimony(III) trioxide used in this study was only 80% pure and was contaminated with arsenic and lead. The concentrations of lead (0.1035 mg/m$^3$) and arsenic (0.0018 mg/m$^3$) in the air were both considered too low to have been the cause of neoplasms. Further, in animal studies, lead predominantly causes kidney neoplasms, which were not observed with antimony(III) trioxide exposure, thus, lead is not likely to have contributed to the carcinogenicity seen in the Groth et al. study (1986). Arsenic causes mice and hamsters to develop lung neoplasms, which were seen in Wistar rats after exposure to antimony. Compared to the concentration of antimony(III) trioxide (36 mg/m$^3$), the concentration of arsenic (0.0018 mg/m$^3$) was inconsequential, which is further supported by (1) much higher levels of antimony than that of arsenic found in the lung in exposed animals (Table 5-5), and (2) higher levels of arsenic in the lung of males, which did not develop lung tumors, compared to that of females, which developed lung tumors. These data suggest that neither arsenic nor lead contributed greatly to the observed incidences of lung cancer in this study, but interaction and other effects cannot be ruled out. Although this assessment is for hazard identification, it is noted that exposure concentrations in the Groth et al. study (1986) varied dramatically (average daily concentrations ranged from less than 10 mg/m$^3$ to more than 80 mg/m$^3$) due to technical difficulties in generating the aerosol, leading to questions about aerosol size and actual exposure level.

Table 5-5. Antimony and arsenic concentrations (µg/g freeze-dried tissue) in the lung and blood of Wistar rats exposed to antimony trioxide containing arsenic by inhalation

<table>
<thead>
<tr>
<th>Tissue conc.</th>
<th>Antimony(III) trioxide</th>
<th>Ratio$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metal and site</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimony in lung</td>
<td>9.2</td>
<td>38,300</td>
</tr>
<tr>
<td>Antimony in blood</td>
<td>12.0</td>
<td>1,160</td>
</tr>
<tr>
<td>Arsenic in lung</td>
<td>6.5</td>
<td>213</td>
</tr>
<tr>
<td>Arsenic in blood</td>
<td>60.0</td>
<td>115</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimony in lung</td>
<td>10.5</td>
<td>25,600</td>
</tr>
<tr>
<td>Antimony in blood</td>
<td>9.6</td>
<td>1,034</td>
</tr>
<tr>
<td>Arsenic in lung</td>
<td>18.5</td>
<td>150</td>
</tr>
<tr>
<td>Arsenic in blood</td>
<td>123.0</td>
<td>230</td>
</tr>
</tbody>
</table>

Source: Groth et al. 1986

$^a$Ratio = Concentration in 45 mg/m$^3$ group/concentration in 0 mg/m$^3$ group. Conc. = concentration.

No increased incidences of neoplasms were observed in the 1-year exposure plus 1-year post-exposure recovery study in male and female F344 rats (Newton et al 1994). The concentrations in that study, 0.06, 0.51, and 4.45 mg/m$^3$, were much lower than the high concentrations used in previously discussed studies (i.e., 45 mg/m$^3$ in Groth et al. [1986], and 30 mg/m$^3$ in NTP...
[2017a]) but the high concentration was comparable to the high dose used by Watt (1983) of 4.2 mg/m³. The aerosol size used in the Newton et al. (1994) study was large, ranging from 2.92 to 4.60 mm and included less respirable aerosols than if they had been < 4.0 mm (EPA 1988, OECD 2017). However, the Watt (1983) study used aerosols that were even larger, averaging 5.06 µm, and Watt reported significant increases in lung tumor incidences. Nonsignificant increases in nonneoplastic alveolar/bronchiolar hyperplasia were found in females, but not in males and significant increases in interstitial inflammation occurred at the termination of the study (Newton et al. 1994). Significant increases in nonneoplastic lesions of alveolar/inter-alveolar macrophages, with or without foreign particulate material, perivascular/peribronchiolar macrophages with lymphoid cells and foreign particulate material, and peribronchial lymph node macrophages with foreign particulate material occurred at both the beginning and the end of the exposure period and at the end of the study in both sexes. Lungs appeared with pinpoint black foci, which the authors believed to be aggregates of macrophages containing antimony(III) trioxide. The strain or stock of rats also differs from that used in the positive studies.

Scirrhous carcinoma in the lung was increased in female CDF rats in a study with one-year exposures at 4.2 mg/m³ (Watt 1983). It is worth noting that scirrhous carcinoma is not a term that NTP currently uses, and it is possible that the same lesions might be classified currently as alveolar/bronchiolar carcinoma. Exposed CDF rats also had significant increases in nonneoplastic lesions of the lung, including focal fibrosis, pneumocyte hyperplasia, and multinucleated giant cells at 1.6 and 4.2 mg/m³, and adenomatous hyperplasia at 4.2 mg/m³.

5.3.2 Other neoplasms

Besides lung neoplasms, benign or malignant pheochromocytoma of the adrenal gland in Wistar Han rats, and benign fibrous histiocytoma or malignant fibrosarcoma of the skin in B6C3F1/N mice, and malignant lymphoma in B6C3F1/N mice, also were increased after antimony(III) trioxide exposure.

Adrenal gland neoplasms

Pheochromocytoma of the adrenal medulla in benign and malignant forms were seen in Wistar Han rats, but not in B6C3F1/N mice, in the NTP (2017a) two-year study.

Female Wistar Han rats in the 30 mg/m³ group had increased incidences of adrenal medullary hyperplasia, increased incidences of benign pheochromocytoma (which also exceeded historical control ranges), one incidence (not significantly increased) of malignant pheochromocytoma, and increased combined incidence of benign or malignant pheochromocytoma (see Table 5-6). Rats exposed to 3 and 10 mg/m³ had higher (but not significant) incidences of adrenal medullary hyperplasia, and the trend for all concentrations was positive. Overall, there is some evidence of adrenal medulla carcinogenicity in female Wistar Han rats (NTP 2017a). The increase in the combined incidences of benign or malignant pheochromocytoma in female Wistar Han rats supports the RoC listing criteria.
Table 5-6. Adrenal medulla neoplasms in Wistar Han rats in the NTP 2017 two-year study.

<table>
<thead>
<tr>
<th>Antimony trioxide concentration →</th>
<th>3 mg/m³</th>
<th>10 mg/m³</th>
<th>30 mg/m³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observations ↓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary overload</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pre-neoplastic*</td>
<td>*M</td>
<td>*F, *M</td>
<td>↑ F, ↑ M</td>
</tr>
<tr>
<td>Benign</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td>↑ F</td>
</tr>
</tbody>
</table>

* Positive trend for dose response, although the increase in incidences was not statistically significant.
↑ F = significant increase in females.
↑ M = significant increase in males.
* Increased incidences of hyperplasia in adrenal medulla.

Male Wistar Han rats in the 30 mg/m³ group had increased incidences of adrenal medullary hyperplasia and increased incidences of benign pheochromocytoma. Incidences of benign pheochromocytoma at 10 mg/m³ were higher, but not significantly increased, compared to concurrent controls. Overall, there is some evidence of adrenal medullary carcinogenicity in female Wistar Han rats (NTP 2017a) based on the increased incidences of benign pheochromocytoma and combined malignant or benign pheochromocytoma.

Adrenal medullary hyperplasia and benign and malignant pheochromocytoma in Wistar Han rats have been seen in other NTP inhalation studies, although the mechanistic association remains unknown. Adrenal medulla pheochromocytoma is known to increase in rats under hypoxic conditions (Chandra et al. 2013). In the antimony(III) trioxide inhalation study (NTP 2017a), Wistar Han rats and B6C3F1/N mice showed abnormal breathing and Wistar Han rats also showed cyanosis in the second year. It is possible that lung-lesion-induced hypoxia chronically stimulates catecholamine secretion from the adrenal medulla, and the constant hypersecretion causes the adrenal medulla to develop hyperplasia (Gosney 1985) and subsequent pheochromocytoma (Ozaki et al. 2002 as cited in NTP 2017a).

**Skin neoplasms**

Skin neoplasms were seen in B6C3F1/N mice, but not in Wistar Han rats, in the NTP (2017a) two-year study. Male B6C3F1/N mice had increased incidences (also exceeding historical control ranges) of benign fibrous histiocytoma at 30 mg/m³ and had a significant positive trend. Two incidences (not significantly increased) of malignant fibrosarcoma were seen at 10 mg/m³, and increased combined incidences of fibrous histiocytoma or fibrosarcoma at 30 mg/m³ which had a significant positive trend also occurred. Overall, there is some evidence of skin carcinogenicity in male B6C3F1/N mice based on increased combined incidences of fibrous histiocytoma or fibrosarcoma. Female B6C3F1/N mice had two incidences (not significantly increased, but exceeding the historical control ranges) of squamous-cell carcinoma at 30 mg/m³ which was considered equivocal evidence of skin carcinogenesis in females.

**Lymphomas**

Increased incidences of malignant lymphoma were seen in female B6C3F1/N mice at all treatment concentrations (3, 10, and 30 mg/m³), with a significant positive dose-response trend.
after two years of exposure (NTP 2017a). The incidences at 10 and 30 mg/m$^3$ also exceeded historical control ranges. After only one year of exposure, a low frequency of female mice developed lymphoma and almost all had lymphocyte infiltration into the lung. The 1-year finding demonstrates an early indication of the development of lymphoma. Preneoplastic proliferation of atypical lymphoid proliferation in the lung and spleen was also seen at the 1-year interim sacrifice. Overall, malignant lymphoma in female B6C3F1/N mice is considered to be clear evidence of carcinogenicity.

None of the other studies (Watt 1983, Groth et al. 1986, Newton et al. 1994) reported significant increases in the incidence of neoplasms other than the lung. Groth et al. (1986) examined most major organs while Newton et al. (1994) examined only a few organs. The extent of necropsy in the Watt study (1983) was not clearly reported. The Groth et al. (1986) and Newton et al. (1994) studies histologically examined the adrenal gland and skin and the Newton et al. (1994) study also examined lymph nodes, but none of these organs was found to have increased incidences of neoplasms. The lack of observed non-lung neoplasms was not due to a lack of examination of the target organ sites.

### 5.4 Synthesis and NTP preliminary level of evidence conclusion

#### 5.4.1 Synthesis

The evidence for the carcinogenic potential from inhalation exposure to antimony(III) trioxide (Table 5-3 and Table 5-8) in experimental animals is strong.

Four antimony trioxide inhalation studies have shown significant increases in the incidences of lung neoplasia in both sexes of rats and mice. Lung neoplasms included scirrhous carcinoma and squamous-cell carcinoma in female Wistar rats and scirrhous carcinoma in female CDF rats, alveolar/bronchiolar carcinoma in male or female B6C3F1/N mice, and alveolar/bronchiolar adenoma in male and female Wistar or Wistar Han rats and female B6C3F1/N mice. Combined incidences of alveolar/bronchiolar adenoma or carcinoma were increased in male Wistar Han rats and male and female B6C3F1/N mice.

Increased incidences of tumors outside the lung were seen in the NTP 2-year antimony(III) trioxide inhalation study (NTP 2017a) and included benign pheochromocytoma of the adrenal gland in male and female Wistar Han rats, combined benign and malignant pheochromocytoma in female Wistar Han rats, benign fibrous histiocytoma and combined fibrous histiocytoma and fibrosarcoma of the skin in male B6C3F1/N mice, and malignant lymphoma in female B6C3F1/N mice.

For all neoplasms, an increase in benign tumors only is not considered to support the RoC listing criteria, but an increase in malignant tumors only or an increase in combined incidences of benign or malignant tumor does meet the criteria. The latter increases were seen for four sites, three sites in rats (two sites in females, one in males) and two sites each in both male and female mice (Table 5-7).
### Table 5-7. Neoplasms that had increased incidences in malignant tumors or combined (benign or malignant) tumors

<table>
<thead>
<tr>
<th>Sites</th>
<th>Rat Malignant</th>
<th>Combined</th>
<th>Mouse Malignant</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>↑ F&lt;sup&gt;a&lt;/sup&gt;</td>
<td>*M&lt;sup&gt;b&lt;/sup&gt;</td>
<td>↑ M&lt;sup&gt;c&lt;/sup&gt;, ↑ F&lt;sup&gt;c&lt;/sup&gt;</td>
<td>↑ F&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>–</td>
<td>↑ F&lt;sup&gt;d&lt;/sup&gt;</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Skin</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>↑ M&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lymphoma (whole body)</td>
<td>–</td>
<td>–</td>
<td>↑ F</td>
<td>–</td>
</tr>
</tbody>
</table>

↑ F = significant increase in females.
↑ M = significant increase in males.
– = No increase reported.
*Considered evidence of antimony(III) trioxide carcinogenicity based on multiple factors, although the increase in incidence was not statistically significant (NTP 2017a).
<sup>a</sup>Squamous-cell carcinoma, scirrhus carcinoma.
<sup>b</sup>Alveolar/bronchiolar adenoma or carcinoma.
<sup>c</sup>Alveolar/bronchiolar carcinoma.
<sup>d</sup>Benign or malignant pheochromocytoma.
<sup>e</sup>Fibrous histiocytoma or fibrosarcoma.

#### 5.4.2 NTP preliminary level of evidence conclusion

Sufficient evidence of carcinogenicity from studies in experimental animals based on the combined increase in the incidences of malignant and benign tumors at several tissue sites in rats and mice.
Table 5.8. Cancer studies in experimental animals from exposure to antimony(III) trioxide

<table>
<thead>
<tr>
<th>Reference and study design</th>
<th>Exposure</th>
<th>Tumor site – Tumor type</th>
<th>Dose levels</th>
<th>Tumor incidence (n/N) (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTP 2017a</td>
<td></td>
<td>Adrenal gland – Benign pheochromocytoma(^a)</td>
<td>0</td>
<td>1/49 (2.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>0/50</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>2/49 (4.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>7/50(^*) (17.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trend P-value: &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung – Alveolar/bronchiolar adenoma(^a)</td>
<td>0</td>
<td>3/50(^b) (7.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>4/50(^b) (9.8%)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>6/50(^b) (13.8%)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>8/50(^c) (19.7%)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Trend P-value: = 0.057</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung – Alveolar/bronchiolar carcinoma(^a)</td>
<td>0</td>
<td>0/50</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>0/50</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>2/50(^c) (4.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>0/50</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung – Alveolar/bronchiolar adenoma or carcinoma(^a)</td>
<td>0</td>
<td>3/50 (7.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>4/50 (9.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>8/50 (18.4%)</td>
<td></td>
</tr>
</tbody>
</table>

**Survival:** Survival had a significant negative trend \((P = 0.025)\), but was not significantly different compared to controls at any exposure level: 30/50, 30/50, 28/50, 18/50.

**Body weight:** Body weight of the 30-mg/m\(^3\) group was lower than untreated controls after 69 weeks.

**Significantly increased preneoplastic lesions:** Lung alveolar epithelium hyperplasia: 4/50, 50/50\(^*\)*, 48/50\(^*\)*, 49/50\(^*\)*

Lung bronchiole epithelium hyperplasia: 3/50, 34/50\(^*\)*, 36/50\(^*\)*, 33/50\(^*\)*

Adrenal medulla hyperplasia: 1/49, 2/50, 4/49, 8/50\(^*\)*

**Overall utility:** [+++] There were no concerns of confounding as the chemical was pure and stable, the exposure was well characterized, and all groups were treated the same. The study had a high level of sensitivity to detect neoplasms as it used large numbers of both sexes of rats, exposed at three dose levels, which reached the maximally tolerated level, for a near life-span duration. However, the stock of rat used was new to NTP and so few historical control data exist compared to other strains. Complete necropsies with histological examination of most organs was performed, so the ability to detect neoplasms was high.

**Footnotes:** * \(P < 0.05\), ** \(P < 0.01\), *** \(P < 0.001\).

\(^a\)Adjusted percent incidence based on Poly-3 estimated
<table>
<thead>
<tr>
<th>Reference and study design</th>
<th>Exposure</th>
<th>Tumor site – Tumor type</th>
<th>Dose levels</th>
<th>Tumor incidence (n/N) (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTP 2017a</td>
<td></td>
<td>Adrenal gland – Benign pheochromocytoma*</td>
<td>30</td>
<td>6/50** (15.2%)</td>
<td></td>
</tr>
<tr>
<td>Animal:</td>
<td></td>
<td></td>
<td>30</td>
<td>8/50 (19.7%)</td>
<td>neoplasm incidence after adjustment for concurrent mortality.</td>
</tr>
<tr>
<td>Rat — Wistar Han [Crl:WI (Han)]</td>
<td></td>
<td></td>
<td>30</td>
<td>8/50 (19.7%)</td>
<td></td>
</tr>
<tr>
<td>Animal age at the beginning of exposure:</td>
<td>6 weeks</td>
<td></td>
<td>30</td>
<td>8/50 (19.7%)</td>
<td></td>
</tr>
<tr>
<td>Study duration:</td>
<td>105 weeks</td>
<td></td>
<td>30</td>
<td>8/50 (19.7%)</td>
<td></td>
</tr>
<tr>
<td>Aerosol size:</td>
<td></td>
<td>Adrenal gland – Malignant pheochromocytoma</td>
<td>0</td>
<td>0/49</td>
<td>Survival: Survival was significantly decreased at 10 and 30 mg/m³ and there was a significant negative trend (P &lt; 0.001): 39/50, 38/50, 28/50 (P = 0.032), 20/50 (P &lt; 0.001).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>2/49 (4.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>2/49 (4.8%)</td>
<td>Body weight: Body weight was lower than controls in the groups exposed to 30, 10, and 3 mg/m³ after 65, 81, and 99 weeks, respectively.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>6/50** (15.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adrenal gland – Benign or malignant pheochromocytoma*</td>
<td>0</td>
<td>0/49</td>
<td>Significantly increased preneoplastic lesions: Lung alveolar epithelium hyperplasia: 5/50, 50/50**, 49/50**, 50/50**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>2/49 (4.5%)</td>
<td>Lung bronchiole epithelium hyperplasia: 6/50, 26/50**, 25/50**, 27/50**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>2/49 (4.8%)</td>
<td>Lung alveolar epithelium squamous metaplasia: 0/50, 5/50*, 3/50, 1/50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>7/50** (17.6%)</td>
<td>Adrenal medulla hyperplasia: 0/49, 0/49, 3/49, 5/50*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung – Alveolar/bronchiolar adenoma*</td>
<td>0</td>
<td>0/50</td>
<td>Overall utility: [+++] There were no concerns of confounding as the chemical was pure and stable, the exposure was well characterized, and all groups were treated the same. The study had a high level of sensitivity to detect neoplasms as it used large numbers of both sexes of rats, exposed at three dose levels, which reached the maximally tolerated level, for a near life-span duration. However, the stock of rat used was new to NTP and so few historical control data exist compared to other strains. Complete necropsies with histological examination of most organs were performed, so the ability to detect neoplasms was high.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>2/50 (4.4%)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>6/50* (13.8%)</td>
<td></td>
</tr>
<tr>
<td>Reference and study design</td>
<td>Exposure</td>
<td>Tumor site – Tumor type</td>
<td>Comments</td>
<td></td>
<td></td>
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<tr>
<td>----------------------------</td>
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</tr>
<tr>
<td></td>
<td>Tumor levels</td>
<td>Tumor incidence (n/N) (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>30</td>
<td>5/50* (12.4%)</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Trend P-value: = 0.029</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Lung – Cystic keratinizing epithelioma or squamous-cell carcinoma*</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>0</td>
<td>0/50</td>
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<td>3</td>
<td>0/50</td>
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<td></td>
<td>10</td>
<td>0/50</td>
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</tr>
<tr>
<td></td>
<td>30</td>
<td>3/50 (7.4%)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Trend P-value: = 0.006</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Lung – Alveolar/bronchiolar adenoma*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>10/50 (21.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>14/50 (32.9%)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>9/50 (21.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>14/50 (34.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTP 2017a</td>
<td>Agent and purity: Antimony(III) trioxide (crystalline form: crystalline, diamond cubic crystal structure) 99.9% Aerosol size: MMAD = 0.9–1.5 µm, GSD 1.7–2.2 Exposure route:</td>
<td>Lung – Alveolar/bronchiolar carcinoma*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal: Mouse — B6C3F1/N M</td>
<td>0</td>
<td>4/50 (8.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal age at the beginning of exposure: 6 weeks</td>
<td>3</td>
<td>18/50*** (40.9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study duration: 105 weeks</td>
<td>10</td>
<td>20/50*** (46.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>27/50*** (62.8%)</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Trend P-value: &lt; 0.001</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Lung – Alveolar/bronchiolar carcinoma, multiple only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0/50</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>3</td>
<td>5/50* (10%)</td>
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</tr>
<tr>
<td></td>
<td>10</td>
<td>6/50** (12%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>30</td>
<td>11/50** (22%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung – Alveolar/bronchiolar adenoma or carcinoma*</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Survival: Survival was significantly decreased at 10 and 30 mg/m³ and there was a significant negative trend (P &lt; 0.001): 38/50, 30/50, 27/50 (P = 0.027), 17/50 (P &lt; 0.001).</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Body weight: Body weights were lower than controls in the 30-mg/m³ group after 73 weeks.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Overall utility: [+++] There were no concerns of confounding as the chemical was pure and stable, the</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Footnotes: * P &lt; 0.05, ** P &lt; 0.01, *** P &lt; 0.001.</td>
<td></td>
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</tr>
</tbody>
</table>

*Adjusted percent incidence based on Poly-3 estimated neoplasm incidence after adjustment for concurrent mortality.
<table>
<thead>
<tr>
<th>Reference and study design</th>
<th>Exposure</th>
<th>Tumor site – Tumor type</th>
<th>Dose levels</th>
<th>Tumor incidence (n/N) (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhalation</strong></td>
<td></td>
<td></td>
<td>0</td>
<td>13/50 (27.5%)</td>
<td>exposure was well characterized, and all groups were treated the same. The study had a high level of sensitivity to detect neoplasms as it used large numbers of both sexes of mice, exposed at three dose levels, which reached the maximally tolerated level, for a near life-span duration. Complete necropsies with histological examination of most organs was performed, so the ability to detect neoplasms was high.</td>
</tr>
<tr>
<td><strong>Exposure concentrations, frequency, and duration:</strong></td>
<td></td>
<td></td>
<td>3</td>
<td>29/50*** (64.5%)</td>
<td><strong>Footnotes:</strong> * P &lt; 0.05, ** P &lt; 0.01, *** P &lt; 0.001.</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td>10</td>
<td>28/50*** (63.6%)</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
<td><strong>Skin – Benign fibrous histiocytoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>0/50</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>1/50 (2.5%)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>1/50 (2.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>4/50* (10.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Skin – Fibrosarcoma</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>0/50</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>0/50</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>2/50 (4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>0/50</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Skin – Fibrous histiocytoma or fibrosarcoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>0/50</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>1/50 (2.5%)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>3/50 (7.3%)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>4/50* (10.6%)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Trend P-value: &lt; 0.001</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>7/50 (15.6%)</td>
<td>Survival was significantly decreased at 10 and 30 mg/m³ and there was a significant negative trend (P &lt; 0.001): 36/50, 31/50, 26/50 (P = 0.032), 15/50 (P &lt; 0.001).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>17/50* (38.1%)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>20/50*** (47.5%)</td>
<td>Body weight: Body weights were lower than controls in the</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Whole body – Malignant lymphoma</strong></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>0/50</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>0/50</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>0/50</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>0/50</td>
<td></td>
</tr>
</tbody>
</table>

A. Antimony (III) trioxide (crystalline form: B6C3F1/N)

B. NTP 2017a

Animal: Mouse — B6C3F1/N

Agent and purity: Antimony (III) trioxide (crystalline form: B6C3F1/N)

Body weight: Body weights were lower than controls in the
<table>
<thead>
<tr>
<th>Reference and study design</th>
<th>Exposure</th>
<th>Tumor site – Tumor type</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dose levels</td>
<td>Tumor incidence (n/N) (%)</td>
</tr>
<tr>
<td>Animal age at the beginning of exposure: 6 weeks</td>
<td>Aerosol size: MMAD = 0.9–1.5 μm, GSD 1.7–2.2</td>
<td>Trend $P$-value: &lt; 0.001</td>
<td>Overall utility: ++[++] There were no concerns of confounding as the chemical was pure and stable, the exposure was well characterized, and all groups were treated the same. The study had a high level of sensitivity to detect neoplasms as it used large numbers of both sexes of mice, exposed at three dose levels, which reached the maximally tolerated level, for a near life-span duration. Complete necropsies with histological examination of most organs was performed, so the ability to detect neoplasms was high.</td>
</tr>
<tr>
<td>Study duration: 105 weeks</td>
<td>Exposure route: Inhalation</td>
<td>Lung – Alveolar/bronchiolar adenoma*</td>
<td>Footnotes: * $P &lt; 0.05$, ** $P &lt; 0.01$, *** $P &lt; 0.001$.</td>
</tr>
<tr>
<td></td>
<td>Exposure concentrations, frequency, and duration: 0 3 10 30 mg/m$^3$ 6 hours/day, 5 days/week × 105 weeks</td>
<td>0</td>
<td>1/50 (2.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>10/50** (22.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>19/50*** (44.9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>8/50** (20.3%)</td>
</tr>
<tr>
<td></td>
<td>Lung – Alveolar/bronchiolar carcinoma*</td>
<td>0</td>
<td>2/50 (4.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>14/50*** (31.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>11/50** (26.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>11/50** (28.8%)</td>
</tr>
<tr>
<td></td>
<td>Lung – Alveolar/bronchiolar carcinoma, multiple only</td>
<td>0</td>
<td>0/50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>7/50** (14%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>6/50* (12%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>4/50* (8%)</td>
</tr>
<tr>
<td></td>
<td>Lung – Alveolar/bronchiolar adenoma or carcinoma*</td>
<td>0</td>
<td>3/50 (6.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>22/50*** (48.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>27/50*** (62.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>18/50*** (43.5%)</td>
</tr>
<tr>
<td></td>
<td>Trend $P$-value: = 0.019</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin – Squamous cell carcinoma</td>
<td>0</td>
<td>0/50</td>
</tr>
<tr>
<td>Reference and study design</td>
<td>Exposure</td>
<td>Tumor site – Tumor type</td>
<td>Dose levels</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------</td>
<td>-------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Groth et al. 1986</td>
<td></td>
<td>Lung – Total neoplasms (M)</td>
<td>0</td>
</tr>
<tr>
<td>Animal:</td>
<td></td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Rat — Wistar M, F</td>
<td></td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Animal age at the beginning of exposure: 8 months</td>
<td></td>
<td>Lung – Squamous cell carcinoma (F)</td>
<td>0</td>
</tr>
<tr>
<td>Study duration: 71 to 73 weeks</td>
<td></td>
<td>Lung – Scirrhous carcinoma (F)</td>
<td>45</td>
</tr>
<tr>
<td>Exposure route: Inhalation</td>
<td></td>
<td>Lung – Bronchioalveolar adenoma (F)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Agent and purity:** Antimony(III) trioxide (crystalline form: not reported) 80% (23 other metals, including Pb 2,300 µg/g, As 40 µg/g, and Ni 1.6 µg/g) Aerosol size: MMAD 2.80 µm
<table>
<thead>
<tr>
<th>Reference and study design</th>
<th>Exposure concentrations, frequency, and duration:</th>
<th>Tumor site – Tumor type</th>
<th>Dose levels</th>
<th>Tumor incidence (n/N) (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newton et al. 1994</td>
<td>45 mg/m³ time-weighted average 7 hours/day, 5 days/week for 6 [5/sex], 9 [5/sex], and 12 [5/sex] months. After 53 weeks (~12 months) the remaining rats [75/sex] were kept unexposed for 18–20 additional weeks before sacrifice [Total time of 71–73 weeks]. Intermediate sacrifices were made to examine distribution of antimony in tissue.</td>
<td>Lung – Carcinoma</td>
<td>0</td>
<td>1/52 (1.9%)</td>
<td>but was found to be only 80% pure, with lead and arsenic as contaminants. The low purity makes distinguishing effects caused by antimony from possible effects caused by the contaminants difficult. The sensitivity of the study to detect neoplasms was low as only one dose level was used and it was based on the level of exposure to workers and not the maximally tolerated dose. Further, the exposure concentration varied widely until 5 months into the study when the target concentration was reached. The exposure duration was more than a year and full necropsies with histological examinations were performed. Neoplasms were reported with statistical analysis as total neoplasms combined per organ site.</td>
</tr>
<tr>
<td>Animal:</td>
<td>Antimony(III) trioxide (crystalline form: not reported)</td>
<td>Lung – Carcinoma</td>
<td>0.06</td>
<td>0/52 (0%)</td>
<td>Footnotes: * P &lt; 0.05, ** P &lt; 0.01, *** P &lt; 0.001. [ ] = Statistical significance calculated by NTP, using Fisher’s Exact test.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung – Carcinoma</td>
<td>0.51</td>
<td>0/53 (0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung – Carcinoma</td>
<td>4.5</td>
<td>1/52 (1.9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung – Carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Survival: Survival was similar to controls.

Body weight: Similar to controls.

Significantly increased preneoplastic lesions: Bronchiolar/alveolar hyperplasia, interstitial inflammation,
### Reference and study design

<table>
<thead>
<tr>
<th>Crl BR)</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal age at the beginning of exposure:</td>
<td>8 weeks (140–169 g males; 99–122 g females)</td>
</tr>
<tr>
<td>Study duration:</td>
<td>24 months</td>
</tr>
</tbody>
</table>

#### Exposure

<table>
<thead>
<tr>
<th>Dose levels</th>
<th>Tumor incidence (n/N) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6/13 (46.2%)</td>
</tr>
<tr>
<td>0.06</td>
<td>11/13[*] (84.6%)</td>
</tr>
<tr>
<td>0.51</td>
<td>9/12 (75%)</td>
</tr>
<tr>
<td>4.5</td>
<td>13/13[***] (100%)</td>
</tr>
</tbody>
</table>

#### Tumor site – Tumor type

<table>
<thead>
<tr>
<th>Alveolar/intra-alveolar macrophages (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>0.06</td>
</tr>
<tr>
<td>0.51</td>
</tr>
<tr>
<td>4.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alveolar/intra-alveolar macrophages with foreign particulates (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>0.06</td>
</tr>
<tr>
<td>0.51</td>
</tr>
<tr>
<td>4.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Perivascular/peribronchiolar macrophages with lymphoid cells and foreign particulates (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>0.06</td>
</tr>
<tr>
<td>0.51</td>
</tr>
<tr>
<td>4.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Peribronchial lymph node macrophages with foreign particulates (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>0.06</td>
</tr>
<tr>
<td>0.51</td>
</tr>
<tr>
<td>4.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lung – Interstitial inflammation (24 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>0.06</td>
</tr>
<tr>
<td>0.51</td>
</tr>
</tbody>
</table>

**Comments**

- interstitial fibrosis, and granulomatous inflammation were increased in the exposed groups.

- An increase in opacities of the eye was seen predominantly in females, but also occurred to a lesser extent in males.

**Overall utility:** [++] There was little concern for confounding as the chemical was pure, exposure conditions were well characterized, and groups were treated consistently with animals randomly assigned to exposure groups. The sensitivity of detecting neoplasms was good as high numbers of both sexes were tested. Exposures were at three concentrations for about half a life-span duration (1 year), though observations (1 year) continued to a near life-span total study duration. However, the highest exposure level did not reach the maximally tolerated level. Most organs were histologically examined, so most neoplasms would have been detected. Although aerosol size was not ideal (slightly over the current upper limit of test guidelines), this study did show Sb₂O₃ accumulation and increased clearance half-life in the lung (by 80% in the 4.5 mg/m³ group). The pulmonary overload was observed at relatively low exposure concentrations (compared to inert particles, such as TiO₂) and Sb₂O₃ toxicity was suspected. It appears conditions that could lead to cancer did persist (Table 9, post-exposure, chronic inflammation in most animals, although hyperplasia was observed in very few animals).
<table>
<thead>
<tr>
<th>Reference and study design</th>
<th>Exposure</th>
<th>Tumor site – Tumor type</th>
<th>Dose levels</th>
<th>Tumor incidence (n/N) (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Bronchiolar/alveolar hyperplasia (24 months)</td>
<td>4.5</td>
<td>48/52[***] (92.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>3/52 (5.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.06</td>
<td>1/52 (1.9%)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0.51</td>
<td>2/53 (3.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.5</td>
<td>4/52 (7.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alveolar/intra-alveolar macrophages (24 months)</td>
<td>0</td>
<td>31/52 (59.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.06</td>
<td>44/52[**] (84.6%)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0.51</td>
<td>46/53[**] (86.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.5</td>
<td>52/52[***] (100%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alveolar/intra-alveolar macrophages with foreign particulates (24 months)</td>
<td>0</td>
<td>0/52 (0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.06</td>
<td>15/52[***] (28.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.51</td>
<td>38/53[***] (71.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.5</td>
<td>51/52[***] (98.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perivascular/peribronchiolar macrophages with lymphoid cells and foreign particulates (24 months)</td>
<td>0</td>
<td>0/52 (0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.06</td>
<td>22/52[**] (42.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.51</td>
<td>46/53[**] (86.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.5</td>
<td>47/52[**] (90.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peribronchial lymph node macrophages with foreign particulates (24 months)</td>
<td>0</td>
<td>0/52 (0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.06</td>
<td>6/52[*] (11.5%)</td>
<td></td>
</tr>
<tr>
<td>Reference and study design</td>
<td>Exposure</td>
<td>Tumor site – Tumor type</td>
<td>Dose levels</td>
<td>Tumor incidence (n/N) (%)</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------------</td>
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<td>-------------</td>
<td>--------------------------</td>
<td>----------</td>
</tr>
<tr>
<td><strong>Newton et al. 1994</strong></td>
<td></td>
<td>Lung – Carcinoma</td>
<td>0.51</td>
<td>34/53[iii] (64.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Animal:</strong> Rat — Fischer 344 (CDF F344 Crl BR)</td>
<td></td>
<td></td>
<td>4.5</td>
<td>39/52[***] (75%)</td>
<td></td>
</tr>
<tr>
<td><strong>Agent and purity:</strong> Antimony(III) trioxide (crystalline form: not reported) 99.68%</td>
<td></td>
<td></td>
<td>0</td>
<td>0/49 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Aerosol size:</strong> MMAD = 3.76 ± 0.84 µm, GSD 1.79 ± 0.32</td>
<td></td>
<td></td>
<td>0.06</td>
<td>0/52 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Exposure route:</strong> Inhalation</td>
<td></td>
<td></td>
<td>0.51</td>
<td>1/54 (1.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Exposure concentrations, frequency, and duration:</strong> 0 0.06 (target 0.05) 0.51 (target 0.5) 4.50 mg/m³ (target 5.0) 6 hours/day, 5 days/week x 12 months</td>
<td></td>
<td></td>
<td>4.5</td>
<td>0/50 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>5 animals/sex were sacrificed at 6 (5/sex), 12</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Survival:</strong> Survival was similar to controls.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Body weight:</strong> Similar to controls.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference and study design</td>
<td>Exposure</td>
<td>Tumor site – Tumor type</td>
<td>Dose levels</td>
<td>Tumor incidence (n/N) (%)</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------</td>
<td>------------------------</td>
<td>-------------</td>
<td>---------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>(5/sex), 18 (5/sex) months and the rest (50/sex) were sacrificed at 24 months.</td>
<td>0</td>
<td>Lung – Interstitial inflammation (24 months)</td>
<td>0/16 (0%)</td>
<td>0.06</td>
<td>0/13 (0%)</td>
</tr>
<tr>
<td></td>
<td>0.06</td>
<td></td>
<td>6/11** (54.5%)</td>
<td>0.51</td>
<td>13/14*** (92.9%)</td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td></td>
<td>4/5 (80%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchiolar/alveolar hyperplasia (24 months)</td>
<td>33/49 (67.3%)</td>
<td>0.06</td>
<td>40/52 (76.9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>48/54*** (88.9%)</td>
<td>0.51</td>
<td>48/50*** (96%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alveolar/intra-alveolar macrophages (24 months)</td>
<td>28/49 (57.1%)</td>
<td>0.06</td>
<td>40/52*** (76.9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>48/54*** (88.9%)</td>
<td>0.51</td>
<td>50/50*** (100%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alveolar/intra-alveolar macrophages with foreign particulates (24 months)</td>
<td>0/49 (0%)</td>
<td>0.06</td>
<td>24/52*** (46.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>49/54*** (90.7%)</td>
<td>0.51</td>
<td>48/50*** (96%)</td>
</tr>
</tbody>
</table>
**Watt 1983**

**Animal:** Rat — CDF F

**Animal age at the beginning of exposure:** NR (Possibly 3 to 5 months)

**Study duration:** 2 years

**Agent and purity:** Antimony(III) trioxide (crystalline form: not reported) 99.4%

**Aerosol size:** MMAD = 5.06 µm

**Exposure route:** Inhalation

<table>
<thead>
<tr>
<th>Dose levels</th>
<th>Tumor incidence (n/N) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0/49 (0%)</td>
</tr>
<tr>
<td>0.06</td>
<td>31/52[***] (59.6%)</td>
</tr>
<tr>
<td>0.51</td>
<td>47/54[***] (87%)</td>
</tr>
<tr>
<td>4.5</td>
<td>47/50[***] (94%)</td>
</tr>
</tbody>
</table>

**Comments**

**Lung — Scirrhous carcinoma**

<table>
<thead>
<tr>
<th>Dose levels</th>
<th>Tumor incidence (n/N) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0/13</td>
</tr>
<tr>
<td>1.6</td>
<td>0/17</td>
</tr>
<tr>
<td>4.2</td>
<td>9/18** (50%)</td>
</tr>
</tbody>
</table>

**Lung — Squamous cell carcinoma**

<table>
<thead>
<tr>
<th>Dose levels</th>
<th>Tumor incidence (n/N) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0/13</td>
</tr>
<tr>
<td>1.6</td>
<td>0/17</td>
</tr>
<tr>
<td>4.2</td>
<td>2/18 (11%)</td>
</tr>
</tbody>
</table>

**Lung — Alveolar/bronchiolar adenoma**

<table>
<thead>
<tr>
<th>Dose levels</th>
<th>Tumor incidence (n/N) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0/13</td>
</tr>
<tr>
<td>1.6</td>
<td>1/17 (5.9%)</td>
</tr>
</tbody>
</table>

**Survival:** Not reported.

**Body weight:** Body weight gain in exposed rats was greater than controls.

**Significantly increased pre-neoplastic lesions:** Lungs from exposed animals appeared grossly mottled – with foci of fibrosis. Focal fibrosis occurred as early as 3 months in the high-dose group and the incidence was significantly increased over controls in the high dose group from 9 months to the end of the study and in the low dose group from 12 months to the end of the study. Significant increases in pneumocyte hyperplasia occurred in both the low and high dose from 12 months to the end of the study.
### Reference and study design

<table>
<thead>
<tr>
<th>Exposure concentrations, frequency, and duration:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1.6 ± 1.5 [avg Feret’s diameter = 0.44 µm w/ geometric std dev 2.23] 4.2 ± 3.2 mg/m³ [avg Feret’s diameter = 0.4 µm w/ geometric std dev 2.13] for 6 hours/day, 5 days/week, for up to 1 year. Sacrifices at 0, 3, 6, 9, 12, and 24 months.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor site – Tumor type</th>
<th>Dose levels</th>
<th>Tumor incidence (n/N) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2</td>
<td>3/18 (16.7%)</td>
<td>study. Significant increases in adenomatous hyperplasia occurred in the high dose group after 9 months to the end of the study. The onset of multinucleated giant cells in the high dose group occurred after 6 months and in the low dose group after 1 year. Significant increases in the incidence of multinucleated giant cells were seen in the high dose group after 9 months and in the low-dose group after 1 year. Other comments: Only the incidence at 2 years is reported here as the denominators of the other time points were all fewer than 10 rats. Scirrhous carcinomas were associated with an unusually large amount of fibrous connective tissue. Overall utility: [++] The chemical purity was high and exposure was characterized, although the particle size (converted by Newton et al. [1994] to be MMAD of approximately 5 µm) was over the recommended (1-4 µm). Only female rats were used, which eliminates the ability to detect sex differences. The sensitivity to detect neoplasms was low as a small number of rats were used at only two dose levels, though the exposure was near life-span duration. The ability to detect neoplasms, if they exist, was moderate as the organs examined during necropsy were not fully reported. The statistical methods used were not reported. The use of large exposure chamber with pigs inside and pine shavings also increased the chance of exposure to non-Sb₂O₃ particles (and possible metabolism alternation due to pine shavings and therefore affecting susceptibility). Footnotes: * P &lt; 0.05, ** P &lt; 0.01, *** P &lt; 0.001.</td>
</tr>
</tbody>
</table>

avg = average; F = female; GSD = geometric standard deviation; M = male; MMAD = mass median aerodynamic diameter; n/N = number of animals with neoplasms divided by the total number of animals tested in that group; NOS = not otherwise specified; NR = not reported; std dev = standard deviation.
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6 Mechanistic and Other Relevant Data

Section 6 provides mechanistic and other relevant data related to understanding the carcinogenicity of antimony trioxide observed in experimental animals (Section 5). Tumor sites observed in animal include lung tumors in rats and mice, adrenal gland tumors in rats, and skin and lymphoma in mice.

Most of the section discusses mechanistic data on antimony(III) trioxide and antimony(III) trichloride, which is similar to antimony(III) trioxide, and is generally organized according to the 10 key characteristics of human carcinogens (Smith et al. 2016) (see Appendix E, Table E-1), with minor exceptions: insufficient studies are available on alterations in cell nutrient supply and immortalization, and receptor-mediated effects are integrated into the section on cell proliferation and cell death. This section is organized as follows: other relevant data on antimony compounds (Section 6.1), electrophilic properties (Section 6.2), genotoxicity (Section 6.3), inhibition of DNA repair (Section 6.4), epigenetic alterations (Section 6.5), oxidative stress (Section 6.6), immunomodulation and inflammation (Section 6.7), and alteration of cell proliferation, cell death, and receptor-mediated effects (Section 6.8). Information derived from analysis of a transcriptome study and high-throughput Tox21/ToxCast screening assays are discussed in Section 6.9. Section 6.10 provides a synthesis of the mechanistic data.

6.1 Other relevant data

This section reviews (1) carcinogenic studies on other antimony compounds because they may help inform whether antimony compounds in general are carcinogenic, and (2) conclusions regarding non-cancer health outcomes because these outcomes could potentially from biological alterations that could also contribute to carcinogenicity.

6.1.1 Carcinogenicity studies of other antimony compounds

Studies of exposure to antimony(III) potassium tartrate in the drinking water in Long-Evans rats (Schroeder et al. 1970) or Swiss CD-1 mice (one study reported in Kanisawa and Schroeder 1969 and Schroeder et al. 1968) showed no increases in tumors (see Appendix E.1 for details on the findings). However, limitations of the study design and reporting leave the question of the carcinogenicity of antimony(III) potassium tartrate unanswered. Limitations in the rat study included the death of many rats from pneumonia and performance of only a gross necropsy (no histopathological examination). In the mouse study, the limitations included testing of only one exposure concentration, which might not have been the maximally tolerated dose; histological evaluation of only gross lesions; and reporting of tumor incidences only for both sexes combined. Antimony(III) potassium tartrate administered orally has relatively low bioavailability (NTP 1992). It is not known whether exposure to antimony(III) potassium tartrate via a more bioavailable route would cause tumors. No carcinogenicity studies of other antimony compounds were identified.

6.1.2 Non-cancer health outcomes

Non-carcinogenic health effects resulting from exposure to antimony are described elsewhere. ATSDR (2017) conducted a systematic review of non-cancer effects in workers and animals exposed to antimony (elemental antimony, antimony ore, and various antimony compounds) and
concluded that antimony is presumed to cause respiratory health effects (e.g., pneumoconiosis, coughing, and laryngitis) in workers following inhalation exposure and gastrointestinal-tract irritation following oral exposure and injections. Suspected human health effects of antimony, based primarily on evidence from animal studies, are cardiovascular (myocardial and electrocardiogram alterations), metabolic (decreased serum glucose levels), and developmental (decreased postnatal growth and birth weight and other effects). While NTP RoC did not investigate the biological alterations leading to these non-cancer health effects or how they might be associated with carcinogenicity, observed respiratory health effects were seen in the lung, a cancer site in laboratory animals exposed to antimony trioxide via inhalation.

6.2 Electrophilic properties
Antimony compounds are electrophilic and might interact directly with nucleic acids (DNA and RNA) and proteins. Antimony, especially in its trivalent form, is highly reactive with sulphydryl groups and, in particular, vicinal thiol groups (reviewed by Wysocki and Tamas 2010). Thiol reactivity may directly affect toxicity by disrupting protein structure, function, and stability. Antimony(III) potassium tartrate directly inhibits glutathione (GSH) reductase (Wyllie and Fairlamb 2006, Moreira et al. 2017) and glutathione S-transferase (GST) in red blood cells (Poon and Chu 2000) (see Section 6.5 for additional details). This antimony compound also reduced protein thiols by 15% to 40% in neonatal cardiac myocytes (Section 6.2). Reaction of antimony(III) with thiols can also target zinc finger domains of DNA-binding proteins and affect their functions, as seen in antimony(III) trichloride displacement of zinc in a DNA repair enzyme (Grosskopf et al. 2010) (see Section 6.3 for additional details).

6.3 Genotoxicity
This section summarizes the results of in vitro, in vivo, and human genotoxicity studies of antimony compounds. The focus is on antimony(III) trioxide, followed by antimony(III) trichloride, and findings from other antimony(III) compounds. Studies with severe limitations are not used for the assessment or discussed in the text, but study details and limitations are summarized in the tables in Appendix E.2 along with studies discussed in the text. This section is organized by genotoxic end point, including mutations, and damage to DNA, chromatids, and chromosomes. Within each end point, the results are generally presented in the order of human studies, in vivo animal studies, in vitro mammalian cell studies, and in vitro bacterial cell studies.

6.3.1 Mutagenicity
Detailed results of the mutagenicity studies are shown in Appendix E.2, Table E.2-1.

Antimony(III) trioxide did not increase mutations in mouse lymphoma L5178Y TK+/− cells in vitro with or without liver S9 metabolic enzymes and cofactors (Elliott et al. 1998).

In bacterial cells (Salmonella typhimurium and Escherichia coli), antimony(III) trioxide (Elliott et al. 1998, Kuroda et al. 1991, Kanematsu et al. 1980) and antimony(III) trichloride (Kuroda et al. 1991, Kanematsu et al. 1980) were not mutagenic in tests conducted with or without S9 metabolic activation in multiple strains that tested both base pair substitutions and frameshift mutations. Overall, the data suggest that antimony(III) compounds are not mutagenic in bacterial assays.
6.3.2 Mutations in antimony(III) trioxide–induced lung tumors

Mutations in tumors seen after a chemical exposure are not direct evidence of a chemical’s mutagenicity, because the mutations might have occurred spontaneously (i.e., not caused by the chemical), by direct effects of the chemical (e.g., mutagenicity), or by indirect effects (e.g., as a result of chemical-induced oxidative stress or inhibition of DNA repair) and progression of tumorigenesis. However, the observation of common mutations in specific types of tumors might still provide information related to carcinogenicity.

Because the epidermal growth factor receptor gene (Egfr) (an oncogene) and Kras (a proto-oncogene) are commonly mutated in human lung neoplasms, the mutations of Egfr and Kras genes were analyzed in the lungs of mice and rats after two-year inhalation exposure to antimony(III) trioxide at 3, 10, or 30 mg/m³ (NTP 2017a). Egfr mutations were seen in the lung tumors of mice (46% of the tissues) and rats (50% of the tissues), whereas no Egfr mutations were seen in non-tumorous lung tissue or in spontaneous lung tumors in the control animals. No Kras mutations were seen in the control rats, and only one Kras mutation was seen in a single lung tumor in antimony(III) trioxide-exposed rats. The incidences of Kras mutations in exposed mice were similar to those in control mice. These data suggest that EGFR signaling might play an important role in pulmonary carcinogenesis resulting from chronic antimony(III) trioxide exposure in both rats and mice (NTP 2017a). Detailed results of the studies are shown in Appendix E.2, Table E.2-2.

6.3.3 DNA damage

Detailed results of DNA damage studies are shown in Appendix E.2, Table E.2-3. Antimony(III) trioxide exposure was associated with DNA damage in mice and in cultured cells.

Although two human studies (Cavallo et al. 2002, El Shanawany et al. 2017) reported an association between increased DNA damage and occupational antimony(III) trioxide exposure, the evidence is inconclusive, because of potential confounding from occupational co-exposures, lack of correlation of urine antimony levels with measured DNA damage, extremely high background levels of DNA damage in one study (El Shanawany et al. 2017), and other limitations.

In animal studies, after 12-month inhalation exposure to antimony(III) trioxide, B6C3F1/N mice of both sexes had significantly increased DNA damage in lung (at 3 mg/m³ or higher in females and 30 mg/m³ in males), but not in blood leukocyte samples at concentrations of up to 30 mg/m³, as measured by the comet assay (NTP 2017a). Wistar Han rats of both sexes with 12-month exposure to antimony(III) trioxide at up to 30 mg/m³ did not show increased DNA damage in the lung or blood leukocytes (NTP 2017a). Oral administration of antimony(III) trioxide to rats did not cause unscheduled DNA synthesis, an indicator of repair of DNA damage, which is less sensitive than the direct measurement of DNA damage (Elliott et al. 1998).

In vitro studies of human whole blood and peripheral blood lymphocytes (Schaumlöffel and Gebel 1998) and V79 Chinese hamster cells (Gebel et al. 1998) exposed to antimony(III) trichloride showed increased DNA damage (single-strand breaks). DNA damage was detected below cytotoxic concentrations and did not involve DNA-protein crosslinks. The latter observation is in contrast to results with arsenic, which is a potent inducer of DNA-protein crosslinks in both hamster and human cells.
In prokaryotes, evidence for DNA damage has been reported from experiments with sensitive
detection capacity. In modified rec assay protocols that increased the sensitivity of the Bacillus subtilis rec assay 20- to 50-fold (Kada 1976, Hirano et al. 1982), antimony(III) trioxide (Kuroda et al. 1991) and antimony(III) trichloride (Kanematsu et al. 1980, Kuroda et al. 1991) both gave positive results. In the very sensitive plasmid pBR322 DNA-nicking assay, trimethylstibine (Sb\textsuperscript{III}(CH\textsubscript{3})\textsubscript{3}) was genotoxic, but antimony(III) potassium tartrate was not (Andrewes et al. 2004). In contrast, in the less sensitive assays, antimony(III) trichloride did not induce SOS DNA repair genes in E. coli (Lantzsch and Gebel 1997) or S. typhimurium (Yamamoto et al. 2002). In the traditional B. subtilis rec assay, antimony(III) trichloride did not inhibit the growth in the repair-deficient bacteria (Nishioka 1975).

6.3.4 Chromosomal aberrations, micronucleus, and sister chromatid exchange

Detailed results of chromosomal aberrations, micronucleus, and sister chromatid exchange (SCE) studies are shown in Appendix E.2, Table E.2-4.

Data in humans are scarce and have many limitations. Occupational inhalation exposure to antimony(III) trioxide did not increase micronucleus formation or SCE in peripheral blood lymphocytes in workers in one study; however, there were few subjects and workers were exposed to relatively low antimony levels (Cavallo et al. 2002).

In animal studies, chromosome aberrations in bone marrow were not increased by oral exposure to antimony(III) trioxide in rats for three weeks, even at a dose that resulted in decreased body weight (Kirkland et al. 2007). Because of the many limitations of the studies in mice (Gurnani et al. 1992a, 1992b), including unknown test-substance purity, lack of positive controls, and mortality at the high dose, it is uncertain whether antimony(III) trioxide (Gurnani et al. 1992b) or antimony(III) trichloride (Gurnani et al. 1992a) induces chromosomal aberrations in mice. Antimony potassium tartrate (described as potassium antimonyl tartrate in the study) administered by intraperitoneal (i.p.) injections increased chromosomal aberrations (excluding gaps and including gaps) in the bone marrow of rats (El Nahas et al. 1982).

In vitro exposure of human leucocytes to antimony(III) trioxide led to increased chromosomal aberrant cells (excluding gaps) in both the presence and absence of S9 mixture (Elliott et al. 1998). Similarly, in vitro exposure to antimony(III) sodium tartrate increased chromatid breaks in human leucocytes (Paton and Allison 1972).

Antimony(III) trioxide increased micronuclei in mature erythrocytes (normochromatic erythrocytes) in mice, but not in rats, after 12 months of inhalation exposure; the increase in mice showed a significant dose-related trend and was significant at the highest dose (30 mg/m\textsuperscript{3}) (NTP 2017a). Micronucleus frequencies in polychromatic erythrocytes were not increased in mice or rats after 12-month inhalation exposure to antimony(III) trioxide (NTP 2017a). Because approximately 1 million erythrocytes per animal were scored by flow cytometry for detection of micronuclei, the method is highly sensitive and able to detect small increases (NTP 2017a). In studies in which 2,000 polychromatic erythrocytes per rat were scored for micronuclei (the current recommendation is to score 4,000 immature erythrocytes per animal, OECD 2016), antimony(III) trioxide did not increase micronuclei in erythrocytes in the bone marrow of mice 24 or 48 hours after a single oral gavage dose of 5,000 mg/kg of body weight (b.w.) or after 8,
15, or 22 days of daily dosing (at up to 1,000 mg/kg b.w.) (Elliott et al. 1998) or in rats after 21 days of daily oral dosing (at up to 1,000 mg/kg b.w. per day) (Kirkland et al. 2007).

In vitro exposure to antimony(III) trioxide increased micronuclei in Chinese hamster V79 cells (Gebel et al. 1998). Following in vitro exposure to antimony(III) trichloride, micronuclei were seen in human peripheral blood lymphocytes (Schaumlöffel and Gebel 1998), V79 Chinese hamster cells (Gebel 1998, Gebel et al. 1998), BES-6 human bronchial epithelial cells, human fibroblasts, and Chinese hamster ovary (CHO)-K1 cells (Huang et al. 1998). Because co-incubation with either superoxide dismutase or catalase did not affect the number of micronuclei detected in human lymphocytes, superoxide or peroxide oxygen species might not have a prominent role in promoting chromosomal damage (Schaumlöffel and Gebel 1998).

SCEs were increased by both antimony(III) trioxide and antimony(III) trichloride in human lymphocytes (Gebel et al. 1997) and Chinese hamster V79 cells (Kuroda et al. 1991).

Studies showed that antimony(III) trioxide and other antimony(III) compounds increased chromosomal aberrations, micronuclei, and sister chromatid exchange. Chromosomal aberrations included chromosome damage (excluding gaps) induced by antimony(III) trioxide by in vitro exposure of human cells (Elliott et al. 1998) and chromatid breaks induced by antimony(III) sodium tartrate by in vitro exposure of human cells (Paton and Allison 1972). Micronuclei were increased by antimony(III) trioxide in vivo and antimony(III) trichloride in vitro exposures. SCEs were increased by antimony(III) trioxide and antimony(III) trichloride in human cells (Gebel et al. 1997) and animal cells (Kuroda et al. 1991).

6.3.5 Summary of genotoxicity results

As summarized in Table 6-1, (1) antimony(III) trioxide and other antimony(III) compounds are not mutagenic in bacterial or mammalian cells, (2) antimony(III) trioxide can cause DNA damage in mouse lung in vivo after long-term inhalation exposure, and (3) antimony(III) trioxide can cause chromosomal aberrations in vitro, micronucleus formation in vivo, and SCE in vitro.

Table 6-1. Summary of genotoxicity data for antimony(III) trioxide and antimony(III) trichloride

<table>
<thead>
<tr>
<th>Endpoint (test system)</th>
<th>Antimony(III) trioxide</th>
<th>Antimony(III) trichloride</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>in vitro</td>
<td>in vivo</td>
</tr>
<tr>
<td><strong>Mutation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any mutation (prokaryotes)</td>
<td>N</td>
<td>–</td>
</tr>
<tr>
<td>Any mutation (eukaryotes)</td>
<td>N</td>
<td>*</td>
</tr>
<tr>
<td><strong>DNA Damage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any DNA damage (prokaryotes)</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Any DNA damage (eukaryotes)</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>DNA-protein crosslinks</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Chromosomal damage/cytogenetic effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromosomal aberrations</td>
<td>P</td>
<td>N a</td>
</tr>
<tr>
<td>Micronucleus induction</td>
<td>–</td>
<td>P</td>
</tr>
<tr>
<td>Sister chromatid exchange</td>
<td>P</td>
<td>–</td>
</tr>
</tbody>
</table>
Results: P = positive, N = negative, – = not reported.
*Mutations were detected in antimony(III) trioxide-induced lung tumors (NTP 2017a). *Negative in rats; uncertain in mice due to severe study limitations. \(^b\) Uncertain because only available study has severe study limitations.

### 6.4 Inhibition of DNA repair

Whether DNA repair pathways are affected by antimony(III) trioxide is of interest because arsenic, a metalloid with similar chemical properties, is known to compromise DNA repair mechanisms (reviewed by Sage et al. 2017). Although effects of antimony(III) trioxide on DNA repair was only investigated indirectly in an unscheduled DNA synthesis study (Elliot et al. 1998), those of antimony(III) trichloride and antimony(III) potassium tartrate have in assays directly measure DNA damage repair and enzymes.

Antimony(III) trioxide did not increase unscheduled DNA synthesis (an indicator of DNA repair) in the liver cells of rats received up to 5000 mg/kg b.w. antimony(III) trioxide via a single oral gavage (Elliot et al. 1998). Because this assay is not very sensitive, the result does not conclusively rule out the possibility that antimony(III) trioxide might affects DNA damage repair.

Antimony(III) trichloride decreased the repair of cyclobutane pyrimidine dimers (CPDs) induced by ultraviolet C (UVC), but not the repair of (6–4) photoproducts (6–4 PP) induced by UVC or DNA adducts induced by benzo[a]pyrene diol epoxide (BPDE), in human lung carcinoma A549 cells (Grosskopf et al. 2010). Proteins in the nucleotide excision repair (NER) pathway were affected differently. Antimony(III) trichloride decreased transcript and protein levels of xeroderma pigmentosum complementation group E (XPE) protein, but it also released zinc from the zinc finger domain of xeroderma pigmentosum complementation group A (XPA) protein and consequently interfered with XPA function, without affecting XPA protein accumulation (Grosskopf et al. 2010). The lesion-specific effect of antimony(III) trichloride can be explained by the need for different enzymes to repair a particular lesion. The repair of the subtler helix disruption associated with CPDs requires XPE and XPA (which coordinates interaction with other NER complex proteins to repair CPDs, but not 6–4 PP), while the repair of the bulkier 6–4 PP is faster and may not require the activity of XPE (Grosskopf et al. 2010).

Antimony(III) trichloride also inhibited \(\gamma\)-radiation-induced DNA repair that correlated with disruption in the signaling cascade controlling the non-homologous end-joining repair (NHEJ) and homologous recombination (HR) repair pathways (Koch et al. 2017). This impairment may be a consequence of antimony’s interaction with critical cysteines in ataxia-telangiectasia mutated kinase (ATM), or RAD51 DNA recombinase, or the zinc finger domain of BRCA1. How antimony influences the function of ATM, RAD51, and BRCA1 is not known.

Antimony(III) potassium tartrate inhibited the repair of UV-induced DNA damage and of \(\gamma\)-radiation-induced DNA double-strand breaks (DSBs) (to less than 10%) in CHO-K1 cells (Takahashi et al. 2002a).

These studies suggest that antimony(III) exposure leads to alterations in the abundance, phosphorylation, or localization of various proteins that regulate or mediate NER, NHEJ, and HR pathways (summarized in Table 6-2). Whether antimony affects other repair pathways, including base-excision repair or mismatch repair, has not been investigated.
Table 6-2. DNA repair pathways and molecules altered by exposure to antimony(III) compounds

<table>
<thead>
<tr>
<th>DNA repair pathway(s)</th>
<th>Effects on DNA repair</th>
<th>Molecules affected</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimony(III) trichloride</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NER</td>
<td>Defect in lesion-specific repair of UVC-induced CPDs in A549 cells (no effect on repair of 6-4PP or BPDE-DNA adducts)</td>
<td>Decreased transcript and protein levels of XPE</td>
<td>Grosskopf et al. 2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Release of zinc from zinc finger domain of XPA</td>
<td></td>
</tr>
<tr>
<td>NHEJ and HR</td>
<td>Inhibition of repair of γ-irradiation-induced DSBs in HeLa cells</td>
<td>Prolonged association of histone H2AX and TP53-binding protein 1 at foci of DSBs</td>
<td>Koch et al. 2017</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diminished phosphorylation of Chk1, but not Chk2, and prolonged DNA-damage-induced cell-cycle arrest at the G2/M checkpoint</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prolonged association of the phosphorylated form of ATM at DSB foci</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diminished phosphorylation and recruitment of repair-associated regulator BRCA1 to DSB foci</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>Inhibition of repair of γ-irradiation-induced DSBs in HeLa cells</td>
<td>Diminished association of the HR-specific marker RAD51 at DSB foci</td>
<td>Koch et al. 2017</td>
</tr>
<tr>
<td><strong>Antimony(III) potassium tartrate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHEJ and HR</td>
<td>Inhibition of repair of γ-irradiation-induced DSBs in CHO-K1 cells</td>
<td>Not reported</td>
<td>Takahashi et al. 2002a</td>
</tr>
</tbody>
</table>

BPDE-DNA adducts = DNA adducts induced by (+)-anti-benzo[a]pyrene diol epoxide, BRCA1 = breast cancer type 1 susceptibility protein, CHK = serine/threonine-protein kinase Chk1 isoform 1 (i.e., checkpoint kinase 1, CHEK1), CHK2 = serine/threonine-protein kinase Chk1 isoform 2 (i.e., checkpoint kinase 2, CHEK2), DSB = double-strand DNA break, RAD51 = DNA repair protein RAD51 homolog (i.e., RAD51 recombinase).

6.5 Epigenetic alterations

Only two studies on DNA and RNA methylation were identified.

In a study of U.S. Native Americans, antimony exposure was linked to increased global methylation of cytosines and, to a lesser extent, increased global methylation of hydroxycytosines of DNA (Tellez-Plaza et al. 2014). Global hypomethylation has been reported to be associated with lung cancer (not from antimony exposure) (Daskalos et al. 2009, Daskalos et al. 2011) and cancer in general, but the change in methylation could also be risk-factor specific (Huang et al. 2016). Both increases and decreases in DNA methylation of various genes have been linked to carcinogenesis at various tissue sites (Witte et al. 2014, Lian et al. 2015), but the global change is less informative.

In cultured embryonic mouse stem cells, exposure to antimony(III) trichloride resulted in a decrease in the levels of modified cytidines, including 5-hydroxymethylcytosine, 5-formylcytosine, and 5-carboxylcytosine, in both DNA and RNA (Xiong et al. 2017). The decrease in 5-hydroxymethylcytosine has been reported to be associated with early stages of epigenetic carcinogenesis in rat liver (Lian et al. 2015).

Overall, although there is some evidence for induction of epigenetic changes by antimony, the data are not sufficient to determine their contribution to the carcinogenicity of antimony(III) trioxide or antimony in general.
6.6 Oxidative stress

Cellular redox imbalance leads to excess accumulation of reactive oxygen species (ROS) and reactive nitrogen species, and causes oxidative stress. Oxidative stress can cause cell damage, affect normal cell processes, and contribute to carcinogenicity (reviewed by Jones 2008, Kim et al. 2015, Smith et al. 2016). Many studies show that trivalent antimony compounds increase oxidative stress in vivo and in vitro.

Although no studies of in vivo oxidative damage by antimony(III) trioxide were found, an in vivo effect of an antimony(V) compound has been reported. Exposure of mice to meglumine antimoniate(V) caused oxidative damage in the forms of protein carbonylation, lipid peroxidation (Bento et al. 2013), and DNA damage (Cantanhêde et al. 2015, Moreira et al. 2017). Organ-specific changes in catalase and superoxide dismutase activities support a role for ROS in protein and lipid damage (Bento et al. 2013, Moreira et al. 2017).

In vitro studies showed that antimony(III) compounds can react with thiol groups on proteins and peptides (e.g., the reduced form of GSH) (see Section 6.1) and consequently inhibit cellular antioxidant defenses. Exposure to antimony(III) trioxide (Mann et al. 2006) and other antimony(III) compounds (antimony trichloride [Hashemzaei et al. 2015] and antimony potassium tartrate [Tirmenstein et al. 1995, Tirmenstein et al. 1997, Poon and Chu 2000, Sudhandiran and Shaha 2003, Wyllie and Fairlamb 2006]) led to an increase in ROS, disruption of mitochondrial membrane potential, or disruption of cellular redox metabolism (through GSH depletion or disruption of GSH production or utilization). The depletion of GSH results in part from the cell’s expulsion of trivalent antimony by binding antimony to GSH or co-transporting antimony and GSH out of the cell (Figure 6-1, #1). Antimony(III) potassium tartrate, but not sodium stibogluconate (which contains pentavalent antimony) inhibits GST activity (Poon and Chu 2000) (Figure 6-1, #3). Also inhibited by antimony are glutathione reductase, by antimony(III) potassium tartrate (Wyllie and Fairlamb 2006), and glutathione peroxidase, by meglumine antimoniate(V) (Moreira et al. 2017) (Figure 6-1, #4, #5).
Figure 6-1. Antimony increases oxidative stress.

The increase in oxidative stress is the overall result of individual effects: (#1) a decrease in the reduced form of glutathione (GSH), (#2) an increase in mitochondrial damage, including decreased mitochondrial membrane potential (MMP) and a consequent increase in ROS, (#3) reduced GST activity, and (#4) inhibition of the activities of GST and (#5) glutathione peroxidase and a consequent imbalance of GSH and its oxidized form (GSSG). Despite protective effects triggered by antimony, such as increased expression and nuclear translocation of nuclear factor (erythroid-derived 2)-like 2 (i.e., Nrf2) caused by antimony(III) trioxide (#6), the overall effect is increased oxidative stress and oxidative damage. Light gray arrows and text indicate effects seen with Sb(V) compounds but not yet studied with Sb(III) compounds.

Studies using antioxidants and inhibitors of various enzymes in the redox process showed that the effects of exposure to antimony(III) trioxide (Mann et al. 2006, Lösler et al. 2009), antimony(III) trichloride (Hashemzaei et al. 2015), and antimony(III) potassium tartrate (Lecureur et al. 2002) are modulated by oxidative stress and/or disruption of antioxidant systems (see Appendix E.3). For example, antimony(III) trioxide–induced apoptosis was further increased by depletion of GSH or inhibition of enzymes (γ-glutamylcysteine synthetase, glutathione peroxidase, or catalase) (Lösler et al. 2009).

Mitochondria can be affected by ROS and can contribute to increased ROS. Antimony(III) trioxide (Lösler et al. 2009), antimony(III) trichloride (Hashemzaei et al. 2015), and antimony(III) potassium tartrate (Lecureur et al. 2002) disrupted mitochondrial membrane potential (Figure 6-1, #2) and induced ROS. Mitochondria, in turn, are a source of antimony(III) trichloride–induced oxidative stress. When primary rat hepatocytes were exposed to both antimony(III) trichloride and a mitochondrial protective agent, the ROS production was less than with exposure to antimony(III) trichloride alone (Hashemzaei et al. 2015). Exposure of cells to...
both antimony(III) trichloride and ROS scavengers prevented the antimony(III) trichloride–
duced decrease in mitochondrial membrane potential.

6.7 Immunomodulation and inflammation

Little is known regarding the effects of antimony(III) compounds on immunity. An
epidemiological study (Kim et al. 1999) reported that workers exposed to high concentrations of
antimony(III) trioxide in the air had altered activation of T and B cells and lowered serum
cytokine and immunoglobulin (Ig) levels. However, this study did not control for potential
confounding factors (e.g., exposure to co-contaminants that could affect immune function), so an
association between antimony exposure and observed changes could not be confirmed.

The majority of studies investigating antimony-mediated effects on immunity involve humans
and animals with parasite infections undergoing treatment with antimony(V) compounds.
Antimony(V) compounds can potentiate inflammatory cytokine responses, macrophage activity,
and expression of interferon-γ by T lymphocytes in vivo and in vitro (Appendix E.4). This
immune-stimulating effect of antimony(V) may be in part from inhibition of Src homology
PTPase1, a key phosphatase involved in regulating cytokine responses and immune-cell
activation (Pathak and Yi 2001).

6.8 Alteration of cell proliferation and receptor-mediated effects

Antimony(III) trioxide has not been reported to inhibit apoptosis, increase cell proliferation, or
encourage angiogenesis. Antimony(III) potassium tartrate inhibits cell differentiation in cultured
skin cells, potentially increasing the chance of tumor development, but in endothelial cells it
decreases angiogenesis, which facilitates tumor growth. It is possible that, like arsenic,
antimony(III) potassium tartrate has both pro- and anti-tumorigenic effects.

In spontaneously immortalized keratinocytes (SIK), exposure to antimony(III) potassium tartrate
or aresnite(III) prevented cell differentiation and preserved colony formation potential at 3 days
post-confluence (Patterson and Rice 2007). Antimony(III) potassium tartrate preserved
proliferation potential via preventing the decrease in EGFR caused by confluence or insulin in
the media, and elevating β-catenin activity as a transcription factor, and preventing the decrease
in active β-catenin level caused by confluence (Patterson and Rice 2007). The effects on EGFR
were also seen in normal human foreskin epithelia cells (Patterson and Rice 2007). These
findings may be relevant to antimony(III) trioxide-induced benign skin tumors (fibrous
histiocytoma) in rats (see Section 5).

The potential role of EGFR in antimony(III) trioxide carcinogenicity is further supported by the
increased Egfr mutation in the alveolar/bronchiolar tumors of mice and rats after long-term
inhalation exposure to antimony(III) trioxide, not seen in non-tumor lung tissue or in

In cultured human umbilical-vein endothelial cells, antimony(III) potassium tartrate suppressed
the activation of several critical receptor kinases involved in angiogenesis, including vascular
endothelial growth factor receptor 2, fibroblast growth factor receptors 1 and 2, tyrosine kinase
with immunoglobulin-like and epithelial growth factor-like domains 2, and erb-b2 receptor
tyrosine kinase 2, at concentrations from 2.5 to 10 µmol/L (Wang et al. 2015). Moreover,
antimony(III) potassium tartrate suppressed the phosphorylation of Src and focal adhesion kinase
in the presence of phosphorylation triggers. These findings support the notion that antimony(III) potassium tartrate has anti-angiogenic properties in endothelial cells; indeed, antimony(III) potassium tartrate inhibited vascularization of non-small-cell lung cancer xenografts in mice.

6.9 Transcriptomics and Tox21/ToxCast high-throughput screening

6.9.1 Transcriptomics

One DNA microarray study (Kawata et al. 2007) of in vitro effects of an antimony(III) compound on a human cell line was found in the National Center for Biotechnology Information Gene Expression Omnibus (NCBI GEO) database (NCBI 2017). HepG2 (human liver carcinoma) cells were exposed to bis(+)–tartarodiantimonate(III) dipotassium trihydrate (i.e., antimony(III) potassium tartrate trihydrate, equivalent to one molecule of antimony(III) potassium tartrate plus three water molecules) at a concentration of 200 µM for 6 hours, and the gene expression changes seen in a Human Genome Focus array (Affymetrix) were compared with changes following exposure to five other substances, including arsenic(III) oxide at 20 µM and nickel(III) chloride hexahydrate at 6.5 nM. The gene expression profile after antimony(III) potassium tartrate trihydrate exposure was most similar to that after nickel(III) chloride hexahydrate exposure.

The microarray data were downloaded from the NCBI GEO database and analyzed in Ingenuity Pathway Analysis (Qiagen) by the NTP ORoC, using the filter of minimal 2-fold change. Of the top ten canonical pathways affected (Appendix E-5, Table E-5-1), seven were related to immune reactions (agranulocyte adhesion and diapedesis, granulocyte adhesion and diapedesis, role of cytokines in mediating communication between immune cells, role of hypercytokinemia or hyperchemokinemia in the pathogenesis of influenza, crosstalk between dendritic cells and natural killer cells, role of interleukin-17A in psoriasis, and role of Wnt/GSK-3β signaling in the pathogenesis of influenza). These findings are consistent with the former use of antimony(III) potassium tartrate as an antiparasitic agent for leishmaniasis. The other three pathways were eicosanoid signaling, bladder-cancer signaling, and detoxification of oxidized guanosine triphosphate (GTP) and deoxyguanosine triphosphate (dGTP). Although antimony is not known to cause urinary-bladder cancer, the chemically similar arsenic increases the incidence of transitional-cell carcinoma of the urinary bladder in humans. An effect on the oxidized GTP and dGTP detoxification pathway is consistent with the observation that various antimony compounds increase oxidative stress (as discussed in Section 6.5).

In the upstream analysis, the top three affected regulators were vascular endothelial growth factor (VEGF), colony-stimulating factor 2 (CSF2) (a cytokine), and the triggering receptor expressed on myeloid cells 1 (TREM1), which stimulates neutrophil- and monocyte-mediated inflammatory responses (Appendix E.6, Table E.6-1). In a 2015 study, antimony(III) potassium tartrate inhibited the VEGF-induced formation of capillary-like structures in endothelial cells (Wang et al. 2015). In other words, antimony(III) potassium tartrate showed anti-tumor effects via anti-angiogenesis in cultured cells. Both CSF2 and TREM1 stimulate immune or inflammatory responses. These top three affected regulators are predominantly involved in skin disease and cancer. Some anti-cancer effects, such as increased differentiation of cells, were also enriched in the gene expression. To identify key factors contributing to potential carcinogenic effects, further analysis is needed. It is also possible that 6-hour exposure leads to mostly acute responses, which may differ from the long-term effects.
6.9.2 Tox21/ToxCast high-throughput screening

A total of six antimony compounds, not including antimony(III) trioxide, were found in the Tox21 (Tice et al. 2013) and ToxCast (Kavlock and Dix 2010, Kavlock et al. 2012) results from the Tox21 Toolbox (NTP 2017b) and iCSS Dashboard (EPA 2017b): (1) acetic acid, antimony(III) salt, (2) antimony potassium(III) tartrate trihydrate, (3) antimony(III) trichloride, (4) antimony(V) sulfide, (5) antimony(III) potassium tartrate hydrate, and (6) triphenylstibine(III).

All of the above antimony compounds except acetic acid, antimony(III) salt and antimony potassium(III) tartrate trihydrate were screened in some of the Tox21 assays, although the assays varied. Among the antimony compounds screened in Tox21, triphenylstibine(III) was also screened in ToxCast in only some of the assays in the Attagene (ATG), CeeTox, and NovaScreen (NVS) platforms. In addition, antimony(III) trichloride was also screened in the ATG platform and three estrogen receptor assays in the NVS platform in ToxCast.

The data are reviewed for antimony compounds screened in the subset of assays (Chiu et al. 2017, IARC 2017b) that relate to the 10 key characteristics of human carcinogens (Smith et al. 2016). For the purpose of comparing different antimony compounds, only the responses from Tox21 assays, in which several antimony compounds were tested, were compared. The half maximal effective concentration (EC$_{50}$) and weighted area under the curve (wAUC) were obtained from the Tox21 Toolbox Activity Profiler. Assay results exhibiting the following characteristics were excluded from the analysis: observed cytotoxicity, autofluorescence, insufficient reporter gene activity readout support, suboptimal National Center for Advancing Translational Sciences fits, or substantial variation between sources. Assays that assessed only cell viability were not included. All effective EC$_{50}$s were within an order of magnitude.

The only pentavalent antimony compound, antimony(V) sulfide, showed no activity in Tox21 assays. Antimony(III) potassium tartrate hydrate was active only in one androgen receptor antagonist assay, which was also activated by antimony(III) potassium tartrate trihydrate. Triphenylstibine was not active in any assays linked with the 10 key characteristics of carcinogens, but was active in assays associated with nuclear receptors, including constitutive androstane receptor, pregnane X receptor, and retinoic acid-related orphan receptors $\gamma$.

Antimony(III) trichloride and antimony(III) potassium tartrate trihydrate had hits in more assays than other screened antimony compounds. Observed hits by both were related to oxidative stress or antagonism of nuclear receptors, including the AR, farnesoid X receptor, and peroxisome proliferator-activated receptor delta. Antimony(III) potassium tartrate trihydrate was also active in an estrogen receptor antagonist assay. One of the common characteristics of nuclear receptors is DNA-binding domain or zinc finger structure. Antimony(III) ions have been reported to displace Zn(II) in zinc finger domains (Nielson et al. 1985, Grosskopf et al. 2010), providing a possible link to the observed antagonist activity of nuclear receptors.

In summary, the activities of antimony compounds in Tox21 assays were mostly antagonistic to nuclear receptors, possibly because of displacement of Zn(II) in the zinc finger structures of these receptors by antimony(III) ions. These assays also indicated an oxidative stress response. Because only one antimony(V) compound was screened, and some of the trivalent compounds...
had very little activity in the Tox21 assays, it is unclear whether antimony(III) compounds are in general more active than antimony(V) compounds.

### 6.10 Integration of mechanistic information

This section summarizes and integrates the primary findings from the mechanistic data on antimony(III) trioxide.

Because of its electrophilicity and affinity to vicinal thiol groups, antimony(III) trioxide is expected to be able to directly interact with GSH and many proteins that have DNA binding domains, such as transcription factors and DNA repair enzymes. Indeed, these effects were seen with antimony(III) trioxide and other antimony compounds.

Generation of oxidative stress appears to be an early event in cells exposed to antimony. Antimony(III) trioxide induces ROS, disrupts mitochondrial membrane potential, and inhibits the enzymes involved in GSH functions, indicating that antimony disrupts enzymes and effectors of the cellular redox system. Excess oxidative stress can cause DNA damage, protein carbonylation, and lipid peroxidation, which were seen after exposure to meglumine antimoniate(V) in vivo.

Antimony(III) trioxide causes DNA damage, chromosomal aberrations, and micronucleus formation in rodents after in vivo exposure, although it is generally not mutagenic. Many studies have shown that various antimony compounds increase oxidative stress and cause oxidative damage. Antimony(III) trioxide also decreases levels of antioxidants in cells. Although antimony(III) trioxide was not used in the DNA repair study, two other antimony(III) compounds decreased DNA repair capacity in human cells in vitro, and the effect was due at least in part to displacement of the zinc(II) in zinc fingers of a DNA repair enzyme.

Antimony(III) trioxide causes mutations in *Egfr* in the lung tumors of mice and rats. Although antimony(III) potassium tartrate inhibits cell differentiation in cultured human skin cells (which is considered to preserve proliferation potential and thereby contribute to possible carcinogenicity) by preventing the decrease in EGFR activity when cells reach confluence, antimony(III) trioxide has not been reported to inhibit cell differentiation or increase cell proliferation.

In summary, based on studies using antimony(III) trioxide and other antimony(III) compounds, antimony(III) trioxide is electrophilic, can cause oxidative stress, likely inhibits DNA repair, can cause oxidative damage, and is likely to decrease cell differentiation. These effects can contribute to carcinogenesis, and all are biologically plausible in humans.
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7 Evidence Integration and Preliminary Listing Recommendation

The purpose of this monograph is to assess the data on the carcinogenicity of antimony(III) trioxide. This section integrates the assessments of the studies on cancer in animals (Section 7.1), mechanistic and other relevant data (Sections 7.2), and studies on cancer in humans (Section 7.3).

7.1 Evidence of carcinogenicity from studies in experimental animals

There is sufficient evidence of the carcinogenicity of antimony(III) trioxide from studies in experimental animals.

The conclusion that antimony(III) trioxide is carcinogenic is based on increased incidences of malignant tumors and increased combined incidences of benign and malignant tumors at several tissue sites in two rodent species exposed to antimony(III) trioxide by inhalation. Increased incidences were observed for lung tumors in rats and mice of both sexes, adrenal-gland tumors in female rats, skin tumors in male mice, and lymphoma in female mice (see Section 5, Tables 5-1 and 5-4). In a two-year study (NTP 2017a), the increased incidences of alveolar/bronchiolar carcinoma and the increased combined incidences of alveolar/bronchiolar adenoma and carcinoma both occurred at exposure levels below the concentration resulting in potential lung overload.

7.2 Summary of mechanistic data

The data from mechanistic studies provide plausible support for carcinogenic activity. Because antimony(III) trioxide may exert its effects through released trivalent antimony ions, effects observed with other trivalent antimony compounds are potentially relevant.

Antimony compounds increase oxidative stress and cause oxidative damage. Antimony(III) trioxide causes DNA damage and micronucleus formation in rodents after in vivo exposure, and causes DNA damage, chromosomal aberrations, and sister chromatid exchange after in vitro exposure, although antimony(III) trioxide is generally not mutagenic.

Although antimony(III) trioxide did not affect unscheduled DNA synthesis (an indicator of DNA repair), two other antimony(III) compounds decreased DNA repair capacity in human cells in vitro, and the effect was due at least in part to displacement of the zinc(II) in the zinc fingers of a DNA repair enzyme.

Antimony(III) potassium tartrate prevents cell differentiation and increases colony formation of human keratinocytes in vitro, at least in part by stabilizing the level of EGFR and elevating the level of β-catenin, a proto-oncogene.

Consistent with antimony’s known high affinity to zinc finger domains of the proteins, several antimony(III) compounds showed antagonist effects on nuclear receptors in high-throughput screening assays, but whether this occurs in vivo has not been confirmed. Although antimony exposure has been associated with global DNA methylation changes in one human study, the role of epigenetic changes in its carcinogenicity is unclear. The immune effects of antimony(III) compounds are unclear.
7.3 Evidence of carcinogenicity from studies in humans

The data from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to antimony(III) trioxide or other antimony compounds.

Elevated mortality was reported in three cohort studies of antimony-exposed workers in the United States (Schnorr et al. 1995, Jones et al. 2007) and the United Kingdom (Jones 1994). In addition, an increased risk of stomach cancer was found in the U.S. antimony smelter cohort study (Schnorr et al. 1995) and a Swedish case-control study of glass workers (Wingren and Axelson 1993), but not in the U.K. antimony smelter cohort study (Jones 1994). However, few studies evaluated each type of cancer, and the results may have been affected by nondifferential exposure misclassification and confounding bias due to co-exposure to other metals.

7.4 Preliminary listing recommendation

This preliminary listing recommendation is based on applying the RoC listing criteria to the body of scientific evidence provided in this monograph.

Antimony(III) trioxide increased the incidences of malignant tumors or the combined malignant and benign tumors at two tissue sites in rats (lung and adrenal gland) and three sites in mice (lung, skin, and lymphoid system).

Biological effects associated with carcinogenicity include increases in oxidative stress and oxidative damage, impairment of DNA damage repair, and possibly inhibition of cell differentiation.

Antimony(III) trioxide is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting data from mechanistic studies.
References


5. Asakura K, Satoh H, Chiba M, Okamoto M, Serizawa K, Nakano M, Omae K. 2009. Genotoxicity studies of heavy metals: lead, bismuth, indium, silver and antimony. *J Occup Health* 51(6): 498-512. (Supported by the IMS (Intelligent Manufacturing Systems) Promotion Center, Manufacturing Science and Technology Center. Authors affiliated with Keio University School of Medicine, Japan; Tohoku University Graduate School of Medicine, Japan; International University of Health and Welfare, Japan; Hitachi Ltd., Japan.)


15. Beyersmann D, Hartwig A. 2008. Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms. *Arch Toxicol* 82(8): 493-512. (Support not reported. Authors affiliated with University of Bremen, Germany; Technical University of Berlin, Germany.)


20. Cantanhêde LF, Almeida LP, Soares REP, Branco PVGC, Pereira SRF. 2015. Soy isoflavones have antimutagenic activity on DNA damage induced by the antileishmanial glucantime (*Meglumine antimoniate*). *Drug Chem Toxicol* 38(3): 312-317. (Supported by FAPEMA (Fundação de Amparo à Pesquisa e ao Desenvolvimento Científico e Tecnológico do Maranhão). Authors affiliated with Federal University of Maranhão, Spain.)


32. Coelho DR, De-Carvalho RR, Rocha RCC, Saint Pierre TD, Paumgarten FJR. 2014. Effects of *in utero* and lactational exposure to Sb-V on rat neurobehavioral development and fertility. *Reprod Toxicol* 50: 98-107. (Supported by the Rio de Janeiro StateAgency for Supporting Research, the the Brazilian National Research Council, and the National School of Public Health. Authors affiliated with Oswaldo Cruz Foundation (FIOCRUZ), Brazil; Pontifical Catholic University of Rio de Janeiro, Brazil.)
33. Colak EH, Yomralioglu T, Nisanci R, Yildirim V, Duran C. 2015. Geostatistical analysis of the relationship between heavy metals in drinking water and cancer incidence in residential areas in the Black Sea region of Turkey. *J Environ Health* 77(6): 86-93. (Supported by the Scientific and Technical Research Council of Turkey. Authors affiliated with Karadeniz Technical University, Turkey; Istanbul Technical University, Turkey.)


35. Cullen A, Kiberd B, Matthews T, Mayne P, Delves HT, O'Regan M. 1998. Antimony in blood and urine of infants. *J Clin Pathol* 51(3): 238-240. (Supported by the National Sudden Infant Death Register of the Irish Sudden Infant Death Association funded by the National Lottery through the Department of Health Authors affiliated with University College Dublin, Ireland; The Irish Sudden Infant Death Association, Ireland; The Children's Hospital, Ireland; University of Southampton, UK; Trinity College, Ireland.)


39. De Oliveira FB, Schettini DA, Ferreira CS, Rates B, Rocha OGF, Frézard F, Demichelis C. 2006. Kinetics of antimony(V) reduction by L-cysteine. Pharmacological implications and application to the determination of antimony in pentavalent antimonal drugs. *J Brazil Chem Soc* 17(8): 1642-1650. (Supported by CNPq, MCT, CAPES and FAPEMIG. Authors affiliated with Universidade Federal de Minas Gerais, Brazil; Fundação Centro Tecnológico de Minas Gerais, Brazil.)


Fondation pour la Recherche Médicale, the Ligue Nationale Francaise contre le Cancer, and the Association pour la Recherche contre la Cancer. Authors affiliated with INSERM, France.)
44. Dopp E, Hartmann LM, Florea AM, von Recklinghausen U, Rabieh S, Shokouhi B, Hirner AV, Rettenmeier AW. 2006. Trimethylantimony dichloride causes genotoxic effects in Chinese hamster ovary cells after forced uptake. *Toxicol Vitro* 20(6): 1060-1065. (Supported by the German Research Foundation. Authors affiliated with University Hospital Essen, Germany; University of Duisburg-Essen, Germany.)
50. Ellegaard L, Cunningham A, Edwards S, Grand N, Nevalainen T, Prescott M, Schuurman T, Steering Group of the Rethink Project. 2010. Welfare of the minipig with special reference to use in regulatory toxicology studies. *J Pharmacol Toxicol Methods* 62(3): 167-183. (Supported by the RETHINK project, a Specific Support Action funded by the European Community 6th Framework Programme. Authors affiliated with Ellegaard Göttingen Minipigs A/S, Denmark; GSK, UK; University of Newcastle School of Agriculture, Food and Rural Development, UK; University of Kuopio, Finland; National Centre for the Replacement, Refinement and Reduction of Animals in Research, UK; Biomedical Research of Wageningen University, Netherlands.)
53. Elshafie AI, Ählin E, Mathsson L, ElGhazali G, Rönnelid J. 2007. Circulating immune complexes (IC) and IC-induced levels of GM-CSF are increased in sudanese patients with acute visceral Leishmania donovani infection undergoing sodium stibogluconate treatment: implications for disease pathogenesis. J Immunol 178(8): 5383-5389. (Supported by the Swedish Society of Medicine, King Gustav V’s 80-years Fund, Swedish League against Rheumatism, Ugglas Foundation, Groschinsky Foundation, Viberg Foundation, and Swedish Fund for Research Without Animal Experiments. Authors affiliated with Uppsala University, Sweden; Alribate University Hospital, Sudan; University of Khartoum, Sudan; King Fahad Medical City, Saudi Arabia.)
62. Fan K, Borden E, Yi T. 2009. Interferon-gamma is induced in human peripheral blood immune cells in vitro by sodium stibogluconate/interleukin-2 and mediates its antitumor activity in vivo. J Interferon Cytokine Res 29(8): 451-460. (Support not reported. Authors affiliated with Lerner Research Institute, OH; Cleveland Clinic Foundation, OH; Taussig Cancer Center, OH.)
64. Felicettti SW, Thomas RG, McClellan RO. 1974b. Retention of inhaled antimony-124 in the beagle dog as a function of temperature of aerosol formation. Health Physics 26(6): 525-531. (Supported by the USAEC. Authors affiliated with Lovelace Foundation for Medical Education and Research, NM.)


67. Filella M, Belzile N, Chen YW. 2002b. Antimony in the environment: A review focused on natural waters I. Occurrence. *Earth Sci Rev* 57(1-2): 125-176. (Supported by the Agence Universitaire de la Francophonie (Programme d’invitation de professeur/chercheur), the Natural Sciences and Engineering Research Council of Canada and the Elliot Lake Research Field Station of Laurentian University. Authors affiliated with University of Geneva, Switzerland; Laurentian University, Canada.)


71. Friedrich K, Vieira FA, Porrozzi R, Marchevsky RS, Miekeley N, Grimaldi G, Jr., Paumgartten FJ. 2012. Disposition of antimony in rhesus monkeys infected with *Leishmania braziliensis* and treated with meglumine antimoniate. *J Toxicol Environ Health A* 75(2): 63-75. (Supported by INOVA-ENSP (National School of Public Health), PAPES-V grants (CNPq-FIOCRUZ) and the the Brazilian National Research Council (CNPq). Authors affiliated with National School of Public Health, Brazil; Oswaldo Cruz Institute, Brazil; Oswaldo Cruz Foundation, Brazil; Pontifical Catholic University of Rio de Janeiro, Brazil.)


73. Gebel T, Christensen S, Dunkelberg H. 1997. Comparative and environmental genotoxicity of antimony and arsenic. *Anticancer Res* 17(4a): 2603-2607. (Support not reported. Authors affiliated with University of Goettingen, Germany.)


76. Gerhardsson L, Brune D, Nordberg GF, Wester PO. 1982. Antimony in lung, liver and kidney tissue from deceased smelter workers. *Scand J Work Environ Health* 8(3): 201-208. (Supported by the Swedish Work Environment Fund. Authors affiliated with Umeå University, Sweden; Scandinavian Institute of Dental Medicine, Norway.)


78. Ghosh M, Roy K, Roy S. 2013. Immunomodulatory effects of antileishmanial drugs. *J Antimicrob Chemother* 68(12): 2834-2838. (Supported by the Network Project and CSIR India. Authors affiliated with CSIR-Indian Institute of Chemical Biology, India.)


82. Grosskopf C, Schwerdtle T, Mullenders LH, Hartwig A. 2010. Antimony impairs nucleotide excision repair: XPA and XPE as potential molecular targets. *Chem Res Toxicol* 23(7): 1175-1183. (Supported by the DFG. Authors affiliated with Technische Universität Berlin, Germany; Westfälische Wilhelms-Universität Münster, Germany; Leiden University Medical Center, Netherlands.)

83. Groth DH, Stettler LE, Burg JR, Busey WM, Grant GC, Wong L. 1986. Carcinogenic effects of antimony trioxide and antimony ore concentrate in rats. *J Toxicol Environ Health* 18(4): 607-626. (Supported by NIOSH and Midwest Research Institute. Authors affiliated with NIOSH, OH; Experimental Pathology Laboratories, VA; College of William and Mary, VA; Midwest Research Institute, MO.)


85. Guan D, Kao HY. 2015. The function, regulation and therapeutic implications of the tumor suppressor protein, PML. *Cell Biosci* 5: 60. (Supported by RO1 HL093269 and DK078965. Authors affiliated with Case Western Reserve University, OH.)


89. Hansen C, Hansen EW, Hansen HR, Gammelgaard B, Stürup S. 2011. Reduction of Sb(V) in a human macrophage cell line measured by HPLC-ICP-MS. Biol Trace Elem Res 144(1-3): 234-243. (Support not reported. Authors affiliated with University of Copenhagen, Denmark; University of Aberdeen, UK.)


91. Hashemzaei M, Pourahmad J, Safaeinejad F, Tabrizian K, Akbari F, Bagheri G, Hosseini MJ, Shahraki J. 2015. Antimony induces oxidative stress and cell death in normal hepatocytes. Toxicol Environ Chem 97(2): 256-265. (Supported by the Zabol University of Medical Sciences. Authors affiliated with Zabol University of Medical Sciences, Iran; Shahid Beheshti University of Medical Sciences, Iran; Zanjan University of Medical Sciences, Iran.)


93. Hebeisen M, Baitzch L, Presotto D, Baumgaertner P, Romero P, Michelin O, Speiser DE, Rufer N. 2013. SHP-1 phosphatase activity counteracts increased T cell receptor affinity. J Clin Invest 123(3): 1044-1056. (Supported by the Swiss National Center of Competence in Research Molecular Oncology, the Ludwig Institute for Cancer Research, and the Swiss Cancer League. Authors affiliated with Lausanne University Hospital Center, Switzerland; University of Lausanne, Switzerland.)

94. Herath I, Vithanage M, Bundschuh J. 2017. Antimony as a global dilemma: Geochemistry, mobility, fate and transport. Environ Pollut 223: 545-559. (Support not reported. Authors affiliated with University of Southern Queensland, Australia; National Institute of Fundamental Studies, Sri Lanka.)

95. Hirano K, Hagiwara T, Ohta Y, Matsumoto H, Kada T. 1982. rec-Assay with spores of Bacillus subtilis with and without metabolic activation. Mutat Res 97(5): 339-347. (Supported by the Ministry of Education, the Ministry of Welfare, the Science and Technology Agency of Japan, the Takamatsu Sunomiya Cancer Research Fund, the Nissan Science Foundation, and the National Institute of Genetics. Authors affiliated with National Institute of Genetics, Japan; Sankyo Co. Ltd., Japan.)

96. Hirano S, Tadano M, Kobayashi Y, Udagawa O, Kato A. 2015. Solubility shift and SUMOylation of promyelocytic leukemia (PML) protein in response to arsenic(III) and fate of the SUMOylated PML. Toxicol Appl Pharmacol 287(3): 191-201. (Supported by the Japan Society for the Promotion of Science. Authors affiliated with National Institute for Environmental Studies, Japan; Chiba University, Japan.)


100. Huang H, Shu SC, Shih JH, Kuo CJ, Chiu ID. 1998. Antimony trichloride induces DNA damage and apoptosis in mammalian cells. *Toxicology* 129(2-3): 113-123. (Supported by the National Science Council, Republic of China. Authors affiliated with National Tsing-Hua University, Taiwan.)


106. ICRP. 1981. Metabolic data for antimony. *Ann ICRP* 6(42403): 46-49. (Support and authors not reported.)


(LSHC-CT-2005- 518417)), the Canceropole programs, and the Leukemia and Lymphoma Society of Canada. Authors affiliated with INSERM/CNRS, France; Hôpital St. Louis, France; Ontario Cancer Institute and McLaughlin Centre for Molecular Medicine, Canada.)


119. Kanisawa M, Schroeder HA. 1969. Life term studies on the effect of trace elements on spontaneous tumors in mice and rats. *Cancer Res* 29(4): 892-895. (Supported by the USPHS, the US Army, the American Cancer Society, and the CIBA Pharmaceutical Company. Authors affiliated with Dartmouth Medical School, NH; Brattleboro Memorial Hospital, VT.)


123. Kentner M, Leinemann M, Schaller KH, Weltle D, Lehnert G. 1995. External and internal antimony exposure in starter battery production. Int Arch Occup Environ Health 67(2): 119-123. (Supported by the VB Autobatterie GmbH. Authors affiliated with University of Gottingen, Germany; University of Erlangen-Nürnberg, Germany.)


126. Kirkland D, Whitwell J, Deyo J, Serex T. 2007. Failure of antimony trioxide to induce micronuclei or chromosomal aberrations in rat bone-marrow after sub-chronic oral dosing. Mutat Res 627(2): 119-128. (Supported by the International Antimony Oxide Industry Association (IAOIA) and the Antimony Trioxide Stakeholders (ATOS). Authors affiliated with Covance Laboratories Ltd., UK; Eastman Chemical Company, TN; Blasland, Bouck & Lee Inc., CA.)

127. Koch B, Maser E, Hartwig A. 2017. Low concentrations of antimony impair DNA damage signaling and the repair of radiation-induced DSB in HeLa S3 cells. Arch Toxicol. (Supported by the Deutsche Forschungsgemeinschaft. Authors affiliated with Karlsruhe Institute of Technology, Germany.)


(Supported by the Ministry of Education, Science and Culture of Japan. Authors affiliated with Osaka City Institute of Public Health and Environmental Sciences, Japan; Osaka City University Medical School, Japan; Seoul Health Junior College, Korea.)


137. Li J, Wei Y, Zhao L, Zhang J, Shangguan Y, Li F, Hou H. 2014. Bioaccessibility of antimony and arsenic in highly polluted soils of the mine area and health risk assessment associated with oral ingestion exposure. Ecotoxicol Environ Saf 110: 308-315. (Supported by the National Natural Science Foundation of China, the Special Environmental Protection Foundation for Public Welfare Projects, THe National Science Foundation for Post-doctoral Scientists of China, and the State Key Laboratory Program. Authors affiliated with Chinese Research Academy of Environmental Sciences, China.)


140. López S, Aguilar L, Mercado L, Bravo M, Quiroz W. 2015. Sb(V) reactivity with human blood components: Redox effects. Plos One 10(1): 12. (Supported by FONDECYT. Authors affiliated with Pontificia Universidad Católica de Valparaíso, Chile.)

1047-1058. (Support not reported. Authors affiliated with Charité Universitätsmedizin Berlin, Germany; Universität Ulm, Germany; Institut für klinische Transfusionsmedizin und Immungenetik, Germany.)


143. Ma DK, Guo JU, Ming GL, Song H. 2009. DNA excision repair proteins and Gadd45 as molecular players for active DNA demethylation. *Cell Cycle* 8(10): 1526-1531. (Supported by NIH, March of Dimes, NARSAD and MSCR. Authors affiliated with Johns Hopkins University School of Medicine, MD.)

144. Majestic BJ, Turner JA, Marcotte AR. 2012. Respirable antimony and other trace-elements inside and outside an elementary school in Flagstaff, AZ, USA. *Sci Total Environ* 435-436: 253-261. (Supported by the Camille and Henry Dreyfus Foundation and the National Science Foundation. Authors affiliated with University of Denver, CO; Northern Arizona University, AZ; Arizona State University, AZ.)


146. Mann KK, Davison K, Colombo M, Colosimo AL, Diaz Z, Padovani AM, Guo Q, Scrivens PJ, Gao W, Mader S, Miller WH, Jr. 2006. Antimony trioxide-induced apoptosis is dependent on SEK1/JNK signaling. *Toxicol Lett* 160(2): 158-170. (Supported by the CIHR, the Montreal Centre for Experimental Therapeutics in Cancer/CIHR/FRSQ, BCRP, Department of the Army, and the U.S. Army Medical Research Acquisition Activity. Authors affiliated with Montreal Centre for Experimental Therapeutics in Cancer and Lady Davis Institute for Medical Research, Canada; Université de Montréal, Canada.)

147. Mansour TE, Bueding E. 1954. The actions of antimonials on glycolytic enzymes of *Schistosoma mansoni*. *Br J Pharmacol Chemother* 9(4): 459-462. (Supported by the Office of Naval Research and NIH. Authors affiliated with Western Reserve University, OH.)


149. Miekeley N, Mortari SR, Schubach AO. 2002. Monitoring of total antimony and its species by ICP-MS and on-line ion chromatography in biological samples from patients treated for leishmaniasis. *Anal Bioanal Chem* 372(3): 495-502. (Supported by CNPq, FAPERJ, and CAPES. Authors affiliated with Pontifical Catholic University, Brazil; Center of Hospital Research Evandro Chagas, Brazil.)

151. Miranda ES, Miekeley N, De-Carvalho RR, Paumgartten FJ. 2006. Developmental toxicity of meglumine antimoniate and transplacental transfer of antimony in the rat. Reprod Toxicol 21(3): 292-300. (Supported by ANVISA, CNPq, and CAPES. Authors affiliated with Oswaldo Cruz Foundation, Brazil; Pontifical Catholic University of Rio de Janeiro, Brazil.)


153. Moreira VR, de Jesus LCL, Soares RP, Silva LDM, Pinto BAS, Melo MN, Paes AMA, Pereira SRF. 2017. Meglumine antimoniate (glucantime) causes oxidative stress-derived DNA damage in BALB/c mice infected by Leishmania (Leishmania) infantum. Antimicrob Agents Chemother 61(6). (Supported by FAPEMA and CAPES. Authors affiliated with Universidade Federal do Maranhão, Brazil; Universidade Federal de Minas Gerais, Brazil)


156. Müller K, Daus B, Mattusch J, Stärk HJ, Wennrich R. 2009. Simultaneous determination of inorganic and organic antimony species by using anion exchange phases for HPLC-ICP-MS and their application to plant extracts of Pteris vittata. Talanta 78(3): 820-826. (Supported by the Deutsche Bundesstiftung Umwelt DBU. Authors affiliated with UFZ Helmholtz Centre for Environmental Research, Germany.)

157. Müller S, Miller WH, Jr., Dejean A. 1998. Trivalent antimonials induce degradation of the PML-RAR oncoprotein and reorganization of the promyelocytic leukemia nuclear bodies in acute promyelocytic leukemia NB4 cells. Blood 92(11): 4308-4316. (Supported by the European Economic Community, the the Association pour la Recherche contre le Cancer, la Fondation pour la Recherche Médicale et le Ministère de la Recherche et de la Technologie, and the Medical Research Council of Canada. Authors affiliated with INSERM, France; McGill University, Canada.)


168. NTP. 2017a. *Draft Toxicology and Carcinogenesis Studies of Antimony Trioxide (CAS No. 1309-64-4) in Wistar Han [Crl:Wi (Han)] Rats and B6C3F1/N Mice (Inhalation Studies).* NTP TR 590. National Toxicology Program, National Institutes of Health. 303 pp.


173. Olmez I, Gulovali MC, Gordon GE, Henkin RI. 1998. Trace elements in human parotid saliva. *Biol Trace Elem Res* 17: 259-270. (Support not reported. Authors affiliated with University of Maryland, MD; Center for Molecular Nutrition and Sensory Disorders, Washington, DC; Massachusetts Institute of Technology, MA; Turkish Aerospace Industries, Inc., Turkey.)


179. Pathak MK, Yi T. 2001. Sodium stibogluconate is a potent inhibitor of protein tyrosine phosphatases and augments cytokine responses in hemopoietic cell lines. *J Immunol* 167(6): 3391-3397. (Supported in part by Grants R01CA79891 and R01MG58893. Authors affiliated with Cleveland Clinic Foundation, OH.)


188. Quiroz W, Arias H, Bravo M, Pinto M, Lobos MG, Cortés M. 2011. Development of analytical method for determination of Sb(V), Sb(III) and TMSb(V) in occupationally exposed human urine samples by HPLC-HG-AFS. *Microchem J* 97(1): 78-84. (Supported by FONDECYT. Authors affiliated with Pontificia Universidad Católica de Valparaíso, Chile; Universidad de Valparaíso, Chile.)

189. Quiroz W, Aguilar L, Barria M, Veneciano J, Martínez D, Bravo M, Lobos MG, Mercado L. 2013. Sb(V) and Sb(III) distribution in human erythrocytes: speciation methodology and the influence of temperature, time and anticoagulants. *Talanta* 115: 902-910. (Supported by FONDECYT and “Dirección de Investigación” of the Pontificia Universidad Católica de Valparaíso. Authors affiliated with Pontificia Universidad Católica de Valparaíso, Chile; Universidad de Valparaíso, Chile.)


191. Ribeiro RR, Ferreira WA, Martins PS, Neto RL, Rocha OG, Le Moyec L, Demicheli C, Frézard F. 2010. Prolonged absorption of antimony(V) by the oral route from non-inclusion meglumine antimoniate-beta-cyclodextrin conjugates. *Biopharm Drug Dispos* 31(2-3): 109-119. (Supported by CNPq and FAPEMIG. Authors affiliated with Universidade Federal de Minas Gerais, Brazil; Universidade Federal do Recôncavo da Bahia, Brazil; Fundação Centro Tecnológico de Minas Gerais, Brazil; CNRS, France.)


194. Sahin U, de Thé H, Lallemand-Breitenbach V. 2014. PML nuclear bodies: assembly and oxidative stress-sensitive sumoylation. *Nucleus* 5(6): 499-507. (Support not reported. Authors affiliated with University Paris Diderot, France; INSERM, France; CNRS, France; Hôpital St. Louis, France; Collège de France, France.)

Nationale contre le Cancer, l’Université Paris Nord, and CNRS. Authors affiliated with Université Paris Nord, France.)


199. Schroeder HA, Mitchener M, Balassa JJ, Kanisawa M, Nason AP. 1968. Zirconium, niobium, antimony and fluorine in mice: effects on growth, survival and tissue levels. J Nutr 95(1): 95-101. (Supported by the Public Health Service, the National Heart Institute, the US Army and CIBA Pharmaceutical Products, Inc. Authors affiliated with Dartmouth Medical School, NH; Brattleboro Memorial Hospital, VT.)

200. Schroeder HA, Mitchener M, Nason AP. 1970. Zirconium, niobium, antimony, vanadium and lead in rats: life term studies. J Nutr 100(1): 59-68. (Supported by the Public Health Service, the National Heart Institute, the U.S. Army, and Cooper Laboratories, Inc. Authors affiliated with Dartmouth Medical School, NH; Brattleboro Memorial Hospital, VT.)


205. Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Bucher JR, Stewart BW, Baan RA, Cogliano VJ, Straif K. 2016. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Environ Health Perspect 124(6): 713-721. (Supported by NIEHS. Authors affiliated with University of California Berkeley, CA; IARC, France; US EPA, Washington, D.C. and NC; ATSDR; Texas A&M University, TX; University of Wisconsin School of Medicine and Public Health, WI; University of Minnesota, MN; NIEHS, NC; University of New South Wales, Australia.)

207. Sudhandiran G, Shaha C. 2003. Antimonial-induced increase in intracellular Ca2+ through non-selective cation channels in the host and the parasite is responsible for apoptosis of intracellular *Leishmania donovani* amastigotes. *J Biol Chem* 278(27): 25120-25132. (Supported by the Indian Council of Medical Research, Department of Biotechnology, Government of India and the National Institute of Immunology, New Delhi. Authors affiliated with National Institute of Immunology, India.)


211. Sunderman Jr FW. 1984. Carcinogenicity of nickel compounds in animals. *IARC Sci Publ* 53: 127-142. (Supported by NIEHS and the U.S. Department of Energy. Author affiliated with University of Connecticut School of Medicine, CT.)


213. Takahashi S, Sato H, Kubota Y, Utsumi H, Bedford JS, Okayasu R. 2002b. Inhibition of DNA-double strand break repair by antimony compounds. *Toxicology* 180(3): 249-256. (Support not reported. Authors affiliated with National Institute of Radiological Sciences, Japan; Kyoto University, Japan; Colorado St. University, CO.)


Occupational Safety and Health at the Johns Hopkins Bloomberg School of Public Health, NIEHS, the Carlos the Third Health Institute at the Spanish Ministry of Economy and Innovation, and FEDER. Authors affiliated with Johns Hopkins Bloomberg School of Public Health, MD; INCLIVA, Spain; Second Military Medical University, China; MedStar Health Research Institute, MD; Georgetown-Howard Universities Center for Clinical and Translational Science, Washington, DC; Karl-Franzens University, Austria; Aragon Health Sciences Institute, Spain; CNIC, Spain; Johns Hopkins Medical Institutions, MD; Texas Biomedical Research Institute, TX.)

216. Tessier S, Martin-Martin N, de Thé H, Carracedo A, Lallemand-Breitenbach V. 2017. Promyelocytic leukemia protein, a protein at the crossroad of oxidative stress and metabolism. Antioxid Redox Signal 26(9): 432-444. (Supported by the the Ramón y Cajal, the Basque Department of Industry, Tourism and Trade, Health, and Education, Marie Curie, the Movember Foundation, FERO, ERC, INSERM, CNRS, the Spanish Association Against Cancer, Université Paris-Diderot, Ligue Contre le Cancer, Institut National du Cancer, ANR (PACRI, SLI, and SUMOPiv projects), Canceropole Ile de France, and the European Research Council. Authors affiliated with Collège de France, France; INSERM, France; CNRS, France; Université Paris Diderot, France; CIC bioGUNE, Spain; Hopital St. Louis, France; IKERBASQUE, Spain; University of the Basque Country, Spain.)


222. Tran CL, Buchanan D, Cullen RT, Searl A, Jones AD, Donaldson K. 2000. Inhalation of poorly soluble particles. II. Influence of particle surface area on inflammation and clearance. Inhal Toxicol 12(12): 1113-1126. (Supported by the UK Health and Safety Executive. Authors affiliated with Institute of Occupational Medicine, UK; Napier University, UK.)


227. Tyrrell J, Melzer D, Henley W, Galloway TS, Osborne NJ. 2013. Associations between socioeconomic status and environmental toxicant concentrations in adults in the USA: NHANES 2001-2010. *Environ Int* 59: 328-335. (Supported by the University of Exeter internal support. Authors affiliated with University of Exeter Medical School, UK.)

228. Ulrich N. 1998. Speciation of antimony(III), antimony(V) and trimethylstiboxide by ion chromatography with inductively coupled plasma atomic emission spectrometric and mass spectrometric detection. *Anal Chim Acta* 359(3): 245-253. (Support not reported. Author affiliated with University of Hannover, Germany.)


234. Verdugo M, Ogra Y, Quiroz W. 2016. Mechanisms underlying the toxic effects of antimony species in human embryonic kidney cells (HEK-293) and their comparison with arsenic species. *J Toxicol Sci* 41(6): 783-792. (Supported by the Chilean Government and JSPS KAKENHI. Authors affiliated with Chiba University, Japan; Avenida Universidad, Chile.)


Chenguang Program from Shanghai Municipal Education Commission, and the Fundamental Research Funds for the Central Universities. Authors affiliated with East China Normal University, China; Texas A&M University Health Science Center, TX.)

237. Watt WD. 1983. *Chronic Inhalation Toxicity of Antimony Trioxide: Validation of the Threshold Limit Value*. Detroit, MI: Wayne State University, PhD Thesis. (Supported by ASARCO, Inc. Author affiliated with Wayne State University, MI.)


245. Wyllie S, Fairlamb AH. 2006. Differential toxicity of antimonial compounds and their effects on glutathione homeostasis in a human leukaemia monocyte cell line. *Biochem Pharmacol* 71(3): 257-267. (Supported by the Burroughs Wellcome Fund and Wellcome Trust Infectious Disease Initiative. Authors affiliated with University of Dundee, UK.)

246. Wysocki R, Tamas MJ. 2010. How *Saccharomyces cerevisiae* copes with toxic metals and metalloids. *FEMS Microbiol Rev* 34(6): 925-951. (Supported by the Swedish Research Council, the Swedish Research Links programme, and the Polish Ministry of Science and Higher Education. Authors affiliated with University of Wroclaw, Poland; University of Gothenburg, Sweden.)
247. Xiong J, Liu X, Cheng QY, Xiao S, Xia LX, Yuan BF, Feng YQ. 2017. Heavy metals induce decline of derivatives of 5-methylcytosine in both DNA and RNA of stem cells. *ACS Chem Biol* 12(6): 1636-1643. (Supported by the National Natural Science Foundation of China. Authors affiliated with Wuhan University, China; University of Science and Technology of China, China; Southern Medical University, China; Chinese Academy of Sciences, China.)


254. Zheng FY, Qian SH, Li SX, Huang XQ, Lin LX. 2006. Speciation of antimony by preconcentration of Sb(III) and Sb(V) in water samples onto nanometer-size titanium dioxide and selective determination by flow injection-hydride generation-atomic absorption spectrometry. *Anal Sci* 22(10): 1319-1322. (Supported by the National Natural Science Foundation of China and the Science & Technology Committee of Fujian Province, China. Authors affiliated with Wuhan University, China; Zhangzhou Teachers College, China.)

Abbreviations

53BP1: TP53-binding protein 1, 6-4PP = 6-4 photoproducts
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AAS: atomic absorption spectrometry
ACGIH: American Conference of Governmental Industrial Hygienists
ADME: absorption, distribution, metabolism, and excretion
ALF: artificial lysosomal fluid
ALL: acute lymphoblastic leukemia
ANOVA: analysis of variance
APL: acute promyelocytic leukemia
APM: airborne particulate matter
APT: antimony potassium tartrate
AR: androgen receptor
ASW: Artificial sweat
AT: 3-amino-1,2,4-azole
ATG: Attagene
ATM: serine-protein kinase ATM
ATSDR: Agency for Toxic Substances and Disease Registry
avg: average
BDL: below detection limit
BPDE: benzo[a]pyrene diol epoxide
BPDE-DNA: benzo[a]pyrene diol epoxide-DNA
BPDE-DNA adducts: DNA adducts induced by (+)-anti-benzo[a]pyrene diol epoxide
BRCA1: breast cancer type 1 susceptibility protein
BSC: Board of Scientific Counselors
BSO: DL-buthionine-[S,R]-sulfoximine
CAR: androstane receptor
CAS: Chemical Abstracts Service
CAT: catalase
CCRF-CEM: acute lymphoblastic leukemia cells
CDC: Centers for Disease Control and Prevention
CDR: Chemical Data Reporting Rule
CHK: serine/threonine-protein kinase Chk1 isoform 1
CHK2: serine/threonine-protein kinase Chk1 isoform 2
CI: confidence interval
Conc: concentration
CPD: cyclobutane pyrimidine dimers
CSF2: colony-stimulating factor 2
CYP: cytochrome P450
DDB2: damage specific DNA binding protein 2 (see also XPE)
dGTP: deoxyguanosine triphosphate
DNA: deoxyribonucleic acid
DSB: double-strand breaks
EC50: effective concentration at 50% maximal activity
EGF: epidermal growth factor
EGFR: epidermal growth factor receptor
EPA: (United States) Environmental Protection Agency
ErbB2: erb-b2 receptor tyrosine kinase 2
EU: European Union
EU RAR: European Union risk assessment report
Exp.: exposed
F: female
FDA: Food and Drug Administration
FXR: farnesoid-X-receptor
GC/MS: gas chromatography/mass spectroscopy
GI: gastrointestinal
GM: geometric mean
GMB: Gamble’s solution
GSD: geometric standard deviation
GSH: glutathione
GSSG: glutathione disulfide
GST: glutathione-S-transferase
GST: artificial gastric fluid
GTP: guanosine triphosphate
H2AX: histone H2AX
HBr: hydrogen bromide
HCl: hydrogen chloride
HG-AAS: hydride generation-atomic absorption spectrometry
HHS: Department of Health and Human Services
HL-60: acute promyelocytic leukemia cells
HPLC-HG-AFS: high performance liquid chromatography-hydride generation-atomic fluorescence spectrometry
HPLC: high-performance liquid chromatography
HR: hazard ratio
HR: homologous recombination repair
hr: hour
HSDB: Hazardous Substances Database
HTS: harmonized tariff schedule
HWSE: healthy worker survival (or survivor) effect
i.p.: intraperitoneal
i.v.: intravenous
IARC: International Agency for Research on Cancer
IC-ICP-AES: inductively coupled plasma atomic emission spectrometric
ICD: International Classification of Diseases
ICD-8: International Classification of Diseases, Eighth Revision
ICD-9: International Classification of Diseases, Ninth Revision
ICP-AES: inductively coupled plasma-atomic emission spectroscopy
ICP-MS: inductively coupled plasma-mass spectrometry
IDLH: immediately dangerous to life and health
IFNα: interferon-alpha
IFNγ: interferon-gamma
Ig: immunoglobulin
IM: infectious mononucleosis
InChi: IUPAC International Chemical Identifier
iNOS KO: inducible nitric oxide synthase knock out (mice)
IRIS: Integrated Risk Information System
IUR: Inventory Update Rule

JEM: job-exposure matrix

K-562 chronic myelogenous leukemia cells

LC-HG-AFS: liquid chromatography-hydride generation-atomic fluorescence spectrometry

LOUCY T cell acute lymphoblastic leukemia cells

M: male or mice

MAP: mitogen-activated protein

MCL: maximum contaminant level

MeSH: Medical Subject Headings

MMAD: mass median aerodynamic diameter

MMP: mitochondrial membrane potential

MN: micronuclei

mo: month

MS: mercaptosuccinic acid

N: number

n/N: number of animals with neoplasms divided by the total number of animals tested in that group

NaAsc: sodium ascorbate

NAC N-acetylcysteine

NAICS: North American Industry Classification System

NB4 acute promyelocytic leukemia cells

NB4-M-AsR3 cells arsenic resistant APL cells derived in Miller lab

nBP: n-bromoheptane

NC: negative control

NCATS: National Center for Advancing Translational Sciences

NCBI GEO: National Center for Biotechnology Information Gene Expression Omnibus database

NCE: normochromatric erythrocyte

NCTR: National Center for Toxicological Research

ND: not detected; not determined; not done; patient and normal donor

NER: nucleotide excision repair

NHANES: National Health and Nutrition Examination Survey
NHEJ: non-homologous end joining
NIEHS: National Institute of Environmental Health Sciences
NIH: National Institutes of Health
NIOSH: National Institute for Occupational Safety and Health
NOES: National Occupational Exposure Survey
NOS: not otherwise specified
NR: not reported; none reported
Nrf2: nuclear factor (erythroid derived-2)-like 2
NS: not significant
NT: not tested
NTP: National Toxicology Program
NVS: NovaScreen
obs: observations
OECD: Organisation for Economic Co-Operation and Development
OR: odds ratio
ORoC: Office of the Report on Carcinogens
OSHA: Occupational Safety and Health Administration
p.o.: per os (oral administration)
PAHs: polycyclic aromatic hydrocarbons
PBS: phosphate-buffered saline
PC: positive control
PCE: polychromatic erythrocyte
PDF: Portable Document Format
PEL: permissible exposure limit
PET: polyethylene terephthalate
PM$_1$: particles less than 1 µm in diameter
PM$_{10}$: particles less than 10 µm in diameter
PPARd: peroxisome proliferator-activated receptor delta
PVC: polyvinyl chloride
R: rats
r: correlation coefficient
RAD51: DNA repair protein RAD51 homolog
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAHC:</td>
<td>reasonably anticipated to be a human carcinogen</td>
</tr>
<tr>
<td>REL:</td>
<td>recommended exposure limit</td>
</tr>
<tr>
<td>RNA:</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>RoC:</td>
<td>Report on Carcinogens</td>
</tr>
<tr>
<td>ROS:</td>
<td>reactive oxygen species</td>
</tr>
<tr>
<td>RQ:</td>
<td>reportable quantity</td>
</tr>
<tr>
<td>RR:</td>
<td>relative risk</td>
</tr>
<tr>
<td>s.c.:</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>Sb:</td>
<td>antimony</td>
</tr>
<tr>
<td>Sb(III):</td>
<td>trivalent form of antimony (valence = +3)</td>
</tr>
<tr>
<td>Sb(V):</td>
<td>pentavalent form of antimony (valence = +5)</td>
</tr>
<tr>
<td>SCE:</td>
<td>sister-chromatid exchange</td>
</tr>
<tr>
<td>SD:</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SHP-1:</td>
<td>PTPases Src homology PTPase1</td>
</tr>
<tr>
<td>SIC:</td>
<td>Standard Industrial Classification</td>
</tr>
<tr>
<td>SMR:</td>
<td>standardized mortality ratio</td>
</tr>
<tr>
<td>SOD:</td>
<td>superoxide dismutase</td>
</tr>
<tr>
<td>std dev:</td>
<td>standard deviation</td>
</tr>
<tr>
<td>Tie2</td>
<td>tyrosine kinase with immunoglobulin like and EGF like domains 2</td>
</tr>
<tr>
<td>TK:</td>
<td>toxicokinetics</td>
</tr>
<tr>
<td>TLV:</td>
<td>threshold limit value</td>
</tr>
<tr>
<td>TWA:</td>
<td>time-weighted average</td>
</tr>
<tr>
<td>TM:</td>
<td>tail moment</td>
</tr>
<tr>
<td>TREM1:</td>
<td>triggering receptor expressed on myeloid cells 1</td>
</tr>
<tr>
<td>TRI:</td>
<td>Toxics Release Inventory</td>
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<tr>
<td>TSCA:</td>
<td>Toxic Substances Control Act</td>
</tr>
<tr>
<td>TWA:</td>
<td>time-weighted average</td>
</tr>
<tr>
<td>U.K.:</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>USITC:</td>
<td>United States International Trade Commission</td>
</tr>
<tr>
<td>UV:</td>
<td>ultraviolet light</td>
</tr>
<tr>
<td>UVC:</td>
<td>ultraviolet C</td>
</tr>
<tr>
<td>VC</td>
<td>vehicle control</td>
</tr>
</tbody>
</table>
VEGF: vascular endothelial growth factor  
wAUC: weighted area under the curve  
X-CGD: X-linked chronic granulomatous disease  
XPA: xeroderma pigmentosum complementation group A  
XPE: xeroderma pigmentosum complementation group E
Units of Measurement

Area

\( \text{cm}^2 \): square centimeter

Concentration

\( \text{g/L} \): grams per liter
\( \text{mg/dL} \): milligrams per deciliter
\( \text{mg/kg b.w.} \): milligrams per kilogram body weight
\( \text{mg/L} \): milligrams per liter
\( \text{mg/m}^3 \): milligrams per meter cubed
\( \text{mg\%} \): milligram percent (milligrams per deciliter)
\( \text{mol/L} \): moles per liter
\( \text{ng/g} \): nanograms/gram
\( \text{ppm} \): parts per million
\( \text{ppt} \): parts per trillion
\( \text{wt\%} \): weight percent
\( \mu\text{M} \): micromolar
\( \mu\text{mol/L} \): micromoles per liter
\( \mu\text{g/g} \): micrograms per gram
\( \mu\text{g/kg} \): micrograms per kilogram
\( \mu\text{g/L} \): micrograms per liter
\( \mu\text{g/m}^3 \): micrograms per meter cubed

Length

\( \text{ft} \): feet
\( \text{in} \): inch

Mass/Weight

\( \text{kg} \): kilogram
\( \text{lb} \): pound
\( \text{mg} \): milligram
mol: mole
ng: nanogram
µg: microgram

**Temperature**
°C degrees Celsius

**Volume**
dL: deciliter
L: liter
m³: cubic meter
mL: milliliter
Glossary

6-4 Photoproducts: DNA photoproducts with (6-4) pyrimidine-pyrimidone adducts

Agranulocyte: A leukocyte (white blood cell) lacking apparent cytoplasmic granules when viewed under light microscopy (in contrast to granulocytes).

Anaerobic: Living, active, occurring, or existing in the absence of free oxygen.

Aneuploidy: The chromosomal variation due to a loss or a gain of one or more chromosomes resulting in the deviation from the normal or the usual number of chromosomes for that species.

Anoxic: A condition or an environment that lacks oxygen, as anoxic water which is devoid of oxygen.

Apoptosis: Cell deletion by fragmentation into membrane-bound particles, which are phagocytosed by other cells.

Atopic dermatitis: A chronic or recurrent inflammatory skin disease (also referred to as eczema). "Atopic" means that there is typically a genetic tendency toward allergic disease. Atopic dermatitis usually begins in the first few years of life and is often the initial indication that a child may later develop asthma and/or allergic rhinitis (hay fever). In infants, eczema usually appears as tiny bumps on the cheeks. Older children and adults often experience rashes on the knees or elbows (often in the folds of the joints), on the backs of hands or on the scalp.

Attrition bias: Systematic differences between comparison groups in withdrawals or exclusions of participants from the results of a study.

Boiling point: The boiling point of the anhydrous substance at atmospheric pressure (101.3 kPa) unless a different pressure is stated. If the substance decomposes below or at the boiling point, this is noted (dec). The temperature is rounded off to the nearest °C.

Chemical Data Reporting Rule: Chemical Data Reporting (CDR) is the new name for Inventory Update Reporting (IUR). The purpose of Chemical Data Reporting is to collect quality screening-level, exposure-related information on chemical substances and to make that information available for use by the U.S. Environmental Protection Agency (EPA) and, to the extent possible, to the public. The IUR/CDR data are used to support risk screening, assessment, priority setting and management activities and constitute the most comprehensive source of basic screening-level, exposure-related information on chemicals available to EPA. The required frequency of reporting currently is once every four years.

Clastogenesis: The process resulting in additions, deletions, or rearrangements of parts of the chromosomes that are detectable by light microscopy.

Comet assay: Single cell gel electrophoresis for assessment of DNA damage in presumptive target tissues.

Diapedesis: The movement of blood cells, particularly leukocytes, from the blood across blood vessel walls into tissues.
**Disposition:** The description of absorption, distribution, metabolism, and excretion of a chemical in the body.

**Endoduplication:** Replication of a nuclear genome in the absence of cell division.

**Enterohemepatic circulation (enterohepatic cycling, enterohepatic recycling):** Circulation of substances such as bile salts that are absorbed from the intestine and carried to the liver, where they are secreted into the bile and again enter the intestine.

**FDA Good Laboratory Practice Regulations:** A quality system codified by the U.S. Food and Drug Administration that prescribes operating procedures for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration.

**Feret’s (or Feret) diameter:** A measure used for analysis of irregular particle sizes that consists of the average of the perpendicular distances between two parallel planes touching each particle on opposite sides.

**Fining agent:** A chemical compound added to glass melts to remove bubbles.

**Fire retardant:** A liquid, solid, or gas that tends to inhibit combustion when applied on, mixed in, or combined with combustible materials.

**Fisher’s exact test:** The test for association in a two-by-two table that is based on the exact hypergeometric distribution of the frequencies within the table.

**Follow-up:** Observation over a period of time of a person, group, or initially defined population whose appropriate characteristics have been assessed to observe changes in health status or health-related variables.

**Granulocyte:** A type of white blood cell that has small granules, which contain proteins. The specific types of granulocytes are neutrophils, eosinophils, and basophils.

**Healthy worker survival effect:** A continuing selection process such that those who remain employed tend to be healthier than those who leave employment.

**Healthy worker survivor effect:** The selection process by which workers affected by their occupational exposure terminate prematurely their working life or transfer from higher to lesser exposed jobs, generally leading to under-estimation of risks and dose-response estimation. The healthy worker survivor effect is most prominent in cross sectional studies of disease prevalence and exposure.

**Hypercytokinemia:** A potentially fatal hyperrelease of inflammatory mediators in response to stimulation of T cells and macrophages by pathogens and immune insults.

**Hypogeusia:** A partial loss of the ability to taste.

**Hyposmia:** The partial loss of the ability to perceive smells.

**In silico:** An expression used to mean “performed on computer or via computer simulation”.
**InChi key:** A 27-character compacted version of the InChI (IUPAC [International Union of Pure and Applied Chemistry] International Chemical Identifier) intended for Internet and database searching and indexing.

**Leishmaniasis:** A parasitic disease that is found in parts of the tropics, sub-tropics, and southern Europe caused by infection with Leishmania parasites, which are spread by the bite of infected sand flies. The most common forms of leishmaniasis in people are cutaneous leishmaniasis, which causes skin sores, and visceral leishmaniasis, which affects several internal organs (usually spleen, liver, and bone marrow).

**Loss of heterozygosity:** If there is one normal and one abnormal allele at a particular locus, as might be seen in an inherited autosomal dominant cancer susceptibility disorder, loss of the normal allele produces a locus with no normal function. When the loss of heterozygosity involves the normal allele, it creates a cell that is more likely to show malignant growth if the altered gene is a tumor suppressor gene.

**Melting point:** The melting point of the substance at atmospheric pressure (101.3 kPa). When there is a significant difference between the melting point and the freezing point, a range is given. In case of hydrated substances (i.e., those with crystal water), the apparent melting point is given. If the substance decomposes at or below its melting point, this is noted (dec). The temperature is rounded off to the nearest °C.

**Metabolic activation:** The chemical alteration of an exogenous substance by or in a biological system. The alteration may inactivate the compound or it may result in the production of an active metabolite of an inactive parent compound.

**Metalloid:** A chemical element that exhibits some properties of metals and some of nonmetals.

**Metaplasia:** A change of cells to a form that does not normally occur in the tissue in which it is found.

**Micronuclei:** Small nuclei separate from, and additional to, the main nucleus of a cell, produced during the telophase of mitosis or meiosis by lagging chromosomes or chromosome fragments derived from spontaneous or experimentally induced chromosomal structural changes.

**Miscible:** A physical characteristic of a liquid that forms one liquid phase with another liquid (e.g., water) when they are mixed in any proportion.

**Mitotic checkpoint:** A molecular safeguard mechanism for cells to ensure accurate chromosome segregation during mitosis.

**Molecular weight:** The molecular weight of a substance is the weight in atomic mass units of all the atoms in a given formula. The value is rounded to the nearest tenth.

**Mucociliary transport:** The process by which cilia move a thin film of mucus from the upper and lower respiratory tracts towards the digestive tract. Particles of dust and microorganisms are trapped on the mucus and thereby removed from the respiratory tract.
Mutations: A change in the structure of a gene, resulting from the alteration of single base units in DNA, or the deletion, insertion, or rearrangement of larger sections of genes or chromosomes. The genetic variant can be transmitted to subsequent generations.

National Health and Nutrition Examination Survey: A program of studies designed to assess the health and nutritional status of adults and children in the United States. The survey is unique in that it combines interviews and physical examinations.

Natural killer cells: A type of white blood cell that contains granules with enzymes that can kill tumor cells or microbial cells. Also called large granular lymphocytes.

Non-differential misclassification: The probability of erroneous classification of an individual, a value, or an attribute into a category other than that to which it should be assigned is the same in all study groups.

Nonferrous: Not containing, including, or relating to iron.

Normochromatic erythrocyte: A mature erythrocyte that lacks ribosomes and can be distinguished from immature, polychromatic erythrocytes by stains selective for RNA.

Nrf2: A protein that controls how certain genes are expressed. These genes help protect the cell from damage caused by free radicals (unstable molecules made during normal cell metabolism). Also called NFE2L2 and nuclear factor (erythroid-derived 2)-like 2.

Octanol/water partition coefficient (log Kow): A measure of the equilibrium concentration of a compound between octanol and water.

Opacifier: A chemical used to make a solution or substance more opaque.

Oxic: Of a process or environment in which oxygen is involved or present.

Personal breathing zone: A sampling area as close as practical to an employee’s nose and mouth, (i.e., in a hemisphere forward of the shoulders within a radius of approximately nine inches) so that it does not interfere with work performance or safety of the employee.

Plate incorporation: A commonly used procedure for performing a bacterial reverse mutation test. Suspensions of bacterial cells are exposed to the test substance in the presence and in the absence of an exogenous metabolic activation system. In the plate-incorporation method, these suspensions are mixed with an overlay agar and plated immediately onto minimal medium. After two or three days of incubation, revertant colonies are counted and compared with the number of spontaneous revertant colonies on solvent control plates.

Poly-3 trend test: A survival-adjusted statistical test that takes survival differences into account by modifying the denominator in the numerical (quantal) estimate of lesion incidence to reflect more closely the total number of animal years at risk.

Polychromatic erythrocyte: A newly formed erythrocyte (reticulocyte) containing RNA.

Primary mineral: In an igneous rock, any mineral that is formed during the original solidification (i.e., crystallization) of the rock. Primary minerals include both the essential...
minerals used to assign a classification name to the rock and the accessory minerals present in lesser abundance.

**Proto-oncogene:** A gene involved in normal cell growth. Mutations (changes) in a proto-oncogene may cause it to become an oncogene, which can cause the growth of cancer cells.

**P\text{trend}:** Level of statistical significance of a change over time in a group selected to represent a larger population.

**QUOSA:** A collection of scientific literature management software and services for researchers and information professionals in the life sciences and related scientific and medical areas designed to retrieve, organize, and analyze full-text articles and documents.

**Reticuloendothelial cells:** Cells with the ability to take up inert particles and vital dyes, e.g., macrophages, macrophage precursors, specialized endothelial cells lining the liver sinusoids, spleen, and bone marrow, and reticular cells of lymphatic tissue and bone marrow (fibroblasts).

**Schistosomiasis:** A disease caused by parasites (genus *Schistosoma*) that enter humans by attaching to the skin, penetrating it, and then migrating through the venous system to the portal veins where the parasites produce eggs and eventually, the symptoms of acute or chronic disease (for example, fever, abdominal discomfort, blood in stools).

**Secondary mineral:** A mineral formed through processes such as weathering and hydrothermal alteration (at a later time in contrast to primary minerals which form during the original solidification of the rock).

**Selection bias:** An error in choosing the individuals or groups to take part in a study. Ideally, the subjects in a study should be very similar to one another and to the larger population from which they are drawn (for example, all individuals with the same disease or condition). If there are important differences, the results of the study may not be valid.

**Sister-chromatid exchange:** The exchange during mitosis of homologous genetic material between sister chromatids; increased as a result of inordinate chromosomal fragility due to genetic or environmental factors.

**Solubility:** The ability of a substance to dissolve in another substance and form a solution. The Report on Carcinogens uses the following definitions (and concentration ranges) for degrees of solubility: (1) *miscible* (see definition), (2) *freely soluble* - capable of being dissolved in a specified solvent to a high degree (> 1,000 g/L), (3) *soluble* - capable of being dissolved in a specified solvent (10–1,000 g/L), (4) *slightly soluble* - capable of being dissolved in a specified solvent to a limited degree (1–10 g/L), and (5) *practically insoluble* - incapable of dissolving to any significant extent in a specified solvent (< 1 g/L).

**Specific gravity:** The ratio of the density of a material to the density of a standard material, such as water at a specific temperature; when two temperatures are specified, the first is the temperature of the material and the second is the temperature of water.

**Spot test:** Qualitative assay in which a small amount of test chemical is added directly to a selective agar medium plate seeded with the test organism, e.g., *Salmonella*. As the chemical diffuses into the agar, a concentration gradient is formed. A mutagenic chemical will give rise to
a ring of revertant colonies surrounding the area where the chemical was applied; if the chemical is toxic, a zone of growth inhibition will also be observed.

**T90**: Additional exposure time used in sub-chronic and chronic inhalation studies in experimental animals; the time required to achieve 90% of the target concentration after the beginning of vapor generation.

**Time-weighted average**: The average exposure concentration of a chemical measured over a period of time (not an instantaneous concentration).

**Toxicokinetics**: The mathematical description (toxicokinetic models) of the time course of disposition of a chemical in the body.

**Transcriptomics**: The study of the RNA transcripts of a cell, tissue, or organism (i.e., the transcriptome) to determine how the transcriptome, and hence pattern of gene expression, changes with respect to various factors, such as type of tissue, stage of development, hormones, drugs, or disease.

**Transitions**: DNA nucleotide substitution mutation in which a purine base is substituted for another purine base (adenine $\rightarrow$ guanine or guanine $\rightarrow$ adenine) or a pyrimidine base for another pyrimidine base (cytosine $\rightarrow$ thymine or thymine $\rightarrow$ cytosine).

**Transversions**: DNA nucleotide substitution mutation in which a purine base (adenine or guanine) is substituted for a pyrimidine base (cytosine or thymine) or vice versa.

**Two-compartment pharmacokinetic model**: A two-compartment pharmacokinetic model resolves the body into a central compartment and a peripheral compartment. The central compartment generally comprises tissues that are highly perfused such as heart, lungs, kidneys, liver and brain. The peripheral compartment comprises less well-perfused tissues such as muscle, fat and skin. A two-compartment model assumes that, following drug administration into the central compartment, the drug distributes between that compartment and the peripheral compartment. However, the drug does not achieve instantaneous distribution (i.e., equilibrium), between the two compartments. After a time interval (t), distribution equilibrium is achieved between the central and peripheral compartments, and elimination of the drug is assumed to occur from the central compartment.

**Vapor density, relative**: A value that indicates how many times a gas (or vapor) is heavier than air at the same temperature. If the substance is a liquid or solid, the value applies only to the vapor formed from the boiling liquid.

**Vapor pressure**: The pressure of the vapor over a liquid (and some solids) at equilibrium, usually expressed as mm Hg at a specific temperature (°C).
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Antimony Trioxide
CAS No. 1309-64-44
Reasonably anticipated to be a human carcinogen\(^1\).

\[
\begin{array}{c}
\text{O} \\
\text{Sb} \\
\text{O} \\
\text{Sb} \\
\text{O}
\end{array}
\]

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

*Cancer Studies in Experimental Animals*
Antimony trioxide administered by inhalation caused lung tumors in rats and mice of both sexes and tumors at several other tissue sites in female rats and in mice of both sexes. This conclusion was based on three studies in three different strains or stocks of rats and one study in mice. NTP studies (2017) examined all organs and tissues in both sexes of Wister Han rats and B6C3F1/N mice, and three other studies examined primarily the lung in both sexes of Wistar rats (Groth *et al.* 1986) or Fischer 344 rats (Newton *et al.* 1994) or female CDF rats (Watt 1983). The NTP studies were most informative based on the study design and detailed report, while other studies are also adequate to inform carcinogenicity after critical evaluation of potential bias.

Exposure of female rats to antimony trioxide significantly increased the incidences of benign lung tumors (alveolar/bronchiolar adenoma) (Groth *et al.* 1986, NTP 2017) and incidences of malignant lung tumors (scirrhous carcinoma and/or squamous-cell carcinoma) (Groth *et al.* 1986, Watt 1983). Although the purity of the antimony trioxide used in one study (Groth *et al.* 1986) was only 80%, the potential for other contaminant metals to have caused the tumors was ruled out based on analysis of the metals in lung tissue. Because the types of benign lung tumors reported can progress to malignancy, the observation of benign tumors provides additional evidence of carcinogenicity. In male rats, the combined incidences of benign lung tumors (alveolar/bronchiolar adenoma) and malignant lung tumors (alveolar/bronchiolar carcinoma) were not significantly increased, but both exceeded the historical control ranges for all past studies (NTP 2017). When this is considered together with a positive trend with dose and increased lung tumors in the other sex and species (female rats, both sexes of mice), the increase in combined incidences was deemed treatment related (NTP 2017). Another study in male and female rats (Newton *et al.* 1994) found no increase in the frequency of lung tumors, possibly because the highest tested concentration was too low (as indicated by the absence of changes in survival or body weight in the high-dose groups). Newton *et al.* (1994) was the only study that reported no increase in tumors.

\(^1\)NTP preliminary listing recommendation proposed for the RoC.
Exposure of mice to antimony trioxide caused statistically significant increases in the incidences of benign lung tumors (alveolar/bronchiolar adenoma) in females, malignant lung tumors (alveolar/bronchiolar carcinoma) in males and females, and combined benign and malignant lung tumors (alveolar/bronchiolar adenoma and carcinoma) in females (NTP 2017).

At other tissue sites, antimony trioxide exposure significantly increased the incidences of malignant lymphoma (cancer of the white blood cells) in female mice; skin tumors (benign fibrous histiocytoma alone and combined with malignant fibrosarcoma) in male mice; benign tumors of the adrenal gland (pheochromocytoma) in male and female rats; and combined benign and malignant adrenal-gland tumors (pheochromocytoma) in female rats (NTP 2017).

<table>
<thead>
<tr>
<th>Rat</th>
<th>Malignant</th>
<th>Combined</th>
<th>Mouse</th>
<th>Malignant</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>↑F</td>
<td>*M</td>
<td>↑M, ↑F</td>
<td>↑F</td>
<td></td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>–</td>
<td>↑F</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Skin</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>↑M</td>
<td></td>
</tr>
<tr>
<td>Lymphatic system</td>
<td>–</td>
<td>–</td>
<td>↑F</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

↑F = Significant increase in tumors in females.
↑M = Significant increase in tumors in males.
* = Increase not statistically significant but considered exposure-related (NTP 2017).
– = No exposure-related increase in tumors.

**Mechanisms of Carcinogenesis and Other Relevant Data**

Antimony trioxide induces several biological effects associated with carcinogenicity that are also observed with other carcinogenic metals (e.g., arsenic); however, the available data did not provide adequate information to determine the overall mechanism by which antimony causes cancer. Because antimony trioxide may exert its effects through released trivalent antimony ions, effects observed with other trivalent antimony compounds are potentially relevant to understanding the carcinogenicity of antimony trioxide.

The strongest evidence for antimony-induced biological effects potentially contributing to carcinogenicity were oxidative stress (and consequently oxidative damage) seen in experimental animals and cultured cells, and inhibition of DNA repair seen in cultured cells. Furthermore, trivalent antimony inhibits cell differentiation in cultured skin cells, and consequently increase the potential for tumor development.

For oxidative stress, antimony induces reactive oxygen species (ROS) and nitric oxide, adversely affects mitochondria, and causes oxidative damage in DNA, proteins, and lipids. Antimony trioxide also decreases antioxidants in cells, specifically lowering levels of reduced glutathione (GSH), and inhibits the enzymes involved in GSH functions, indicating that antimony disrupts enzymes and effectors of the cellular redox system. When external antioxidant and ROS scavengers were added to cells exposed to antimony(III) compounds, the cells were at least partially protected from antimony(III)-induced oxidative damage.

Antimony trioxide causes damages in DNA, chromosome, and chromatid in experimental animals and/or cultured cells, although antimony trioxide does not cause mutations in classical bacterial tests except under very specific conditions. In mice exposed to antimony trioxide by inhalation, lung tissue showed increased DNA damage, and red blood cells showed increased...
micronucleus formation, indicating chromosomal instability (NTP 2017). Increased chromosomal aberrations, micronucleus, and sister chromatid exchange were seen after antimony trioxide exposure in cultured cells. The genotoxicity could be the result of oxidative stress, decreased DNA repair, or the combination of both.

Antimony trichloride, another trivalent antimony compound, decreased the repair of DNA damage induced by ultraviolet and ionizing radiation; antimony trioxide is likely to have similar effects. Trivalent antimony can directly disrupt XPA, a key protein in a specific type of DNA repair pathway (nucleotide excision repair), by displacing zinc (an essential metal in stabilizing the protein structure) in the protein’s DNA-binding region, thus hindering the protein’s function. Other repair proteins also are affected by antimony through alteration of protein concentration, structure, or location.

Antimony trioxide–induced lung tumors in rats and mice showed high incidences of specific mutations in the epidermal growth factor receptor gene (Egfr) (NTP 2017). These Egfr mutations lead to increased cell survival and can lead to cancer growth. The fact that Egfr mutations were not seen in spontaneous alveolar/bronchiolar carcinomas or non-tumor lung tissues in rats or mice suggests a role for antimony trioxide exposure in their occurrence.

An antimony(III) compound has been shown to prevent cell differentiation in cultured human skin cells, giving cells the potential to continue proliferating and possibly cause cancer. Once skin cells are fully differentiated they lose the ability to divide, and are not likely to become cancer cells. Prevention of cell differentiation by antimony trioxide results in part from inhibition of the decrease in the number of epidermal growth factor receptors that naturally occurs when cells in culture grow into a certain density (e.g., nearly covering the whole bottom of a petri dish). With an excess of epidermal growth factor receptors, cells can continue to divide even at high cell density (e.g., grow into more than one layer of cells on the same growth surface). Consistent with this potential mechanism, skin tumors were seen in mice exposed to antimony trioxide by inhalation, and dermatitis was reported in workers exposed to antimony trioxide.

**Cancer Studies in Humans**

The data available from studies in humans are inadequate to evaluate the relationship between human cancer and exposure specifically to antimony trioxide or antimony in general.

The relevant data for evaluation of antimony exposure are two cohort studies of antimony smelter workers in the United Kingdom (Jones 1994) and the United States (Schnorr et al. 1995), a cohort study of tin smelter workers in the United Kingdom (Jones et al. 2007), and a case-control study of art glass workers in Sweden (Wingren and Axelson 1993). For lung cancer, elevated mortality was seen in all studies of antimony-exposed smelter worker cohorts. Results may be impacted due to potential confounding bias from concurrent exposure to other lung carcinogens. An increased risk of stomach cancer was found in the U.S. antimony smelter cohort study (Schnorr et al. 1995) and the Swedish case-control study (Wingren and Axelson 1993), but not in the U.K. antimony smelter cohort study (Jones 1994).

**Properties**

Antimony trioxide is the oxide of trivalent (+3) antimony, and it occurs naturally as well as from human activities. Antimony exists in four main oxidation states: −3, 0, +3, and +5. The most
common in environmental, biological, and geochemical systems are Sb(III) (the trivalent form) and Sb(V) (the pentavalent form). In nature, antimony trioxide (Sb$_2$O$_3$) exists in minerals such as valentinite and senarmontite (ATSDR 2017, Roper et al. 2012). Humans purposely oxidize elemental antimony to produce antimony trioxide for various industrial uses. Other forms of antimony can also transform into antimony trioxide during the life cycles of products containing antimony. For instance, at high temperature (e.g., during incineration, combustion, or use of the brakes in vehicles), other forms of antimony can be oxidized and give rise to antimony trioxide.

Antimony trioxide exists as an odorless white powder or polymorphic crystals (HSDB 2013). It is slightly soluble in water, dilute sulfuric acid, dilute nitric acid, or dilute hydrochloric acid. It is soluble in solutions of alkali hydroxides or sulfides and in warm solutions of tartaric acid or of bitartrates. Physical and chemical properties of antimony trioxide are listed in the following table.

<table>
<thead>
<tr>
<th>Property</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>291.5$^a$</td>
</tr>
<tr>
<td>Specific gravity, at 24°C</td>
<td>5.9$^b$</td>
</tr>
<tr>
<td>Melting point</td>
<td>655°C$^b$</td>
</tr>
<tr>
<td>Boiling point</td>
<td>1425°C$^b$</td>
</tr>
<tr>
<td>Water solubility, at 22.2°C</td>
<td>[3.3 x 10$^{-4}$] g/100 mL$^{b,c}$</td>
</tr>
<tr>
<td>Vapor pressure, at 574°C</td>
<td>1 mm Hg$^b$</td>
</tr>
</tbody>
</table>

Sources: $^a$ChemIDplus 2017 $^b$PubChem 2017 $^c$IPCS 2017. $^d$Reported as 0.0033 g/L; brackets denote conversion of units.

The bioaccessibility of antimony trioxide was highest (81.7%) in artificial lysosomal fluid with pH = 4.5 and lowest (13.6%) in artificial gastric fluid with pH = 1.6. Intermediate values were found for artificial fluids representing human blood serum (41.5%) and interstitial lung fluid (56.7%), both with pH = 7.4, and sweat (60.8%) with pH = 6.5 (ECHA 2017).

**Use**

The major industrial use of antimony trioxide (EPA 2014, NTP 2016) is as a synergist for halogenated flame retardants in plastics, rubber, and textiles, all of which are used in a wide variety of consumer products. The final concentration of antimony trioxide in textiles as a fire-retardant synergist is 4% to 6%, but back coatings for textiles may contain up to 24% (EU 2008). Another important use of antimony trioxide (EPA 2014, EU 2008, NTP 2016) is as a catalyst for polyethylene terephthalate (PET) plastics, which results in final antimony concentrations of 180 to 550 ppm in the plastic. The major current use for PET plastic is in bottles for water and other beverages, often intended for single use and then disposal, and the major use for recycled PET is as PET fibers for use in fleece fabrics for clothing, soft toys, rugs, carpets, and upholstery, including in automobiles. Antimony trioxide is used in art and other specialty glasses at a concentration of about 0.8% antimony in finished glass (its main use is as a fining agent to remove gaseous inclusions that could leave bubbles in the glass product). It is also used as a white pigment and an opacifier in paints and pigments, which are used in a broad range of industries and consumer products such as plastics, coatings, enamels, and ceramics, and building
materials. An additional minor use of antimony trioxide is to reduce the amount of hexavalent chromium used in cement.

Antimony trioxide is ultimately disposed of as waste during either production processes or through disposal of the final consumer products. Some products are recycled, such as PET beverage bottles for production of PET fibers, but the antimony itself in these recycled products is generally not recovered for reuse.

**Production**

Antimony trioxide is produced primarily by re-volatilization of crude antimony trioxide or by oxidation of antimony metal (EU 2008). The only current domestic producer of primary antimony metal and oxide identified was a company in Montana that used imported feedstock (USGS 2017); no marketable antimony has been mined in the United States since 2015 (USGS 2017). The production of antimony trioxide in 2015 was reported to be between 1 million and 10 million pounds (EPA 2017). The most recent U.S. mine production was in Nevada in 2013 and 2014, when about 800 tons of stibnite (Sb₂S₃), the principal antimony ore, was extracted. That mine has been on care-and-maintenance status (i.e., production has ceased but management for public health and safety continues) since 2015 (USGS 2017).

Antimony trioxide accounts for 80% of total antimony use in the United States (EPA 2014, NTP 2016). Reports under the U.S. Environmental Protection Agency’s (EPA’s) Chemical Data Reporting rule indicate that about 1,000,000 to 10,000,000 pounds of antimony trioxide is produced in the United States; however, consumption of antimony trioxide is likely much higher. EPA (2014) reported that most (approximately 87%) of the roughly 70 million pounds of antimony trioxide consumed in the United States each year between 2007 and 2011 was imported (EPA 2014). The majority of total antimony (83%) used in the United States is also imported, mostly from China, and the remainder (17%) is recovered from antimony-lead batteries (USGS 2017). In 2012, data reported to EPA identified three companies manufacturing and ten facilities importing antimony trioxide (EPA 2012).

**Exposure**

A significant number of people in the United States are exposed to antimony trioxide, as evidenced by occupational exposure data and supporting data on industrial and consumer uses, production, consumption, and predicted environmental exposure. In addition to exposure to antimony trioxide in the workplace, people are potentially exposed when using consumer products containing antimony trioxide or breathing contaminated air. Because the chemical form of antimony changes during manufacturing, in the environment, and in vivo, people can be exposed to antimony trioxide produced by oxidation of other forms of antimony and can be exposed to other antimony forms from sources releasing antimony trioxide. Although levels of antimony are low in biological samples, several studies have reported an association between levels of antimony biomarkers (e.g., antimony in urine or cord blood) and adverse biological effects (Scinicariello and Buser 2016) or non-cancer health outcomes, such as cardiovascular-related diseases (e.g., Guo et al. 2016, Shiue and Hristova 2014) and adverse pregnancy outcomes (Zheng et al. 2014), suggesting that chronic exposure to low levels of antimony may be a potential public health concern. A summary of the major sources of antimony trioxide is presented in the table and text below.
Sources of antimony trioxide and the final forms of antimony (Sb$_2$O$_3$ and others) to which people are exposed

<table>
<thead>
<tr>
<th>Source of antimony trioxide</th>
<th>Exposure route</th>
<th>Expected form of antimony exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sb$_2$O$_3$ production: Occupational</td>
<td>Inhalation of Sb$_2$O$_3$</td>
<td>Sb$_2$O$_3$</td>
</tr>
<tr>
<td></td>
<td>Dermal exposure</td>
<td>Sb$_2$O$_3$</td>
</tr>
<tr>
<td>Environmental antimony trioxide (Sb$_2$O$_3$): Sb$_2$O$_3$ and some non-Sb$_2$O$_3$ releasing sources</td>
<td>Inhalation of Sb$_2$O$_3$</td>
<td>Sb$_2$O$_3$</td>
</tr>
<tr>
<td></td>
<td>Ingestion (from consuming contaminated soil)</td>
<td>Sb ions</td>
</tr>
<tr>
<td></td>
<td>Ingestion (from drinking contaminated water)</td>
<td>Sb(V) ion in oxic environments, and Sb(III) ion in anoxic environments</td>
</tr>
<tr>
<td>Sb$_2$O$_3$ in flame retardant: Occupational and general population exposure</td>
<td>Inhalation (from breathing indoor air in the workplace and home from containing house dust)</td>
<td>Mainly Sb$_2$O$_3$</td>
</tr>
<tr>
<td></td>
<td>Dermal (workplace and from sitting on flame-retardant-treated upholstery)</td>
<td>Sb ions</td>
</tr>
<tr>
<td></td>
<td>Ingestion (from mouthing flame-retardant-treated toys)</td>
<td>Sb ions</td>
</tr>
<tr>
<td>Sb$_2$O$_3$ in PET: Occupational and consumer products</td>
<td>Inhalation: Workers in PET production</td>
<td>Sb$_2$O$_3$</td>
</tr>
<tr>
<td></td>
<td>Inhalation: Workers in downstream PET operations</td>
<td>Sb ions</td>
</tr>
<tr>
<td></td>
<td>Ingestion (from drinking liquid in PET bottles)</td>
<td>Sb ions</td>
</tr>
<tr>
<td>Sb$_2$O$_3$ glass, paint and other uses:</td>
<td>Inhalation and dermal: Occupational</td>
<td>Sb$_2$O$_3$ and Sb ions (depending on process step)</td>
</tr>
<tr>
<td>Occupational</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Occupational Exposure**

The highest occupational exposure to antimony trioxide occurs in workplaces that produce or use antimony trioxide. In the United States, roughly 70 million pounds of antimony trioxide are used annually as a synergist for halogenated flame retardants in plastics, rubber, and textiles, as a catalyst in PET production, and as an additive in optical and art glass, pigments, paints, ceramics, and cement. Workers at an estimated 273 U.S. facilities (based on information from EPA’s Toxics Release Inventory) were exposed to antimony trioxide in 2010. More than 200,000 workers were exposed to antimony trioxide and other antimony compounds in the 1981 to 1983 U.S. National Occupational Exposure Survey, indicating extensive past exposure to antimony.

The highest occupational exposure to antimony trioxide in the United States, exceeding current regulatory levels by at least tenfold, occurred during smelting and refining operations and production of antimony trioxide in the 1970s and 1980s (antimony air levels ranged from 50 to over 5,000 µg/m$^3$) (Donaldson 1976). Antimony is no longer mined in the United States, although three companies still produce antimony trioxide and twelve companies import it (EPA 2012). Global data collected since the 1980s suggest that the highest exposure to antimony
Antimony trioxide occurs during production of antimony trioxide; mean exposure at an antimony trioxide manufacturing facility was 766 µg/m³ (ATSDR 2017), and worst-case exposure was estimated at 790 µg/m³ (EU 2008). The next-highest exposures have been reported for the flame-retardant industry, at up to 200 µg/m³ (ATSDR 1992), with worst-case exposure estimated at 570 µg/m³ (EU 2008). Lower exposures occur during the use of antimony trioxide in the PET industries (with an estimated worst-case exposure of 26 µg/m³) and glass industries (1980s measurements were 40 to 840 µg/m³, Lüdersdorff et al. (1987); estimated worst-case exposure is 15 µg/m³ (EU 2008)). Because other forms of antimony can be oxidized to antimony trioxide, workers in industries using other forms of antimony as raw material can also be exposed to antimony trioxide. For example, when antimonial lead in automobile batteries (antimony makes up as much as 2% of the battery’s total weight) is recycled, the metals are frequently oxidized and produce antimony(III) trioxide (Grund et al. 2006, Dupont et al. 2016). The table above provides information on the form of antimony in these different industries.

Workers can also be exposed to antimony trioxide from emissions from high traffic areas. A study in Chile found very high levels of antimony in the blood (average concentration of 27±9 ng antimony/kg) from port workers exposed to high vehicle traffic. Antimony exposure most likely results from oxidative of antimony trisulfide lubricant to antimony trioxide, which occurs by frictional heating during braking (Quiroz et al. 2009).

**Exposure of the General Population**

Antimony has been detected in urine, whole blood, and saliva from U.S. residents. Data from the National Health and Nutrition Examination Survey reported low levels of urinary antimony (0.043 µg/L for 2013 to 2014), and levels have been decreasing over time. Higher urinary antimony levels were found in individuals with lower income living in economically deprived neighborhoods (Belova et al. 2013, Gonzales et al. 2016, Tyrrell et al. 2013). These biomonitoring studies measure total antimony; the proportion of antimony that resulted from exposure to antimony trioxide is not known.

Members of the general population are exposed to antimony trioxide primarily by breathing contaminated indoor and outdoor air. In 2010, EPA estimated from Toxics Release Inventory data that approximately 11,635 lb of antimony were released into the air from 273 U.S. facilities that likely produced, processed, or used antimony trioxide-containing flame retardants (EPA 2014). Antimony concentrations in outdoor air are highest near facilities that release antimony trioxide into the air, such as mines and smelting operations; levels reported in the 1970s ranged from 0.146 to 300,000 µg/m³. People can also be exposed to antimony trioxide released into the air by oxidation of various forms of antimony, such as antimony trisulfide in brake pads oxidized during braking of automobiles, burning of coal and petroleum, and incineration of waste containing antimony. Levels of antimony in the air of U.S. cities (not associated with specific sources) are low (0.00037 to 0.002 µg/m³ for total suspended particulates).

Soil, water, drinking water and food are not major environmental sources of exposure to antimony trioxide, because it occurs at low concentrations. Environmental exposure is most likely to other forms of antimony, because antimony trioxide is converted to different forms in these media. Antimony trioxide in solution produces the trivalent antimony ion, which hydrolyzes to either the neutral trivalent species antimony (III) hydroxide, Sb(OH)₃, or the charged pentavalent species (the antimonate ion), Sb(OH)₆⁻ (EU 2008). Exposure to antimony in
the soil is expected to be minimal because of antimony’s low solubility and mobility (EPA 2014, Li et al. 2014). Low levels of antimony have been found in U.S. groundwater (at a median concentration of less than 1 µg/L), drinking water (at concentrations ranging from 0.02 to 9.6 µg/L) (ATSDR 2017), and food (at concentrations ranging from not detected to 1.7 µg/g of dry weight) (Belzile et al. 2011).

Consumers are potentially exposed to antimony from consumer products as a result of the use of antimony trioxide as a flame retardant or in PET containers. Exposure of the general population to antimony trioxide from consumer products is generally by inhalation of dust from these products; the estimated worst-case daily exposure to antimony trioxide from inhalation of house dust is 60 µg/g of dust and 0.0032 µg/m³ of air (EU 2008). Exposure is likely higher for children, especially infants, because of their direct contact with carpet material containing antimony trioxide as a fire retardant while crawling and their mouthing of other fabrics containing fire retardants or toys with antimony-containing paint or plastics; the estimated worst-case daily exposure from this source is 0.6 µg/kg of body weight (EU 2008). (See Table above for the route of exposure and most likely form of antimony.)

**Regulations**

**Consumer Product Safety Commission**

Maximum soluble migrated elemental antimony for surface coatings and substrates other than modeling clay included as part of a toy = 60 mg/kg product.

Maximum soluble migrated elemental antimony for modeling clays included as part of a toy = 60 mg/kg product.

**Department of Transportation (DOT)**

Antimony compounds (inorganic, liquid, not otherwise specified), antimony compounds (inorganic, solid, not otherwise specified), and other liquid and solid antimony compounds as specified by the DOT are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

**Environmental Protection Agency (EPA)**

**Clean Air Act**

*National Emission Standards for Hazardous Air Pollutants:* Antimony compounds are listed as hazardous air pollutants.

**Clean Water Act**

*Effluent Guidelines:* Elemental antimony and antimony compounds are listed as toxic pollutants.

*Water Quality Criteria:* Based on fish or shellfish and water consumption = 5.6 µg/L for elemental antimony; based on fish or shellfish consumption only = 640 µg/L for elemental antimony.

Antimony trioxide and other antimony compounds as specified by EPA are designated as hazardous substances.
Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 5,000 lb for elemental antimony;
= 1,000 lb for antimony and other antimony compounds
as specified by EPA.

Emergency Planning and Community Right-To-Know Act
Toxics Release Inventory: Elemental antimony and antimony compounds are listed substances subject to reporting requirements.

Resource Conservation and Recovery Act
Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of antimony or its compounds = K021, K161, K176, K177.
Elemental antimony and antimony compounds are listed as hazardous constituents of waste.

Safe Drinking Water Act
Maximum contaminant level (MCL) = 0.006 mg/L for elemental antimony.

Food and Drug Administration (FDA)
Test systems designed to measure antimony in urine, blood, vomitus, and stomach contents in the diagnosis and treatment of antimony poisoning are designated as Class I medical devices requiring a premarketing application for FDA clearance to market.
Maximum permissible level of elemental antimony in bottled water = 0.006 mg/L.
Antimony (as Sb) content of color additive mixtures for food use made with titanium dioxide may not exceed 2 parts per million.

Occupational Safety and Health Administration (OSHA)
This legally enforceable PEL was adopted from the 1968 ACGIH TLV-TWA shortly after OSHA was established; it may not reflect the most recent scientific evidence and may not adequately protect worker health.

Permissible exposure limit (PEL) (8-h TWA) = 0.5 mg/m$^3$ for elemental antimony and compounds (as Sb).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)
Threshold limit value – time-weighted average (TLV-TWA) = 0.5 mg/m$^3$ for elemental antimony and compounds (as Sb).$^2$

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$^2$ A revision of the ACGIH TLV-TWA for antimony trioxide from “L” (i.e., exposure by all routes should be carefully controlled to levels as low as possible) to 0.03 mg/m$^3$ for antimony trioxide respirable particulate matter has been proposed and placed on the 2017 Notice of Intended Changes (NIC).
Exposure to antimony trioxide by all routes should be carefully controlled to levels as low as possible.

**Environmental Protection Agency (EPA)**

IRIS inhalation reference concentration (RfC) = \(2 \times 10^{-4} \text{ mg/m}^3\) for antimony trioxide.

Regional Screening Levels (formerly Preliminary Remediation Goals):

- **Residential soil** = 3.1 mg/kg for elemental antimony;  
  = 28,000 mg/kg for antimony trioxide.
- **Industrial soil** = 47 mg/kg for elemental antimony.
- **Residential air** = 0.021 \(\mu\text{g/m}^3\) for antimony trioxide.
- **Industrial air** = 0.088 \(\mu\text{g/m}^3\) for antimony trioxide.
- **Tapwater** = 0.78 \(\mu\text{g/L}\) for elemental antimony.

**National Institute for Occupational Safety and Health (NIOSH)**

Recommended exposure limit (REL) = 0.5 mg/m\(^3\) (10-h TWA) for elemental antimony and other antimony compounds (as Sb).

Immediately dangerous to life and health (IDLH) limit = 50 mg/m\(^3\) for elemental antimony.

**References**


