National Toxicology Program
U.S. Department of Health and Human Services

Report on Carcinogens

Monograph on Antimony Trioxide

RoC MONOGRAPH 13

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Foreword

The National Toxicology Program (NTP), established in 1978, is an interagency program within the Public Health Service of the U.S. Department of Health and Human Services. Its activities are executed through a partnership of the National Institute for Occupational Safety and Health (part of the Centers for Disease Control and Prevention), the Food and Drug Administration (primarily at the National Center for Toxicological Research), and the National Institute of Environmental Health Sciences (part of the National Institutes of Health), where the program is administratively located. NTP offers a unique venue for the testing, research, and analysis of agents of concern to identify toxic and biological effects, provide information that strengthens the science base, and inform decisions by health regulatory and research agencies to safeguard public health. NTP also works to develop and apply new and improved methods and approaches that advance toxicology and better assess health effects from environmental exposures.

The Report on Carcinogens Monograph series began in 2012. Report on Carcinogens Monographs present the cancer hazard evaluations of environmental agents, substances, mixtures, or exposure circumstances (collectively referred to as "substances") under review for the Report on Carcinogens. The Report on Carcinogens is a congressionally mandated, science-based, public health document that provides a cumulative list of substances that pose a cancer hazard for people in the United States. Substances are reviewed for the Report on Carcinogens to (1) be a new listing, (2) reclassify the current listing status, or (3) be removed.

NTP evaluates cancer hazards by following a multistep process and using established criteria to review and integrate the scientific evidence from published human, experimental animal, and mechanistic studies. General instructions for the systematic review and evidence integration methods used in these evaluations are provided in the *Handbook for the Preparation of Report on Carcinogens Monographs*. The handbook's instructions are applied to a specific evaluation via a written protocol. The evaluation's approach as outlined in the protocol is guided by the nature, extent, and complexity of the published scientific information and tailored to address the key scientific issues and questions for determining whether the substance is a potential cancer hazard and should be listed in the Report on Carcinogens. Draft monographs undergo external peer review before they are finalized and published.

The Report on Carcinogens Monographs are available free of charge on the NTP website and cataloged in PubMed, a free resource developed and maintained by the National Library of Medicine (part of the National Institutes of Health). Data for these evaluations are included in the Health Assessment and Workspace Collaborative. Information about the Report on Carcinogens is also available on the NTP website.

For questions about the monographs, please email NTP or call 984-287-3211.

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This report has been reformatted to meet new NTP publishing requirements;
its content has not changed. The proposed substance profile is no longer part of the document
because it is published in the 14th Report on Carcinogens.

About This Report

National Toxicology Program[1]

[1]Division of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA

Collaborators

H.S. Amy Wang, Andrew D. Ewens, Sanford C. Garner, Ruth M. Lunn, Suril S. Mehta, Alton F. Peters, Joanne Trgovcich, Kristine L Witt

Division of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA
Responsible for executing and coordination of project activities, including conception, design, planning, conduct, and technical review of cancer hazard
H.S. Amy Wang, Ph.D.
Ruth M. Lunn, Dr.P.H.

RoC Evaluation Team
Contributed to design, conduct, technical review, and interpretation and integration of studies in the evaluation
Andrew D. Ewens, Ph.D., ILS, Inc., Research Triangle Park, North Carolina, USA
Sanford C. Garner, Ph.D., ILS, Inc., Research Triangle Park, North Carolina, USA
Alton F. Peters, M.S. ILS, Inc., Research Triangle Park, North Carolina, USA
Suril S. Mehta, M.P.H., Division of the National Toxicology Program (DNTP), National Institute of Environmental Health Sciences (NIEHS)
Joanne Trgovcich, Ph.D., ICF, Durham, North Carolina, USA
Kristine L. Witt, M.S., Division of the National Toxicology Program (DNTP), National Institute of Environmental Health Sciences (NIEHS)

Contributors

Division of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA
Provided scientific input or technical assistance with the monograph preparation
Jui-Hua Hsieh, Ph.D.
Gloria D. Jahnke, D.V.M.

Provided technical input of review
Alison H. Harrill, Ph.D.
Nisha S. Sipes, Ph.D.

Developed a web-based database
Andy J. Shapiro, M.S.

Organized the peer review of the monograph
Mary S. Wolfe, Ph.D.

RoC Internal Review Group
Provided critical scientific review of the monograph
Stephen S. Ferguson, Ph.D., DNTP, NIEHS
Gordon P. Flake, M.D. (deceased), DNTP, NIEHS
Michelle J. Hooth, Ph.D., DNTP, NIEHS
B. Alex Merrick, Ph.D. (chair), DNTP, NIEHS
Daniel L. Morgan, Ph.D., DNTP, NIEHS
Arun K.R. Pandiri, B.V.Sc., Ph.D., DNTP, NIEHS
Matthew D. Stout, Ph.D., DNTP, NIEHS
Kyla W. Taylor, Ph.D., DNTP, NIEHS
Erik J. Tokar, Ph.D., DNTP, NIEHS
Suramya Waidyanatha, Ph.D., DNTP, NIEHS

External Reviewers
Provided scientific input or technical assistance with the monograph preparation
Michael A. Babich, Ph.D., U.S. Consumer Product Safety Commission (CPSC), Rockville, Maryland, USA
Melanie C. Buser, M.P.H., Center for Disease Control and Prevention (CDC), Atlanta Georgia, USA
Kristina M. Hatlelid, Ph.D., CPSC, Rockville, Maryland, USA
Sharon L. Oxendine, Ph.D., U.S. Environmental Protection Agency (EPA), Washington, District of Columbia, USA
Linda M. Sargent, Ph.D., CDC, Atlanta Georgia, USA
Yin-tak Woo, Ph.D., EPA, Washington, District of Columbia, USA

ILS, Inc., Research Triangle Park, North Carolina, USA
Provided scientific input or technical assistance with the monograph preparation
Whitney D. Arroyave, Ph.D.

Provided technical input or review
Stanley T. Atwood, M.S.

Provided administrative assistance
Ella J. Darden, B.S.
Tracy L. Saunders, B.S.

Designed and performed literature searches
Jessica A. Geter, M.S.L.S.
Lara Handler, M.S.L.S.

ICF International, Inc., Durham, North Carolina, USA
Provided editorial assistance
Susan Dakin, Ph.D.

Provided logistical support for the peer-review meeting
F. Louise Assem, Ph.D.
Susan Blaine, B.A.
Canden N. Byrd, B.S.
Anna N. Stamatogiannakis, B.S.

Peer Review

Peer review of the Draft RoC Monograph on Antimony Trioxide was conducted by an ad hoc expert panel at a public meeting held on January 24, 2018, in the Rodbell Auditorium at the National Institute of Environmental Health Sciences, David P. Rall Building, Research Triangle Park, NC (see http://ntp.niehs.nih.gov/go/38854 for materials, minutes, and panel recommendations from meeting). The selection of panel members and conduct of the peer review were performed in accordance with the Federal Advisory Committee Act and Federal policies and regulations. The panel members served as independent scientists, not as representatives of any institution, company, or governmental agency.

The charge to the Peer-Review Panel was as follows:

(1) Comment on whether the Draft RoC Monograph on Antimony Trioxide is technically correct, clearly stated, and objectively presented.

(2) Provide opinion on whether there is currently or was in the past significant human exposure to antimony trioxide.

The Panel was asked to vote on the following questions:

(1) Whether the scientific evidence supports NTP's conclusions on the level of evidence for carcinogenicity from cancer studies in animals for antimony trioxide.

(2) Whether the scientific evidence supports NTP's preliminary policy decision on the listing status of antimony trioxide.

The monograph has been revised based on NTP's review of the Panel's peer-review comments. The Peer-Review Panel Report, which captures the Panel recommendations for listing status of antimony trioxide in the RoC and their scientific comments, are available on the Peer-Review Meeting webpage for antimony trioxide (http://ntp.niehs.nih.gov/go/38854).

Peer Reviewers

Rebecca Fry, Ph.D. (Chair)
Professor, Department of Environmental Sciences and Engineering
Director, UNC Superfund Research Program
Director, Institute for Environmental Health Solutions
Gillings School of Global Public Health
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina, USA

Richard Peterson II, D.V.M., Ph.D., DACVP
Senior Investigative Pathologist
Global Preclinical Safety
Investigative Toxicology and Pathology
AbbVie
Libertyville, Illinois, USA

Elaine Symanski, Ph.D.
Professor and Chair, Southwest Center for Occupational and Environmental Health
Department of Epidemiology, Human Genetics and Environmental Sciences
School of Public Health
The University of Texas Health Science Center at Houston
Houston, Texas, USA

Michael Waalkes, Ph.D.
Retired, Senior Advisor
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
Raleigh, North Carolina, USA

Elizabeth Ward, Ph.D.
Retired, Senior Vice President for Intramural Research
American Cancer Society
Asheville, North Carolina, USA

John Wise, Sr., Ph.D.
Professor, Department of Pharmacology and Toxicology
University of Louisville
Louisville, Kentucky, USA

Hao Zhu, Ph.D.
Associate Professor, Department of Chemistry
The Rutgers Center for Computational and Integrative Biology
Rutgers University-Camden
Camden, New Jersey, USA

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Erratum

An error was identified in the *Report on Carcinogens Monograph on Antimony Trioxide*. The time to steady state for the 30 mg/m^3 exposure level has been corrected to 1,310 in this document. [September 9, 2021]

Abstract

Introduction: Antimony trioxide (Sb_2O_3) is a synergist in flame retardants, a catalyst in polyethylene terephthalate (PET) production, and a material used in various industrial process and consumer goods. Antimony trioxide is a potential public health concern because of occupational exposure and a suggested association with cancer based on animal studies. The National Toxicology Program (NTP) conducted a cancer hazard assessment of Sb_2O_3 for possible listing in the Report on Carcinogens (RoC), a document mandated by the U.S. Congress to provide information on cancer hazards for people residing in the United States.

Methods: Using a systematic review approach, NTP evaluated evidences on human exposure, cancer studies in humans and experimental animals, mechanisms, and other relevant information. Studies identified via a systematic literature search of three databases were selected using pre-defined inclusion and exclusion criteria. Using a structured framework, multiple reviewers assessed human and animal cancer studies for the study quality (potential biases and study sensitivity) and utility of informing Sb_2O_3 carcinogenicity. NTP also evaluated mechanistic data, using the 10 key characteristics of carcinogens as a guide, and reviewed other relevant data, such as metabolism and toxicokinetic studies. Because Sb_2O_3 may exert its effects through released trivalent antimony ions, biological effects observed with other compounds containing trivalent antimony were also considered. Conclusions on the level of evidence (e.g., sufficient, limited, or inadequate) of the carcinogenicity of antimony trioxide from cancer studies in experimental animals and humans, and the final listing recommendation (not to list, *known* or *reasonably anticipated to be a human carcinogen*) were reached by applying the RoC listing criteria to the body of evidence.

Results and Discussion: Among over 5,500 references identified, 256 references were cited in the monograph. This included an evaluation of five cancer studies in experimental animals and four human cancer studies of independent populations. Antimony trioxide administered by inhalation caused lung tumors (i.e., malignant tumors and/or combined benign and malignant tumors) in rats and mice of both sexes and tumors at several other tissue sites (adrenal gland in female rats, skin in male mice, and lymphatic system in female mice). All studies, except one study in which the high dose was too low, reported increase in tumors. In human cancer studies, elevated mortality of lung cancer was seen in all three cohort studies of antimony-exposed smelter workers; however, it is unclear whether the increased risk was due to exposure to antimony or concurrent exposure to other lung carcinogens. An increased risk of stomach cancer was found in one case-control study and only one of two antimony smelter cohort studies. Evidence for antimony-induced biological effects potentially contributing to carcinogenicity include oxidative stress (and consequently oxidative damage) seen in cultured cells treated with Sb_2O_3 or other antimony compounds, and inhibition of DNA repair seen in cultured cells treated with antimony trichloride. Furthermore, trivalent antimony inhibits cell differentiation in cultured skin cells treated with antimony trichloride or antimony potassium tartrate, which also contains trivalent antimony, and consequently increase the potential for tumor development.

Conclusions: NTP recommends that 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 Sb_2O_3 or antimony in general.

Introduction

Antimony is a metalloid found in nature in over 100 mineral species; it can exist in four oxidation states, −3, 0, +3, 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. Table 1 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 1. Summary of Evidence Streams, Exposures of Interest, and Outcomes

Scientific Evidence Stream	Exposure	Outcome
Primary evidence		
Experimental animal studies	Antimony(III) trioxide	All reported neoplasms
Human studies	Antimony(III) trioxide (primarily) and other antimony(III) compounds	Lung and stomach cancer
Supporting evidence		
Human studies	Antimony(III) compounds	Biological effects related to carcinogenicity or toxicity
Experimental animal studies	Antimony(III) compounds	Carcinogenicity and biological effects related to carcinogenicity or toxicity
In vitro studies	Antimony(III) compounds	Biological effects related to carcinogenicity or toxicity

The monograph also assesses exposure information (summarized in Table 2) 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.

Table 2. Summary of Exposure Information

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

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).

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, NTP posted its protocol for preparing the draft RoC monograph on antimony trioxide for public input on the RoC webpage (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 NTP's 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:

- Chemical Identification and 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 Data (Section 6)
- Other Relevant Data (Section 7)
- Evidence Integration and Listing Recommendation (Section 8)

The overall cancer hazard evaluation in Section 8 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?

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, 232 references were selected for final inclusion in the monograph. Literature searches were updated on a monthly basis prior to posting the peer review draft online (November 29, 2017) and the last update of these searches was received on November 13, 2017. References recommended by the peer reviewers were also considered for the final revisions.

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 carcinogenesis. Mechanistic data, toxicokinetics data, and other relevant data (such as non-cancer health outcomes and carcinogenicity studies of other antimony compounds) are discussed for other inorganic trivalent 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 listing recommendation. The evidence from the cancer studies in humans 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.

1. Chemical Identification and Properties

This section provides information on the physical and chemical properties of antimony(III) trioxide (Sb_2O_3) and on antimony compounds with toxicological and other relevant information (Sections 3, 4, 5, and 6). As mentioned in the Introduction 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.

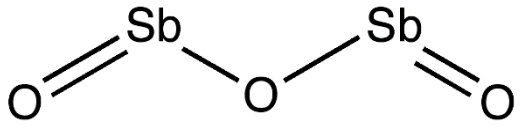


Figure 1-1. Structure for Antimony(III) Trioxide

Table 1-1. Physical and Chemical Properties for Antimony(III) Trioxide

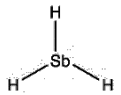
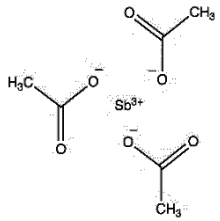
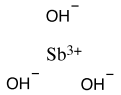
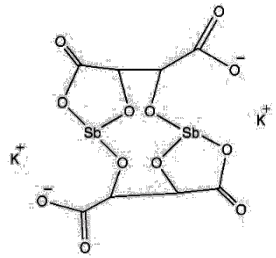
Property	Information
Chemical formula	Sb_2O_3[a]
CAS No.	1309-64-4[b]
InChi key	GHPGOEFPKIHBNM-UHFFFAOYSA-N[c]
Molecular weight	291.5[a]
% Antimony by weight	83.6
Antimony charge	+3[a]
Specific gravity, at 24°C	5.9[c]
Melting point	655°C[c]
Boiling point	1,425°C[c]
Water solubility, at 22.2°C	[3.3×10^{-4}] g/100 mL[d,e]
Vapor pressure, at 574°C	1 mm Hg[c]

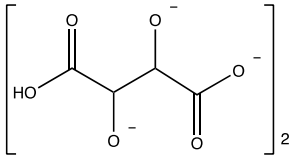
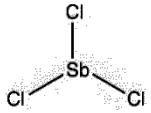
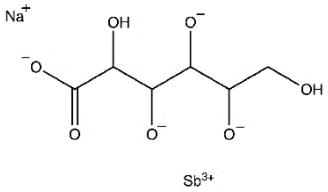
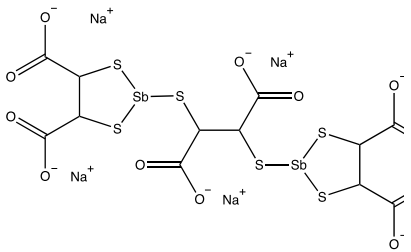
[a]ChemIDplus (2017).
[b]U.S. EPA (2017a).
[c]PubChem (2017).
[d]IPCS (2017).
[e]Reported as 0.0033 g/L; brackets denote conversion of units.

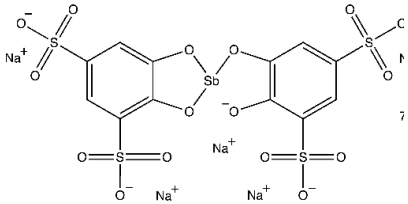
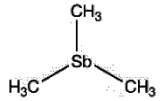
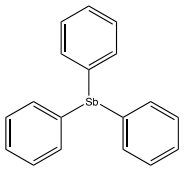
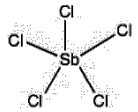
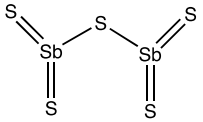
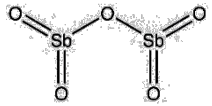
Physical and chemical properties for other antimony compounds discussed in this monograph are listed in Table 1-2 together with their structures; the compounds listed are those with carcinogenicity (Sections 4 and 5), mechanistic (Section 6), or disposition (Section 3) data. In

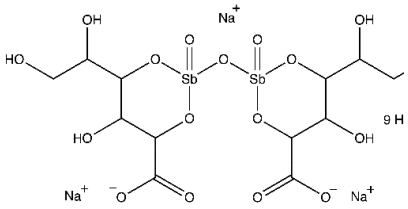
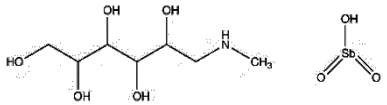
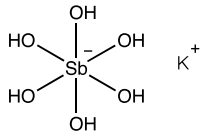
addition to elemental antimony (valence = 0), most antimony compounds have valences of either +3 (11 compounds) or +5 (6 compounds) although one compound with valence −3 is also included in the table. Compounds with +3 valence are likely to share more similarity with antimony(III) oxide but as discussed 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(V) (the active ingredient in Pentostam).

Table 1-2. Physical and Chemical Properties for Metallic (Elemental) Antimony and Other Antimony Compounds with Carcinogenicity or Mechanistic Data

Name	CAS No. (InChI Key)	Formula	Chemical Structure	Molecular Weight (% Sb by Weight)	Density or Specific Gravity	Solubility in Water (g/100 mL), Descriptive Level[c]
Valence = 0						
Antimony (elemental)	7440-36-0[a] (WATWJIUSRGPENY-UHFFFAOYSA-N[a])	Sb[a]	Sb	121.8[a] (100.0[a])	6.68[a, b]	Insoluble[a]
Valence = −3						
Stibine	7803-52-3[a] (OUULRIDHGPHMNQ-UHFFFAOYSA-N[a])	SbH_3[a]		124.8[a] (97.6a)	2.26[a,d]	$[4.1 \times 10\text{-}1]$[a,e] Slightly soluble
Valence = +3						
Antimony acetate; acetic acid antimony (+3) salt	6923-52-0[a] (JVLRYPRBKSMEBF-UHFFFAOYSA-K[a])	$C_6H_9O_6Sb$[a]		298.9[a] (40.7[a])	–	–
Antimony hydroxide	39349-74-1[f] (SZOADBKOANDULT-UHFFFAOYSA-K[a])	H_3O_3Sb[a]		172.8[a] (70.5[a])	–	–
Antimony potassium tartrate[g]	28300-74-5[a] (WBTCZEPSIIFINA-MSFWTACDSA-J[a])	$C_8H_4K_2O_{12}Sb_2$[g]		667.8[a] (36.5[a])	2.6[a]	$[8.3 \times 10^0]$[a,h] Soluble

Name	CAS No. (InChI Key)	Formula	Chemical Structure	Molecular Weight (% Sb by Weight)	Density or Specific Gravity	Solubility in Water (g/100 mL), Descriptive Level[c]
Antimony tartrate[i]	12544-35-3[f] (JFVMOLRNQCNLCHI-WZZCOQPSA-J[f])	$C_8H_4O_{12}Sb_2$[f]		535.6[f] (45.5[f])	–	[2.8×10^2][j] Very soluble
Antimony trichloride	10025-91-9[a] (FAPDDOBMIUGHIN-UHFFFAOYSA-K[a])	$SbCl_3$[a]		228.1[a] (53.4[a])	3.14[a,k]	[10×10^0][a,l] Soluble
Sodium antimony(III) gluconate (antimony(III) sodium gluconate)	12550-17-3[f] (JEKOQEIHGHQVEI-ZBHRUSISSA-M[f])	$C_6H_8NaO_7Sb$[f]		336.9[f] (36.2[f])	–	–
Sodium antimony 2,3-mesodimercaptosuccinate (active ingredient in Astiban)	3064-61-7[a] (AOGOCZMBIYQOFE-UHFFFAOYSA-B[a])	$C_{12}H_6Na_6O_{12}S_6Sb_2$[a]		916.0[a] (26.6[a])	–	–

Name	CAS No. (InChI Key)	Formula	Chemical Structure	Molecular Weight (% Sb by Weight)	Density or Specific Gravity	Solubility in Water (g/100 mL), Descriptive Level[c]
Stibophen[m]	15489-16-4[f] (ZDDUXABBRATYFS-UHFFFAOYSA-F[f])	$C_{12}H_4O_{16}S_4Sb•7H_2O.5Na$[f]		895.2[f] (13.6[f])	–	–
Trimethylstibine	594-10-5[a] (PORFVJURJXKREL-UHFFFAOYSA-N[a])	C_3H_9Sb[a]		166.9[a] (73.0[a])	–	–
Triphenylstibine	603-36-1[a] (HVYVMSPIJIWUNA-UHFFFAOYSA-N[a])	$C_{18}H_{15}Sb$[a]		353.1[a] (34.5[a])	–	$[4.3 \times 10^{-6}]$[f,n] Insoluble
Valence = +5						
Antimony pentachloride	7647-18-9[a] (VMPVEPPRYRXYNP-UHFFFAOYSA-I[a])	$SbCl_5$[a]		299.0[a] (40.7[a])	2.35[a, k]	–
Antimony pentasulfide	1315-04-4[a] (PPKVREKQVQREQD-UHFFFAOYSA-N[a])	S_5Sb_2[a]		403.8[a] (60.3[a])	–	$[9.9 \times 10^{-6}]$[o] Insoluble
Antimony pentoxide	1314-60-9[f] (LJCFOYOSGPHIOO-UHFFFAOYSA-N[f])	Sb_2O_5[f]		323.5[f] (75.3[f])	–	$[4.3 \times 10^{-6}]$[p] Insoluble

Name	CAS No. (InChI Key)	Formula	Chemical Structure	Molecular Weight (% Sb by Weight)	Density or Specific Gravity	Solubility in Water (g/100 mL), Descriptive Level[c]
Sodium stibogluconate (active ingredient in Pentostam)	16037-91-5[f] (CUEDNFKBTFCOSV-UZVLBLASSA-L[f])	$C_{12}H_{20}O_{17}Sb_2.3Na•9H_2O$[f]		908.9[f] (26.8[f])	–	–
Meglumine antimoniate	133-51-7[a] (XOGYVDXPYVPAAQ-SESJOKTNSA-M[a])	$C_7H_{18}NO_8Sb$[a]		366.0[a] (33.3[a])	–	–
Potassium hexahydroxy antimonate	12208-13-8[q] (IAYJQRROUBIPRX-UHFFFAOYSA-H[f])	H_6KO_6Sb[q]		262.9[q] (46.3[q])	–	–

– = No data found; CAS = Chemical Abstracts Service; InChI = IUPAC International Chemical Identifier.
[a]PubChem (2017).
[b]At 77°F.
[c]Descriptive levels are converted from solubility in water (Solubility of Things 2018).
[d]At −25°C.
[e]Reported as 4.1 g/L at 0°C in water. Brackets denote unit conversion.
[f]ChemIDplus (2017).
[g]Formula and structure shown are for anhydrous form of antimony potassium tartrate.
[h]Reported as 83,000 mg/L at 20°C. Brackets denote unit conversion.
[i]Antimony tartrate ion. Felicetti et al. (1974a) reported starting solution as 124Sb-tartrate complex.
[j]EPA CompTox Chemistry Dashboard (2017b). Reported as mean of 5.55 mol/L. Brackets denote unit conversion.
[k]At 68°F.
[l]At 25°C.
[m]The anhydrous form of Stibophen is C12H4Na5O16S4Sb (CAS number = 23940-36-5, molecular weight = 769.1 g/mol).
[n]Reported as 0.043 mg/L at 25°C. Brackets denote unit conversion. Accessed 11/29/2017.
[o]EPA CompTox Chemistry Dashboard (2017b). Reported as 2.46 × 10-7 mol/L. Brackets denote unit conversion.
[p]EPA CompTox Chemistry Dashboard (2017b). Reported as 1.32 × 10-7 mol/L by EpiSuite (2017). Brackets denote unit conversion.
[q]ChemSpider (2017).

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

Antimony Compound	Percent (%) Solubility in Simulated Human Fluid after 24 Hours of Exposure				
	Gamble's Solution[a] (pH = 7.4)	Phosphate-buffered Saline[b] (pH = 7.4)	Artificial Sweat[c] (pH = 6.5)	Artificial Lysosomal Fluid[d] (pH = 4.5)	Artificial Gastric Fluid[e] (pH = 1.6)
Antimony(III) trioxide	56.7	41.5	60.8	81.7	13.6
Antimony(V) pentoxide	32.5	29.2	60.8	71.4	94.3
Antimony(III) sulfide	3.9	8.5	3.6	5.1	4

Source: ECHA (2017).
[a]Gamble's solution mimics interstitial fluid within the deep lung under normal health conditions.
[b]Phosphate-buffered saline mimics the ionic strength of human blood serum.
[c]Artificial sweat mimics hypo-osmolar fluid excreted upon sweating.
[d]Artificial lysosomal fluid mimics intracellular conditions in lung cells during phagocytosis.
[e]Artificial gastric fluid mimics stomach acid.

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. 2002a; 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 ORoC 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. 2002a). 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_3SbO_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 $H_2SbO_4^-$) 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. Positively charged species are reported to generally exist only under very acidic conditions (i.e., pH < 2) (Herath et al. 2017).

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; 2002b).

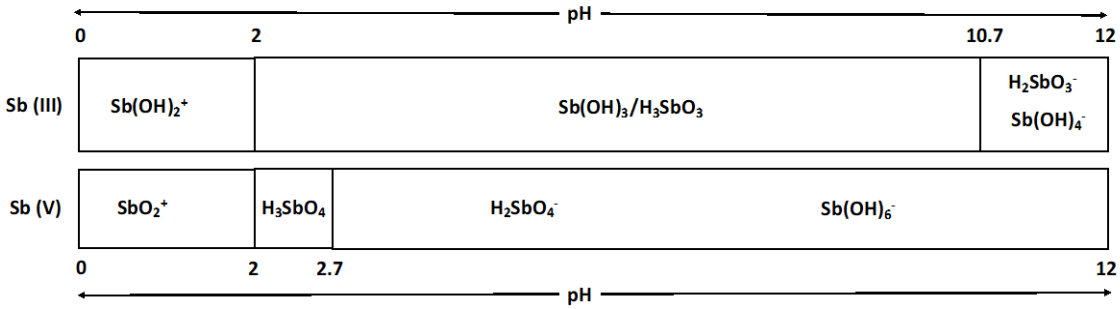


Figure 1-2. Antimony Speciation for Antimony(III) and Antimony(V) Species over a Range of pH Values

$Sb(OH)_2^+$ = dihydroxoantimony (III); $Sb(OH)_3/H_3SbO_3$ = trihydroxy antimony (III)/antimonous acid (III); H_2SbO_3- = dissociated form of Sb_2O_3 (III); $Sb(OH)_4^-$ = tetrahydroxoantimony (III), dissociated form of Sb_2O_3; SbO_2^+ = cation (V); H_3SbO_4 = antimonic acid (V); $H_2SbO_4^-$ = dihydrogen antimonate (V); $Sb(OH)_6^-$ = antimonate ion (V), hexahydroxoantimonate.
Source: Adapted from Herath et al. (2017).

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

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

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_2O_3) is the most commercially significant form of processed antimony. In nature, Sb_2O_3 exists in minerals such as valentinite and senarmontite (ATSDR 2017; Roper et al. 2012). 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 antimony(III) trioxide is the focus of this section. 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 starts with antimony and antimony(III) trioxide consumption in the U.S. (Section 2.1), 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, 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 processes (Section 2.1) Occupational exposure from those uses is discussed in Section 2.2 (occupational exposure), and exposure among the general population is discussed in Sections 2.3.1 (consumer products) and 2.3.2 (environmental exposure).

2.1. Manufacturing Processes, Uses, and Production-related Information

2.1.1. Manufacturing Processes

The life cycle of antimony trioxide from raw material to consumer product is depicted in Figure 2-1. 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). Antimony trioxide is used to make various products and may change forms during the manufacturing of those products (see Section 2.1.2) The life cycle 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 2018), as no marketable antimony has been mined in the United States since 2015 (USGS 2018). The most recent U.S. mine production was in Nevada in 2013 and 2014, when about 800 tons of stibnite (Sb_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 2018).

Antimony trioxide changes its chemical form during the formulation and processing stages for many products. 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.

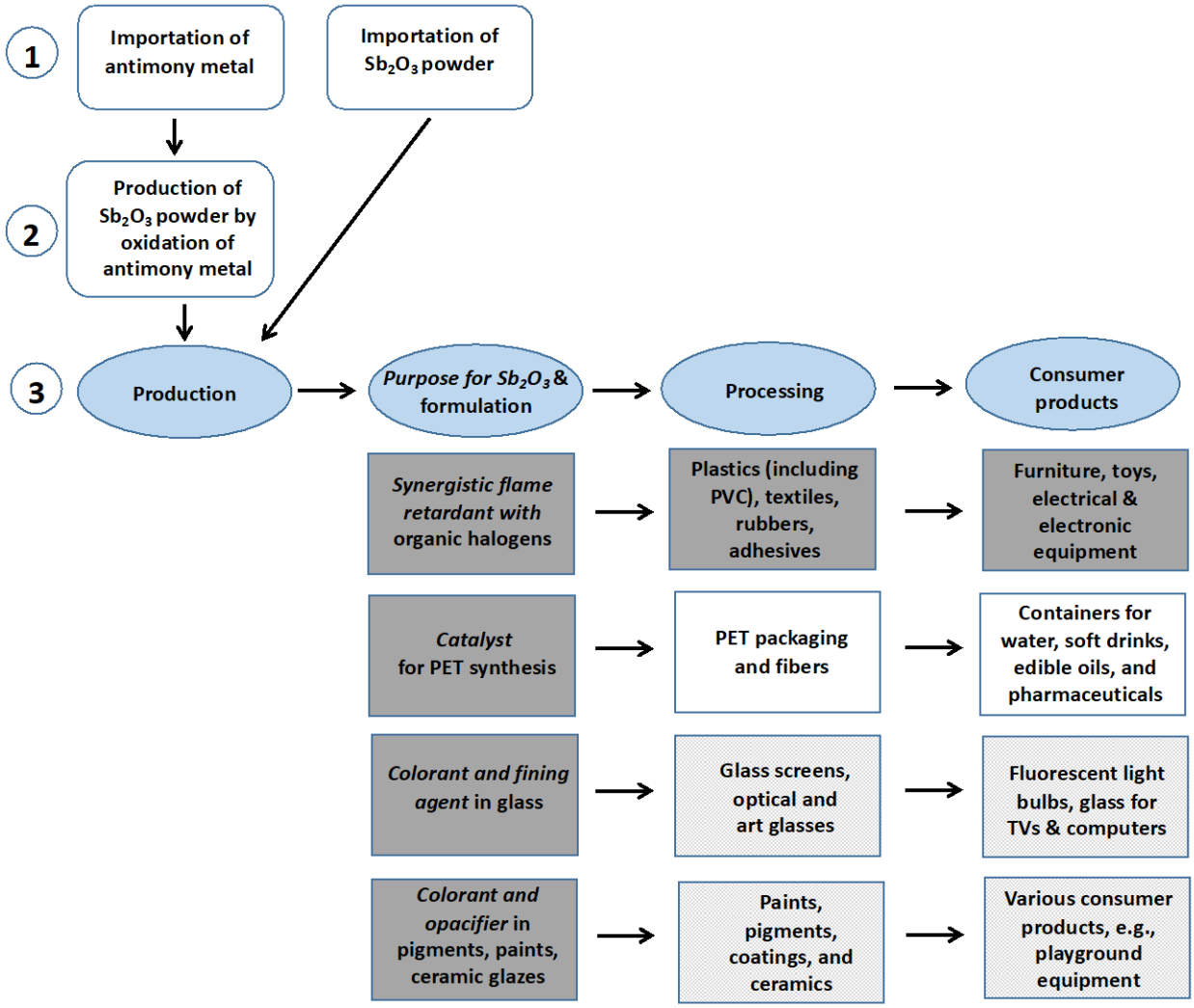


Figure 2-1. Antimony(III) Trioxide Used in Manufacturing Processes

Antimony(III) trioxide (Sb_2O_3) powder can (1) be imported directly or as antimony metal that can then (2) converted to antimony(III) trioxide powder by oxidation in some circumstances; together these processes can be described as (3) the production of antimony(III) trioxide for use in multiple products. Darker shading in the grey rectangular boxes indicates that antimony is believed to be present as the trioxide while lighter shading indicates transformation to other forms of antimony during processing, and intermediate shading indicates possible mixed forms where some, often most, of the antimony is chemically altered.

2.1.2. Uses

Antimony(III) Trioxide

The major industrial use of antimony(III) trioxide (NTP 2017a; USEPA 2014) 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, and an additive in art and specialized glasses, pigments, paints, and ceramics.

Flame retardant synergist: The bromine- or chlorine-containing flame retardants work by quenching free radicals in the gas phase of combustion. Hydrogen halides (e.g., hydrogen chloride, HCl; and hydrogen bromide, 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). Transformation of antimony(III) trioxide does occur if the product is burned (e.g., form antimony halides).

PET production: 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(III) glycolate with antimony concentration ranging from below the detection limit to above 300 mg/kg in the PET bottles (Takahashi et al. 2008). 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. 2011).

Specialty glass, paints, and pigments: 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. 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. During the production process of specialty glass and pigments, antimony(III) trioxide may be chemically transformed to antimony(V) pentoxide by oxidation, and the resulting antimony(V) form may either present as antimony(V) pentoxide in glass or be chemically bonded in a crystal matrix in pigments. Approximately 0.8% antimony is found in finished glass.

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 Sb_2O_3 to the SbO_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.

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(V) pentoxide

and sodium(III) antimonite) are used as synergists for flame-retardant additives in plastics (ATSDR 2017; EU 2008). 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(III) 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 2017a) 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 2016b), 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.

2.1.3. 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(III) 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 (NTP 2017a; USEPA 2014). 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. In 2017, U.S. imports for consumption were approximately 52.8 million pounds of antimony oxide (weight of antimony content) (USGS 2018). EPA (2014) reported that most (approximately 87%) of the roughly 70 million pounds (gross weight) of antimony(III) trioxide consumed in the United States each year between 2007 and 2011 was imported (USEPA 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 2018). In 2012, the U.S. EPA identified three companies manufacturing and ten companies importing antimony(III) trioxide (USEPA 2012).

Table 2-1. U.S. Antimony(III) Trioxide and Antimony Compound Production Volumes for 2015 Exceeding 1 Million Pounds per Year Ranked by Quantity

CAS Number[a]	Antimony Compound	Quantity (lb)[a]
68937-20-2	1,2-Ethanediol, reaction products with antimony(III) trioxide	28,926,800
7440-36-0	Antimony (elemental)	10,000,000–50,000,000
1309-64-4	Antimony(III) trioxide	1,000,000–10,000,000
1314-60-9	Antimony(V) pentoxide	1,000,000–10,000,000
15890-25-2	Antimony(III) diamyldithiocarbamate[b]	1,000,000–10,000,000

[a]USEPA (2017a). Production volumes for antimony (elemental), antimony(III) trioxide, antimony(V) pentoxide, and antimony(III) diamyldithiocarbamate were reported as ranges by EPA.
[b]Antimony(III) diamyldithiocarbamate is a form of antimony(III) dialkyldithiocarbamate with 5-carbon alkyl chains.

Table 2-2. U.S. Imports and Exports of Antimony Metal and Compounds for 2016[a]

Antimony Compound/Category	Imports (lb)	Exports (lb)
Antimony and articles thereof, not elsewhere specified or included	1,940,267	612,439
Antimony ores and concentrates	383,137	25,428
Antimony oxides[b]	42,921,232	3,524,784
Antimony waste and scrap	91,085	389,788
Unwrought antimony (powders)	13,581,996	393,526

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

2.2. Occupational Exposure

The highest exposures to antimony(III) trioxide and total antimony occur in the workplace including transportation workers exposed to antimony trioxide in the air. 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 2017). 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 (USEPA 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 (measured personal breathing zone values), as total antimony, ranged from 0.2 $\mu g/m^3$ to 54,500 $\mu g/m^3$ 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 (this category would likely

include antimony-containing flame retardants) (3.3 μg/m^3 to 54,500 μg/m^3); SIC Code 3341, secondary smelting and refining of nonferrous metals (this category would likely include antimonial lead refining) (1.8 μg/m^3 to 47,700 μg/m^3), and SIC Code 3339, primary smelting and refining of nonferrous metals (including antimony) (5 μg/m^3 to 18,500 μg/m^3). 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; however, the levels most likely reflect other antimony compounds in addition to antimony trioxide.

Workers in the United States and other countries 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 resulting in increased excretion in the urine (see Table 2-3). The studies reported in Table 2-3 were identified primarily from the ATSDR (2017) draft toxicological profile for antimony and compounds and supplemented by literature searches. All results are reported from the primary publication cited.

Among industries using or producing antimony(III) trioxide, the highest levels (up to 5,000 to 6,000 μg/m^3, 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_2O_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 2016a) 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).

Workers in the transportation industry can be exposed to antimony trioxide from oxidation of antimony sulfide or sulfate in brake pads. Port workers in Valparaiso City, Chile were exposed to elevated air concentrations of antimony from heavy vehicular traffic (Quiroz et al. 2009) that resulted in very high levels of antimony in the blood (average concentration of 27 ± 9 ng antimony/kg), which were 5 to 10 times higher than in two control groups (1) from another part of the city or (2) from a rural area outside Valparaiso.

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 2-4 together with studies that reported air levels only. The current TLV for elemental antimony and antimony compounds in air is 500 μg/m^3 (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 Workers Occupationally Exposed to Various Antimony Compounds in the Air

Exposure Scenario (N)	Location[#]	Year of Monitoring	Form of Sb Used	Air Sb Levels (as Total Sb) (μg/m^3), Mean ± Standard Deviation (Range)	Urine Sb Levels (as Total Sb Below, Mean ± Standard Deviation (Range)	Reference
Industries that produce or use antimony(III) trioxide						
Antimony(III) trioxide production	**U.S.A. (Gloucester City, NJ)**	**1975**	**Sb_2O_3**			**Donaldson and Gentry (1975)[a]**
Personal samples (2)				(2,700–5,000)	NR	
General area samples (2)				(1,800–5,600)	NR	
Antimony & antimony(III) trioxide production (smelting and refining)	**U.S.A. (Laredo, TX)**	**1976**	**Sb_2S_3 & Sb_2O_3**			**Donaldson (1976)[a]**
Breathing zone (55)				(50–6,210)	NR	
Area samples (NR)				(140–2,020)	NR	
Antimony oxide production	**U.S.A.**	**1975**	**Sb_2S_3 & Sb_2O_3**			**Cassady and Etchison (1976)**
Personal samples (5)				(210–3,250)	NR	
Antimony(III) trioxide production	South Korea (Seoul)[*]	NR	Sb_2O_3			Kim et al. (1999)
Personal samples (12)				766	410.8 μg/L	
Flame-retardant industry (injection molding of antimony-containing, ignition-resistant polystyrene) (NR)	NR	NR	NR	(BDL–200)		ATSDR (1992)
Flame-retardant industry (textile manufacturing)	Italy[*]	NR	Sb_2O_3			Iavicoli et al. (2002)
Personal samples (42)				(<0.01–0.55)	0.31 ± 0.24 (0.10–1.37) μg/L[b]	
Area samples (24)				(<0.01–1.45)	0.36 ± 0.29 (0.13–1.77) μg/L[c]	
Glass production facility	**U.S.A. (Columbus, NE)**	**1979**	**NR**	**~5**	**NR**	**Burroughs and Horan (1981)**
Personal samples (5)				(ND–1)		

Exposure Scenario (N)	Location[#]	Year of Monitoring	Form of Sb Used	Air Sb Levels (as Total Sb) (µg/m^3), Mean ± Standard Deviation (Range)	Urine Sb Levels (as Total Sb Below, Mean ± Standard Deviation (Range)	Reference
Area samples (1)				2		
Glass industry- batch bunker	Germany[*]	NR	Sb_2O_3			Lüdersdorf et al. (1987)
Personal air (3)				<50, 720, 840		
Stationary air (4)				40, 60, 70, 290		
Batch mixer (45)					5.0 (1.5–15.7) µg/L	
Art glass production (10)	Italy[*]	NR	Sb_2O_3	NR	12.49 ± 13.68 (3.7–50) µg/L	Goi et al. (2003)
Rubber company	**U.S.A. (Marysville, MI)**	**1979**	**Antimony oxide**			**Salisbury (1980)**
Compounding area				(100–150)	NR	
Other industries						
Lead battery production	Germany	NR				Kentner et al. (1995)
Personal samples:						
Casters (7)			Sb_2O_3	4.5 (1.18–6.6)	3.9 (2.8–5.6) µg/g creatinine	
Formers (14)			SbH_3	12.4 (0.6–41.5)	15.2 (3.5–23.4) µg/g creatinine	
Lead-acid battery plant			**SbH_3**			
Area samples (10)	U.S.A.	NR		(ND–2,500)	NR	Jones and Gamble (1984)
Area samples (1)	U.S.A. (San Antonio, TX)	1978			7.0 µg/g creatinine	Young (1979b)
Area samples (1)	U.S.A. (Dallas, TX)	1978			350 µg/g creatinine	Young (1979a)
Secondary lead smelter (reclaiming scrap batteries)	**U.S.A.**	**1979**	**NR**			**Craig et al. (1981)**
Breathing zone (2 of 21 time-weighted averages)				37, 51	NR	

Exposure Scenario (N)	Location[#]	Year of Monitoring	Form of Sb Used	Air Sb Levels (as Total Sb) (µg/m^3), Mean ± Standard Deviation (Range)	Urine Sb Levels (as Total Sb Below, Mean ± Standard Deviation (Range)	Reference
Manufacture of pentavalent antimony compounds	Belgium[*]	NR	Sb_2O_5 Na_3SbO_4			Bailly et al. (1991)
Personal samples:						
Wet process (26)				86 ± 78	12.3 ± 5.0 µg/g creatinine	
Dry process (14)				927 ± 985	110 ± 76 µg/g creatinine	
Refinery workers	United Kingdom[*]	NR				Smith et al. (1995)
Static and personal monitoring within the working areas of the refinery (NR)			NR	(<10–80)	(0.08–32.6 µg/L urine)	
Chemical manufacturers (NR)			NR	NR	(0.1–36.1 µg/L)	
Battery manufacturers (NR)			NR	NR	(1.5–149.2 µg/L)	
Resinoid grinding wheel manufacture (NR)	**U.S.A.[*]**	**NR**	**Sb_2S_3**	**~3,000**	**(800–9,600 µg/L)**	**Brieger et al. (1954)**
Iron foundry (NR)	Belgium[*]	NR	NR	0.15	NR	Zhang et al. (1985)

NR = not reported; BDL = below detection limit (level of detection reported as 0.3 µg/m^3); ND = not detectable.
[#]U.S. locations are in bold.
[*]Location not specifically reported in publication, but likely location inferred from content of paper.
[a]Also reported by Schnorr et al. (1995) (see Section 5).
[b]All operators, beginning of shift (N = 39).
[c]All operators, end of shift (N = 39).

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 2-4 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)

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

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 (50th percentile) exposure level.
[c]Job-specific (reasonable) worst-case exposure is equal to the 90th 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_2O_3 (inhalation) or as total Sb (dermal) with conversion to equivalent concentration of Sb_2O_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.

2.3. 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 level of exposure to antimony, with antimony (all forms of antimony) geometric means urine concentration of 0.132 µg/L for years 1999 to 2000 and 0.043 µg/L for years 2013 to 2014 (Table 2-5). Although the mean concentration (not considering the samples with antimony at below detection limit) appeared to be decreasing over time, this could reflect the use of more sensitive analytical methods, primarily inductively coupled plasma mass spectrometry (ICP-MS) in recent years, rather than an actual

decrease in exposure, an explanation supported by reports of values close to the lower detection limits for the methods used (Filella et al. 2013a). On the other hand, Pang et al. (2016) (see Table 2-5) analyzing urine samples collected from 1998 to 2003 with a sensitive ICP-MS method reported urine antimony concentrations of 0.1 μg/L or higher, suggesting the exposure was higher.

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; Gonzales et al. 2016; Tyrrell et al. 2013). Slightly higher urinary antimony levels were reported for smokers than non-smokers in 2013 to 2014 data, as well as for younger people (6 to 11 years old, and 12 to 19 years old) than 20 years and older in 1999 to 2000 data and 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 2-5). Antimony concentrations in whole blood (Filella et al. 2013a; 2013b; Whitworth et al. 2017) and saliva (Olmez et al. 1998) were available in only few samples, and the concentrations were much higher than that in urine.

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., 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.

Table 2-5. Ranges of Geometric Mean and 95th Percentile Antimony Levels in Urine, Blood, and Saliva Samples of U.S. Populations

Sample	No. of Individuals	Concentration (μg Sb/L) Geometric Mean with (95% Confidence Interval)	Concentration (μg Sb/L) 95th Percentile with (95% Confidence Interval)	References
Urine				
Urine of general U.S. population in 1999–2000 (total)	**2,276**	**0.132 (0.120–0.145)**	**0.430 (0.390–0.470)**	NHANES (CDC 2017a)
6–11 years	316	0.176 (0.154–0.200)	0.440 (0.320–0.600)	
12–19 years	663	0.158 (0.141–0.178)	0.460 (0.350–0.510)	
20 years and older	1,297	0.123 (0.112–0.137)	0.430 (0.390–0.470)	
Urine of general U.S. population in 2013–2014 (total)	**2,664**	**0.043 (0.039–0.048)**	**0.189 (0.170–0.214)**	NHANES (CDC 2017a)
6–11 years	402	0.052 (0.045–0.060)	0.228 (0.168–0.254)	
12–19 years	451	0.051 (0.043–0.061)	0.203 (0.152–0.235)	
20 years and older	1,811	0.042 (0.038–0.045)	0.184 (0.161–0.215)	
Urine of adult (18–49 years) U.S. population in 2013–2014				NHANES (CDC 2017b)
Non-smokers	822	0.042 (0.037–0.047)	NR	
Smokers	592	0.053 (0.048–0.059)	NR	

Sample	No. of Individuals	Concentration (µg Sb/L) Geometric Mean with (95% Confidence Interval)	Concentration (µg Sb/L) 95th Percentile with (95% Confidence Interval)	References
Urine	15	0.061–0.74[a]	NR	Filella et al. (2013a; 2013b)
Urine of Multi-Ethnic Study of Atherosclerosis (MESA) participants in 2000–2002	308	0.10	NR	Pang et al. (2016)
Urine of Strong Heart Study (SHS) participants in 1998–2003	277	0.15	NR	Pang et al. (2016)
Blood				
Whole blood	9	2.53–4.07	NR	Filella et al. (2013a; 2013b)
Whole blood of Healthy Eating Active Living (HEAL) pilot study participants in Houston, TX	22	3.3	NR	Whitworth et al. (2017)
Saliva				
Saliva of healthy volunteers	4	BDL to 3	NR	Olmez et al. (1998)
Saliva of 3 patients with hypogeusia, 6 with hyposmia, and 3 with both hypogeusia and hyposmia	12	BDL to 10[b]	NR	Olmez et al. (1998)

BDL = below detection limit; hypogeusia = decreased taste acuity; hyposmia = decreased smell acuity; NR = not reported.
[a]Filella et al. (2013a; 2013b) also reported a single arithmetic (rather than geometric) mean that falls outside this range- 1.3 µg/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 2.3.1)or indirectly from the environment by inhaling contaminated air (Section 2.3.2)or by consuming contaminated food or drinking water (Section 2.3.3)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 (Antimony(III) Trioxide and Others) to Which People Are Exposed

Source	Exposure Route	Expected Form of Antimony Exposure
Sb_2O_3 (e.g., industrial facility releases)	Inhalation of Sb_2O_3	Sb_2O_3
	Ingestion (from consuming contaminated soil)	Sb ions
	Ingestion (from drinking contaminated water)	Sb(V) ion in oxic environments, and Sb(III) ion in anoxic environments
Sb_2O_3 in flame retardant	Inhalation (from breathing indoor air containing house dust)	Mainly Sb_2O_3 from flame-retardant-treated fabric wear and tear, but also Sb(V) and Sb(III) from outside soil
	Dermal (from sitting on flame-retardant-treated upholstery)	Sb ions
	Ingestion (from mouthing flame-retardant-treated toys)	Sb ions
Sb_2O_3 in PET	Ingestion (from drinking liquid in PET bottles)	Sb ions

Sources: ATSDR (2017); EU (2008).

2.3.1. 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 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 $Sb(OH)_3$ or H_3SbO_3 and Sb(V) as $Sb(OH)_6^-$ or $H_2SbO_4^-$ 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

Exposure Scenario (Exposure Route)	Form of Antimony in Exposure	Weight of Exposed Subject (kg)	Typical Level (Sb_2O_3 µg/kg b.w./day)[a]	Reasonably Worst-Case Level (µg Sb_2O_3/kg b.w./day)
Sitting on **flame-retardant-treated** upholstery **fabric** (dermal)	in hydro-complexed form	60	ND	1.800
Ingesting **house dust** via hand-to-mouth behavior (oral)	largely antimony(III) trioxide	10	0.156	0.600
Sucking on **toys** (oral)	ions	10	ND	0.250
Drinking from a **PET bottle** (oral)	ions	60	0.014	0.035
Breathing in **house dust**; corresponds to indoor air level (inhalation)	largely antimony(III) trioxide	–	15.6 µg Sb_2O_3/g dust; 0.00082 µg Sb_2O_3/m^3 air[b]	60 µg Sb_2O_3/g dust; 0.0032 µg Sb_2O_3/m^3 air[c]

Source: EU (2008).
ND = not determined.
[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]Reported as 0.82×10^{-6} mg/m^3.
[c]Reported as 3.2×10^{-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 <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 measuring antimony in costume cosmetic products purchased in the San Francisco Bay area reported measurements of antimony in eyeshadows (mean = 0.34 mg/kg; range = 0.13 to 0.57 mg/kg; N = 5) and in body paint (mean = 1.5 mg/kg; range = 0.12 to 6.2 mg/kg; N = 5) (Perez et al. 2017).

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.

2.3.2. 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 (USEPA 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 (ATSDR 2017; EU 2008). 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 $\mu g/m^3$] (HSDB 2013). U.S. antimony air particulate matter levels ranged from not detectable (the lower limit of detection was not reported) to 1.21 $\mu g/m^3$, which was reported for a site close to a lead smelter (Ragaini et al. 1977). Elevated mean air levels of 0.146 $\mu g/m^3$ 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 $\mu g/m^3$ 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; ATSDR 2017; EU 2008). 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 2017). Recycling of antimony as part of antimonial 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 (Dupont et al. 2016; Grund et al. 2011). 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). Antimony concentration measurements taken at a roadside site in London, England were 6.73 ± 3.49 ng/m^3 (0.00673 ± 0.00348 $\mu g/m^3$) while the background level was 1.31 ± 0.807 ng/m^3 (0.00131 ± 0.000807 $\mu g/m^3$) (Gietl et al. 2010). 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/m^3 for total suspended particulate, 0.0013 to 0.0206 μg/m^3 for particles <10 μm in diameter (PM_{10}), and 0.0019 to 0.022 μg/m^3 for particles <2.5 μm in diameter ($PM_{2.5}$) (see Table 6-4 in ATSDR (2017).) Antimony levels in areas unpolluted by anthropogenic activity are low (approximately 0.001 μg/m^3) (ATSDR 2017). The EU (2008) estimated that the reasonable worst-case background concentration of antimony in outdoor air is 0.0026 μg/m^3.

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. 2002a).

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 <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 (Li et al. 2014; USEPA 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 <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).

2.3.3. 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 $Sb(OH)_3$, 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

Exposure Category[a]	Typical (µg Sb_2O_3/kg b.w./day)[b]	Worst Case (µg Sb_2O_3/kg b.w./day)[b]
Food	0.074	0.096
Breast milk (children 0–3 months)	0.023	0.087
Drinking water[c]	ND	0.029

Source: EU (2008).
ND = not determined.
[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.

2.4. Summary and Synthesis

A significant number of people in the United States are exposed to antimony(III) trioxide (Sb_2O_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 Sb_2O_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 (EU 2008; Mak 2007) 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 (2017a), 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 2017a). 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 two to three 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 (2017a). In the Newton et al. (1994) study, antimony (III) trioxide levels were detected at several timepoints in red blood cells, but not plasma, from male and female Fisher 344 rats exposed to antimony trioxide by inhalation (at 0.055, 0.51, or 4.50 mg/m^3) for up to 12 months and observed for another 12 months (Table B-1). The antimony levels increased proportionally with exposure level and nearly so with an exposure duration of 12 months compared with 6 months. Lung burdens also increased with exposure concentrations during the 2-year study in male and female Fischer 344 rats (Newton et al. 1994) (see Table 3-1 in Section 3.4, Toxicokinetics).

NTP (2017a) 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 increased with exposure concentration in rats and mice for both the short-term (data not shown) and the long-term exposure periods. Blood levels for the long-term exposure period were measured on days 61, 124, 269, 369, and 551 (see Appendix B, Table B-2 and Figure 3-1). Blood concentrations increased with exposure duration for rats by approximately 4 to 5-fold when concentration at day 551 was compared with that at day 61. Although NTP (2017a) concluded that the increase over time was not as clear for mice in the 2-year study, no statistical comparisons for different time points were reported. Blood

concentrations were also normalized by division of the blood levels by the exposure concentration; the normalized blood levels decreased with increasing exposure concentration, particularly at higher concentrations (data not shown).

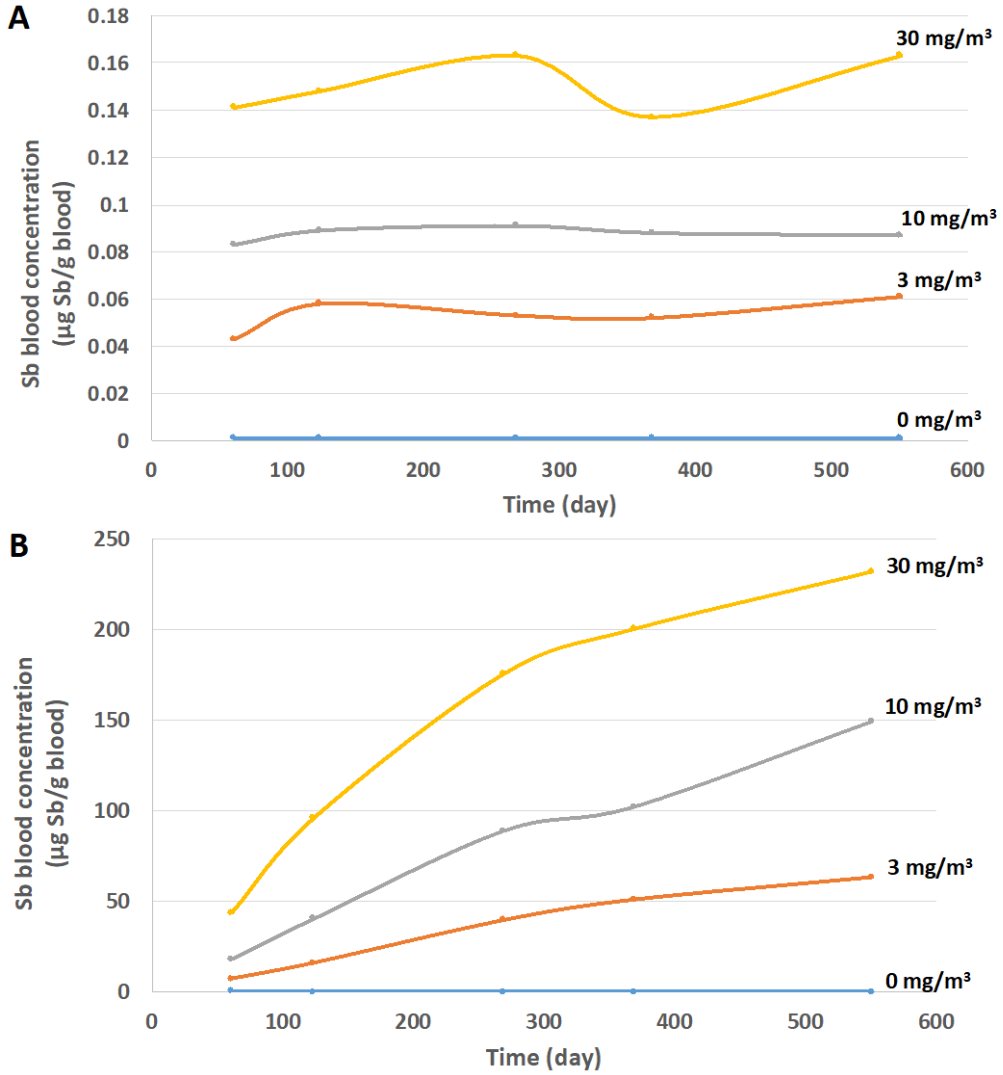


Figure 3-1. Blood Antimony Levels (µg/L) in Female Mice (Panel A) and Rats (Panel B) Exposed to Antimony(III) Trioxide by Inhalation at 0, 3, 10, or 30 mg/m³ in a Two-year Study

Blood antimony levels are reported in Appendix B, Table B-1.
Source: NTP (2017a).

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. Leffler et al. (1984) exposed adult male Syrian golden hamsters to 19.5-µm or 7-µm particles of antimony(III) trioxide by intratracheal 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 intratracheal instillation was >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 (T. N. O. 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 (T. N. O. 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 14 days, tissue levels increased at least 10 fold, and sometimes >100-fold in thyroid, lung, spleen, heart, kidney, liver, bone marrow, bone or femur, muscle and whole blood levels in males and females (see Appendix B, Table B-3). Two additional studies, Westrick (1953), which exposed male Sprague-Dawley rats to 2% antimony(III) trioxide in the diet for 49 days, and Gross et al. (1955), which also exposed rats (sex and strain not specified) to 2% antimony(III) trioxide in the diet but for a total period of 8 months, reported tissue levels of antimony. If food consumption by the rats is assumed to be 5 g per day per 100 g body weight (Johns Hopkins University 2017) then the exposures by either gavage or dietary consumption would be approximately 0.1 g per 100 g body weight and the tissue levels can be compared across the different studies (see Appendix B, Table B-3). The 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 compared with rats exposed by repeated gavage for 14 days (T. N. O. Quality of Life 2005), but the differences between tissue levels at 49 days and 8 months (Gross et al. 1955) were relatively small and levels were lower after 8 months of exposure in some tissues. Different experimental conditions likely contributed to differences across these studies, but the general pattern of increasing tissue levels with increasing duration of oral exposure is likely meaningful.

3.1.2. 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 enterohepatic 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 2-4). 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/m^3 (ACGIH 2017), but one study (Kim et al. 1999) reported a geometric mean air level of 766 μg/m^3, which was associated with a urinary excretion level of approximately 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/m^3 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).

Experimental Animal Studies

Inhalation and intratracheal instillation. In experimental 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 exposed to antimony(III) trioxide by intratracheal instillation, 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 (SbH_3) 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 (Bailly et al. (1991); Dunn (1928); Lauwers et al. (1990) 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 (approximately 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 >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 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; ICRP 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 male and female Sprague-Dawley rats, the levels in thyroid, bone marrow, liver, spleen, and whole blood ranged from 0.028 (2.8 ng Sb/g in whole blood) to 0.195 µg/g (195 ng Sb/g in thyroid) (T. N. O. Quality of Life 2005) (see Table B-3, column for controls [M/F]). Higher levels in liver were reported for 50 dogs (26 females, 23 males, and one of unknown sex) (12.2 µg/kg [ng/g] in males and 135 µg/kg [ng/g] in females) (Paßlack et al. 2015) and for 47 cats (22 males and 25 females) (132 µg/kg [ng/g] for males and females combined) (Paßlack et al. 2014). However, the tissue samples were collected from dogs and cats euthanized for medical reasons and no information on the animals was reported by the authors except for the age range of 3 days to 15 years for the dogs and 2 months to 18 years for the cats. The diet consumed by the dogs and cats could have been an important factor in the difference in antimony levels compared with rats, but the dietary composition was not specified.

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 via either inhalation (as antimony tartrate), 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 intratracheal instillation have been reported for different species. For example, following exposure to antimony(III) trichloride, blood levels in rabbits and dogs were <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(V)) by subcutaneous (s.c.) injections transferred antimony to fetuses via the placenta (Coelho et al. 2014; Miranda et al. 2006), 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/m^3, far above the current threshold limit value for antimony and antimony compounds in air of 500 μg/m^3 (ACGIH 2017).

In seven workers exposed to radioactive antimony (reported as ^{124}Sb 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).

Experimental Animal Studies

Both urinary and fecal elimination have been reported for experimental 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 (^{124}Sb) 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 ($SbCl_3$) 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 (T. N. O. 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. 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 (Barrera et al. 2016; Quiroz et al. 2013) 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) (Miekeley et al. 2002; Petit de Peña et al. 1990), 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, liver, 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 approximately 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 (2017a) 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 3-1). 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 approximately 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[a] (µg/g) in Lung Tissue During a One-year Chronic Exposure (Six-month and 12-month Samples) and a One-year Observation Period (Six-month and 12-month Samples) in Fischer 344 Male and Female Rats

Group	6 mo	12 mo	18 mo (6 mo obs)	24 mo (12 mo obs)
Males				
I- Control	0.0	0.0	0.0	0.0
II- 0.055 mg/m^3	19.6 ± 4.9	11.5 ± 1.6	1.4 ± 1.3	0.4 ± 0.6
III- 0.51 mg/m^3	75.4 ± 10.1	132.0 ± 35.1	28.9 ± 5.1	8.1 ± 3.2
IV- 4.5 mg/m^3	1190.0 ± 167.0	1420.0 ± 238.0	991.0 ± 194.0	554.0 ± 189.0
Females				
I- Control	0.0	0.0	0.0	0.0
II- 0.055 mg/m^3	15.1 ± 4.0	9.6 ± 1.1	2.2 ± 0.6	0.2 ± 0.5
III- 0.51 mg/m^3	76.9 ± 10.6	107.0 ± 28.3	33.2 ± 9.9	14.7 ± 8.2
IV- 4.5 mg/m^3	1100.0 ± 332.0	1500.0 ± 183.0	757.0 ± 59.0	663.0 ± 54.0

Source: Newton et al. (1994).
mo = months.
[a]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 2017a). 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 2-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 (2017a) 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 Figure 3-2 and Figure 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 Two Years

Parameter	Exposure Level (mg/m^3)		
	3	**10**	**30**
Deposition rates (μg Sb_2O_3 per total lung per day)	17	44	119
Percent deposition efficiency (%)	3.3	3.7	4.7
Clearance half-life (days)	136	203	262
Time to steady state (days)	680	1,015	1,310[a]

Source: NTP (2017a).
[a]ERRATUM: An error was identified in the *Report on Carcinogens Monograph on Antimony Trioxide*. The time to steady state for the 30 mg/m^3 exposure level has been corrected to 1,310 in this document. [September 9, 2021]

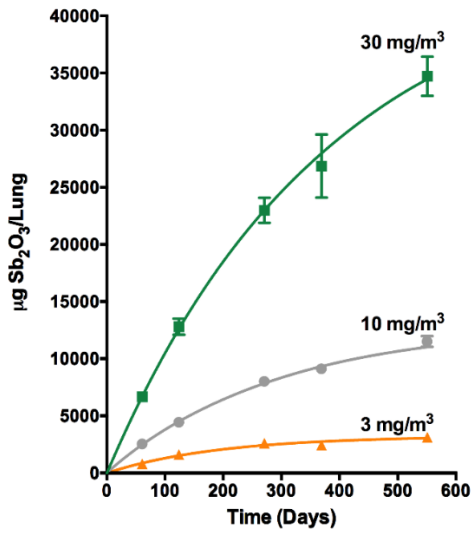


Figure 3-2. Lung Antimony(III) Trioxide Burdens in Female Rats in the Two-year Inhalation Study

Symbols represent the mean ± standard error for 5 rats exposed to either 3, 10, or 30 mg/m^3 antimony(III) trioxide by inhalation for the times indicated. The lines represent the lung deposition and clearance data based on the model fit as in NTP (2017a).

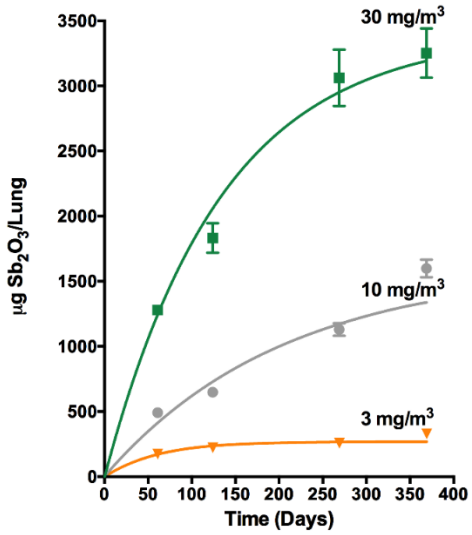


Figure 3-3. Lung Antimony(III) Trioxide Burdens in Female Mice in the Two-year Inhalation Study

Symbols represent the mean ± standard error for 5 mice exposed to either 3, 10, or 30 mg/m^3 antimony(III) trioxide by inhalation for the times indicated. The lines represent the lung deposition and clearance data, without the results for day 551, based on the model fit as in NTP (2017a). NTP (2017a) noted that the day 551 lung burdens were considerably higher than the curves generated with the model fit.

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 (2017a) 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. 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.

3.5. Summary

3.5.1. Absorption and Distribution

Humans exposed occupationally to antimony(III) trioxide by inhalation excreted more antimony in urine, which increased with increasing levels in the air, and some workers were shown to retain antimony in their lungs for months or years. Rats and mice exposed to antimony(III) trioxide by inhalation showed increased concentrations of antimony in blood and in the lung. Absorption of antimony was greater in rats than in mice. Inhalation exposure can also result in gastrointestinal absorption if larger particles of antimony are cleared from the lung by mucociliary transport and then swallowed. Absorption is estimated to be low or very low for both inhalation and oral exposure, and limited data indicate similar absorption of antimony(III) and antimony(V).

Information from studies with exposure to antimony(III) trioxide and other forms of antimony indicated that this element is distributed through the body via the blood, and distribution to tissues is generally similar for different routes of exposure. Both antimony(III) and antimony(V) 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 (2017a) 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 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.) 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 (2017b)] 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 (2017b)]).
2. Evaluation of risk of bias and study sensitivity (Section 4.2, and Appendix C, Table C-1, Table C-2, Table C-3, Table C-4, Table C-5, Table 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's 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 2017b).

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 (Jones 1994; Jones et al. 2007; Schnorr et al. 1995; Wingren and Axelson 1993) 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 the table in Section 4.3.

In both cohort and case-control studies, participants were occupationally exposed to antimony via metal smelting (Jones 1994; Jones et al. 2007; Schnorr et al. 1995) 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 (Jones 1994; Schnorr et al. 1995; Wingren and Axelson 1993) 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 (Jones 1994; Schnorr et al. 1995; Wingren and Axelson 1993), 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; Jones et al. 2007; Schnorr et al. 1995), and two cohort studies and one case-control study reported on gastric cancer mortality (Jones 1994; Schnorr et al. 1995; Wingren and Axelson 1993). 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

Reference	Study Design (Location), Years, Population	Outcome, Including Cancer Sites, Data Analysis	Exposure: Antimony Compounds, Source of Information, Assessment, Metrics
Jones (1994)	Antimony smelter worker cohort (United Kingdom) 1961–1992 (study enrollment and follow-up period) N = 1,420 male workers	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	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, time of hire
Schnorr et al. (1995)	**Antimony smelter worker cohort (United States)** 1937–1989 (employment and follow-up period) N = 1,014 male workers	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	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
Jones et al. (2007); methods described in Binks et al. (2005)	Tin smelter worker cohort (United Kingdom) 1937–2001 (employment and follow-up period) N = 1,462 male workers	Poisson regression analysis (relative risk [RR]) Lung cancer (ICD-8 code: 162.0–162.1 and ICD-9 code: 162.0–162.9)	Antimony species NR *Exposure sources:* area and personal air sampling, personnel records, JEM Quantitative cumulative inhalation exposure (mg-year/m^3)
Wingren and Axelson (1993); methods described in Wingren and Axelson (1985)	Case-control study of men in art glass-producing area (Sweden) 1950–1982 (mortality period) N for cases and controls = NR	Case-control analysis (OR) Cases: stomach cancer (ICD-8 code: 151); colon cancer (code: NR) Controls: death other than cancer or cardiovascular disease	Antimony(III) trioxide *Exposure status:* Determined by listed occupation in death registry Intensity (based on glass works consumption patterns)

ICD = International Classification of Diseases, ICD-8 = ICD Revision 8 (1965), ICD-9 = ICD Revision 9 (1978), JEM = job-exposure matrix, NR = not reported, OR = odds ratio, RR = relative risk, SMR = standardized mortality ratio, U.K. = United Kingdom, U.S. = United States.

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 Table C-1, Table C-2, Table C-3, Table C-4, Table C-5, Table 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

Study Type, Citation	Concern for Potential Bias[a]						Quality[a]	Utility[b]
	Selection	Exposure	Outcome	Confounding Methods	Adequacy of Analysis	Selective Reporting	Sensitivity	Integration
Cohort studies								
Antimony smelter workers								
Jones (1994)	++	+++/++	+++	+	+++	+++	++	+++/++
Schnorr et al. (1995)	++	++	+++	+++	++	+++	++	+++/++
Tin smelter workers								
Jones et al. (2007)	++	++	+++	++	++	+++	+	++
Case-control study								
Wingren and Axelson (1993)	+++	+	++	+	++	++	+	+

[a]Levels 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.

[b]Utility 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; Jones et al. 2007; Schnorr et al. 1995) 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; Jones et al. 2007; Schnorr et al. 1995) 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 (Jones et al. 2007; Wingren and Axelson 1993), 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. It should be noted that while individual-level exposure estimates are generally more precise than imprecise group-level estimates, they may be more subject to bias which may impact the validity of the results (Tielemans et al. 1998). 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), some concern in the study of tin smelter workers (Jones et al. 2007), and minimal concern in the study of antimony smelter workers (Schnorr et al. 1995) (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 (Jones 1994; Wingren and Axelson 1993) 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 5-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

Reference, Location, Study Design and Year	Population Description & Exposure Assessment Method	Exposure Category	Risk Estimate (95% CI)	Exposed Cases	Covariates	Comments, Strengths, and Limitations
Jones (1994) Cohort Northeast England, United Kingdom **Enrollment or follow-up:** 1961–1992 (study enrollment and follow-up period)	**Population:** Antimony smelter workers N = 1,420 men **Exposure assessment method:** company records	**Lung cancer: Ever employed antimony workers, SMR (95% CI)**			Age	**Exposure information:** *Exposure level:* Ever-exposure to antimony defined as employment in antimony plant for 3+ months. *Exposure duration:* 6–50 years based on employment. **Confounding concern:** Likely co-exposure to arsenic and PAHs (lung carcinogens). Smoking not controlled for despite 72% prevalence. **Strengths:** Antimony workers exposed primarily to antimony compounds. Stratified by hiring date, years since first exposure. Additional analysis on other job titles. **Limitations:** External analysis only. Small number of exposed cases for lung and stomach cancers. Potential confounding by smoking and occupational co-exposures. Individual-level data on exposure not available. **Level of evidence:** Inconclusive (lung), inconclusive (stomach)
		Ever antimony worker	[1.55 (1.11–2.11)]	37		
		Before 1/1/1961	[2.18 (1.49–3.07)]	32		
		After 12/31/1960	[0.54 (0.18–1.27)]	5		
		Stomach cancer: Ever employed antimony workers, SMR (95% CI)				
		Ever antimony worker	[0.42 (0.05–1.51)]	2		
Schnorr et al. (1995) Cohort Southern Texas, United States	Population: Antimony smelter workers N = 1,014 men	**Lung cancer: External analysis – U.S. white male mortality rates, SMR (95% CI)**			Age, calendar year, latency period	**Exposure information:** *Exposure level:* Ever-exposure to antimony defined as employment in antimony plant for 3+ months from 1937–1971.
		Ever antimony worker	[0.75 (0.51–1.07)]	30		
		Lung cancer: External analysis – Texas ethnic-specific mortality rates, SMR (90% CI)				

Reference, Location, Study Design and Year	Population Description & Exposure Assessment Method	Exposure Category	Risk Estimate (95% CI)	Exposed Cases	Covariates	Comments, Strengths, and Limitations
Enrollment or follow-up: 1937–1989 (employment and follow-up period)	**Exposure assessment method:** company records	Ever antimony worker	1.39 (1.01–1.88)	28		*Exposure duration:* <5 years to >10 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)
		<5 years employment	SMR only: 0.83	11		
		5–10 years employment	SMR only: 2.24	8		
		>10 years employment	SMR only: 2.73	9		
		Stomach cancer: External analysis – U.S. white male mortality rates, SMR (95% CI)				
		Ever antimony worker	1.49 (0.71–2.74)	10		
		Stomach cancer: External analysis – Texas ethnic-specific mortality rates, SMR (95% CI)				
		Ever antimony worker	1.24 (0.50–2.55)	7		
Jones et al. (2007) Cohort Northern England, United Kingdom **Enrollment or follow-up:** 1937–2001 (Employment and follow-up period)	**Population:** Tin smelter workers N = 1,462 men **Exposure assessment method:** job-exposure matrix and air sampling measurements	**Lung cancer: Cumulative exposure, RR (90% CI)**			Age, calendar year, time since exposure	**Exposure information:** *Exposure level:* cumulative antimony inhalation over employment duration. Exposure duration: Modeled three exposure scenarios from 1937–1971 using annual air sampling estimates from 1972–1991. **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 cumulatively estimated.
		Model 1a (unweighted)	[1.23 (0.79–1.92)]	62		
		Model 1a (weighted)	[5.26 (1.75–43.38)]			
		Model 2b (unweighted)	[1.13 (0.80–1.60)]			
		Model 2b (weighted)	[3.25 (1.32–21.76)]			
		Model 3c (unweighted)	[1.12 (0.80–1.55)]			
		Model 3c (weighted)	[3.32 (1.42–8.08)]			
		Lung cancer: Cumulative exposure, beta coefficient (β) (90% CI)				
		Model 1[a] (unweighted)	0.21 (−0.24–0.65)	62		
		Model 1[a] (weighted)	1.66 (0.56–3.77)			

Reference, Location, Study Design and Year	Population Description & Exposure Assessment Method	Exposure Category	Risk Estimate (95% CI)	Exposed Cases	Covariates	Comments, Strengths, and Limitations
		Model 2[b] (unweighted)	0.12 (0.22–0.47)			**Limitations:** Small number of exposed cases for lung cancer. No information on smoking status; did not control for highly correlated occupational co-exposures. Exposure not at an individual level; air concentrations modeled over 34-year period. **Level of evidence:** Inconclusive (lung)
		Model 2[b] (weighted)	1.18 (0.28–3.08)			
		Model 3[c] (unweighted)	0.11 (−0.22–0.44)			
		Model 3[c] (weighted)	1.20 (0.35–2.09)			
Wingren and Axelson (1993) Case-control Southeast Sweden **Enrollment or follow-up:** 1950–1982 (mortality period)	**Population:** Population-based study of art glass producing area N cases = NR (~ 73 cases of stomach cancer, Wingren and Axelson (1985)). N controls: NR (~833 controls, Wingren and Axelson (1985)) **Exposure assessment method:** occupation (i.e., art glass worker) listed on death records	**Stomach cancer: Antimony use in parish of subject death, OR (90% CI)**			Age	**Exposure information:** Occupation listed as glass worker on death record, and subject died in a parish where antimony use was reported. *Exposure level:* Reported antimony usage levels from companies within study's geographic area. **Confounding concern**: Likely co-exposure to lead; minimal concern for smoking and asbestos. **Strengths**: Population-based study; cases and controls from same geographic area. **Limitations**: Unknown number of cases and controls; exposure status based on factory antimony use at one time point; likely confounding from occupational co-exposure to lead. **Level of evidence**: Inconclusive (stomach)
		No use	2.00 (1.30–3.10)	NR		
		Low level of use	1.60 (0.90–2.60)			
		High level of use	0.80 (0.30–2.00)			
		Any level of use (pooled estimate)	[1.36 (0.85 to 2.15)]			

NR = not reported; [ ] = NTP calculated risk estimates and CI.
[a]Model 1: back-extrapolated missing air concentrations, holding 1972–1974 concentrations constant.
[b]Model 2: back-extrapolated missing air concentrations, assuming two-fold higher concentrations than 1972–1974.
[c]Model 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 <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 $\mu g/m^3$ arsenic and 551 $\mu g/m^3$ for 8-hour area samples; in 1976, mean airborne concentrations were 5 $\mu g/m^3$ arsenic and 747 $\mu g/m^3$ 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. (2007) study 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. Furthermore, the use of weighting factors (time since exposure and attained age) to modify cumulative exposure estimates are less than ideal as they were based on assumptions from a prior study of uranium workers (NRC 1999). It is unclear whether weighted or unweighted estimates are the best metric to evaluate the relationship.

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/m^3-year) were higher than either arsenic (0.28 mg/m^3-year) or antimony (0.37 mg/m^3-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.

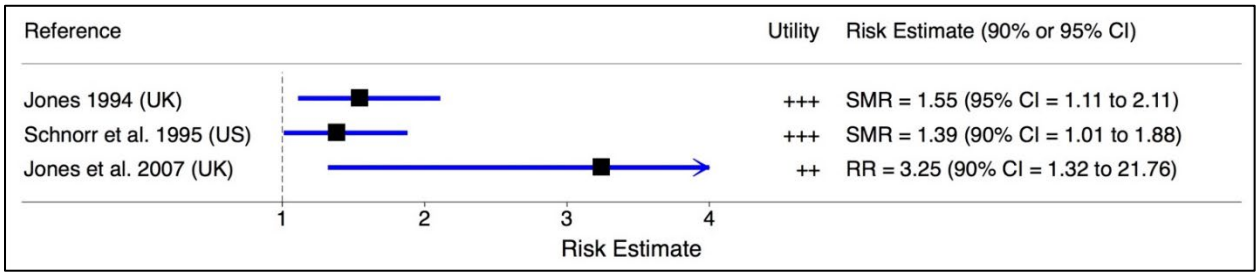


Figure 4-1. Forest Plot of Effect Estimates of Lung Cancer Mortality (SMR or RR, 90% or 95% CI) in Metal Smelter Workers Exposed to Antimony in Available Cohort Studies

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 (SEER 2018). 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 5-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, Table C-1, Table C-2, Table C-3, Table C-4, Table C-5, Table 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, 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, 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. Since there was likely substantial exposure misclassification between the low and high consumption estimates due to imprecise assessment methods, in a post-hoc analysis NTP pooled both the low and high exposure for an ever-exposure risk estimate, which resulted in a weighted odds ratio of 1.36 which was not statistically significant (95% CI = 0.85 to 2.15). 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 a nonsignificant 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.

A prospective mortality linkage study of National Health and Nutrition Examination Survey (NHANES) participants by Guo et al. (2016) saw an increased risk of death from malignant neoplasms 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 Section 4.1, all malignant neoplasms (i.e., all sites as one outcome) are insensitive for evaluating potential cancer hazards.

4.4. NTP's 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; however, it is not clear whether the increased risk was due to exposure to antimony. 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 and applies the RoC listing criteria to reach a 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 <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 Jr 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 (Groth et al. 1986; NTP 2017a; Newton et al. 1994; Watt 1983), 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 1-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's 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, 2 years, with interim sacrifice at 6 months and 12 months (NTP 2017a). Three studies exposed rats for approximately 1 year, followed by at least 4 months of post-exposure observation (Groth et al. 1986; Newton et al. 1994; Watt 1983). 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

Species, Strain or Stock (Sex)	Route	Exposure/Whole-study Duration	Reference
Rat, Wistar Han (M&F)	Inhalation	105 weeks/105 weeks	NTP (2017a)
Mouse, B6C3F1/N (M&F)	Inhalation	105 weeks /105 weeks	NTP (2017a)
Rat, F344 (M&F)	Inhalation	12 months/24 months	Newton et al. (1994)
Rat, CDF (F)	Inhalation	1 year/2 years	Watt (1983)
Rat, Wistar (M&F)	Inhalation	53 weeks /71–73 weeks	Groth et al. (1986)

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.
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 elements of study potential bias and study sensitivity were used: study design, exposure conditions, outcome, confounding, reporting, and analysis (NTP 2015). 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 (NTP 2017a; Newton et al. 1994), 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.

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.

Three antimony(III) trioxide studies were considered of moderate overall utility for assessing cancer hazard. The Groth et al. (1986) study used antimony(III) trioxide that was estimated to be 95.8% pure based on the assumption that all of the antimony (80% by weight) was in the trioxide form, which is consistent with the grade of antimony tested. Trace amounts of arsenic and lead contaminated the antimony(III) trioxide, but the low levels were not thought to contribute significantly to carcinogenicity. 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.

Table 5-2. Quality Assessments of Antimony Trioxide Cancer Studies in Experimental Animals

Areas	NTP (2017a)	NTP (2017a)	Newton et al. (1994)	Watt (1983)	Groth et al. (1986)
Species	R	M	R	R	R
Sex	MF	MF	MF	F	MF
Study design					
Animal randomization	+++	+++	+++	NR	NR
Concurrent controls	+++	+++	+++	+++	+++
Animal model[a]	+++	+++	+++	++	+++
Statistical power[a]	+++	+++	+++	+	+++
Exposure					
Chemical characterization	+++	+++	+++	+++	++
Dosing regimen[a]	+++	+++	++	+++	++
Exposure duration[a]	+++	+++	+++	+++	++
Dose/response	+++	+++	+++	++	+
Outcome					
Outcome methodology	+++	+++	++	++	+++
Group methodology consistency	+++	+++	+++	+++	++
Adequacy of study duration[a]	+++	+++	+++	+++	++
Confounding					
Consideration of confounding	+++	+++	+++	++	+
Analysis and reporting					
Reporting and statistics	+++	+++	+++	++	+++
Tumor combining	+++	+++	+++	+++	+++
Study judgment					
Overall utility	+++	+++	++	++	++

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.
[a]Elements related primarily to the sensitivity of the study.

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 (Groth et al. 1986; NTP 2017a; Watt 1983). 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 the second table in Section 5.4.2. Four studies were performed in rats; three studies were in both sexes (Groth et al. 1986; NTP 2017a; Newton et al. 1994) 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

Species[a], Strain or Stock	Site	Classification	Neoplasms (Sex of Animal)	Reference
Rat, Wistar Han	Adrenal gland	Benign	Pheochromocytoma (M and F)	NTP (2017a)
	Adrenal gland	Combined	Pheochromocytoma (F)	
	Lung	Benign	Alveolar/bronchiolar adenoma (M[b] and F)	
	Lung	Combined	Alveolar/bronchiolar adenoma or carcinoma (M[b])	
Mouse, B6C3F1/N	Lung	Benign	Alveolar/bronchiolar adenoma (F)	NTP (2017a)
	Lung	Malignant	Alveolar/bronchiolar carcinoma (M and F)	
	Lung	Combined	Alveolar/bronchiolar adenoma or carcinoma (F)	
	Skin	Benign	Fibrous histiocytoma (M)	
	Skin	Combined	Fibrous histiocytoma or fibrosarcoma (M)	
	Whole body	Malignant	Lymphoma (F)	
Rat, Wistar	Lung	Benign	Bronchiolar/alveolar adenoma or carcinoma (F)	Groth et al. (1986)
	Lung	Malignant	Squamous-cell carcinoma (F)	
	Lung	Malignant	Scirrhous carcinoma (F)	
Rat, Fischer 344	None	None	None (M and F)	Newton et al. (1994)
Rat (F only), CDF	Lung	Malignant	Scirrhous carcinoma (F)	Watt (1983)

Studies are presented in the order of descending overall utility.
In the Classification column, combined = benign or malignant (total number of animals with tumors).
F = female; M = male.
[a]Both sexes, unless specified.
[b]Considered evidence of antimony trioxide based on multiple factors, although the increase in incidence was not statistically significant.

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 (2017a) 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 2 years (NTP 2017a).

Table 5-4. Lung Tumors in the Two-year NTP (2017a) Studies

	Antimony Trioxide Concentration		
	3 mg/m^3	**10 mg/m^3**	**30 mg/m^3**
Mouse			
Pulmonary overload	No	Yes	Yes
Preneoplastic[a]	↑F, ↑M	↑F, ↑M	↑F, ↑M
Benign	↑F	↑F	↑F
Malignant	↑F, ↑M	↑F, ↑M	↑F, ↑M
Combined	↑F, ↑M	↑F, ↑M	↑F, ↑M
Rat			
Pulmonary overload	No	Yes	Yes
Preneoplastic[a]	↑F, ↑M	↑F[b], ↑M	↑F[b], ↑M
Benign	*M	↑F, *M	↑F[c], *M
Malignant	–	–	–
Combined	*M	*M	*M

↑ = significant increase; F = in females; M = in males; * = considered evidence of antimony(III) trioxide carcinogenicity based on multiple factors, although the increase in incidence was not statistically significant.
[a]Increased hyperplasia of both alveolar and bronchiolar epithelium.
[b]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.

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. Alveolar/bronchiolar 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 there was a significant positive trend and it was considered an

equivocal finding. NTP (2017a) noted that "cystic keratinizing epitheliomas are considered part of a spectrum of lesions that form a continuum considered to progress from squamous metaplasia to keratin cysts to cystic keratinizing epithelioma to squamous-cell carcinoma." NTP also reported lung squamous-cell carcinoma in male or female rats as part of the evidence for carcinogenicity of five substances with exposure by inhalation (tetranitromethane (NTP 1990), nickel(II) oxide (NTP 1996a), nickel subsulfide (NTP 1996b), cobalt sulfate heptahydrate (NTP 1998), and indium phosphide (NTP 2001)) and 2 substances with exposure by oral gavage (dimethyl hydrogen phosphide (NTP 1985) and 3,3',4,4',5-pentachlorobiphenyl (PCB 126), a type of polychlorinated biphenyl (PCB) compound (NTP 2006)).

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 2 years. Carcinomas were increased in both sexes of mice and adenomas were increased in female mice. Compared to rats that had incidence rates of adenomas and carcinomas lower than 20% at all dose levels, mice had incidence rates that were all >20% and carcinomas that were over 60% at 30 mg/m^3 in males. The incidences of carcinomas exceeded historical controls at all dose levels in both sexes and adenomas exceeded historical control at all dose levels in females. During the 1-year interim sacrifice a low frequency of alveolar/bronchiolar adenoma were seen in female mice. 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 2 years. After just 1 year, males had a low frequency of alveolar/bronchiolar adenoma and alveolar/bronchiolar carcinoma. These early findings indicate lung carcinogenesis related to antimony exposure (NTP 2017a). Significant increases in the incidences of adenomas and carcinomas were observed at exposure concentrations as low as 3 mg/m^3, which did not cause pulmonary overload.

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. (1986) study. 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.

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

	Tissue Concentration (µg/g Freeze-dried Tissue)		Ratio (Concentration in 45 mg/m^3 group/concentration in 0 mg/m^3 group)
Exposed antimony trioxide level	**0 mg/m^3**	**45 mg/m^3**	
Metal and site			
Male			
Antimony in lung	9.2	38,300	4,163
Antimony in blood	12.0	1,160	97
Arsenic in lung	6.5	213	33
Arsenic in blood	60.0	115	<2
Female			
Antimony in lung	10.5	25,600	2,438
Antimony in blood	9.6	1,034	108
Arsenic in lung	18.5	150	8
Arsenic in blood	123.0	230	<2

Source: Groth et al. (1986).

The data in Table 5-5 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. (1986) study varied dramatically (average daily concentrations ranged from <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.

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 4.5 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/m^3. The aerosol size used in the Newton et al. (1994) study was large, ranging from 3.76 to 4.55 μm (depending on the instrument used) and included less respirable aerosols than if they had been <4.0 μm (OECD 2017; USEPA 1988). However, the Watt (1983) study used aerosols that were even larger, averaging 5.06 μm, and Watt reported significant increases in lung tumor incidences. 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 1-year exposures at 4.2 mg/m^3 (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 pneumocyte hyperplasia at 1.6 and 4.2 mg/m^3, and adenomatous hyperplasia in the lung at 4.2 mg/m^3.

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 (NTP 2017a).

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) 2-year study.

Female Wistar Han rats in the 30 mg/m^3 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/m^3 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.

Male Wistar Han rats in the 30 mg/m^3 group had increased incidences of adrenal medullary hyperplasia and increased incidences of benign pheochromocytoma. Incidences of benign pheochromocytoma at 10 mg/m^3 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.

Table 5-6. Adrenal Medulla Neoplasms in Wistar Han Rats in the NTP (2017a) Two-year Study

	Antimony Trioxide Concentration		
	3 mg/m^3	**10 mg/m^3**	**30 mg/m^3**
Observations			
Pulmonary overload	No	Yes	Yes
Pre-neoplastic[a]	*M	*F, *M	↑F, ↑M
Benign	–	–	↑F, ↑M
Malignant	–	–	–
Combined	–	–	↑F

* = positive trend for dose response, although the increase in incidences was not statistically significant; ↑F = significant increase in females; ↑M = significant increase in males – = no increase reported.
[a]Increased incidences of hyperplasia in adrenal medulla.

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) 2-year study. Male B6C3F1/N mice had increased incidences (also exceeding historical control ranges) of benign fibrous histiocytoma at 30 mg/m^3 and had a significant positive trend. Two incidences (not significantly increased) of malignant fibrosarcoma were seen at 10 mg/m^3, and increased combined incidences of fibrous histiocytoma or fibrosarcoma at 30 mg/m^3 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/m^3, 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/m^3), with a significant positive dose-response trend after 2 years of exposure (NTP 2017a). The incidences at 10 and 30 mg/m^3 also exceeded historical control ranges. After only 1 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 (Groth et al. 1986; Newton et al. 1994; Watt 1983) 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 (1983) study 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's Level-of-evidence Conclusion

5.4.1. Synthesis

The evidence for the carcinogenic potential from inhalation exposure to antimony(III) trioxide (Table 5-7 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 or 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).

5.4.2. NTP's 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 5-7. Neoplasms That Had Increased Incidences in Malignant Tumors or Combined (Benign or Malignant) Tumors

Sites	Rat		Mouse	
	Malignant	Combined	Malignant	Combined
Lung	↑F[a]	*M[b], ↑F[b]	↑M[c], ↑F[c]	↑F[b]
Adrenal gland	–	↑F[d]	–	–
Skin	–	–	–	↑M[e]
Lymphoma (whole body)	–	–	↑F	–

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

Table 5-8. Cancer Studies in Experimental Animals from Exposure to Antimony(III) Trioxide

Reference and Study Design	Exposure	Tumor Site – Tumor Type Dose Levels (mg/m^3)	Tumor Incidence (n/N) (%)	Comments
NTP (2017a) **Animal:** Rat – Wistar Han [Crl:WI (Han)] M **Animal age at the beginning of exposure:** 6 weeks **Study duration:** 105 weeks	**Agent and purity:** Antimony(III) trioxide (crystalline form: crystalline, diamond cubic crystal structure) 99.9% Aerosol size: Mass median aerodynamic diameter (MMAD) 0.9–1.5 µm, GSD 1.7–2.2 **Exposure route:** Inhalation **Exposure concentrations, frequency, and duration:** 0 3 10 30 mg/m^3 6 hours/day, 5 days/week × 105 weeks	**Adrenal gland – Benign pheochromocytoma**[a]		**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* **Other comments**: 12 Month interim evaluation: Perivascular lymphocytic infiltrate 0/10, 4/10*, 4/10*, 3/10. **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.
		0	1/49 (2.5%)	
		3	0/50	
		10	2/49 (4.8%)	
		30	7/50*[b] (17.2%)	
		Trend p value: < 0.001		
		Lung – Alveolar/bronchiolar adenoma[a]		
		0	3/50[c] (7.1%)	
		3	4/50[c] (9.8%)	
		10	6/50[c] (13.8%)	
		30	8/50[c] (19.7%)	
		Trend p value: = 0.057		
		Lung – Alveolar/bronchiolar carcinoma[a]		
		0	0/50	
		3	0/50	
		10	2/50[d] (4.7%)	
		30	0/50	
		Lung – Alveolar/bronchiolar adenoma or carcinoma[a]		
		0	3/50[c] (7.1%)	
		3	4/50[c] (9.8%)	
		10	8/50[c] (18.4%)	
		30	8/50[c] (19.7%)	

Reference and Study Design	Exposure	Tumor Site – Tumor Type Dose Levels (mg/m^3)	Tumor Incidence (n/N) (%)	Comments
NTP (2017a) **Animal:** Rat – Wistar Han [Crl:WI (Han)] F **Animal age at the beginning of exposure:** 6 weeks **Study duration:** 105 weeks	**Agent and purity:** Antimony 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:** Inhalation **Exposure concentrations, frequency, and duration:** 0 3 10 30 mg/m^3 6 hours/day, 5 days/week × 105 weeks	**Adrenal gland – Benign pheochromocytoma**[a]		**Survival**: Survival was significantly decreased at 10 and 30 mg/m^3 and there was a significant negative trend ($p < 0.001$): 39/50, 38/50, 28/50 ($p = 0.032$), 20/50 ($p < 0.001$). **Body weight**: Body weight was lower than controls in the groups exposed to 30, 10, and 3 mg/m^3 after 65, 81, and 99 weeks, respectively. **Significantly increased preneoplastic lesions**: Lung alveolar epithelium hyperplasia: 5/50, 50/50**, 49/50**, 50/50** Lung bronchiole epithelium hyperplasia: 6/50, 26/50**, 25/50**, 27/50** Lung alveolar epithelium squamous metaplasia: 0/50, 5/50*, 3/50, 1/50 Adrenal medulla hyperplasia: 0/49, 0/49, 3/49, 5/50* **Other comments**: 12 Month interim evaluation: Alveolar/bronchiolar adenoma 0/10, 0/10 0/10, 1/10; Perivascular lymphocytic infiltrate 0/10, 4/10*, 5/10*, 3/10. **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.
		0	0/49	
		3	2/49[e] (4.5%)	
		10	2/49[e] (4.8%)	
		30	6/50**[e] (15.2%)	
		Trend p value: = 0.004		
		Adrenal gland – Malignant pheochromocytoma		
		0	0/49	
		3	0/49	
		10	0/49	
		30	1/50 (2%)	
		Adrenal gland – Benign or malignant pheochromocytoma[a]		
		0	0/49	
		3	2/49[f] (4.5%)	
		10	2/49[f] (4.8%)	
		30	7/50**[f] (17.6%)	
		Trend p value: < 0.001		
		Lung – Alveolar/bronchiolar adenoma[a]		
		0	0/50	
		3	2/50[g] (4.4%)	
		10	6/50*[g] (13.8%)	
		30	5/50*[g] (12.4%)	
		Trend p value: = 0.029		
		Lung – Cystic keratinizing epithelioma or squamous-cell carcinoma[a,h]		
		0	0/50	
		3	0/50	
		10	0/50	
		30	3/50[g,h] (7.4%)	
		Trend p value: = 0.006		

Reference and Study Design	Exposure	Tumor Site – Tumor Type Dose Levels (mg/m^3)	Tumor Incidence (n/N) (%)	Comments
NTP (2017a) **Animal:** Mouse – B6C3F1/N M **Animal age at the beginning of exposure:** 6 weeks **Study duration**: 105 weeks	**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:** Inhalation **Exposure concentrations, frequency, and duration:** 0 3 10 30 mg/m^3 6 hours/day, 5 days/week × 105 weeks	**Lung – Alveolar/bronchiolar adenoma**[a] 0 3 10 30 **Lung – Alveolar/bronchiolar carcinoma**[a] 0 3 10 30 Trend p value: < 0.001 **Lung – Alveolar/bronchiolar carcinoma, multiple only** 0 3 10 30 **Lung – Alveolar/bronchiolar adenoma or carcinoma**[a] 0 3 10 30 Trend p value: < 0.001 **Skin – Benign fibrous histiocytoma**[a] 0 3 10 30 Trend p value: = 0.012 **Skin – Fibrosarcoma** 0 3 10 30 **Skin – Fibrous histiocytoma or fibrosarcoma**[a] 0 3 10 30 Trend p value: = 0.023	10/50 (21.5%) 14/50 (32.9%) 9/50 (21.8%) 14/50 (34.6%) 4/50 (8.5%) 18/50***[i] (40.9%) 20/50***[i] (46.2%) 27/50***[i] (62.8%) 0/50 5/50* (10%) 6/50** (12%) 11/50** (22%) 13/50 (27.5%) 29/50*** (64.5%) 28/50*** (63.6%) 34/50*** (75.3%) 0/50 1/50[j] (2.5%) 1/50[j] (2.5%) 4/50*[j] (10.6%) 0/50 0/50 2/50[j] (4%) 0/50 0/50 1/50[k] (2.5%) 3/50[k] (7.3%) 4/50*[k] (10.6%)	**Survival:** Survival was significantly decreased at 10 and 30 mg/m^3 and there was a significant negative trend (p < 0.001): 38/50, 30/50, 27/50 (p = 0.027), 17/50 (p < 0.001). **Body weight:** Body weights were lower than controls in the 30 mg/m^3 group after 73 weeks. **Significantly increased preneoplastic lesions: Lung lymphocyte infiltration: 13/50, 47/50[l]***[l], 48/50[l]***[l], 45/50[l]***[l];** Lung alveolar epithelium hyperplasia: 6/50, 39/50**, 45/50**, 49/50** Lung bronchiole epithelium hyperplasia: 0/50, 32/50**, 44/50**, 44/50**. **Other comments:** 12 Month interim evaluation: Alveolar/bronchiolar adenoma 0/10, 0/10, 2/10, 0/10; Alveolar/bronchiolar carcinoma 0/10, 0/10, 1/10, 2/10; Lung lymphocyte infiltration 0/10, 10/10**, 10/10**, 10/10**. **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 were performed, so the ability to detect neoplasms was high.

Reference and Study Design	Exposure	Tumor Site – Tumor Type Dose Levels (mg/m^3)	Tumor Incidence (n/N) (%)	Comments
NTP (2017a) **Animal:** Mouse – B6C3F1/N F **Animal age at the beginning of exposure:** 6 weeks **Study duration:** 105 weeks	**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:** Inhalation **Exposure concentrations, frequency, and duration:** 0 3 10 30 mg/m^3 6 hours/day, 5 days/week × 105 weeks	**Whole body – Malignant lymphoma[a]**		**Survival:** Survival was significantly decreased at 10 and 30 mg/m^3 and there was a significant negative trend ($p < 0.001$): 36/50, 31/50, 26/50 ($p = 0.032$), 15/50 ($p < 0.001$). **Body weight:** Body weights were lower than controls in the 30 mg/m^3 group after 85 weeks. **Significantly increased preneoplastic lesions: Lung lymphocyte infiltration: 7/50, 37/50[l***l], 37/50[l***l], 26/50[l***l];** Lung alveolar epithelium hyperplasia: 1/50, 36/50**, 49/50**, 48/50** Lung bronchiole epithelium hyperplasia: 1/50, 34/50**, 48/50**, 45/50**. **Other comments:** 12 Month interim evaluation: Alveolar/bronchiolar adenoma 0/10, 0/10, 0/10, 1/10; peribronchial and perivascular lymphoid infiltrates 3/10, 10/10**, 10/10**, 9/10**; malignant lymphoma 0/10, /10, 0/10, 3/10. **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 were performed, so the ability to detect neoplasms was high.
		0	7/50 (15.6%)	
		3	17/50*[l] (38.1%)	
		10	20/50***[l] (47.5%)	
		30	27/50***[l] (60.7%)	
		Trend p value: < 0.001		
		Lung – Alveolar/bronchiolar adenoma[a]		
		0	1/50 (2.3%)	
		3	10/50**[m] (22.8%)	
		10	19/50***[m] (44.9%)	
		30	8/50**[m] (20.3%)	
		Lung – Alveolar/bronchiolar carcinoma[a]		
		0	2/50 (4.4%)	
		3	14/50***[n] (31.2%)	
		10	11/50**[n] (26.8%)	
		30	11/50**[n] (28.8%)	
		Lung – Alveolar/bronchiolar carcinoma, multiple only		
		0	0/50	
		3	7/50** (14%)	
		10	6/50* (12%)	
		30	4/50* (8%)	
		Lung – Alveolar/bronchiolar adenoma or carcinoma[a]		
		0	3/50 (6.6%)	
		3	22/50***[o] (48.8%)	
		10	27/50***[o] (62.6%)	
		30	18/50***[o] (43.5%)	
		Trend p value: = 0.019		
		Skin – Squamous-cell carcinoma		
		0	0/50	
		3	0/50	
		10	0/50	
		30	2/50[p] (4%)	

Reference and Study Design	Exposure	Tumor Site – Tumor Type Dose Levels (mg/m^3)	Tumor Incidence (n/N) (%)	Comments
Groth et al. (1986) **Animal:** Rat – Wistar M, F **Animal age at the beginning of exposure:** 8 months **Study duration:** 71 to 73 weeks	**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 **Exposure route:** Inhalation **Exposure concentrations, frequency, and duration:** 0 45 mg/m^3 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.	**Lung – Total neoplasms (M)** 0 45 **Lung – Total neoplasms (F)** 0 45 **Lung – Squamous-cell carcinoma (F)** 0 45 **Lung – Scirrhous carcinoma (F)** 0 45 **Lung – Bronchioalveolar adenoma or carcinoma combined (F)** 0 45	 None None 0/89 19/89[***] (21%) 0/89 9/89[**] (10%) 0/89 5/89[*] (5.6%) 0/89 11/89[***] (12%)	**Survival:** Survival was similar to controls. **Body weight**: Body weights were similar to controls, although males did weigh 6.2% less than controls at 26 to 50 weeks. **Significantly increased preneoplastic lesions**: Interstitial fibrosis and alveolar-wall cell hypertrophy and hyperplasia, as well as cuboidal and columnar cell metaplasia occurred at lung foci. Occasionally, neoplasms developed from these foci, suggesting a pre-neoplastic lesion. **Other comments**: Total neoplasms included squamous-cell carcinoma, bronchioalveolar adenoma, bronchioalveolar carcinoma, and scirrhous carcinoma. Incidences of lung neoplasms were not reported in males but were said not to have been significantly different from controls. **Overall utility: [++]** The chemical was well characterized, 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 a statistical analysis as total neoplasms combined per organ site.

Reference and Study Design	Exposure	Tumor Site – Tumor Type Dose Levels (mg/m^3)	Tumor Incidence (n/N) (%)	Comments
Newton et al. (1994) **Animal:** Rat – Fischer 344 (CDF F344 Crl BR) M **Animal age at the beginning of exposure:** 8 weeks (140–169 g males; 99–122 g females) **Study duration:** 24 months	**Agent and purity:** Antimony(III) trioxide (crystalline form: not reported) 99.68% **Aerosol size:** MMAD = 3.76 ± 0.84 µm, GSD 1.79 ± 0.32 **Exposure route:** Inhalation **Exposure concentrations, frequency, and duration:** 0 0.06 (target 0.05) 0.51 (target 0.5) 4.50 mg/m^3 (target 5.0) 6 hours/day, 5 days/week × 12 months 5 animals/sex were sacrificed at 6 (5/sex), 12 (5/sex), 18 (5/sex) months and the rest (50/sex) were sacrificed at 24 months.	**Lung – Carcinoma** 0 0.06 0.51 4.5	1/52 (1.9%) 0/52 (0%) 0/53 (0%) 1/52 (1.9%)	**Survival:** Survival was similar to controls. **Body weight:** Similar to controls. **Significantly increased preneoplastic lesions:** Lungs were examined after 12 months and 24 months. 12 Month results: **Alveolar/intraalveolar macrophage:** 6/13 (46.2%), 11/13 (84.6%)[*], 9/12 (75.0%), 13/13 (100.0%)[**]; **Alveolar/intraalveolar macrophage with foreign particulates:** 0/13, 13/13 (100.0%)[***], 12/12 (100.0%)[***], 13/13 (100.0%)[***]; **Perivascular/peribronchiolar macrophage with lymphoid cells and foreign particulates:** 0/13, 2/13 (15.3%), 6/12 (50.0%)[**], 7/13 (53.8%)[**]; **Peribronchial lymph node macrophage with foreign particulates:** 0/13, 3/13 (23.1%), 5/12 (41.7%)[*], 13/13 (100.0%)[***]. 24 Month results: **Interstitial inflammation:** 32/52 (61.5%), 37/52 (71.2%), 36/53 (67.9%), 48/52 (92.3%)[***]; **Bronchiolar/alveolar hyperplasia:** 3/52 (5.8%), 1/52 (1.9%), 2/53 (3.8%), 4/52 (7.7%); **Alveolar/intraalveolar macrophage:** 31/52 (59.6%), 44/52 (84.6%)[**], 46/53 (86.8%)[**], 52/52 (100.0%)[***]; **Alveolar/intraalveolar macrophage with foreign particulates:** 0/52, 15/52 (28.8%)[***], 38/53 (71.7%)[***], 51/52 (98.1%)[***]; **Perivascular/peribronchiolar macrophage with lymphoid cells and foreign particulates:** 0/52, 22/52 (42.3%)[***], 46/53 (86.8%)[***], 47/52 (90.4%)[***]; **Peribronchial lymph node macrophage with foreign particulates:** 0/52, 6/52 (11.5%)[*], 34/53 (64.2%)[***], 39/52 (75.0%)[***]. **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 Sb_2O_3 accumulation and decreased clearance in the lung (by 80% in the 4.5 mg/m^3 group). The pulmonary overload was observed at relatively low exposure concentrations (compared to inert particles, such as TiO_2) and Sb_2O_3 toxicity was suspected. It appears conditions that could lead to cancer did persist (Table 9, page 572 of Newton et al.), post-exposure, chronic inflammation in most animals, although hyperplasia was observed in very few animals).

Reference and Study Design	Exposure	Tumor Site – Tumor Type		Comments
		Dose Levels (mg/m^3)	Tumor Incidence (n/N) (%)	
Newton et al. (1994) **Animal:** Rat – Fischer 344 (CDF F344 Crl BR) F **Animal age at the beginning of exposure:** 8 weeks (140–169 g males; 99–122 g females) **Study duration:** 24 months	**Agent and purity:** Antimony(III) trioxide (crystalline form: not reported) 99.68% Aerosol size: MMAD = 3.76 ± 0.84 µm, GSD 1.79 ± 0.32 **Exposure route:** Inhalation **Exposure concentrations, frequency, and duration**: 0 0.06 (target 0.05) 0.51 (target 0.5) 4.50 mg/m^3 (target 5.0) 6 hours/day, 5 days/week × 12 months 5 animals/sex were sacrificed at 6 (5/sex), 12 (5/sex), 18 (5/sex) months and the rest (50/sex) were sacrificed at 24 months.	**Lung – Carcinoma** 0 0.06 0.51 4.5	0/49 (0%) 0/52 (0%) 1/54 (1.9%) 0/50 (0%)	**Survival**: Survival was similar to controls. **Body weight**: Similar to controls. **Significantly increased preneoplastic lesions**: Lungs were examined after 12 months and 24 months. 12 Month results: **Alveolar/intraalveolar macrophage:** 6/16 (37.5%), 10/13 (76.9%)[*], 8/11 (72.7%), 14/14 (100.0%)[***]; **Alveolar/intraalveolar macrophage with foreign particulates:** 0/16, 13/13 (100.0%)[***], 11/11 (100.0%)[***], 14/14 (100.0%)[***]; **Perivascular/peribronchiolar macrophage with lymphoid cells and foreign particulates:** 0/16, 6/13 (46.2%)[**], 4/11 (36.4%)[*], 7/14 (50.0%)[**]; **Peribronchial lymph node macrophage with foreign particulates:** 0/16, 0/13, 6/11 (54.5%)[**], 13/14 (92.9%)[***]. 24 Month results: **Interstitial inflammation:** 33/49 (67.3%), 40/52 (76.9%), 48/54 (88.9%)[**], 48/50 (96.0%)[***]; **Bronchiolar/alveolar hyperplasia:** 1/49 (2.0%), 0/52, 0/54, 6/50 (12.0%); **Alveolar/intraalveolar macrophage:** 28/49 (57.1%), 40/52 (76.9%)[*], 48/54 (88.9%)[***], 50/50 (100.0%)[***]; **Alveolar/intraalveolar macrophage with foreign particulates:** 0/49, 24/52 (46.2%)[***], 49/54 (90.7%)[***], 48/50 (96.0%)[***]; **Perivascular/peribronchiolar macrophage with lymphoid cells and foreign particulates:** 0/49, 31/52 (59.6%)[***], 47/54 (87.0%)[***], 47/50 (94.0%)[***]; **Peribronchial lymph node macrophage with foreign particulates:** 0/49, 6/52 (11.5%)[*], 29/54 (53.7%)[***], 39/50 (78.0%)[***]. **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 Sb_2O_3 accumulation and decreased clearance in the lung (by 80% in the 4.5 mg/m^3 group). The pulmonary overload was observed at relatively low exposure concentrations (compared to inert particles, such as TiO_2) and Sb_2O_3 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).

Reference and Study Design	Exposure	Tumor Site – Tumor Type Dose Levels (mg/m^3)	Tumor Incidence (n/N) (%)	Comments
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 Exposure concentrations, frequency, and duration: 0 1.6 ± 1.5 [avg Feret's diameter = 0.44 µm w/ geometric std dev 2.23] 4.2 ± 3.2 mg/m^3 [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.	**Lung – Scirrhous carcinoma** 0 1.6 4.2 **Lung – Squamous-cell carcinoma** 0 1.6 4.2 **Lung – Alveolar/bronchiolar adenoma** 0 1.6 4.2	0/13 0/17 9/18** (50%) 0/13 0/17 2/18 (11%) 0/13 1/17 (5.9%) 3/18 (16.7%)	**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. 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 ~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-Sb_2O_3 particles (and possible metabolism alternation due to pine shavings and therefore affecting susceptibility).

*p < 0.05, **p < 0.01, ***p < 0.001.
[ ] = Statistical significance calculated by NTP, using Fisher's Exact test.
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; geometric std dev = standard deviation.
[a]Adjusted percent incidence based on Poly-3 estimated neoplasm incidence after adjustment for concurrent mortality.
[b]Exceeds historical controls from inhalation studies: 5/149 (range 0%–8%); exceeds historical controls from studies of all routes: 6/297 (range 0%–8%).
[c]Exceeds historical controls from inhalation studies: 4/150 (range 0%–6%); exceeds historical controls from studies of all routes: 4/299 (range 0%–6%).
[d]Exceeds historical controls from inhalation studies: 0/150; exceeds historical controls from studies of all routes: 0/299.
[e]Exceeds historical controls from inhalation studies: 1/148 (range 0%–2%); exceeds historical controls from studies of all routes: 5/297 (range 0%–4%).
[f]Exceeds historical controls from inhalation studies: 2/148 (range 0%–2%); exceeds historical controls from studies of all routes: 7/297 (range 0%–4%).
[g]Exceeds historical controls from inhalation studies: 0/150; exceeds historical controls from studies of all routes: 0/300.
[h]Includes two cystic keratinizing epithelioma and one squamous-cell carcinoma, tumors that NTP considered to be part of a continuum of lesions.
[i]Exceeds historical controls from inhalation studies: 42/250 (range 8%–22%); exceeds historical controls from studies of all routes: 75/550 (range 4%–22%).
[j]Exceeds historical controls from inhalation studies: 1/250 (range 0%–2%); exceeds historical controls from studies of all routes: 2/550 (range 0%–2%).
[k]Exceeds historical controls from inhalation studies: 2/250 (range 0%–2%); exceeds historical controls from studies of all routes: 5/550 (range 0%–2%).
[l]Exceeds historical controls from inhalation studies: 63/250 (range 14%–36%); exceeds historical controls from studies of all routes: 109/550 (range 12%–36%).
[m]Exceeds historical controls from inhalation studies: 12/249 (range 2%–8%); exceeds historical controls from studies of all routes: 27/549 (range 0%–10%).
[n]Exceeds historical controls from inhalation studies: 17/249 (range 2%–10%); exceeds historical controls from studies of all routes: 24/549 (range 0%–10%).
[o]Exceeds historical controls from inhalation studies: 28/249 (range 6%–18%); exceeds historical controls from studies of all routes: 50/549 (range 2%–18%).
[p]Exceeds historical controls from inhalation studies: 0/250; exceeds historical controls from studies of all routes: 0/550.

6. Mechanistic Data

Section 6 provides mechanistic 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 Characteristics in Table 6-1), with minor exceptions (see next paragraph). The order of the presentation is by both possible chronological sequence of events (e.g., being electrophilic leads to binding with GSH, and the efflux of antimony GSH complex in turn causes oxidative stress) and the weight of evidence (evidence from antimony(III) trioxide carries more weight than evidence from other antimony compounds). No metabolic activation is needed for the antimony effects seen.

The section (see Section number and Section header in Table 6-1) starts with electrophilic properties (Section 6.1), oxidative stress (Section 6.2), genotoxicity (Section 6.3), and inhibition of DNA repair (Section 6.4). Due to limited information available, receptor-mediated effects are integrated into the section on cell proliferation and cell death (i.e., alteration of cell proliferation, cell death, and receptor-mediated effects (Section 6.5). Little information is available for antimony immunomodulation and inflammation (Section 6.6) and epigenetic alterations (Section 6.7) contributing to antimony trioxide carcinogenicity, and therefore are presented last. Insufficient studies are available on alterations in cell nutrient supply and immortalization and these topics are not discussed. The relative abundance of the data in each section could be a reflection of available studies (e.g., genotoxicity has been studied much longer than epigenetic changes), rather than the nature of the effects.

Table 6-1. Ten Characteristics of Carcinogens (Smith et al. 2016) and Organization of Section 6

Number	Characteristic	Section Number	Section Header
1	Act as an electrophile either directly or after metabolic activation	6.1	Electrophilic properties
2	Be genotoxic	6.3	Genotoxicity
3	Alter DNA repair or cause genomic instability	6.4	Inhibition of DNA repair
4	Induce epigenetic alterations	6.7	Epigenetic alterations
5	Induce oxidative stress	6.2	Oxidative stress
6	Induce chronic inflammation	6.6	Immunomodulation and inflammation
7	Be immunosuppressive	–	(combined with inflammation)
8	Modulate receptor-mediated effects	–	(combined with cell proliferation)
9	Cause immortalization	–	(no information)
10	Alter cell proliferation, cell death, or nutrient supply	6.5	Alteration of cell proliferation, cell death, and receptor-mediated effects (no information on altered nutrient supply)

6.1. 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 sulfhydryl 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.

While direct effects of antimony(III) trioxide electrophilicity were not found, antimony(III) potassium tartrate directly inhibits glutathione (GSH) reductase (Moreira et al. 2017; Wyllie and Fairlamb 2006) and glutathione *S*-transferase (GST) in red blood cells (Poon and Chu 2000) (see Section 6.2 for additional details). Antimony(III) potassium tartrate also reduced protein thiols by 15% to 40% in neonatal cardiac myocytes (Tirmenstein et al. (1997) in 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 6.4 for additional details). In the high-throughput screening using cultured cells, four antimony compounds, not including antimony(III) trioxide, were screened in various Tox21 assays (see Appendix E.1). They showed mostly antagonistic effects to nuclear receptors, possibly because of displacement of Zn(II) in the zinc finger structures of these receptors by antimony(III) ions.

6.2. Oxidative Stress

Cellular redox imbalance leads to excess accumulation of reactive oxygen species (ROS) and reactive nitrogen species, both of which can cause 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 (Poon and Chu 2000; Sudhandiran and Shaha 2003; Tirmenstein et al. 1997; Tirmenstein et al. 1995; 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).

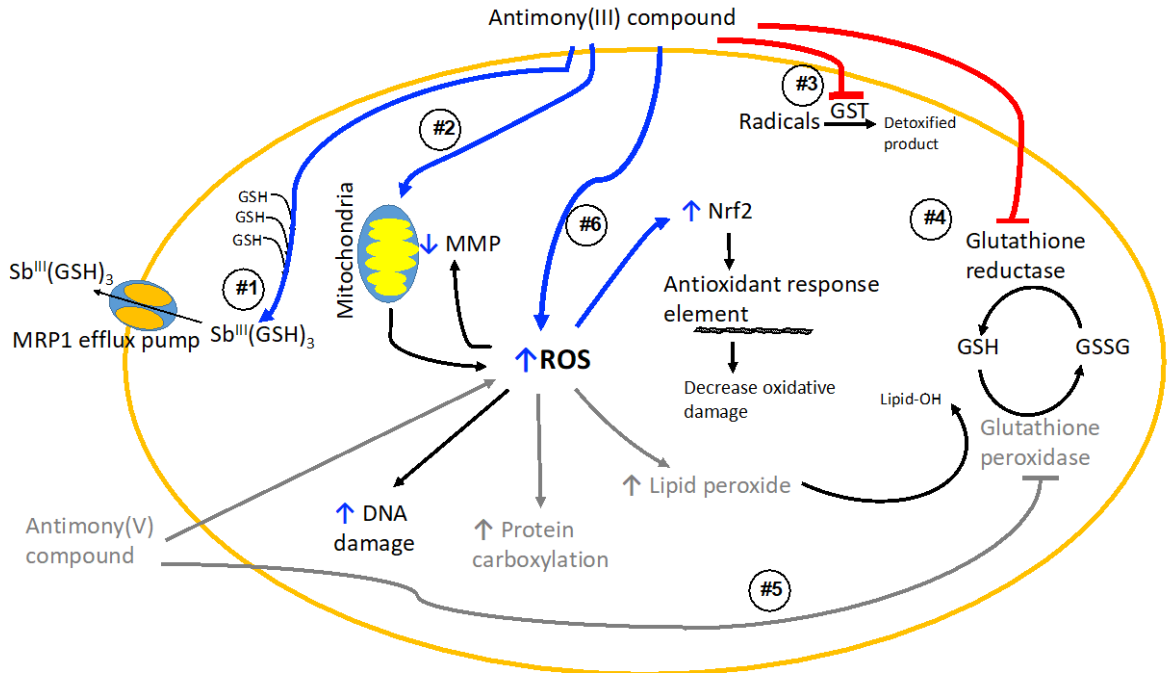


Figure 6-1. Antimony Increases Oxidative Stress

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 (Lösler et al. 2009; Mann et al. 2006), 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.2). 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 (Blond and Whittam 1965) (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-induced decrease in mitochondrial membrane potential.

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.

As summarized in Table 6-2, (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 6-2. Summary of Genotoxicity Data for Antimony(III) Trioxide and Antimony(III) Trichloride

Endpoint (Test System)	Antimony(III) Trioxide		Antimony(III) Trichloride	
	In Vitro	In Vivo	In Vitro	In Vivo
Mutation				
Any mutation (prokaryotes)	Neg	–	Neg	–
Any mutation (eukaryotes)	Neg	*	–	–
DNA Damage				
Any DNA damage (prokaryotes)	Pos	Pos	Pos	–
Any DNA damage (eukaryotes)	Pos	Pos	Pos	–
DNA-protein crosslinks	–	–	Neg	–
Chromosomal damage/cytogenetic effects				
Chromosomal aberrations	Pos	Neg[a]	–	[b]
Micronucleus induction	–	Pos	Pos	Pos
Sister chromatid exchange	Pos	–	Pos	–

Results: Pos = positive, Neg = negative. – = not reported.
*Mutations were detected in antimony(III) trioxide-induced lung tumors (NTP 2017a).
[a]Negative in rats; uncertain in mice due to severe study limitations.
[b]Uncertain because only available study has severe study limitations.

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.3 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: Base Substitution and Frame Shift

Detailed results of the mutagenicity studies regarding base change and fame shift are shown in Appendix E.3, Table E-2.

No human cell study was found. In mouse lymphoma L5178Y $TK^{+/-}$ cells in vitro antimony(III) trioxide did not increase mutations 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; Kanematsu et al. 1980; Kuroda et al. 1991) and antimony(III) trichloride (Kanematsu et al. 1980; Kuroda et al. 1991) 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. DNA Damage

Detailed results of DNA damage studies are shown in Appendix E.3, Table E-3. Antimony(III) trioxide exposure was associated with DNA damage in mice and in cultured cells. No study specifically measuring DNA adduct was found.

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/m^3 or higher in females and 30 mg/m^3 in males), but not in blood leukocyte samples at concentrations of up to 30 mg/m^3, 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/m^3 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.

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 (Hirano et al. 1982; Kada 1976), antimony(III) trioxide (Kanematsu et al. 1980; 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 ($Sb(CH_3)_3$) 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).

6.3.3. Chromosomal Aberrations, Micronucleus, and Sister Chromatid Exchange

Detailed results of chromosomal aberrations, micronucleus, and sister chromatid exchange (SCE) studies are shown in Appendix E.3, Table E-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 3 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 oral exposure to antimony(III) trioxide (Gurnani et al. 1992a) or antimony(III) trichloride (Gurnani et al. 1992b) 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(IIII) 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^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 ells (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(IIII) 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).

6.4. Inhibition of DNA Repair

Although effects of antimony(III) trioxide on DNA repair was only investigated indirectly in an unscheduled DNA synthesis study (Elliott et al. 1998), those of antimony(III) trichloride and antimony(III) potassium tartrate have in assays directly measure DNA damage repair and enzymes. As summarized in Table 6-3, 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 homologous recombination pathways. Whether antimony affects other repair pathways, including base-excision repair or mismatch repair, has not been investigated.

Antimony(III) trioxide did not increase unscheduled DNA synthesis (an indicator of DNA repair) in the liver cells of rats received up to 5,000 mg/kg b.w. antimony(III) trioxide via a single oral gavage (Elliott 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 γ-radiation-induced DNA repair that correlated with disruption in the signaling cascade controlling the non-homologous end-joining repair (NHEJ) and homologous recombination-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 γ-radiation-induced DNA double-strand breaks (DSBs) (to <10%) in CHO-K1 cells (Takahashi et al. 2002).

Table 6-3. DNA Repair Pathways and Molecules Altered by Exposure to Antimony(III) Compounds

DNA Repair Pathway(s)	Effects on DNA Repair	Molecules Affected	Reference
Antimony(III) trichloride			
NER	Defect in lesion-specific repair of UVC-induced CPDs in A549 cells (no effect on repair of 6-4PP or BPDE-DNA adducts)	Decreased transcript and protein levels of XPE Release of zinc from zinc finger domain of XPA	Grosskopf et al. (2010)
NHEJ and homologous recombination	Inhibition of repair of γ-irradiation-induced DSBs in HeLa cells	Diminished phosphorylation (i.e., activation) and recruitment of BRCA1 to DSB Antimony(III) trioxide itself had no impact on CHK1 or CHK2 phosphorylation, but it diminished γ-irradiation-induced phosphorylation of CHK1, but not CHK2 Prolonged presence of phosphorylated ATM foci at DSB, but ATM activity did not appear to be impaired	Koch et al. (2017)
homologous recombination	Inhibition of repair of γ-irradiation-induced DSBs in HeLa cells	Diminished association of the homologous recombination-specific marker RAD51 at DSB	Koch et al. (2017)
Antimony(III) potassium tartrate			
NHEJ and homologous recombination	Inhibition of repair of γ-irradiation-induced DSBs in CHO-K1 cells	Not reported	Takahashi et al. (2002)

BPDE-DNA adducts = DNA adducts induced by (+)-anti-benzo[*a*]pyrene diol epoxide; BRCA1 = breast cancer type 1 susceptibility protein; CHK1 = checkpoint kinase 1 (protein); CHK2 = checkpoint kinase 2 (protein); ; RAD51 = DNA repair protein RAD51 (i.e., RAD51 recombinase).

6.5. Alteration of Cell Proliferation and Receptor-mediated Effects

Antimony(III) trioxide has not been reported to inhibit apoptosis, increase cell proliferation, or encourage angiogenesis, but it increased the mutation of *Egfr* genes in mouse lung tumors.

Among the many receptors related to tumor development, the epidermal growth factor receptor gene (*EGFR*) (an oncogene) is commonly mutated in human lung neoplasms, and so is *KRAS* (a proto-oncogene), which does not code for a receptor but a G-protein influencing cells to divide or differentiate. The mutations of *Egfr* and *Kras* genes were analyzed in the lungs of mice and rats after 2-year inhalation exposure to antimony(III) trioxide at 3, 10, or 30 mg/m^3 (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.4, Table E-5.

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 antimony(III) potassium tartrate has both pro- and anti-tumorigenic effects.

In spontaneously immortalized keratinocytes (SIK), exposure to antimony(III) potassium tartrate 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).

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. In HepG2 (human liver carcinoma) cells, bis[(+)-tartato]diantimonate(III) dipotassium trihydrate (i.e., antimony(III) potassium tartrate trihydrate, equivalent to one molecule of antimony(III) potassium tartrate plus three water molecules), one of the top three affected regulators[1] based on upstream analysis of the microarray data (see Appendix E.5, Table E-6) was vascular endothelial growth factor (VEGF). 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.

6.6. Immunomodulation and Inflammation

Little is known regarding the effects of antimony(III) compounds on immunity. No in vivo or in vitro studies of antimony(III) trioxide effects on the immune system or function were found. In vitro exposure to an organic antimony(III) compound was found to affect expression of genes related to immune function, and in vivo intentional exposure to organic and inorganic antimony(V) compounds were used to increase immune response to parasites.

[1]IPA (Ingenuity Pathway Analysis)'s definition of upstream transcriptional regulator is quite broad—any molecule that can affect the expression of other molecules, which means that upstream regulators can be almost any type of molecule, from transcription factor, to microRNA, kinase, compound or drug (Ingenuity Systems 2018). Consequently, the abbreviations in the discussion of upstream regulators do not necessarily follow the format rule of gene names in italic and protein names not.

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.

In contrast to the lack of information of inorganic antimony immune effects, an organic compound containing antimony(III) was found to affect expression of many genes related to immune reactions. Based on the gene expression profile of HepG2 cells after 6-hour-exposure to bis[(+)-tartato]diantimonate(III) dipotassium trihydrate (equivalent to one molecule of antimony(III) potassium tartrate plus three water molecules) (Kawata et al. 2007) analyzed by ORoC (see Appendix E.5), of the top ten canonical pathways affected (see Table E-7), 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. In the upstream analysis (Appendix E.5, Table E-6**)**, besides VEGF, the top three affected regulators were 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. Both CSF2 and TREM1 stimulate immune or inflammatory responses.

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.6, Table E-8). 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).

6.7. Epigenetic Alterations

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.

Only two studies on DNA and RNA methylation were identified, and none was specific for antimony(III) trioxide. This might reflect the relative newness of epigenetic research, besides DNA methylation, compared to other characteristics (particularly for genotoxicity and oxidative stress), rather than the degree or breadth of changes.

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. 2011; Daskalos et al. 2009) 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 (Lian et al. 2015; Witte et al. 2014), 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).

6.8. Integration of Mechanistic Information

This section summarizes and integrates the primary findings from the mechanistic data on antimony(III) trioxide (Figure 6-2).

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.

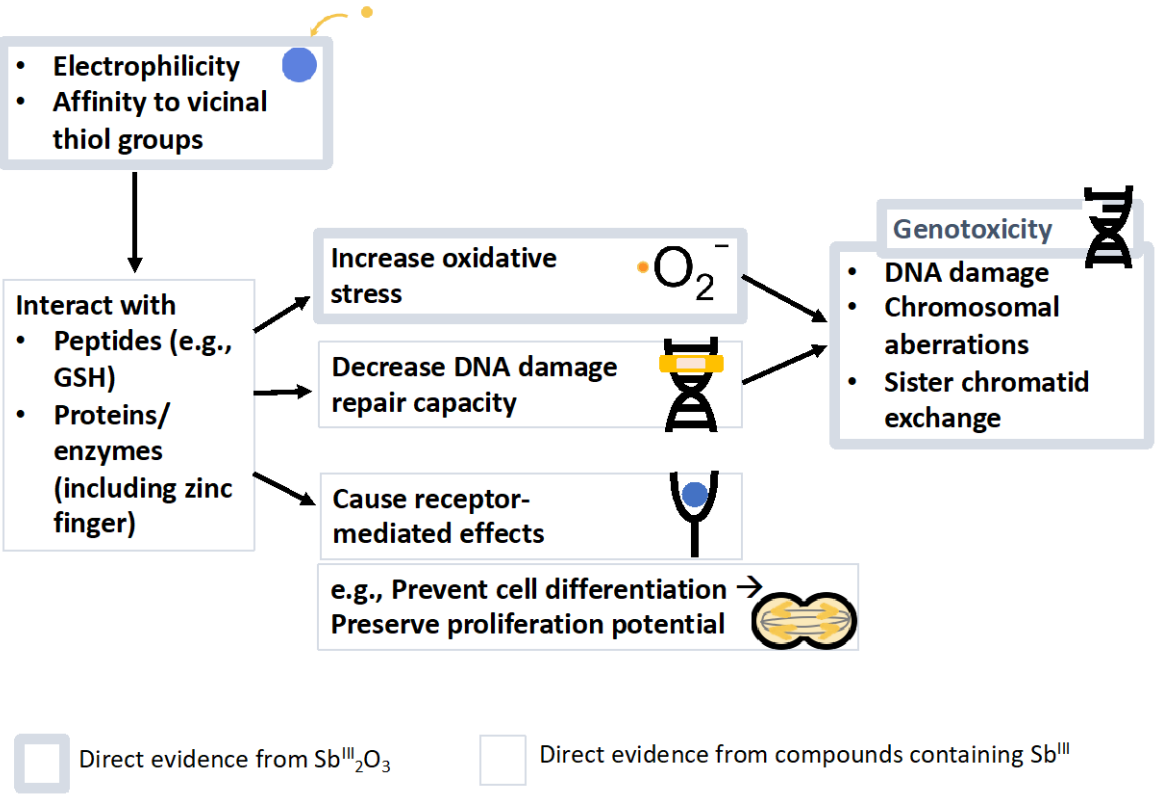


Figure 6-2. Key Mechanistic Information for Antimony(III) Trioxide Carcinogenicity

Antimony(III) trioxide causes DNA damage, chromosomal aberrations, and micronucleus formation in rodents after in vivo exposure, Bacterial assays indicate it does not change the base-sequence in DNA, which is supported by the only available mammalian mutation study. 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.

7. Other Relevant Data

This section reviews (1) carcinogenic studies on other antimony compounds and (2) conclusions regarding non-cancer health outcomes.

7.1. 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 F.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.

7.2. Noncancer 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 experimental animals exposed to antimony trioxide via inhalation.

8. Evidence Integration and 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 8.1), mechanistic and other relevant data (Section 8.2), and studies on cancer in humans (Section 8.3).

8.1. 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, Table 5-1 and Table 5-4). In a 2-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.

8.2. 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.

Although electrophilicity of antimony(III) trioxide has not been reported, antimony compounds are electrophilic and might interact directly with nucleic acids and proteins. Trivalent antimony is highly reactive with sulfhydryl groups and, in particular, vicinal thiol groups. Proteins containing vicinal thiol groups include GSH and enzymes that bind to DNA.

Antimony(III) trioxide and other 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 indirect and not sensitive 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.

8.3. 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 (Jones et al. 2007; Schnorr et al. 1995) 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.

8.4. Listing Recommendation

This 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.

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Abbreviations

AAS	atomic absorption spectrometry
ADME	absorption, distribution, metabolism, and excretion
ATG	Attagene
ATM	ataxia-telangiectasia mutated kinase
avg	average
b.w.	body weight
BDL	below detection limit
BPDE	benzo[a]pyrene diol epoxide
BPDE-DNA adducts	DNA adducts induced by (+)-anti-benzo[a]pyrene diol epoxide
BRCA1	breast cancer type 1 (protein)
BSC	NTP Board of Scientific Counselors
BSO	dl-buthionine-[S,R]-sulfoximine
CCRF-CEM	name of a cell line from acute lymphoblastic leukemia cells
CDC	Centers for Disease Control and Prevention
CI	confidence interval
conc. (Conc.)	concentration
CPDs	cyclobutane pyrimidine dimers
CSF2	colony-stimulating factor 2
dGTP	deoxyguanosine triphosphate
DNA	deoxyribonucleinc acid
DSB(s)	double-strand DNA break(s)
EC50	half maximal effective concentration
Egfr	epidermal growth factor receptor (mouse and rat gene)
EGFR	epidermal growth factor receptor (human gene)
EGFR	epidermal growth factor receptor (protein)
ELISA	enzyme-linked immunosorbent assay
EPA	U.S. Environmental Protection Agency
EU	European Union
F	female(s)
FDA	U.S. Food and Drug Administration
FISH	fluorescence in situ hybridization

FPG	formamidopyrimidine-DNA glycosylase
GI	gastrointestinal
GLP	Good Laboratory Practice
GSD	geometric standard deviation
GSH	glutathione
GSSG	glutathione disulfide
GST	glutathione *S*-transferase
GTP	guanosine triphosphate
HBr	hydrogen bromide
HCl	hydrogen chloride
HepG2	a cell line from human liver carcinoma
HG-AAS	hydride generation-atomic absorption spectrometry
HHS	Department of Health and Human Services
HIC	highest ineffective concentration
HPLC-HG-AFS	high-performance liquid chromatography-hydride generation-atomic fluorescence spectrometry
HPLC-UV-HG-AFS	high-performance liquid chromatography-ultraviolet-hydride generation-atomic fluorescence spectrometry
hr	hour(s)
HR	hazard ratio
HTS	USITC harmonized tariff schedule
HWSE	healthy worker survival effect
i.m.	intramuscular(ly)
i.p.	intraperitoneal(ly)
i.v.	intravenous(ly)
IC-ICP-AES	ion chromatography with inductively coupled plasma-atomic emission spectrometry
ICD	International Classification of Diseases
ICD-8	ICD Revision 8
ICD-9	ICD Revision 9
ICF	ICF Incorporated, LLC
ICP-AES	Inductively coupled plasma-atomic emission spectroscopy
ICP-MS	mass spectrometry

iCSS	interactive Chemical Safety for Sustainability (dashboard)
ILS	Integrated Laboratory Systems, Inc.
JEM	job-exposure matrix
K-562	chronic myelogenous leukemia cells
LC-HG-AFS	liquid chromatography-hydride generation-atomic fluorescence spectrometry
LEC	lowest effective concentration
LOUCY	T cell acute lymphoblastic leukemia cells
M	male(s)
MMAD	mass median aerodynamic diameter
MMP	mitochondrial membrane potential
mo	month(s)
MPPD	multiple path particle deposition (model)
N	number (e.g., total number of animals tested in a group)
n/N	number of animals with neoplasms divided by the total number of animals tested in that group
NAICS	North American Industry Classification System
NAWQA	National Water-Quality Assessment
NB4	acute promyelocytic leukemia cells
NB4-M-AsR3	arsenic-resistant APL cells derived in Miller laboratory
NC	negative control
NCBI GEO	National Center for Biotechnology Information Gene Expression Omnibus
NCTR	National Center for Toxicological Research
ND	not determined
Neg	negative
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
NTP	National Toxicology Program
NVS	NovaScreen
OR	odds ratio
ORoC	Office of the Report on Carcinogens
OSHA	Occupational Safety and Health Administration
PAHs	polycyclic aromatic hydrocarbons
PC	positive control
PET	polyethylene terephthalate
pH	potential of hydrogen (a logarithmic scale used to specify the acidity or basicity of an aqueous solution)
PHS	Public Health Service
Pos	positive
PVC	polyvinyl chloride
r	correlation coefficient
R	rat(s)
REACH	European Union Registration, Evaluation and Authorisation of CHemicals
RNA	ribonucleic acid
RoC	Report on Carcinogens
ROS	reactive oxygen species
RR	relative risk
s.c.	subcutaneous(ly)
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SEER	Surveillance, Epidemiology, and End Results (program)
SIC	standard industrial classification
SIK	a cell line from spontaneously immortalized human keratinocytes
SMR	standardized mortality ratio
std dev	(geometric) standard deviation
TK	toxicokinetics
TLV	threshold limit value
TREM1	triggering receptor expressed on myeloid cells 1

TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
U.K.	United Kingdom
U.S.	United States of America
USGS	United States Geological Survey
UVC	ultraviolet C
VC	vehicle control
VEGF	vascular endothelial growth factor
XPA	xeroderma pigmentosum complementation group A
XPE	xeroderma pigmentosum complementation group E

Units of Measurement

Area	
cm^2	square centimeter
Concentration	
g/L	grams per liter
mg/kg b.w.	milligrams per kilogram body weight
mg/L	milligrams per liter
mg/m^3	milligrams per cubic meter
mg%	milligram percent (equivalent to milligrams per deciliter)
mol/L	moles per liter
ng/g	nanograms per gram
ppm	parts per million
µM	micromolar
µmol/L	micromoles per liter
µg/g	micrograms per gram
µg/kg	micrograms per kilogram
µg/L	micrograms per liter
$µg/m^3$	micrograms per cubic meter
Length	
ft	feet
in	inch
Mass/Weight	
kg	kilogram
lb	pound
mg	milligram
mol	mole
ng	nanogram
µg	microgram
Temperature	
°C	degrees Celsius
Volume	
dL	deciliter
L	liter
m^3	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).

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.

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. 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 4 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.

Enterohepatic 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 elevated release 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: A 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, subtropics, 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. 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.

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 exposure misclassification: The probability of erroneous classification of an exposed individual into a category other than that to which they 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 *K*ow): 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 9 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 2 or 3 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_{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 determination and quantification of the time course of absorption, distribution, biotransformation, and excretion of a chemical in the body.

Transcriptomics: The study of all 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 → guanine or guanine → adenine) or a pyrimidine base for another pyrimidine base (cytosine → thymine or thymine → cytosine).

Vapor pressure: The pressure of the vapor over a liquid (and some solids) at equilibrium, usually expressed as mm Hg at a specific temperature.

Appendix A. Literature Search Strategy

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A.1. Introduction

The objective of the literature search approach is to identify published literature that is relevant for evaluating the potential carcinogenicity of antimony trioxide (https://ntp.niehs.nih.gov/ntp/about_ntp/bsc/2016/december/meetingmaterials/draftantimonytrioxide_508.pdf). The literature search strategy was used to identify publications in the following areas:

- Properties and human exposure (focusing on the U.S. population)
- Disposition (ADME) and toxicokinetics
- Human cancer studies
- Studies of cancer in experimental animals
- Mechanistic data and other relevant effects
  - Genetic and related effects
  - Mechanistic considerations

A.2. General Approach

Database searching encompasses selecting databases and search terms and conducting the searches. Searches of several citation databases are generally conducted using search terms for antimony, combined with search terms for cancer and/or specific topics, including epidemiological and mechanistic studies. A critical step in the process involves consultation with an information specialist to develop relevant search terms. These terms are used to search bibliographic databases. Table A-1 highlights the general concepts searched and databases consulted. To review all the terms used, please refer to the full search strings in Antimony: RoC Protocol (https://ntp.niehs.nih.gov/ntp/roc/protocols/antimonytrioxide_508.pdf).

Table A-1. Major Topics Searched

Topic	Search Method	Databases Searched
Exposure	Antimony String **AND** occur*[tiab]	PubMed
Human Studies	Antimony String **AND** ORoC Epidemiological (Human) Studies Search **AND** ORoC Cancer Search	PubMed, Scopus, Web of Science
Animal Studies	Antimony String **AND** Experimental Animals Studies Search **AND** ORoC Cancer Search	PubMed, Scopus, Web of Science
Mechanism and Genotoxicity	Antimony String **AND** ORoC Characteristics of Carcinogens Search	PubMed, Scopus, Web of Science

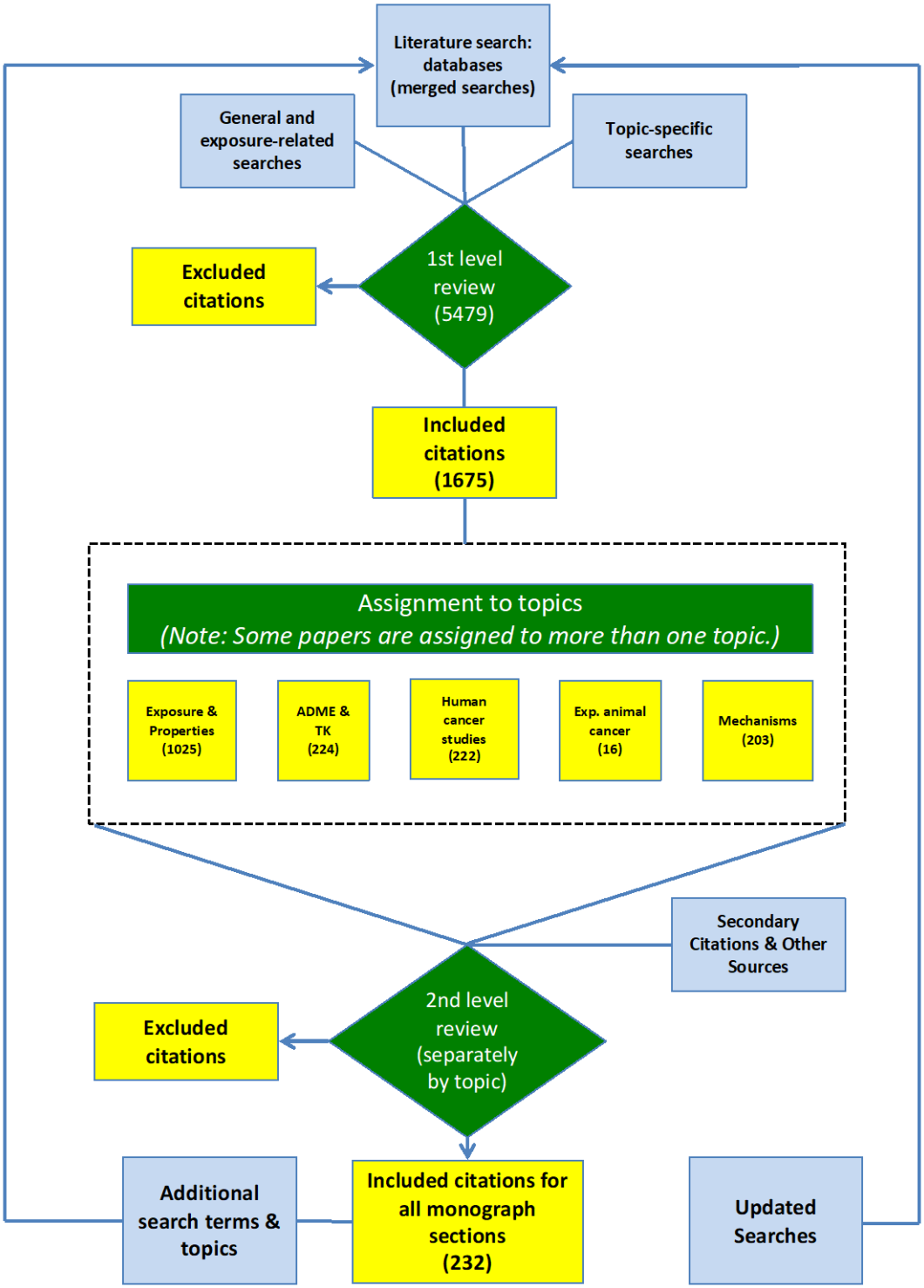

Figure A-1. Literature Search Strategy and Review

A.3. Search Strategies

Relevant literature is identified using search terms, data sources, and strategies as discussed below.

General data search: This search covers a broad range of general data sources for information relevant to many or all of the wide range of monograph topics pertaining to antimony.

Exposure-related data search: This search covers a broad range of potential sources for exposure-related information and physical-chemical properties.

Database searches in PubMed, Scopus, and Web of Science: The majority of the primary literature used to draft the antimony monograph was identified from searches of these three extensive databases available through the NIEHS Library. Searches for antimony were combined with the search terms for each of the monograph topics listed above to create the specific literature searches.

Searches for human cancer studies are somewhat unique because they involve the identification of search terms for exposure scenarios that might result in exposure of people to antimony. For antimony, these exposure-related search terms were based on uses of antimony identified from the EPA's TRI database and the Chemical Data Report rule website.

QUOSA library of occupational case-control studies search of the QUOSA-based library of more than 6,000 occupational case-control studies, approximately 95% of which are currently available as searchable full-text pdfs, was conducted using the term "antimony."

Secondary sources: Citations identified from authoritative reviews or from primary references located by literature search, together with publications citing key papers identified using the Web of Science, "Cited Reference Search," were also added.

A.4. Exclusion of Treatment for Leishmaniasis from Human Cancer Searches

The use of antimony for the treatment of leishmaniasis is considered an intentional medical exposure and out of the scope of this monograph. The large corpus of literature related to leishmaniasis treatment was excluded when identifying human studies. Unlike other parts of the monograph, in which leishmaniasis related content was excluded via search terms, the mechanisms section literature search did not exclude leishmaniasis via the use of search terms. The studies on the *Leishmania* parasite itself were excluded at levels 1 and 2 by reviewers, and studies on the host or cells not infected by leishmaniasis were included for information related to mechanism.

A.5. Updating the Literature Search

The literature searches were last updated in PubMed, Scopus, and Web of Science on November 13, 2017, prior to submitting the draft monograph for peer review on November 29,

2017. References recommended by the peer reviewers were also considered for the final revisions.

A.6. Review of Citations Using Web-based Systematic Review Software

Citations retrieved from literature searches were uploaded to web-based systematic review software and screened using inclusion and exclusion criteria. Multi-level reviews of the literature were conducted, with initial reviews (Level 1) based on titles and abstracts only to identify citations that could be excluded and to assign the included literature to one or more monograph topics; subsequent reviews (Level 2) for literature assigned to the various monograph topics (Exposure, ADME & TK, Human cancer studies, etc.) were based on full-text (i.e., PDFs) of the papers and were carried out by the writer and scientific reviewer for each monograph section. Two reviewers, at least one of whom is a member of the ORoC at NIEHS, participated at each level of review.

Appendix B. ADME Tables

Tables

Table B-1. Antimony(III) Trioxide Levels[a] (µg/g) in Red Blood Cells during a One-year Chronic Inhalation Exposure (after Six Months and 12 Months of Exposure) and a One-year Observation Period (Six Months and 12 Months after Exposure) in Fischer 344 Male and Female Rats

Group	6 mo	12 mo	18 mo (12 mo exposure and 6 mo obs)	24 mo (12 mo exposure and 12 mo obs)
Males				
I- Control	BDL	BDL	0.17 ± 0.39	BDL
II- 0.055 mg/m^3	0.53 ± 0.31	1.09 ± 0.21	0.86 ± 0.68	BDL
III- 0.51 mg/m^3	5.07 ± 0.29	7.55 ± 0.60	3.93 ± 0.25	2.53 ± 0.27
IV- 4.5 mg/m^3	34.50 ± 3.8	70.70 ± 6.3	38.60 ± 4.8	30.50 ± 7.5
Females				
I- Control	BDL	BDL	BDL	BDL
II- 0.055 mg/m^3	0.74 ± 0.06	1.48 ± 0.10	0.81 ± 0.30	BDL
III- 0.51 mg/m^3	5.69 ± 0.62	9.94 ± 1.32	6.53 ± 0.90	3.39 ± 0.28
IV- 4.5 mg/m^3	75.60 ± 8.4	121.00 ± 10.6	74.60 ± 18.3	36.60 ± 15.5

Source: Newton et al. (1994).
mo = month; BDL = below detection limit (lowest limit of detection = 0.02 µg of antimony/mL, i.e., 0.024 µg of antimony(III) trioxide/mL); obs = observation
[a]Total antimony in red blood cells was reported as total antimony(III) trioxide using the relationship 1 mole Sb_2O_3 = 1.197 mole Sb_2.

Table B-2. Blood Antimony Concentrations (µg/g Blood) in Female Rats and Mice Exposed to Antimony Trioxide (N = 5 Except Where Indicated)

	Day 61	Day 124	Day 269	Day 369	Day 551
Female Mice					
Controls	0.001 ± 0.000	0.001 ± 0.001	0.001 ± 0.000	0.001 ± 0.000	0.001 ± 0.000
3 mg/m^3	0.043 ± 0.002**	0.058 ± 0.001**	0.053 ± 0.006**	0.052 ± 0.003**	0.061 ± 0.010**
10 mg/m^3	0.083 ± 0.002**	0.089 ± 0.002**	0.091 ± 0.002**	0.088 ± 0.003**	0.087 ± 0.004**
30 mg/m^3	0.141 ± 0.003**	0.148 ± 0.005**	0.163 ± 0.008** [a]	0.137 ± 0.007**	0.163 ± 0.006**[a]
Female Rats					
Controls	0.139 ± 0.012	0.050 ± 0.002	0.077 ± 0.002	0.084 ± 0.008	0.066 ± 0.005
3 mg/m^3	7.352 ± 0.375**	16.135 ± 0.995**	39.590 ± 3.915**	50.917 ± 2.296**	63.297 ± 3.906**
10 mg/m^3	18.079 ± 0.793**	40.350 ± 1.543**	88.833 ± 2.210**	102.083 ± 2.738**	149.192 ± 8.472**[a]
30 mg/m^3	43.574 ± 1.741**	96.082 ± 3.940**	175.437 ± 6.471**	200.239 ± 10.302**	231.934 ± 8.681**

Source: NTP (2017a).
**Significantly different ($p < 0.01$) from the chamber control group by Shirley's test.
[a]N = 4.

Table B-3. Tissue Distribution of Antimony (µg Antimony/g Tissue) in Rats after Oral Exposure to Antimony(III) Trioxide by Gavage or in the Diet

Tissue	Controls (M/F)[a]	1,000 mg/kg Sb_2O_3 Suspension p.o. for 1 Day (M/F)[a]	1,000 mg/kg Sb_2O_3 Suspension p.o. for 14 Days (M/F)[a]	2% Sb_2O_3 in Diet[b] for 49 Days[c]	2% Sb_2O_3 in Diet[b] for 8 Months[d]
Thyroid	0.098/0.195	1.507/2.103	2.639/2.280	88.9	156.0
Adrenal	NR	NR	NR	67.8	NR
Lung	0.004/0.002	0.041/0.061	0.746/0.882	14.0	3.7
Spleen	0.010/0.032	0.197/0.113	1.485/1.386	18.9	8.1
Heart	0.004/0.003	0.042/0.041	0.643/0.356	7.6	5.1
Kidney	0.003/0.002	0.012/0.023	0.323/0.261	6.7	6.0
Liver	0.004/0.003	0.041/0.064	0.823/0.675	8.9	15.5
Bone marrow	0.080/0.142	1.192/1.996	2.486/3.517	NR	NR
Bone or femur	0.019/0.010	0.048/0.032	0.254/0.265	NR	2.5
Muscle	0.003/0.003	0.005/0.005	0.039/0.044	NR	0.3
Whole blood	0.003/0.003	0.708/0.640	8.278/6.886	NR	NR

F = female; M = male; NR = not reported; p.o. = per os (by mouth).
[a]T. N. O. Quality of Life (2005) as cited by EU (2008).
[b]Based on consumption of 5 g of food per day per 100 g body weight (Johns Hopkins University 2017), rats exposed to 2% Sb_2O_3 in the diet or by gavage at 1,000 mg/kg body weight would be exposed to ~0.1 g per 100 g body weight.
[c]Westrick (1953).
[d]Gross et al. (1955) as cited by EU (2008).

Appendix C. Human Studies Tables

Tables

Table C-1. Evaluation of Selection Bias in Human Cancer Studies

Study	Selection Bias
Jones (1994)	*Rating*: ++; *Direction*: ↓ *Rationale*: Only an external analysis was conducted. Although the impact of healthy worker survivor effect (HWSE) is mitigated by stratification by time since exposure, HWSE is still possible and may bias results toward the null.
Schnorr et al. (1995)	*Rating*: ++; ↓ *Rationale*: Only an external analysis was conducted. HWSE was not accounted for in this analysis, which may result in an underestimating of the risk estimates.
Jones et al. (2007)	*Rating*: ++; ↓ *Rationale*: Missing death information for 5.7% of untraced individuals would slightly bias results if they experienced the outcome. HWSE was not accounted for in the analyses, however, the impact of the smelter closing during follow-up would reduce the residual survival advantage.
Wingren and Axelson (1993)	*Rating*: +++; ↔ *Rationale*: Cases and controls were selected from the same parishes. No evidence suggests that the selection of subjects was related to both antimony exposure and disease.

↓ = results bias toward the null; ↔ = unknown direction of bias.

Table C-2. Evaluation of Exposure Assessment Methods in Human Cancer Studies

Study	Exposure Assessment Rating
Jones (1994)	*Rating*: ++/+++; *Direction*: ↔ *Rationale*: Exposure assessment methods have decent sensitivity and specificity, leading to reliable classification with respect to ever-exposure to antimony and exposure duration. Antimony exposure is assumed based on job description at smelter site.
Schnorr et al. (1995)	*Rating*: ++; ↓ *Rationale*: Exposure was reliably characterized as ever-exposure to antimony and duration of antimony exposure, but not with respect to concentration of exposure. Based on the reported environmental sampling data, antimony air exposure varied by plant location and year sampled; however, exposure is not captured at the individual level due to lack of information on job duties, and therefore, may be subject to misclassification.
Jones et al. (2007)	*Rating*: ++; ↓ *Rationale*: Given the modeling efforts used to account for the uncertainty in early air contamination levels, and because air sampling concentrations are likely an underestimate of true individual antimony exposure, exposure levels and timing may not represent true antimony concentrations and worker exposure prior to 1972. Authors mention changes in plant processes before NIOSH collected exposure estimates. The 3 scenarios for back-extrapolation (1. twice as high air concentrations in 1937, 2. average concentration from 1937 to 1972, and 3. a doubling in concentrations from 1937 through 1960, then a decrease to 1972 levels) are assumptions based on little empirical data.
Wingren and Axelson (1993)	*Rating*: +; ↑ *Rationale*: Exposure to antimony was based on reported job title at death. Those classified as unexposed who may have worked in a glass producing facility or had other antimony occupational exposure over a lifetime may have misclassified exposure. Reported level of antimony used by surveyed glass-working facilities may not represent individual-level exposure to employees. Facility surveys of antimony use was taken at one time point; unknown if antimony use patterns were consistent.

↑ = results bias away from the null; ↓ = results bias toward the null; ↔ = unknown direction of bias.

Table C-3. Evaluation of Outcome Assessment in Human Cancer Studies

Study	Outcome Assessment Rating
Jones (1994)	*Rating*: +++; *Direction*: ↔ *Rationale*: Outcome methods distinguish between diseased and non-diseased subjects. Follow-up and diagnoses are conducted independent of exposure status.
Schnorr et al. (1995)	*Rating*: +++; ↔ *Rationale*: Outcome methods distinguish between diseased and non-diseased subjects. Follow-up and diagnoses are conducted independent of exposure status.
Jones et al. (2007)	*Rating*: +++; ↔ *Rationale*: Outcome methods distinguish between diseased and non-diseased subjects. Follow-up and diagnoses are conducted independent of exposure status.
Wingren and Axelson (1993)	*Rating*: ++; ↑ *Rationale*: Outcome methods distinguish between diseased and non-diseased subjects. Occupational title (i.e., exposure status) was collected from the death and burial register, which noted mortality status. Given the lack of information on the blinding status, diagnostic bias cannot be ruled out. If coder identified diseased subjects as being exposed, it would bias the results away from the null.

↑ = results bias away from the null; ↔ = unknown direction of bias.

Table C-4. Evaluation of Study Sensitivity in Human Cancer Studies

Study	Sensitivity Rating
Jones (1994)	Rating: ++; Direction: ↔ Rationale: Study has few exposed cases but a substantial duration of exposure with a long range for follow-up. Stratification by exposure duration and years increase sensitivity.
Schnorr et al. (1995)	*Rating*: ++; ↔ *Rationale*: Study had a small-to-moderate number of exposed cases. There was adequate duration for follow-up, with a substantial duration of exposure. Duration and ever-exposure were measured, but not the range of antimony concentrations.
Jones et al. (2007)	*Rating*: +; ↔ *Rationale*: Adequate number of potentially exposed subjects but a small number of exposed cases. Exposure characterized by job-exposure matrix and detailed work histories. Exposure was modeled with a substantial range and level of exposure with adequate duration for latency. However, exposure was not at an individual level and exposure was extrapolated based on assumptions.
Wingren and Axelson (1993)	*Rating*: +; ↔ *Rationale*: Study captures variability in antimony use by parish where cases and controls died. However, given the unknown number of exposed subjects, exposed cases, the unknown number of controls, and the unknown individual-level exposure to antimony in glass workers, this study has poor sensitivity.

↔ = unknown direction of bias.

Table C-5. Evaluation of Potential for Confounding Bias for Human Cancer Studies

Study	Confounding Rating
Jones (1994)	*Rating*: +; *Direction*: ↑ *Rationale*: No control for smoking or occupational co-exposures in statistical analysis. Likely co-exposure to arsenic and PAHs (lung carcinogens) based on smelting source materials. Smoking not controlled for, despite high prevalence in the study population.

Study	Confounding Rating
Schnorr et al. (1995)	*Rating*: +++; ↔ *Rationale*: No control for smoking or occupational co-exposures in statistical analysis. Confounding from occupational co-exposures to arsenic and lead are minimal based on source information and environmental testing. Smoking prevalence rates were assumed to be low in this particular population.
Jones et al. (2007)	*Rating*: ++; ↑ *Rationale*: No attempt to statistically account for measured occupational co-exposures in analysis. High level of correlation between antinomy, lead, and arsenic air concentrations suggests likely occupational co-exposure. Minimal concern for smoking, but not controlled for in analysis.
Wingren and Axelson (1993)	*Rating*: +; ↑ *Rationale*: Smoking and occupational co-exposures lead and asbestos were not statistically controlled for in analysis. Lead and antimony use patterns were highly correlated, and lead was associated with an increased risk of stomach cancer mortality in this population; therefore, risk of confounding bias is high.

↑ = results bias away from the null; ↔ = unknown direction of bias.

Table C-6. Evaluation of Analysis and Selective Reporting for Human Cancer Studies

Study	Analysis Rating	Reporting Rating
Jones (1994)	*Rating*: +++ *Rationale*: The study used relevant data and appropriate assumptions and methods of analysis.	*Rating*: +++ *Rationale*: No evidence that reporting of the data or analyses were limited to only a subset of data that were collected.
Schnorr et al. (1995)	*Rating*: ++ *Rationale*: 95% CI are generally favorable to 90% CI regardless of a priori outcome status.	*Rating*: +++ *Rationale*: No evidence that reporting of the data or analyses were limited to only a subset of the data that were collected.
Jones et al. (2007)	*Rating*: ++ *Rationale*: 95% CI are generally favorable to 90% CI regardless of a priori outcome status.	*Rating*: +++ *Rationale*: No evidence that reporting of the data or analyses were limited to only a subset of the data that were collected.
Wingren and Axelson (1993)	*Rating*: ++ *Rationale*: 95% CI are generally favorable to 90% CI regardless of a priori outcome status.	*Rating*: ++ *Rationale*: It is unknown whether reporting was done on only a subset on data. Sample size for cases, controls, and exposure groups were not reported.

Appendix D. Animal Study Quality Tables

Tables

Table D-1. Schroeder et al. (1970) Study of Male Rats Exposed to Antimony Potassium Tartrate in the Drinking Water

Utility Question	Rating	Rationale
Study design		
Randomization	NR	Randomization and initial body weights were not reported.
Controls	+++	Concurrent control group, exposed to untreated drinking water, had the same number of animals as exposure group did.
Historical data		No.
Animal model	+++	Both sexes of a random bred strain, which increases external validity.
Statistical power	+++	Large numbers of animals (51 males, 59 females) per concentration group were used.
Exposure		
Chemical characterization	NR	Not reported, not even purity.
Dosing regimen	++	The maximally tolerated dose level was not reached, because the treated group did not show decreased body weight compared to the control group, although the median life spans and longevity (mean age of the last surviving 10%) for both sexes were decreased by the treatment. The dose might not have been high enough to detect neoplastic effects.
Exposure duration	+++	Though exposure duration was never clearly stated, this study appears to use a lifetime exposure.
Dose-response	+	Only one dose level was tested and no basis for that level was reported. All other elements were administered at the same level, except for lead.
Outcome		
Pathology	+	Only grossly visible tumors were reported. The methods stated that gross tumors were fixed but did not state that they were stained or microscopically examined. Consequently, small tumors might have been missed.
Consistency between groups	++	A pneumonia epidemic killed many rats and the death rates varied among the groups.
Study duration	+++	Lifetime study because the animals were observed until their natural death (as compared to scheduled euthanization after a predetermined exposure period).
Confounding		
Confounding	++	Pneumonia killed various numbers of animals per group, before penicillin treatment controlled the disease. It is unclear that all rats, or only visibly sick rats, received penicillin. Furthermore, the disease might in effect select stronger/healthier animals (than the general population) to complete the study. Additionally, test substance purity was unknown.
Reporting and analysis		
Reporting data and statistics	++	The statistical methods and results of survival measures were reported, but statistical analysis of tumor incidences was not reported.
Combining lesions	+	Tumors were counted based on gross observation, not histological analysis occurred.

Overall utility: +. The study has low utility because of many limitations, including only reporting grossly visible tumors without organ site or tumor type.

Table D-2. Schroeder et al. (1970) Study of Female Rats Exposed to Antimony Potassium Tartrate in the Drinking Water

Utility Question	Rating	Rationale
Study design		
Randomization	NR	Randomization and initial body weights were not reported.
Controls	+++	Concurrent control group, exposed to untreated drinking water, had the same number of animals as exposure group did.
Historical data		No
Animal model	+++	Both sexes of a random bred strain, which increases external validity.
Statistical power	+++	Large numbers of animals (51 males, 59 females) per concentration group were used.
Exposure		
Chemical characterization	NR	Not reported, not even purity.
Dosing regimen	++	The maximally tolerated dose level was not reached, because the treated group did not show decreased body weight compared to the control group, although the median life spans and longevity (mean age of the last surviving 10%) for both sexes were decreased by the treatment. The dose might not have been high enough to detect neoplastic effects.
Exposure duration	+++	Though exposure duration was never clearly stated, this study appears to use a lifetime exposure.
Dose-response	+	Only one dose level was tested and no basis for that level was reported.
Outcome		
Pathology	+	Only grossly visible tumors were reported. The methods stated that gross tumors were fixed but did not state that they were stained or microscopically examined. Consequently, small tumors might have been missed.
Consistency between groups	++	A pneumonia epidemic killed many rats and the death rates varied among the groups.
Study duration	+++	Lifetime study because the animals were observed until their natural death (as compared to scheduled euthanization after a predetermined exposure period).
Confounding		
Confounding	++	Pneumonia killed various numbers of animals per group, before penicillin treatment controlled the disease. It is unclear that all rats, or only visibly sick rats, received penicillin. Furthermore, the disease might in effect select stronger/healthier animals (than the general population) to complete the study. Additionally, test substance purity was unknown.
Reporting and analysis		
Reporting data and statistics	++	The statistical methods and results of survival measures were reported, but statistical analysis of tumor incidences was not reported.
Combining lesions	+	Tumors were counted based on gross observation, not histological analysis occurred.

Overall utility: +. The study has low utility because of many limitations, including only reporting grossly visible tumors without organ site or tumor type.

Table D-3. Kanisawa and Schroeder (1969) and Schroeder et al. (1968) Study of Male and Female (Combined) Mice Exposed to Antimony Potassium Tartrate in Drinking Water for the Life Span of the Animals

Utility Question	Rating	Rationale
Study design		
Randomization	NR	Not reported.
Controls	+++	Concurrent control group, exposed to doubly deionized water with added essential trace elements, had the same number of animals as the exposure group did.
Historical data		No
Animal model	+++	Both sexes of random bred mice were used, giving a high level of external validity.
Statistical power	+++	A large number (54) of mice per sex per group were used.
Exposure		
Chemical characterization	NR	No chemical characterization was reported, not even purity.
Dosing regimen	+	The maximally tolerated dose level was not reached, because the treated group did not show decreased body weight compared to the control group. The dose might not have been high enough to detect neoplastic effects.
Exposure duration	+++	Mice were exposed for their lifetimes.
Dose-response	+	Only one concentration was tested and no rational for the dose selection was reported. Dose response relationships cannot be evaluated due to only one dose level.
Outcome		
Pathology	++	Only gross lesions were microscopically evaluated.
Consistency between groups	++	The treated and control groups were treated the same while mice were alive. The examination of organs/tissues varied, because only gross lesions (not all major organs) were examined microscopically.
Study duration	+++	The study duration was lifetime, up to the animals' natural death.
Confounding		
Confounding	+++	Testing substance purity and supplier were unknown. Exposure to antimony via other sources (feed, housing) was negligible because the feed was antimony free and metal exposure via housing was minimized.
Reporting and analysis		
Reporting data and statistics	++	Although tumor incidents were not statistically analyzed in the study, the data were reported and enabled us to conduct statistical analysis. Statistical methods were described as “numerical data were treated by Chi-squire analysis and by Student’s t test,” but the reported probability in tables did not specify the result was from which method.
Combining lesions	++	Tumor incidence was reported for two sexes combined only, instead of male and female separately. Site-specific (lung, liver, mammary gland, and other) information was limited to tumor incidence, with no subtype. Tumors were also grouped by origin (epithelial, non-epithelial) along with being benign or malignant. Overall information did not allow detecting of specific tumor type increase in either sex.

Overall utility: +. Due to many limitations, including only one tested concentration (below maximally tolerated dose), unknown test substance purity, tumor incidences only reported in combined sexes with no histologic information, and lack of site-specific information (except incidences of three sites in sexes combined), this study is of low utility. Data lack sufficient details to allow us to determine whether any specific type of tumor had increased.

Table D-4. NTP (2017a) Study of Male Rats Exposed to Antimony Trioxide by Inhalation for 105 Weeks

Utility Question	Rating	Rationale
Study design		
Randomization	+++	Animals were randomly assigned to groups.
Controls	+++	Concurrent chamber control was used. Data was also compared with historical control.
Historical data		Yes
Animal model	+++	Standard model.
Statistical power	+++	A large number, 50/sex/group, of animals were used.
Exposure		
Chemical characterization	+++	The chemical and exposure chamber were well characterized, showing high purity, stability, and homogeneity. Concentration inside the exposure chamber was measured in real-time and alarmed if readings were not within limits of acceptable concentrations. Aerosol size, measured monthly, was also consistently <4 μm (MMAD = 1–1.4 μm, GSD 1.8–2.2. Stability in the generation and exposure system was tested before the test, during the test (at 4 weeks for rats), and the end of 2-year study.
Dosing regimen	+++	Consistent and very close to target concentrations. The highest exposure level was near maximally tolerated levels as evidenced by the trend of decreased survival and a significant decrease in body weight. Neoplasms were significantly increased.
Exposure duration	+++	Exposure duration was near life span.
Dose-response	+++	Three dose levels spanning a range of 30-fold were used.
Outcome		
Pathology	+++	Detailed and covering all tissues. Full necropsy with histological exam of all major organs was conducted and verified by an independent quality control pathologist.
Consistency between groups	+++	Nothing was reported to suggest that animals from different groups were treated differently.
Study duration	+++	Near life-span study duration was used.
Confounding		
Confounding	+++	No concerns of confounding were reported.
Reporting and analysis		
Reporting data and statistics	+++	Statistical analysis was clearly reported.
Combining lesions	+++	No indication of concern. Detailed groupings were provided.

Overall utility: +++. There were no concerns of confounding as the chemical was pure, 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 little historical control data existed compared to the previously used Fischer 344 rat stock. Complete necropsies with histological examination of most organs were performed, so the ability to detect neoplasms was high.

Table D-5. NTP (2017a) Study of Female Rats Exposed to Antimony Trioxide by Inhalation for 105 Weeks

Utility Question	Rating	Rationale
Study design		
Randomization	+++	Animals were randomly assigned to groups.
Controls	+++	Concurrent chamber control was used. Data was also compared with historical control.
Historical data		No.
Animal model	+++	Standard model.
Statistical power	+++	A large number, 50/sex/group, of animals were used.
Exposure		
Chemical characterization	+++	The chemical and exposure chamber were well characterized, showing high purity, stability, and homogeneity. Concentration inside the exposure chamber was measured in real-time and alarmed if readings were not within limits of acceptable concentrations. Aerosol size, measured monthly, was also consistently <4 μm (MMAD = 0.9−1.5 μm, GSD = 1.7−2.1). Stability in the generation and exposure system was tested before the test, during the test (at 4 weeks for rats), and the end of 2-year study.
Dosing regimen	+++	Consistent, and very close to target, concentrations. The highest exposure level was near maximally tolerated levels as evidenced by the trend of decreased survival and a significant decrease in body weight. Neoplasms were significantly increased.
Exposure duration	+++	Exposure duration was near life span.
Dose-response	+++	Three dose levels spanning a range of 30-fold were used.
Outcome		
Pathology	+++	Detailed and covering all tissues. Full necropsy with histological exam of all major organs was conducted and verified by an independent quality control pathologist.
Consistency between groups	+++	Nothing was reported to suggest that animals from different groups were treated differently.
Study duration	+++	Near life-span study duration was used.
Confounding		
Confounding	+++	No concerns of confounding were reported.
Reporting and analysis		
Reporting data and statistics	+++	Statistical analysis was clearly reported.
Combining lesions	+++	No indication of concern. Detailed groupings were provided.

Overall utility: +++. There were no concerns of confounding as the chemical was pure, 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 little historical control data existed compared to the previously used Fisher 344 rat stock. Complete necropsies with histological examination of most organs were performed, so the ability to detect neoplasms was high.

Table D-6. NTP (2017a) Study of Male Mice Exposed to Antimony Trioxide by Inhalation for 105 Weeks

Utility Question	Rating	Rationale
Study design		
Randomization	+++	Animals were randomly assigned to groups.
Controls	+++	Concurrent chamber control was used. Data was also compared with historical control.
Historical data		Yes
Animal model	+++	Standard model.
Statistical power	+++	A large number, 50/sex/group, of animals were used.
Exposure		
Chemical characterization	+++	The chemical and exposure chamber were well characterized, showing high purity, stability, and homogeneity. Concentration inside the exposure chamber was measured in real-time and alarmed if readings were not within limits of acceptable concentrations. Aerosol size, measured monthly, was also consistently <4 μm (MMAD = 0.9−1.5 μm, GSD 1.7−2.1). Stability in the generation and exposure system was tested before the test, during the test (at 4 weeks for rats), and the end of 2-year study.
Dosing regimen	+++	Consistent, and very close to target, concentrations. The highest exposure level was near maximally tolerated levels as evidenced by the trend of decreased survival and a significant decrease in body weight. Neoplasms were significantly increased.
Exposure duration	+++	Exposure duration was near life span.
Dose-response	+++	Three dose levels spanning a range of 30-fold were used.
Outcome		
Pathology	+++	Detailed and covering all tissues. Full necropsy with histological exam of all major organs was conducted and verified by an independent quality control pathologist.
Consistency between groups	+++	Nothing was reported to suggest that animals from different groups were treated differently.
Study duration	+++	Near life-span study duration was used.
Confounding		
Confounding	+++	No concerns of confounding were reported.
Reporting and analysis		
Reporting data and statistics	+++	Statistical analysis was clearly reported.
Combining lesions	+++	No indication of concern. Detailed groupings were provided.

Overall utility: +++. There were no concerns of confounding as the chemical was pure, 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 were performed, so the ability to detect neoplasms was high.

Table D-7. NTP (2017a) Study of Female Mice Exposed to Antimony Trioxide by Inhalation for 105 Weeks

Utility Question	Rating	Rationale
Study design		
Randomization	+++	Animals were randomly assigned to groups.
Controls	+++	Concurrent chamber control was used. Data were also compared with historical control.
Historical data		No
Animal model	+++	Standard model.
Statistical power	+++	A large number, 50/sex/group, of animals were used.
Exposure		
Chemical characterization	+++	The chemical and exposure chamber were well characterized, showing high purity, stability, and homogeneity. Concentration inside the exposure chamber was measured in real-time and alarmed if readings were not within limits of acceptable concentrations. Aerosol size, measured monthly, was also consistently <4 μm (MMAD = 0.9−1.5 μm, GSD = 1.7−2.1). Stability in the generation and exposure system was tested before the test, during the test (at 4 weeks for rats), and the end of 2-year study.
Dosing regimen	+++	Consistent, and very close to target, concentrations. The highest exposure level was near maximally tolerated levels as evidenced by the trend of decreased survival and a significant decrease in body weight. Neoplasms were significantly increased.
Exposure duration	+++	Exposure duration was near life span.
Dose-response	+++	Three dose levels spanning a range of 30-fold were used.
Outcome		
Pathology	+++	Detailed and covering all tissues. Full necropsy with histological exam of all major organs was conducted and verified by an independent quality control pathologist.
Consistency between groups	+++	Nothing was reported to suggest that animals from different groups were treated differently.
Study duration	+++	Near life-span study duration was used.
Confounding		
Confounding	+++	No concerns of confounding were reported.
Reporting and analysis		
Reporting data and statistics	+++	Statistical analysis was clearly reported.
Combining lesions	+++	No indication of concern. Detailed groupings were provided.

Overall utility: +++. There were no concerns of confounding as the chemical was pure, 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 were performed, so the ability to detect neoplasms was high.

Table D-8. Groth et al. (1986) Study of Male Rats Exposed to Antimony Trioxide by Inhalation for 53 Weeks Followed by Post-exposure Observation for 71 to 73 Weeks

Utility Question	Rating	Rationale
Study design		
Randomization	NR	Not reported.
Controls	+++	Concurrent untreated chamber controls (filtered air) were used.
Historical data		No
Animal model	+++	Male and female inbred rats were used.
Statistical power	+++	A large number of rats (90/sex/group) were used.
Exposure		
Chemical characterization	++	The purity was estimated to be 95.8%, however the authors did not explicitly report the purity of antimony trioxide. The purity of elemental antimony was reported as 80%, and NIH calculated this to mean a purity of antimony trioxide of 95.8%, assuming all of the antimony present was as antimony trioxide. Trace levels of contamination by carcinogens (arsenic and lead) and others (tin, cesium aluminum, and bromine) were not considered to have significantly contributed to carcinogenic effects. The aerosol concentrations didn't reach target levels of 50 mg/m^3 until after 5 months of adjustment and modifications on the exposure equipment. MMAD of aerosol of 2.80 μm was fine, but the GSD was not reported. Aerosol size appeared only measured once at 6 months of exposure.
Dosing regimen	++	The exposure level was based on the middle of the concentration range that workers are exposed to, so it would not be expected to be at the maximally tolerated level. The concentrations fluctuated dramatically, up to 191.1 mg/m^3 for daily TWAs, while a mean daily TWA was 45, 46 mg/m^3 (two chambers) and the target concentration was 50 mg/m^3. It is not clear whether the chamber air was humidified. Survival and body weights were similar to controls, but total neoplasms in the lung were significantly increased over untreated controls.
Exposure duration	++	Exposure duration was 53 weeks.
Dose-response	+	Only one exposure level was used, and it was based on the middle of the concentration range that workers are exposed to (i.e., well below animals' maximal tolerated dose). The actual exposure concentration fluctuated greatly until about 5 months into the study when the target concentration was reached.
Outcome		
Pathology	+++	Most organs were histologically examined.
Consistency between groups	++	No indication of differential treatments.
Study duration	++	The study duration was 71 to 73 weeks long, roughly 1.4 years, with only 5 months of observation after the end of 53 week-long exposure. These lengths were likely limited because the rats were 8 months old at the beginning of the study.
Confounding		
Confounding	+	The chemical was only 80% antimony, with various other metal contaminants, such as tin, lead, cesium, aluminum, arsenic, and bromine. Lead and arsenic are carcinogenic.

Utility Question	Rating	Rationale
Reporting and analysis		
Reporting data and statistics	+++	Statistical analysis was reported for body weights, tissue levels of antimony. Neoplasms were not reported as they were stated to have not occurred.
Combining lesions	+++	Neoplasms were combined by site. While no numbers of each pathological type were provided, the tumor combining is fine

Overall utility: ++. The chemical was not fully characterized, but was estimated to be 95.8% pure, with trace levels of lead and arsenic as contaminants that were not considered to have significantly contributed to carcinogenic effects. 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.

Table D-9. Groth et al. (1986) Study of Female Rats Exposed to Antimony Trioxide by Inhalation for 53 Weeks Followed by Post-exposure Observation for 71 to 73 Weeks

Utility Question	Rating	Rationale
Study design		
Randomization	NR	Not reported.
Controls	+++	Concurrent untreated chamber controls (filtered air) were used.
Historical data		No
Animal model	+++	Male and female inbred rats were used.
Statistical power	+++	A large number of rats (90/sex/group) were used.
Exposure		
Chemical characterization	++	The purity was estimated to be 95.8%, however the authors did not explicitly report the purity of antimony trioxide. The purity of elemental antimony was reported as 80%, and NIH calculated this to mean a purity of antimony trioxide of 95.8%, assuming all of the antimony present was as antimony trioxide. Trace levels of contamination by carcinogens (arsenic and lead) and others (tin, cesium aluminum, and bromine) were not considered to have significantly contributed to carcinogenic effects. The aerosol concentrations didn't reach target levels of 50 mg/m^3 until after 5 months of adjustment and modifications on the exposure equipment. MMAD of aerosol of 2.80 μm was fine, but the GSD was not reported. Aerosol size appeared only measured once at 6 months of exposure.
Dosing regimen	++	The exposure level was based on the middle of the concentration range that workers are exposed to, so it would not be expected to be at the maximally tolerated level. The concentrations fluctuated dramatically, up to 191.1 mg/m^3 for daily TWAs, while a mean daily TWA was 45, 46 mg/m^3 (two chambers) and the target concentration was 50 mg/m^3. It is not clear whether the chamber air was humidified. Survival and body weights were similar to controls, but total neoplasms in the lung were significantly increased over untreated controls.
Exposure duration	++	Exposure duration was 53 weeks.
Dose-response	+	Only one exposure level was used, and it was based on the middle of the concentration range that workers are exposed to (i.e., well below animals' maximal tolerated dose). The actual exposure concentration fluctuated greatly until about 5 months into the study when the target concentration was reached.

Utility Question	Rating	Rationale
Outcome		
Pathology	+++	Most organs were histologically examined.
Consistency between groups	++	No indication of differential treatments.
Study duration	++	The study duration was 71 to 73 weeks long, roughly 1.4 years, with only 5 months of observation after the end of 53 week-long exposure. These lengths were likely limited because the rats were 8 months old at the beginning of the study.
Confounding		
Confounding	+	The chemical was only 80% antimony, with various other metal contaminants, such as tin, lead, cesium, aluminum, arsenic, and bromine. Lead and arsenic are carcinogenic
Reporting and analysis		
Reporting data and statistics	+++	Statistical analysis was reported for body weights, tissue levels of antimony. Statistical significance was not reported for neoplasm incidences but was calculated by NTP.
Combining lesions	+++	Neoplasms were combined by site. While no numbers of each pathological type were provided, the tumor combining is fine.

Overall utility: ++. The chemical was not fully characterized, but was estimated to be 95.8% pure, with trace levels of lead and arsenic as contaminants that were not considered to have significantly contributed to carcinogenic effects. 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.

Table D-10. Newton et al. (1994) Study of Male Rats Exposed to Antimony Trioxide by Inhalation for 12 Months Followed by Post-exposure Observation for 24 Months

Utility Question	Rating	Rationale
Study design		
Randomization	+++	Used a computer program to randomly sort animals so that mean group weights were comparable.
Controls	+++	Use concurrent control at the same number of animals as exposure groups.
Historical data		No
Animal model	+++	Normal Fischer rats, which are often used in carcinogenicity studies.
Statistical power	+++	A large number of rats (65/sex/group) were used.
Exposure		
Chemical characterization	+++	A blend of lots from nine producers of antimony trioxide. Highly pure material. Particle size was characterized as having a mass median aerodynamic diameter (MMAD) of 3.76 +/− 0.84 μm and a geometric standard deviation (GSD) of 1.79 +/− 0.32. Exposure concentration was analyzed four times a day and particle sizes were analyzed before the study and every 3 months. Homogeneity of the exposure chamber was verified by measuring 10 different locations.
Dosing regimen	++	There were not differences in body weight, survival, or neoplasm incidence, suggesting the dose was not at the maximally tolerated dose.

Utility Question	Rating	Rationale
Exposure duration	+++	12-month exposure.
Dose-response	+++	Three exposed levels were used, which covered a 100-fold range.
Outcome		
Pathology	++	Only heart, airway, and peribronchial lymph nodes were histologically examined.
Consistency between groups	+++	Consistent treatment and evaluation of groups.
Study duration	+++	The study duration was 2 years, with 12 months of exposure and 12 months of observation.
Confounding		
Confounding	+++	Material of high purity. Animal husbandry reported in detail. No significant body weight loss in the treated groups, compared to the control.
Reporting and analysis		
Reporting data and statistics	+++	Since neoplasm incidences were not reported, as they were negative, statistical analysis wasn't reported.
Combining lesions	+++	No tumor combining, as only three cases [two males (including one from control), one female] were seen.

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. Exposure was at three concentrations for about half a life-span duration (1 year), though observations (1 year) continued to a near life-span duration. However, the highest exposure level did not reach the maximally tolerated level. Most organs were histologically examined, so most neoplasms had the ability of being detected. Although aerosol size was not ideal (slightly over the current upper limit of test guidelines), this paper did show Sb_2O_3 accumulation and decreased clearance in the lung (by 80% in the 4.5 mg/m^3 group). For inert particle, such overload would/could cause lung tumor. The overload was observed at relatively low exposure concentrations (compared to inert particles, such as TiO_2) and Sb_2O_3 toxicity was suspected. It appears conditions that could potentially lead to cancer did persist (Table 9, post-exposure, chronic inflammation in most animals, although hyperplasia was in only very few animals).

Table D-11. Newton et al. (1994) Study of Female Rats Exposed to Antimony Trioxide by Inhalation for 12 Months Followed by Post-exposure Observation for 24 Months

Utility Question	Rating	Rationale
Study design		
Randomization	+++	Used a computer program to randomly sort animals so that mean group weights were comparable.
Controls	+++	Use concurrent control at the same number of animals as exposure groups.
Historical data		No
Animal model	+++	Normal Fischer rats, which are often used in carcinogenicity studies.
Statistical power	+++	A large number of rats (65/sex/group) were used.
Exposure		
Chemical characterization	+++	A blend of lots from nine producers of antimony trioxide. Highly pure material. Particle size was characterized as having a mass median aerodynamic diameter (MMAD) of 3.76 +/− 0.84 μm and a geometric standard deviation (GSD) of 1.79 +/− 0.32. Exposure concentration was analyzed four times a day and particle sizes were analyzed before the study and every 3 months. Homogeneity of the exposure chamber was verified by measuring 10 different locations.

Utility Question	Rating	Rationale
Dosing regimen	++	There were not differences in body weight, survival, or neoplasm incidence, suggesting the dose was not at the maximally tolerated dose.
Exposure duration	+++	12-month exposure.
Dose-response	+++	Three exposed levels were used, which covered a 100-fold range.
Outcome		
Pathology	++	Only heart, airway, and peribronchial lymph nodes were histologically examined.
Consistency between groups	+++	Consistent treatment and evaluation of groups.
Study duration	+++	The study duration was 2 years, with 12 months of exposure and 12 months of observation.
Confounding		
Confounding	+++	Material of high purity. Animal husbandry reported in detail. No significant body weight loss in the treated groups, compared to the control.
Reporting and analysis		
Reporting data and statistics	+++	Since neoplasm incidences were not reported, as they were negative, statistical analysis wasn't reported.
Combining lesions	+++	No tumor combining, as only three cases [two males (including one from control), one female] were seen.

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. Exposure was at three concentrations for about half a life-span duration (1 year), though observations (1 year) continued to a near life-span duration. However, the highest exposure level did not reach the maximally tolerated level. Most organs were histologically examined, so most neoplasms had the ability of being detected. Although aerosol size was not ideal (slightly over the current upper limit of test guidelines), this paper did show Sb_2O_3 accumulation and decreased clearance in the lung (by 80% in the 4.5 mg/m^3 group). For inert particle, such overload would/could cause lung tumor. The overload was observed at relatively low exposure concentrations (compared to inert particles, such as TiO_2) and Sb_2O_3 toxicity was suspected. It appears conditions that could potentially lead to cancer did persist (Table 9, post-exposure, chronic inflammation in most animals, although hyperplasia was in only very few animals).

Table D-12. Watt (1983) Study of Female Rats Exposed to Antimony Trioxide by Inhalation for One Year Followed by Post-exposure Observation for Two Years

Utility Question	Rating	Rationale
Study design		
Randomization	NR	Not reported.
Controls	+++	Concurrent controls were used, although animals were housed in different rooms (housing chambers separated to control, low concentration, and high concentration). Otherwise, treatments were the same.
Historical data		No.
Animal model	++	Only female rats were used.
Statistical power	+	Small number of animals were used; 13–18 animals per group sacrificed at the end of exposure. Fewer than 10 per group sacrificed between 2 and 12 months post exposure. Fewer than 20 per group sacrificed 12 months post exposure.

Utility Question	Rating	Rationale
Exposure		
Chemical characterization	+++	Detailed chemical analysis verified that Sb_2O_3 was of high purity. Small amounts of arsenic (0.02%) and lead (0.2%) were found as contaminates. Dust size (measured by SEM) was reported as Feret diameter. Presumably, this is average from the same particle with rotation. Aerosol concentration in the exposure chamber. The equipment generated aerosols of MMAD <15 μm, but aerosol sizes were not measured. Based on conversion done in Newton et al. (1994) paper Table 2, the MMAD is 5.06 μm, which is above the ideal range of rat inhalation study (no more than 4 μm).
Dosing regimen	+++	Another potential concern is the use of pine shaving in the exposure chamber. The rats were not in direct contact with shaving, but metabolism change from pine cannot be excluded. This does not affect the interpretation of this study as all groups were treated the same, but has been suggested by Newton et al. (1994) as a factor affecting outcome even though it is based on concerns of increased particulates (rather than rat metabolism). Survival was not reported, but body weight gain was greater than controls, indicating the dose is not close to maximal tolerant dose. Significant increases in neoplasia occurred, indicating the dose level was high enough to cause carcinogenesis.
Exposure duration	+++	Exposure occurred for up to 1 year, with intermediate sacrifices at 3, 6, 9 months.
Dose-response	++	Only two dose levels, ranging over 2.5 folds, were used, limiting the examination of a dose response curve.
Outcome		
Pathology	++	Major organs were examined microscopically.
Consistency between groups	+++	Consistent treatment among groups, except housed in different rooms.
Study duration	+++	The study duration was 2 years, with 1 year of exposure and 1 year of observation.
Confounding		
Confounding	++	Animals in high dose group were heavier than low dose group at the beginning, suggesting slightly different development level. Not all organs appear to have been examined during necropsy.
Reporting and analysis		
Reporting data and statistics	++	While statistic methods were not specified, the data were reported with raw numbers and therefore enables statistical analysis.
Combining lesions	+++	Tumor types were not combined. Scirrhous carcinomas, a pathologically distinctive lung cancer, alone, was significantly increased compared to negative controls.

Overall utility: ++. The chemical purity was high and exposure was characterized, though the particle size (converted by Newton et al. (1994) to be around MMAD 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 shaving also increased the chance of exposure to non-Sb_2O_3 particles (and possible metabolism alternation due to pine shaving and therefore affecting susceptibility).

Appendix E. Mechanistic and Other Relevant Information

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Tables

This appendix lists Tox21/ToxCast high-throughput screening (Appendix E.1), effects of antioxidant and inhibitors of enzymes on antimony effects (Appendix E.2), genotoxicities of antimony compounds (Appendix E.3), effects related to cell proliferation (Appendix E.4), transcriptomic of antimony(III) potassium tartrate trihydrate in HepG2 cells (Appendix E.5), and immune effects of compounds containing pentavalent antimony (Appendix E.6).

E.1. 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 et al. 2012; Kavlock and Dix 2010) results from the Tox21 Toolbox (NTP 2017c) and iCSS Dashboard (USEPA 2017c): (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 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. Please note that analysis via different criteria, such as dose-response fit threshold, will result in different hits, and therefore the results shown here might be different from others.

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 γ.

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 androgen receptor, 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 (Grosskopf et al. 2010; Nielson et al. 1985), 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.

E.2. Effects of Antioxidants and Inhibitors of Oxidative Stress Related Enzymes on Cells Exposed to Compounds Containing Trivalent Antimony

Table E-1. Effects of Antioxidants and Inhibitors of Oxidative Stress Related Enzymes on Cells Exposed to Compounds Containing Trivalent Antimony

Cell Types	Additional Treatment (Besides Antimony Exposure)	Oxidative Stress and Damage	MMP and Cell Death	Comparison Group (Cells)	Reference
Antimony (III) trioxide					
LOUCY, CCRF-CEM, HL-60, K-562	BSO, an inhibitor of γ-glutamylcysteine synthetase	↓ GSH	↓ MMP[a] ↑ cell death	exposed to Sb_2O_3 alone	Lösler et al. (2009)
HL-60, K-562	Mercaptosuccinic acid, an inhibitor of glutathione peroxidase		↑ cell death	exposed to Sb_2O_3 alone	Lösler et al. (2009)
K-562	3-amino-1,2,4-azole, an inhibitor of catalase		↑ cell death	exposed to Sb_2O_3 alone	Lösler et al. (2009)
CCRF-CEM, K-562	Sodium ascorbate, an antioxidant, but able to act as an oxidant under oxidative stress		↑ cell death	exposed to Sb_2O_3 alone	Lösler et al. (2009)
NB4	None	↑ ROS	↑ cell death	negative control	Mann et al. (2006)
NB4-M-AsR3	None	↑ GSH	↓ cell death	parental NB4 cells	Mann et al. (2006)
NB4	BSO, an inhibitor of γ-glutamylcysteine synthetase	↓ GSH ↑ ROS	↑ cell death	cells not treated with BSO	Mann et al. (2006)
NB4-M-AsR3	BSO, an inhibitor of γ-glutamylcysteine synthetase	↓ GSH	↑ cell death	cells not treated with BSO	Mann et al. (2006)
Antimony (III) trichloride					
Primary rat hepatocytes	none	↑ ROS ↑ lipid peroxidation	↓ MMP ↑ cell death	–	Hashemzaei et al. (2015)

Cell Types	Additional Treatment (Besides Antimony Exposure)	Oxidative Stress and Damage	MMP and Cell Death	Comparison Group (Cells)	Reference
Primary rat hepatocytes	*n*-bromoheptane, a GSH-depleting agent	↓ GSH ↑ ROS ↑ lipid peroxidation	↓ MMP ↑ cell death	exposed to $SbCl_3$ alone	Hashemzaei et al. (2015)
Primary rat hepatocytes	Dimethyl sulfoxide, a ROS scavenger	↓ ROS ↓ lipid peroxidation	↑ MMP ↑ cell death	exposed to $SbCl_3$ alone	Hashemzaei et al. (2015)
Primary rat hepatocytes	Mannitol, a ROS scavenger	↓ ROS ↓ lipid peroxidation	↑ MMP ↓cell death	exposed to $SbCl_3$ alone	Hashemzaei et al. (2015)
Primary rat hepatocytes	Trifluoperazine, a mitochondria permeability transition pore sealing agent	↓ ROS ↓ lipid peroxidation	↑ MMP ↑ cell death	exposed to $SbCl_3$ alone	Hashemzaei et al. (2015)
Primary rat hepatocytes	Carnitine, a mitochondria permeability transition pore sealing agent	↓ ROS ↓ lipid peroxidation	↑ MMP ↓cell death	exposed to $SbCl_3$ alone	Hashemzaei et al. (2015)
Primary rat hepatocytes	L-Glutamine, an adenosine triphosphate (ATP) generating agent	↓ ROS ↓ lipid peroxidation	↑ MMP ↑ cell death	exposed to $SbCl_3$ alone	Hashemzaei et al. (2015)
Antimony (III) potassium tartrate					
HL-60	none	↑ ROS	↓ MMP ↑ cell death	negative control	Lecureur et al. (2002)
HL-60	BSO	–	↑ cell death	exposed to antimony alone	Lecureur et al. (2002)
HL-60	N-acetylcysteine	–	↓ cell death	exposed to antimony alone	Lecureur et al. (2002)

↑ = increased; ↓ = decreased; NB4-M-AsR3 = arsenic-resistant subclone of parental NB4 due to increased GSH levels; BSO = DL-buthionine-[*S,R*]-sulfoximine; CCRF-CEM = a cell line derived from acute lymphoblastic leukemia cells; HL-60 = a cell line derived from human promyelocytic leukemia; K-562 = chronic myelogenous leukemia cells; LOUCY = a cell line derived from T cell acute lymphoblastic leukemia; MMP = mitochondrial membrane potential; NB4 = a cell line derived from human acute promyelocytic leukemia cells; NB4-M-AsR3 cells = arsenic-resistant APL cells (derived in Miller lab).

E.3. Genotoxicity Tables

The genotoxic tables are organized by endpoints: mutations (Table E-2), DNA damage (Table E-3), chromosomal aberrations (Table E-4).

Table E-2. Genotoxicity of Antimony Compounds: Mutations[a]

Genotoxicity Endpoint	Antimony Form	Testing System/Exposure Duration	Assay Endpoint	Comments	Reference
Mammalian cells					
Point mutations and chromosome deletions	**Antimony trioxide**	L5178Y mouse lymphoma cell line (+/−S9, two experiments) 4-hour exposure duration	Negative (concentrations tested: 6–50 μg/mL)	Precipitate formed at top dose level; authors report no significant toxicity at these doses	Elliott et al. (1998)
Bacteria					
A/T base pair substitutions	**Antimony trioxide**	*E. coli* B/r WP2 *try* and WP2 *hcr try* (−S9, spot test method)	Negative (concentrations tested: 0.05–0.5 M)	Microbial toxicity not reported	Kanematsu et al. (1980)
A/T base pair substitution	**Antimony trioxide**	*E. coli* WP2P (+/−S9; plate incorporation and pre-incubation protocols) 3-day exposure duration	Negative (concentrations tested: 100–5,000 μg/plate)	Microbial toxicity not reported	Elliott et al. (1998)
A/T base pair substitution	**Antimony trioxide**	*E. coli* WP2P*uvr*A (+/−S9; plate incorporation and pre-incubation protocols) 3-day exposure duration	Negative (concentrations tested: 100–5,000 μg/plate)	–	Elliott et al. (1998)
A/T base pair substitutions	**Antimony trichloride**	*E. coli* B/r WP2 *try* and WP2 *hcr try* (−S9, spot test method)	Negative (concentrations tested: 0.05–0.5 M)	Microbial toxicity not reported	Kanematsu et al. (1980)
G/C base pair substitutions	**Antimony trioxide**	*S. typhimurium* TA 1535, TA 1537, TA100, TA98 (+/−S9; plate incorporation and pre-incubation protocols) 3-day exposure duration	Negative (concentrations tested: 100–5,000 μg/plate)	Microbial toxicity not reported	Elliott et al. (1998)

Genotoxicity Endpoint	Antimony Form	Testing System/Exposure Duration	Assay Endpoint	Comments	Reference
Frameshift mutations	**Antimony trioxide**	*S. typhimurium* TA 1537 and 98 (+/−S9; plate incorporation and 60 min pre-incubation protocols) 3-day exposure duration	Negative (concentrations tested: 100–5,000 μg/plate)	Microbial toxicity not reported	Elliott et al. (1998)
Base pair substitution and frameshift mutations	**Antimony trioxide**	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1568 (−S9, spot test method)	Negative (concentrations tested: 0.05–0.5 M)	Duration of chemical exposure for spot test assay not reported; microbial toxicity not reported	Kanematsu et al. (1980)
Base pair substitution and frameshift mutations	**Antimony trioxide**	*S. typhimurium* TA100, TA98 (+/−S9; 20 min pre-incubation modification)	Negative in three experiments (concentrations tested: 0.43–1.71 μg/plate)	Survival after pre-incubation step reported	Kuroda et al. (1991)
Base pair substitution and frameshift mutations	**Antimony trichloride**	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1568 (−S9, spot test method)	Negative (concentrations tested: 0.05–0.5 M)	Duration of chemical exposure for spot test assay not reported; microbial toxicity not reported	Kanematsu et al. (1980)
Base pair substitution and frameshift mutations	**Antimony trichloride**	*S. typhimurium* TA100, TA98 (+/−S9; 20 min pre-incubation modification)	Negative in three experiments (concentrations tested: 625–5,000 μg/plate)	Survival after pre-incubation step reported	Kuroda et al. (1991)

Levels of significance are designated as follows: *p < 0.05; **p < 0.01.
Mutation studies are listed hierarchically according to the following criteria: (1): by genotoxicity endpoints; (2): by domain of target species (eukaryote and then prokaryote); (3): by testing system (e.g., *E. coli* strains and then *Salmonella* strains); and (4): by compound in the order of antimony(III) trioxide (bold) and then antimony(III) trichloride. Other forms of antimony, such as elemental antimony (Asakura et al. 2009) were not included in the table.
[a]All data in prokaryotes were derived bacterial reverse mutation assays. The single eukaryotic study data was derived from the mouse lymphoma TK gene mutation assay.

Table E-3. Genotoxic DNA Damaging Effects of Antimony Compounds

Genotoxicity Endpoint	Antimony Form	Assay Name	Testing System	Assay Endpoint	Comments	References
DNA Damage (epidemiological studies)[a]						
DNA strand breaks, alkali labile sites, oxidized purines	Occupational **antimony trioxide**	Alkaline FPG-modified comet assay	Blood lymphocytes from occupationally exposed workers (−S9)	**Frequency of subjects with oxidative DNA damage** **Conc. (µg/m³)** / **# with oxidative damage/total** 0 / 3/23 0.120 ± 0.110 / 11/17 0.052 ± 0.038 / 1/6 **Relative risk of DNA damage** **Conc. (µg/m³)** / **Adjusted relative risk** / **95% CI** 0 / 1 / n/a 0.120 ± 0.110 / 14.2** / 2.7–73.4 0.052 ± 0.038 / 1.7 / 0.1–22.5 **Tail moment values for FPG-treated cells** **Conc. (µg/m³)** / **Mean ± SD** 0 / 24.4 ± 9.51 0.120 ± 0.110 / 32.4 ± 16.3 0.052 ± 0.038 / 28.8 ± 5.61 **Tail moment values for untreated cells** **Conc. (µg/m³)** / **Mean ± SD** 0 / 16.3 ± 6.59 0.120 ± 0.110 / 14.6 ± 8.29 0.052 ± 0.038 / 18.3 ± 8.78	Sb_2O_3 levels for direct and indirect exposure groups lower than OSHA/NIOSH PEL and REL for workplace. Moderate oxidative DNA damage observed in direct exposure group (0.12 ± 0.11 µg/m³); potential concomitant exposures not addressed.	Cavallo et al. (2002)

Genotoxicity Endpoint	Antimony Form	Assay Name	Testing System	Assay Endpoint	Comments	References
DNA strand breaks, alkali labile sites, oxidized purines	Occupational **antimony trioxide**	AP sites quantified using ELISA technique	Blood lymphocytes from occupationally exposed workers (−S9)	The quantity of DNA damage (determined by the number of AP sites/1 × 10^5 bp) among the studied workers was significantly ($p = 0.004$) higher compared to that recorded for the control group and a significant positive correlation was found between the quantity of DNA damage (in the form of increased AP sites) and urinary antimony level among workers ($r = 0.873$, $p < 0.001$). Total oxidative capacity (also measured by ELISA) was not different between workers and controls.	The number of measured basic sites ranged from 17.22 (control group) to 26.88 (exposed workers)/1 × 10^5 bp. This range is higher than expected.	El Shanawany et al. (2017)
DNA damage (in vitro studies in human cells)						
DNA strand breaks, alkali labile sites, DNA-protein crosslinks	Antimony trichloride (concentrations tested: 1–50 μM)	Alkaline comet assay +/− proteinase K	Human whole blood or human lymphocytes exposed ex vivo (−S9)	**Mean tail moment in human whole blood in comet assay without proteinase K** **Conc. (μM) / Time. (hrs) / Mean ± SD** 0 / 2.5 / 1.28 ± 0.10 1 / 2.5 / 1.26 ± 0.01 5 / 2.5 / 1.32 ± 0.08 10 / 2.5 / 1.32 ± 0.04 25 / 2.5 / 1.47 ± 0.07 50 / 2.5 / 1.75 ± 0.08* **Mean tail moment in human lymphocytes in comet assay without proteinase K** **Conc. (μM) / Time (hrs) / Mean ± SD** 0 / 2.5 / 1.00 ± 0.02 1 / 2.5 / 1.23 ± 0.28 5 / 2.5 / 1.39 ± 0.19* 10 / 2.5 / 1.56 ± 0.04*	Significance tested by Kruskal-Wallis one-way ANOVA on ranks.	Schaumlöffel and Gebel (1998)

Genotoxicity Endpoint	Antimony Form	Assay Name	Testing System	Assay Endpoint			Comments	References
				25	2.5	1.64 ± 0.03***		
				50	2.5	2.14 ± 0.01***		
				Mean tail moment in human lymphocytes in comet assay with proteinase K				
				Conc. (µM)	**Time (hrs)**	**Mean ± SD**		
				0	2.5	1.08 ± 0.11		
				1	2.5	1.13 ± 0.09		
				5	2.5	1.30 ± 0.20		
				10	2.5	1.47 ± 0.13*		
				25	2.5	1.53 ± 0.08*		
				50	2.5	1.94 ± 0.30***		
DNA damage (animal studies)								
DNA strand breaks and alkali labile sites	**Antimony trioxide** NC: air	In vivo exposure (inhalation) Alkaline comet assay		**Percent tail DNA**			Trend tests show significant increase for both lung tissue of males and females exposed to trioxide; no increase in percent tail DNA observed in leukocytes of males or females exposed to trioxide. Normally distributed data analyzed by independent sample's t-test and linear regression; data that were not normally distributed were analyzed by the Mann-Whitney test followed by the Kendall rank correlation test.	NTP (2017a)
				Dose (mg/m^3)	**Time (mo.)**	**Mean ± SE**		
				0	12	25.6 ± 0.78		
				3	12	33.7 ± 2.62*		
				10	12	33.5 ± 2.02**		
				30	12	37.5 ± 2.28***		
			Lung of female mice exposed via inhalation for 12 months	**Percent tail DNA**				
				Dose (mg/m^3)	**Time (mo.)**	**Mean ± SE**		
				0	12	32.8 ± 1.11		
				3	12	35.8 ± 2.09		
				10	12	36.4 ± 2.65		
				30	12	45.5 ± 2.32***		

Genotoxicity Endpoint	Antimony Form	Assay Name	Testing System	Assay Endpoint	Comments	References
DNA strand breaks and alkali labile sites	**Antimony trioxide** NC: air	In vivo exposure (inhalation) Alkaline comet assay	Lung and blood leukocytes of male and female rats exposed via inhalation for 12 months	No statistically significant increases were observed in percent tail DNA in blood leukocytes or lung tissue in exposed rats of either sex	Normally distributed data analyzed by independent sample's t-test; data that were not normally distributed were analyzed by the Mann-Whitney test followed by the Kendall rank correlation test.	NTP (2017a)
DNA damage (in vitro studies in non-human mammalian cells)						
DNA strand breaks and alkali labile sites	Antimony trichloride	Alkaline comet assay	V79 Chinese hamster cells exposed in vitro (−S9)	Tail moment was significantly elevated at a minimum dose of 1 µM Sb(III); no difference could be found comparing the results obtained in presence and absence of proteinase K.	DNA damage observed below cytotoxic levels; antimony uptake measured.	Gebel et al. (1998)
DNA damage (bacterial systems)						
Growth in recombination-repair deficient bacterial strain	**Antimony trioxide** NC: Kanamycin (5, 10 20 µg/plate) PC: Mitomycin C (0.05, 0.1, and 0.2 µg/plate)	B. subtilis rec assay	B. subtilis M45(rec-) and H17(rec+)	**HI17 (Rec+) and M45 (Rec-) inhibition length** **Conc. (µg/plate)** / **Difference in Inhibition length (mm)** NC (5) / 0 NC (10) / 0 NC (20) / 0.5 PC (0.05) / 8.0 PC (0.1) / 8.0 PC (0.2) / 7.0 0.3 / 2.5 0.6 / 4.0 1.1 / 4.5	Used spore plate method.	Kuroda et al. (1991)

Genotoxicity Endpoint	Antimony Form	Assay Name	Testing System	Assay Endpoint		Comments	References
Growth in recombination-repair deficient bacterial strain	**Antimony trioxide** PC and NC: other metals tested	*B. subtilis* rec assay	*B. subtilis* M45(rec-) and H17(rec+) (−S9)	**HI17 (Rec+) and M45 (Rec-) inhibition length** **Solution conc. (M)** 0.05	**Difference in inhibition length (mm)** 5	Examined 127 metals; used streak plate method; included cold incubation step to increase contact of metal with bacteria.	Kanematsu et al. (1980)
Growth in recombination-repair deficient bacterial strain	Antimony trichloride NC: Kanamycln (5, 10 20 µg/plate) PC: Mitomycin C (0.05, 0.1, and 0.2 µg/plate)	B. subtilis rec assay	B. subtilis M45(rec-) and H17(rec+) (−S9)	**HI17 (Rec+) and M45 (Rec-) inhibition length** **Conc. (µg/plate)** NC (5) NC (10) NC (20) PC (0.05) PC (0.1) PC (0.2) 6.3 12.5 23	**Difference in inhibition length (mm)** 0 0 0.5 8.0 8.0 7.0 1.5 4.5 4.5	Used spore plate method.	Kuroda et al. (1991)
Growth in recombination-repair deficient bacterial strain	Antimony trichloride	*B. subtilis* rec assay	*B. subtilis* M45(rec-) and H17(rec+) (−S9)	Antimony trichloride result was negative in rec assay (tested at 0.05 M)		Antimony pentachloride also negative.	Nishioka (1975)
Growth in recombination-repair deficient bacterial strain	Antimony trichloride	*B. subtilis* rec assay	*B. subtilis* M45(rec-) and H17(rec+) (−S9)	**HI17 (Rec+) and M45 (Rec-) inhibition length** **Solution Conc. (M)**	**Difference in inhibition length (mm)**	Examined 127 metals; used streak plate method; included cold incubation step to increase contact of metal with bacteria.	Kanematsu et al. (1980)

Genotoxicity Endpoint	Antimony Form	Assay Name	Testing System	Assay Endpoint	Comments	References
	PC and NC: other metals tested			0.01 7		
Induction of recombination-repair genes	Antimony trichloride	SOS chromotest for genotoxicity	*E. coli* PQ37 derived from strain GC4436 (−S9)	SOS chromotest was negative for antimony trichloride (concentration tested: 11–707 µM)	Cytotoxicity observed at 354 µM.	Lantzsch and Gebel (1997)
Induction of recombination-repair genes	Antimony trichloride	Umu test for genotoxicity	*S. typhimurium* TA1535/pSK1002 (−S9)	Umu test was negative for antimony trichloride (concentrations tested: 1.6–820 µM)	Data not reported.	Yamamoto et al. (2002)
DNA Damage (biochemical assay)						
Plasmid DNA nicking	Trimethyl-stibine Potassium antimony tartrate PC: Trimethyl-arsine	Plasmid DNA-nicking assay	Plasmid pBR322 exposed in vitro (gaseous phase) to test reactions for 30 min.	**Estimated Quantity of Open Circular form of Plasmid[d]** **Dose (µM)** / **Result** Trimethyl-stibine: NC +/−; 5 +/−; 20 +/−; 50 +; 200 ++; 500 +++; 5,000 +++	Chemical reactions to produce trimethylstibine were conducted in situ; plus and minus designations were estimated from images only (no quantitation of nicked and supercoiled forms). Negative results were reported for potassium antimony tartrate.	Andrewes et al. (2004)

Levels of significance are designated as follows: *p < 0.05; **p < 0.01; ***p < 0.001.
Listing order of the studies are as follows: (1): assay, in the order of metaphase analysis, micronucleus assay, and sister chromatid exchange assay; (2): target system, in the order of studies in human cells, animal studies, in vitro studies, and biochemical studies; (3): compound, in the order of antimony(III) trioxide (bold), antimony(III) trichloride, and other antimony(III) compounds.
AP = apurinic/apyrimidinic; avg = average; CI = confidence interval; conc. = concentration; ELISA = enzyme-linked immunosorbent assay; FPG = formamidopyrimidine-DNA glycosylase; hr = hour(s); mo = month(s); NC = negative control; NR = not reported; PC = positive control; SD = standard deviation; SE = standard error; VC = vehicle control.
[a]DNA damage estimated as quantity of open circular (vs supercoiled) forms from images of plasmids electrophoretically separated in ethidium bromide-stained agarose gels.

Table E-4. Genotoxicity of Antimony Compounds – Chromosomal Aberrations, Micronucleus, and Sister Chromatic Exchange[a,b]

Substance	Exposure and Assay Name	Testing System and Exposure Duration	Assay Endpoint			Comments	References
Chromosomal aberrations							
Antimony trioxide NC: dimethyl sulfoxide (10 µL/mL) PC: mitomycin C (0.2 µg/mL for-S9) or cyclo-phosphamide (50 µg/mL for +S9)	In vitro exposure Metaphase analysis	Human peripheral lymphocytes with 2 hr exposure to colcemid (−S9) Exposure time: 20 hr and 44 hr Dose: 10, 50, 100 µg/mL	**Mean % aberrant cells excluding gaps**			Precipitate formed at top dose level.	Elliott et al. (1998)
			Group	**HIC/LEC (µg/mL, unless specified)**	**Mean (%)**		
			NC	–	0.5–1.5		
			PC	–	22.0–32.0**		
			Donor 1, 20 hr	100	2.0		
			Donor 2, 20 hr	100	12.5**		
			Donor 2. 44 hr	100	4.5*		
		Human peripheral lymphocytes with 2 hr exposure to colcemid (+S9) Dose: Same as above	NC	–	1.0–1.5		
			PC	–	26–34.0**		
			Donor 1, 20 hr	50	4.5*		
			Donor 2, 20 hr	100	9.5**		
			Donor 2. 44 hr	100	2.0		
Antimony sodium tartrate	In vitro exposure Metaphase analysis	Human leucocytes Exposure time: 48 hr Concentration: 2.3 nM	12% of cells with chromatid breaks ($p < 0.05$)			Purity of test compound not reported; toxicity (marked reduction in mitotic index) reported at 10 nM.	Paton and Allison (1972)
Antimony trioxide	In vivo exposure	Sprague-Dawley rat bone marrow cells (−S9)	**Frequency of cells with chromosomal aberration excluding gaps in male rats**			Body weight gain was reduced (<10%) in the	Kirkland et al. (2007)

Substance	Exposure and Assay Name	Testing System and Exposure Duration	Assay Endpoint			Comments	References
VC: HPMC/poly-sorbate PC: Cyclo-phosphamide	Ex vivo metaphase analysis	Exposure time: Once daily for 21 consecutive days by oral gavage (except PC administered on only on day 21) Dose: 250, 500, 1,000 mg/kg	**Group**	**HIC/LEC (mg/kg)**	**Mean% ± SD**	top dose group of treated rats of both sexes over the 3-week dosing period.	
			VC	20	0 ± 0		
			PC	20	13 ± 6.63***		
			Male rat	1,000	0 ± 0		
			Female rat	1,000	0 ± 0		
Antimony trioxide NC: distilled water	In vivo exposure Ex vivo metaphase analysis	Male Swiss albino mice bone marrow cells (−S9) Exposure by daily oral gavage on days 7, 14 and 21 Dose: 400, 666.7, 1,000 mg/kg	**Frequency of aberrations excluding gap**			Purity of test compound not reported. Test for trend significant for 7 and 14 days for analysis including and excluding gaps (not shown in this table). No increases in chromosomal aberrations were observed after single acute exposure at same doses and measured 6, 12, 18 and 24 hours); Highest dose was lethal.	Gurnani et al. (1992a)
			LEC (mg/kg)	**Time (days)**	**Mean % ± SD**		
			NC	7	1.4 ± 1.140		
			400	7	2.2 ± 0.447*		
			NC	14	1.6 ± 0.547		
			400	14	3.2 ± 0.447*		
			NC	21	1.6 ± 0.547		
			400	21	4.6 ± 0.547*		
Antimony trichloride NC: distilled water	In vivo exposure Ex vivo metaphase analysis	Female Swiss albino mice bone marrow cells (−S9) Dose: 70, 140, 233.3 mg/kg Single exposure by oral gavage analyzed at 6, 12, 18 and 24 hrs	**Frequency of aberrations including gap**			Source and purity of test compound not reported. Test for trend significant for 6, 12, 18, and 24 hr analysis including and excluding gaps (not shown in this table).	Gurnani et al. (1992b)
			LEC (mg/kg)	**Time (hrs)**	**Mean% ± SD**		
			NC	6	1.6 ± 0.547		
			70	6	2.6 ± 0.547		
			NC	12	1.0 ± 1.0		
			70	12	3.0 ± 0.0		
			NC	18	1.6 ± 0.547		
			70	18	3.2 ± 0.836		
			NC	24	1.0 ± 0.0		

Substance	Exposure and Assay Name	Testing System and Exposure Duration	Assay Endpoint			Comments	References
			70	24	4.2 ± 1.095		
Potassium antimony tartrate Control: untreated animals	In vivo exposure Ex vivo metaphase analysis	Male rats bone marrow (−S9) Exposure via single intraperitoneal injection at each dose. Also, tested repeated exposure (daily for 5 days) at each dose. Dose: 2.0, 8.4, 14.8 mg/kg	**Metaphases with aberrations excluding gap**			Similar findings for aberrations including gaps but statistical analysis not performed.	El Nahas et al. (1982)
			LEC (mg/kg, unless specified)	**Time after treatment (hr, unless specified)**	**%**		
			NC	n/a	0.7		
			2.0	6	2.0*		
			2.0	24	2.4*		
			8.4	48	5.2*		
			2.0 mg/kg/day × 5 days	–	7.6*		
Micronuclei							
Occupational **antimony trioxide**	Epidemiology study Sister chromatid exchange assay	Blood lymphocytes from textile workers exposed to low levels of antimony trioxide. 23 exposed workers: 17 high exposure (0.12 ± 11 μg/m^3) and 6 lower exposure (0.052 ± 0.038 μg/m^3) 23 controls	Mean micronuclei/1,000 binucleated cells did not differ between controls and two exposure groups			High exposure well below OHSA permissible exposure levels and NIOSH recommended exposure levels. Exposure groups had similar ages, and smoking habits.	Cavallo et al. (2002)
Antimony trichloride NC: DMSO PC: mitomycin C (data not shown)	In vitro exposure Micronucleus test	Human peripheral lymphocytes (−S9) Doses: 0, 0.5, 2, 5, 25 μM	**Induction of micronuclei by Sb(III)**			Co-incubation with SOD or CAT had no effect on micronucleus frequency; statistically significant in MN observed in second experiment at 5, 10 and 25 μ M.	Schaumlöffel and Gebel (1998)
			LEC (μM)	**Time (hrs)**	**MN/1000 BN, mean ± SD**		
			0	20	10 ± 1.4		
			5	20	30.5 ± 2.1		
Antimony trioxide	In vivo exposure	Male mice peripheral blood erythrocytes	No significant increase in micronucleated PCEs/1,000 PCEs in male mice			Twenty thousand CD71+ reticulocytes (PCE)	NTP (2017a)

Substance	Exposure and Assay Name	Testing System and Exposure Duration	Assay Endpoint	Comments	References
NC: air	Ex vivo micronucleus test	exposed via inhalation for 12 months Dose: 0, 3, 10, 30 mg/m^3	**Micronucleated NCEs/1,000 NCEs** **LEC (mg/m^3) Time (mo.) Mean ± SE** 30 12 1.93 ± 0.10***	were scored per animal for the presence of micronuclei and 1 × 10^6 erythrocytes (NCE) were counted for micronuclei. Williams's and Dunn's tests were used for pairwise significance, and Jonckheere's test and linear regression used for trend significance. MN frequency in NCEs but not PCEs significant by trend test ($p < 0.001$) in both sexes.	
		Female mice peripheral blood erythrocytes exposed via inhalation for 12 months Dose: 0, 3, 10, 30 mg/m^3	No significant increase in micronucleated PCEs/1,000 PCEs in female mice **Micronucleated NCEs/1,000 NCEs** **LEC (mg/m^3) Time (mo.) Mean ± SE** 30 12 1.38 ± 0.09***		
Antimony trioxide NC: air	In vivo exposure Ex vivo micronucleus test	Male rat peripheral blood erythrocytes exposed via inhalation for 12 months	No significant increase in micronucleated PCEs/1,000 PCEs or micronucleated NCEs/1,000 NCEs in male rats.	Twenty thousand CD71+ reticulocytes (PCE) were scored per animal for the presence of micronuclei and 1 × 10^6 erythrocytes (NCE) were counted for micronuclei. Williams's and Dunn's tests were used for pairwise significance, and Jonckheere's test and linear regression used for trend significance. No significant changes were observed in MN frequency in rats of either sex.	NTP (2017a)
		Female rat peripheral blood erythrocytes exposed via inhalation for 12 months	No significant increase in micronucleated PCEs/1,000 PCEs or micronucleated NCEs/1,000 NCEs in female rats.		

Substance	Exposure and Assay Name	Testing System and Exposure Duration	Assay Endpoint	Comments	References
Antimony trichloride	In vitro exposure Micronucleus test	Human fibroblast cells (−S9) Human bronchial epithelial cells (BES-6) (−S9) Chinese hamster ovary cells (CHO-K1) (−S9) Exposure time: 4 hr, Dose: 50–400 µM	Positive findings for all cell types at all doses	LD_{50} = 40 µM in fibroblast cells LD_{50} = 80 µM in BES-6 cells LD_{50} = 180 µM in CHO-K1 cells	Huang et al. (1998)
Antimony trioxide VC: DMSO PC: Cyclo-phosphamide (20 mg/kg)	In vivo exposure Micronucleus test	Mouse bone marrow (−S9) male and females Single dose study Exposure time: 24 and 48 hr Dose: 5,000 mg/kg by oral gavage Repeated dose study: Exposure time: 8, 15 and 22 days Dose: 400, 667, or 1,000 mg/kg by oral gavage	No increases in mean incidence of MPE/1,000 PE in the single dose study (males and females) or in the repeated dose study (sex not identified).	Significantly decreased frequency of polychromatic erythrocytes observed in females at 24 hr in the single dose experiment.	Elliott et al. (1998)
Antimony trioxide VC: HPMC/poly-sorbate PC: Cyclo-phosphamide (20 mg/kg)	In vivo exposure Micronucleus test	Sprague-Dawley male and female rat bone marrow cells (−S9) Exposure time: 21 days (except for PCs) by oral gavage Dose: 250, 500, 1,000 mg/kg	No increase in the frequency of micronucleated PCE in male and female rats	–	Kirkland et al. (2007)
Antimony trioxide	In vitro Micronucleus	Chinese hamster V79 cells	**Mean number of micronuclei** **Group** **LEC (µM)** **Mean**	Study measured both antimony uptake in cells	Gebel et al. (1998)

Substance	Exposure and Assay Name	Testing System and Exposure Duration	Assay Endpoint			Comments	References
VC: DMSO (25 µL) PC: Mitomycin C (0.5 µM)	test with cytokinesis block	Exposure time: 24 hr Dose: 2–50 µM	VC PC Antimony trioxide	– – 25	9.5 45.5 17.5	and cytotoxicity (50% neutral red uptake was found with $SbCl_3$ at 83 µM).	
Sister chromatid exchange							
Occupational antimony trioxide	Epidemiology study Sister chromatid exchange assay	Peripheral blood lymphocytes from textile workers exposed to low levels of antimony trioxide 23 exposed workers: 17 high exposure (0.12 ± 11 µg/m^3) and 6 lower exposure (0.052 ± 0.038 µg/m^3) 23 controls	Mean SCE did not differ between controls and two exposure groups			High exposure well below OHSA permissible exposure levels and NIOSH recommended exposure levels. Exposure groups had similar ages, and smoking habits.	Cavallo et al. (2002)
Antimony trioxide (dissolved in distilled water) NC: DMSO	In vitro exposure Sister chromatid exchange assay	Human peripheral blood lymphocytes from healthy non-smokers aged 25–35 years (−S9) Exposure time: 24 hrs	**LEC (µM)** 0 0.5	**SCE/cell** **Mean ± SD** 8.6 ± 3.4 11.5 ± 4.4*		NC was DMSO, and it is unclear whether the 0 µM result was from distilled water or DMSO. No PC was stated in the study. Results are from 60 metaphase cells scored on two slides.	Gebel et al. (1997)
Antimony trichloride	In vitro exposure	Human peripheral blood lymphocytes from	**LEC (µM)** 0	**SCE/cell** **Mean ± SD** 8.8 ± 4.0		No PC was stated in the study. Results are from 60 metaphases scored on	Gebel et al. (1997)

Substance	Exposure and Assay Name	Testing System and Exposure Duration	Assay Endpoint			Comments	References
(dissolved in DMSO) NC: DMSO	Sister chromatid exchange assay	healthy non-smokers aged 25–35 years (−S9) Exposure time: 24 hr	1		13.8 ± 5.5**	two slides.NC was DMSO, and it is unclear whether the 0 µM result was from distilled water or DMSO.	
Antimony trioxide NC: Water (100 µL) PC: Mitomycin C (0.01 µg/mL)	In vitro exposure Sister chromatid exchange assay	Chinese hamster V79 cells Exposure time: 28 hr Dose: 0.09–0.34 µg/mL	**Frequency of sister chromatid exchanges/metaphase**			Sb_2O_5 was negative in the SCE assay; similar results in experiment 1, although LEC was 0.17 µg/mL.	Kuroda et al. (1991)
			LEC (µg/mL)	**Time (hrs)**	**Mean ± SD**		
			NC	28	6.3 ± 2.5		
			PC	28	56.0 ± 9.3**		
			0.09	28	10.6 ± 3.7**		
Antimony trichloride NC: Water (100 µL) PC: Mitomycin C (0.01 µg/mL)	In vitro exposure Sister chromatid exchange assay	Chinese hamster V79 cells Exposure time: 28 hr Dose: 1.3–20 µg/mL	**Frequency of sister chromatid exchanges/metaphase**			$SbCl_5$ was negative in the SCE assay. Toxic at 20 µg/mL; similar results in experiment 2, although LEC was 5 µg/mL.	Kuroda et al. (1991)
			Conc. (µg/mL)	**Time (hrs)**	**Mean ± SD**		
			NC	28	4.5 ± 2.2		
			PC	28	46.8 ± 8.6**		
			2.5	28	7.5 ± 4.3*		

*p < 0.05, **p < 0.01, ***p < 0.001.
Studies are listed hierarchically according to the following criteria (1): Assay, in the order of assays for chromosomal aberrations, micronucleus, and sister chromatid exchange. (2): Target system, in the order of studies in human cells, animal studies, in vitro studies, biochemical studies. (3) Compound, in the order of antimony trioxide (bold), antimony trichloride, other antimony(III) compounds.
b.w. = body weight; FISH = fluorescence in situ hybridization; HIC = highest ineffective concentration; hr = hour(s); LEC = lowest effective concentration; mo = months; NC = negative control; NR = not reported; PC = positive control; VC = vehicle control.
[a]Provided are the form of the test compound, study details including the testing system and exposure duration, assay endpoint results for test compounds and positive and negative controls, comments provided by reviewers, and reference.
[b]Compounds containing pentavalent antimony are not included. For instance, trimethylantimony dichloride in Dopp et al. (2006) (no increase of MN formation, chromosome aberration, or sister chromatid exchange in the Chinese hamster ovary cells after exposure to at up to 1 mM. When the cells underwent electroporation to double the intake of trimethylantimony dichloride, the formation of MN was increased.) and KSbO3 in Migliore et al. (1999) (nonsignificant increase of centromere-negative MN) were not included in the table.

E.4. Studies Related to Cell Proliferation

Table E-5. Mutations in the Lung of Mice and Rats after Two-year Inhalation Exposure to Antimony Trioxide (NTP 2017a)

Genotoxicity Endpoint	Testing System	Mutation Frequency		Comments	Reference
		Concentration (mg/m^3)	# with mutation/# tissues assayed		
Egfr mutations	Lung tumors from exposed B6C3F1/N mice.	0 (nontumor lung)	0/10	–	NTP (2017a)
		0 (tumor lung)	0/9*		
	Both nontumor lung and spontaneous tumors from control mice.	3 (tumor lung)	11/28**		
		10 (tumor lung)	11/26**		
		30 (tumor lung)	15/26***		
Egfr mutations	Lung tumors from exposed Wistar Han rats.	0 (nontumor lung)	0/11	Increase was not statistically significant.	NTP (2017a)
		0 (tumor lung)	0/4		
	Both nontumor lung and spontaneous tumors from control mice.	3 (tumor lung)	3/5		
		10 (tumor lung)	6/11		
		30 (tumor lung)	4/10		
Kras mutations	Lung tumors from exposed Wistar Han rats.	0 (nontumor lung)	0/11	Increase was not statistically significant.	NTP (2017a)
		0 (tumor lung)	0/4		
	Both nontumor lung and spontaneous tumors from control mice.	3 (tumor lung)	0/5		
		10 (tumor lung)	1/11		
		30 (tumor lung)	0/10		
Kras mutations	Lung tumors from exposed B6C3F1/N mice.	0 (nontumor lung)	0/10	Increase was not statistically significant.	NTP (2017a)
		0 (tumor lung)	3/9		
	Both nontumor lung and spontaneous tumors from control mice.	3 (tumor lung)	9/28		
		10 (tumor lung)	15/26		
		30 (tumor lung)	10/26		

*Significant exposure-concentration trend ($p \leq 0.01$) by the Cochran-Armitage trend test.
**Significantly different ($p \leq 0.05$) from the chamber control group by the one-sided Fisher's exact test.
***$p \leq 0.005$.

E.5. Transcriptomic of Antimony(III) Potassium Tartrate Trihydrate in HepG2 Cells

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[(+)-tartato]diantimonate(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 (Table E-6), seven were related to immune reactions (pathways 1, 2, 4, 5, 7, 8, and 9). 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 6.2).

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.5, Table E-6**)**. 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.

Table E-6. Top 10 Upstream Regulators for Antimony

	Upstream Regulator	Expr Fold Change	Molecule Type	Predicted Activation State	Activation z-score	Flags	P Value of Overlap	Target Molecules in Dataset	Mechanistic Network
1	**Vegf**	–	group	Activated	9.487	bias	1.88E-09	ANGPT2,ANGPTL4,AQP4,ATF3,AURKA,AURKB,BCL2A1,BIRC5,BNC1,BTN1A1,CA2,CALB1,CALCRL,CCL7,CCNF,CD3EAP,CDC14A,CDC20,CDC25A,CDC25B,CDC25C,CDC45,CDH5,CDK1,CDKN2C,CDKN3,CELSR1,CHI3L1,CHIA,CHRNB2,CHST7,CKS1B,CLCF1,CNN1,CNTFR,CPA3,CRLF1,CRYAB,CSF2,CXCL1,CXCL8,CXCR2,CXCR4,CYR61,DBF4,DPF3,DRD3,DTYMK,DUSP4,DUSP5,EDN1,EGR1,EGR3,EMCN,EMP2,ESM1,FABP4,FAIM2,FANCG,FGF16,FGF2,FLNA,FOSB,FOSL1,GATA1,GEM,GH1,GPR4,GPRC5B,HBE1,HBEGF,HDC,HMOX1,HOXB8,HPSE,HTR7,IL18,IL1A,IL3RA,IL4,ITGB3BP,JAM2,JUN,KIF15,KIF22,KIF2C,KITLG,LEF1,LPAR1,LRAT,LYVE1,MCM2,MCM5,MID1,MKI67,MMP10,MMP14,MT1G,MYCN,NDC80,NEK2,NFATC1,NGB,NR4A2,NR4A3,NRCAM,NRG1,PLK1,PLXNA2,PMAIP1,PRC1,PRKCB,PSMC3IP,PTH,RGS2,RGS20,SOCS2,SOCS3,ST8SIA4,STK10,TAAR5,TACR1,TACSTD2,TBXA2R,THBD,TNC,TNFRSF9,TNFSF15,TPX2,TRAF5,TRAIP,TRPC4,TTK,UBE2C,XCR1	–

	Upstream Regulator	Expr Fold Change	Molecule Type	Predicted Activation State	Activation z-score	Flags	P Value of Overlap	Target Molecules in Dataset	Mechanistic Network
2	**CSF2**	8.025	cytokine	Activated	8.308	bias	1.85E-08	ADA,ADAM8,ADGRE5,ANXA1,AURKA,BCL2A1,BIRC5,C5AR1,CCL4,CCNF,CCR1,CCR5,CCR7,CD1C,CD209,CD28,CD33,CD40LG,CD69,CD8A,CDC20,CDK1,CDKN1A,CDKN2B,CDKN2C,CENPE,CHAF1A,CHAF1B,CKS1B,CLCF1,COL8A1,CSF1,CSF2,CTLA4,CXCL1,CXCL2,CXCL8,CXCR4,CYBB,EDN1,EGR1,EGR2,EGR3,EPOR,EXO1,FANCA,FCGR2B,FOLR2,FOS,FOSL1,FPR2,GATA1,GCLM,GDF15,HBEGF,HDC,HLA-DQB1,HRH4,HRK,HSPH1,IER3,IFNG,IGF1,IL1A,IL1RN,IL24,IL3RA,IL4,ITGA4,ITGAM,LEP,MCM5,MKI67,MMP1,MMP14,MRC1,NEK2,NFATC1,NFE2,NFKBIA,NR4A2,NUSAP1,OSM,PDE1B,PIM1,PLK1,POLD1,POLE,PPP1R15A,PRC1,PTGER2,RARA,RECQL4,RELB,RRM2,SERPINB9,SLC1A5,SOCS2,SOCS3,SPAG5,SPI1,STMN1,THBS1,TLR2,TLR4,TNFAIP3,TNFRSF1B,TNFRSF9,TNFSF14,TNFSF15,TNFSF8,TPM4,TPX2,UBE2C, ZFP36	352 (5)
3	**TREM1**	1.62	transmembrane receptor	Activated	4.945	bias	0.000000203	ATF3,CASP5,CCL7,CCR7,CCRL2,CDK1,CDKN2B,CEBPB,CKS2,CSF1,CSF2,CXCL1,CXCL2,CXCL3,CXCL5,CXCL8,CXCR4,DCSTAMP,DEFB4A/DEFB4B,DUSP4,EDN1,EGR1,EGR2,EGR3,FOSL1,GADD45B,GCLM,GEM,GIPR,GLA,HAS1,HBEGF,IFNG,IL17A,IL36RN,IL4,LPL,MAD1L1,MAFF,MMP1,MMP10,MMP19,NFKBIA,NOD2,NR4A2,OSGIN1,RGS1,RRAD,SLC1A3,SNAPC1,TCEAL9,THBD,THBS1,TLR2,TLR4,TNFSF14,TNFSF15,WNT5A	–

	Upstream Regulator	Expr Fold Change	Molecule Type	Predicted Activation State	Activation z-score	Flags	P Value of Overlap	Target Molecules in Dataset	Mechanistic Network
4	**GATA2**	2.854	transcription regulator	–	1.922	–	0.000000237	ADGRE5,ANGPT2,ANGPTL4,ARPP21,C9,CCL21,CCR8,CD177,CD34,CD36,CD69,CD96,CDH5,CDK6,CDKN1A,CEL,CELSR3,CHGA,CHI3L1,CLDN18,CMA1,CPA1,CPA3,CST7,CYBB,CYP2F1,CYP4F11,DDX4,DLK1,E2F2,EDN1,ELANE,EMCN,EPHA3,FABP4,FCN1,GABRP,GATA1,GATA2,GP5,GP9,GPR65,GUCA2A,HBQ1,HDC,HOXA10,HSD17B1,ICAM2,IKZF1,IL3RA,IL4,IL4R,ITGAM,KLF2,KLK3,LYL1,MAFB,MEP1A,MMRN1,MPIG6B,NFE2,PAX3,PDE9A,PLK2,PRG3,RAG1,REG1A,S100A5,S100A9,S100G,SERPINB10,SLC4A1,SLC9A5,SOX18,SPI1,SSTR2,TAC3,TACSTD2,TAL1,THBS1,TUBA8,UBASH3A	–
5	**calcitriol**	–	chemical drug	–	0.412	–	0.000000494	ADAM19,ALPI,ANGPT2,ANKRD2,ATP5D,BIRC5,CA2,CALB1,CALCB,CASR,CCNA1,CCR8,CDC20,CDC45,CDK1,CDK5R1,CDKN1A,CEBPB,CELSR3,CHAF1A,CHAF1B,CHGA,CKM,COL4A1,CSF1,CSF2,CXCL2,CXCL3,CXCL8,CYP24A1,CYP2C9,CYP3A4,CYP46A1,CYR61,DCSTAMP,DEFB4A/DEFB4B,DUSP1,DUSP10,EDN1,EGR1,ETFB,EXO1,FABP4,FAM107A,FCER2,FOS,GADD45A,GADD45G,GEM,HBEGF,HSPB7,IER3,IFITM1,IFNG,IGF1,IGFBP5,IL10RA,IL17A,IL18,IL1A,IL1RN,IL4,INCENP,INS,ITGA4,ITGAM,ITGB7,JUN,KIF20A,KIF22,KL,KLK13,KLK5,LEP,LIG1,LPAR1,LPL,LTBP1,MAOA,MCM2,MCM5,MMP1,MRC1,MYH8,NEK2,NFATC1,NKX2-1,NME4,NPHS1,NTHL1,NUPR1,NUSAP1,PDE9A,POLE,POU1F1,PRC1,PRKCB,PRKCD,PTGER2,PTGFR,PTH,RAB38,RAD51AP1,RARRES1,RBPMS,REL,RRM2,RUNX1T1,S100A9,S100G,SERPINB7,SERPINB9,SLC2A4,SLC7A7,SNPH,SOCS3,SPAG5,STMN1,SUV39H1,TACC3,TERT,THBD,THBS1,THRA,TK1,TLR2,TLR4,TNFAIP3,TPX2,TSPO,WNT11	140 (2)

	Upstream Regulator	Expr Fold Change	Molecule Type	Predicted Activation State	Activation z-score	Flags	P Value of Overlap	Target Molecules in Dataset	Mechanistic Network
6	**ID2**	1.706	transcription regulator	–	−1.136	–	0.000000514	AICDA,ASCL2,BATF,CCR10,CCR7,CCR8,CD40LG,CDC25B,CDK1,CDKN1A,CDKN2C,CEBPB,CSF1,CXCR4,CXCR5,DUSP1,DUSP10,DUSP4,E2F2,EGR2,EGR4,FLT3LG,FOXO3,FSHB,GADD45B,GADD45G,IFNG,IL10RA,IL4,IL4R,IL9R,IRF8,KLF6,LTA,MAP3K14,MPZ,NFAT5,NFATC1,NR4A3,PDCD1,PTPN13,PTPN14,PTPN22,RAPGEF4,REL,RPS6KA2,SELL,SEMA3F,SH2D1A,SOCS3,SOX4,SOX5,TNFRSF25,TNFSF14,TNFSF8,TRAF1,TRAF5	–

	Upstream Regulator	Expr Fold Change	Molecule Type	Predicted Activation State	Activation z-score	Flags	P Value of Overlap	Target Molecules in Dataset	Mechanistic Network
7	**phorbol myristate acetate**	–	chemical drug	Activated	7.684	bias	0.000000604	ADAM28,ADAM8,ADM,ADRB3,AGER,ALOX12,ANGPT2,ANGPTL4,ANXA1,AQP4,ATP2A3,AURKA,AURKB,BCL2A1,BDNF,BIRC5,BLM,BTG2,C5AR1,CA2,CA8,CAV1,CCL1,CCL4,CCNA1,CCR7,CD209,CD28,CD36,CD40LG,CD69,CDK1,CDK5R1,CDK5R2,CDKN1A,CDKN2B,CGA,CHGA,CKM,CLCF1,CRH,CRHR1,CSF1,CSF2,CTLA4,CXCL13,CXCL2,CXCL3,CXCL8,CXCR2,CXCR4,CYBB,CYP24A1,CYP2A6 (includes others),CYR61,DEFB4A/DEFB4B,DSG1,DUSP1,DUSP2,DUSP5,E2F1,E2F3,EGR1,EGR2,EGR3,EGR4,EIF4EBP1,ELANE,EN1,EP300,EPOR,ERBB4,FGF2,FGF7,FOS,FOSB,FOSL1,FSHB,FUT9,GABRP,GAP43,GATA1,GATA2,GDF15,GEM,GML,GNRH1,GRIN2A,H1FX,HAS1,HBEGF,HDC,HMGA1,HPSE,HSD11B1,HSD17B1,HSD3B1,HTR2A,HTR7,IFNG,IGF1,IGFBP2,IGFBP5,IL12RB1,IL17A,IL18,IL1A,IL1RN,IL20RA,IL24,IL4,ITGAM,ITM2A,JUN,JUNB,JUND,KCNJ10,KIF2C,KLF2,KLF6,KLK3,KRT35,LAMB3,LOR,LPL,LTA,LYVE1,MAD1L1,MMP1,MMP11,MMP12,MMP14,MMP19,MMP7,MPZ,MRC1,MSR1,MST1R,MT2A,MUC4,MYH7,MYOZ2,NCR1,NFAT5,NFATC1,NFKBIA,NFKBIE,NKX2-1,NOCT,NR4A2,NTS,OLR1,OSM,OSR2,PAK2,PDCD1,PDE1C,PDPN,PIM1,PLIN3,PODXL2,PON1,POU1F1,PPP1R15A,PRKCB,PRKCD,PRKD1,PTGER2,PTGES,PTGFR,PTPRE,PTPRN,PTPRO,RAE1,RARA,RARB,RASGRP1,RECQL4,REL,RELB,RGS1,RGS2,RUVBL2,S100A9,SELL,SELPLG,SERPINB10,SERPINB7,SERPINB9,SLC22A1,SLC6A2,SLC6A7,SLC7A11,SNAI1,SNAP25,SOCS3,SP4,SPHK1,SRC,SRD5A2,SSTR2,STATH,TACR1,TBXAS1,TEAD4,TERT,TH,THBS1,TIE1,TK1,TLR2,TLR4,TLR6,TMOD2,TNFAIP3,TNFRSF1B,TNFSF14,TRAF1,TRPC6,ULBP2,USF2,VIP,WT1,XCR1,ZFP36	276 (3)

	Upstream Regulator	Expr Fold Change	Molecule Type	Predicted Activation State	Activation z-score	Flags	P Value of Overlap	Target Molecules in Dataset	Mechanistic Network
8	**HDAC1**	0.743	transcription regulator	–	−0.945	–	0.000000942	ADIPOQ,AMPD3,ANGPT2,ASCL2,ATF3,BDNF,CCNA1,CCNB2,CCR8,CD27,CD34,CDC25A,CDC25C,CDK1,CDKN1A,COL1A2,COL9A1,CXCL8,E2F2,EGR1,EHMT2,FABP4,FAM107A,FOS,H2AFX,HBE1,HBG2,IFNB1,IL17A,IL24,IL4,INA,ITGB4,KLK3,LIG1,MAD1L1,MCM5,MPZ,MT1G,MUC4,MYH7,NEFH,NFATC1,NFKBIA,NKX2-5, PAX3, PLK1, PMAIP1, POLL, PPP2R2B,PRIM2,PTH,RAD54L,RAG1,RECQL4,RELB,RGS10,RRM2,RUNX2,S100A9,SATB1,SNAI1,SOX10,TAGLN,TAL1,TBX1,TBX2,TERT,TUBB3, TYMS	414 (12)
9	**PTGER2**	2.853	g-protein coupled receptor	Activated	5.127	bias	0.00000162	AURKA,CCNB2,CCR7,CDKN3,CENPE,CFP,CKS2,CXCL8,CXCR2,CXCR4,EGR1,FPR1,H2AFX,HAMP,HDC,HIST1H2AB,IFNG,IL17A,IL1A,KIF15,KIF20A,KIF22,KIF2C,KLRD1,MKI67,NEK2,NUSAP1,PIM1,PLK1,PRC1,PTGER3,PTGES,SPAG5,THBS1,TPX2,TROAP,TTK	–
10	**TNF**	1.621	cytokine	Activated	8.752	bias	0.00000184	ACTA1,ADAM8,ADAMTS5,ADIPOQ,ADM,ADRB1,ADRB3,AEBP1,AGER,AICDA,AMPD3,ANGPT2,ANGPTL4,ANXA1,ARHGDIB,ATF3,AURKC,BCL2A1,BDKRB1,BDKRB2,BDNF,BIK,BIRC5,BTG2,BTG3,C5AR1,CA2,CABP1,CAV1,CCK,CCL1,CCL22,CCL4,CCL7,CCR1,CCR5,CCR7,CCR8,CD1C,CD209,CD247,CD28,CD36,CD3E,CD40LG,CD5,CD69,CD82,CDC25C,CDH13,CDH5,CDK5R1,CDKN1A,CDKN2C,CDX1,CEBPB,CEBPG,CHI3L1,CHRNA4,CHRNB2,CHRNE,CHRNG,CHST4,CHST7,CIB2,CKM,CLCF1,CLDN7,CNN1,COL15A1,COL16A1,COL1A2,COLQ,COTL1,CPA3,CRH,CRHR1,CRLF1,CRYAB,CSF1,CSF2,CSN2,CST7,CTLA4,CTSF,CX3CR1,CXCL1,CXCL13,CXCL2,CXCL3,CXCL5,CXCL8,CXCR2,CXCR4,CXCR5,CYBB,CYP26B1,CYP2C8,CYR61,CYTH3,DCSTAMP,DEFB4A/DEFB4B,DPF3,DUSP1,DUSP10,DUSP2,DUSP4,DUSP5, DVL1,E2F1,EDN1,EGR1,EGR2,EGR3,ELF3,EMCN,EMP2,ENG,ENPP3,EREG,ESM1,FABP4,FAT2,F	611 (12)

Upstream Regulator	Expr Fold Change	Molecule Type	Predicted Activation State	Activation z-score	Flags	P Value of Overlap	Target Molecules in Dataset	Mechanistic Network
							CAR,FCER2,FCGR2B,FGF2,FGF5,FOS,FOSB,FOSL1,FOXF1,FOXF2,FPR1,FPR2,FSCN1,G0S2,GABRA1,GADD45A,GADD45B,GADD45G,GATA2,GCLM,GDF15,GEM,GNA15,GNL1,GPR176,GPRC5B,GRIA1,HAS1,HBEGF,HDC,HIVEP1,HLA-F, HMOX1,HOXB8,HRK,HSD11B1, HSPA1A/HSPA1B,HSPG2,ICAM2,IER2,IER3,IFI27,IFITM1,IFNA1/IFNA13,IFNB1,IFNG,IGF1,IGFBP2,IGFBP5,IL10RA,IL17A,IL18,IL18R1,IL1A,IL1RN,IL24,IL3,IL36RN,IL3RA,IL4,IL4R,INS,IRF8,ITGA4,ITGAM,ITGB7,JUN,JUNB,JUND,KIF20A,KITLG,KL,KLF10,KLF2,KLF6,KLK3,LAMA4,LAMB3,LBP,LEP,LPL,LTB4R2,LYVE1,MADCAM1,MAFF, MAP3K14,MC1R,MCF2,MECOM,MFHAS1,MGMT,MMP1,MMP10,MMP12,MMP14,MMP28,MMP7, MSR1,MST1R,MSTN,MT2A,MUC1,MUC4,MYH7, NCAN,NCF2,NEFH,NFATC1,NFKBIA,NFKBIE,NKX21, NKX6-1, NOCT,NOD2,NPHS1,NPPB,NR4A2,NR4A3,NR6A1, OAS2,OLR1,OSM,OTUD7B,P2RY6,PAK2,PAX6,PDCD1,PDE2A,PDGFRA,PDPN,PIM1,PLA2G3,PLA2G4C,PLA2G5,PLIN1,PLK2,PLP1,PMAIP1,PPP1R15A,PRKCD,PRSS23,PTGES,PTGFR,PTPRN,PYCARD,RARA,RBPMS,RCAN2,REL,RELB,RFX2,RGS1,RGS2,RGS20,RGS3,RGS5,RND1,RRAD,RRM1, RRM2,RUNX2,S100A9,SCNN1B,SCO2,SCUBE2,SELL,SELPLG,SERPINB10,SERPINB9,SLC12A1,SLC16A2,SLC1A3,SLC2A4,SLC7A8,SNAI1,SNN,SOCS2,SOCS3,SOX4,SPHK1,ST8SIA4,STMN1,SYNGR3,TAGLN,TBXAS1,TERT,TH,THBD,THBS1,THBS2,TIE1,TK1,TLR2,TLR4,TNC,TNFAIP3,TNFRSF1B,TNFRSF9,TNFSF14,TNFSF15,TNFSF8,TNFSF9,TNNC1,TRAF1,TRAF2,TRAF5,TREM2,TRIM15,TRPC3,TRPC6,TWIST1,TXNRD1,VIP,WNT10B, WNT5A,WNT7A,YY1,ZFP36	

Table E-7. Top 10 Canonical Pathways Affected by Six-hour Exposure to 20 µM Antimony(III) Potassium Tartrate Trihydrate

Order	Ingenuity Canonical Pathways	-log(P value)	Ratio	Molecules
1	Agranulocyte Adhesion and Diapedesis	4.29	0.358	CLDN7,CCL8,SELL,CLDN8,PODXL2,MYH3,CXCR4,IL1RN,CLDN14,C5AR1,MYH11,CXCL1,MYH7,MMP11,MADCAM1,MYL6B,CDH5,CXCL8,IL18,XCL2,CXCR2,SELPLG,IL1A,IL36RN,ITGA4,ACTA1,CXCL3,CD34,CXCL14,MMP1,MMP25,ITGA3,MMP12,ITGB7,CXCL5,CCL4,MMP28,ICAM2,CLDN17,CCL7,CLDN18,CCL1,MMP17,CCL21,CXCL2,MMP7,CCL22,MMP19,CXCL13,MMP20,MMP10,MYH8,MMP14
2	Granulocyte Adhesion and Diapedesis	3.79	0.35	CLDN7,CCL8,SELL,CLDN8,CXCR4,IL1RN,CLDN14,C5AR1,CXCL1,MMP11,TNFRSF1B,FPR2,CDH5,CXCL8,HSPB1,IL18,XCL2,CXCR2,SELPLG,IL1A,IL36RN,ITGA4,CXCL3,CXCL14,MMP1,HRH2,MMP25,ITGAM,ITGA3,MMP12,FPR1,HRH4,CXCL5,CCL4,MMP28,ICAM2,CLDN17,CCL7,CLDN18,CCL1,MMP17,CCL21,CXCL2,MMP7,CCL22,MMP19,CXCL13,MMP20,MMP10,MMP14
3	Eicosanoid Signaling	3.63	0.449	DPEP3,ALOX12,FPR2,PTGER1,LTB4R2,PLA2G7,PLA2G6,DPEP1,PLA2G3,PLA2G5,PTGER2,PTGIS,PTGFR,PLA2G4C,TBXA2R,PLA2G2E,ALOX12B,PTGES,PTGIR,PTGER3,ALOX15,TBXAS1
4	Role of Cytokines in Mediating Communication between Immune Cells	3.28	0.444	IFNA10,IL3,CSF2,IFNG,IL4,IFNA7,IFNA14,CXCL8,IL26,IL18,IL1RN,IL25,IFNA1/IFNA13,IL24,IL1A,IL36RN,IL17A,IFNA16,IFNB1,IFNA4
5	Role of Hypercytokinemia/hyperchemokinemia in the Pathogenesis of Influenza	2.91	0.447	IFNA10,IFNG,CCR1,IFNA7,IFNA14,CXCL8,CCR5,IL18,IL1RN,IFNA1/IFNA13,IL1A,IL36RN,IL17A,CCL4,IFNA16,IFNB1,IFNA4
6	Bladder Cancer Signaling	2.33	0.351	FGF5,MMP25,FGF1,MMP12,E2F1,THBS1,FGF20,SUV39H1,CDKN1A,MMP28,FGF12,MMP11,FGF21,FGF7,FGF3,FGF2,MMP17,CXCL8,MMP7,MMP19,FGF16,MMP20,MMP10,FGF8,MMP1,FGF9,MMP14
7	Crosstalk between Dendritic Cells and Natural Killer Cells	2.24	0.346	CAMK2B,CCR7,IL3,CSF2,IFNG,TREM2,HLA-F,FSCN2,TLR4,CD209,FSCN1,FSCN3,KIR2DL2,TNFRSF1B,PRF1,IL4,LTA,NECTIN2,CD69,IL3RA,KLRD1,IL18,CD40LG,CD28,IFNA1/IFNA13,ACTA1,IFNB1
8	Role of IL-17A in Psoriasis	2.2	0.583	S100A9,CXCL1,IL17A,DEFB4A/DEFB4B,CXCL3,CXCL5,CXCL8
9	Role of Wnt/GSK-3β Signaling in the Pathogenesis of Influenza	2.1	0.362	IFNA10,IFNG,WNT5A,LEF1,FZD2,WNT5B,IFNA7,IFNA14,FZD7,DVL1,FZD9,WNT2B,WNT11,WNT8B,IFNA1/IFNA13,WNT7A,IFNA16,IFNB1,APC2,IFNA4,WNT10B
10	Oxidized GTP and dGTP Detoxification	1.99	1	RUVBL2,NUDT1,DDX6

Pathways 1, 2, 4, 5, 7, 8, and 9 (green background) are related to immune reactions. Pathway 6 (with orange background) is related to cancer. Pathway 10 (with yellow background) is related to oxidative stress.

E.6. Immune Effects from Compounds Containing Pentavalent Antimony

This appendix lists immune function from compounds containing pentavalent antimony (Table E-8).

Table E-8. Effects of Compounds Containing Pentavalent Antimony on Immunity

Patients, Species, or Experimental System	Antimony Compound	Immune Effects	Functional or Mechanistic Association	Reference
Human studies				
Healthy active-duty soldiers treated for leishmaniasis	Sodium stibogluconate	Transient lymphopenia (decreased $CD4^+$ and $CD8^+$ T cells)	Increased susceptibility to Herpes Zoster infections	Wortmann et al. (1998)
Patients treated for cutaneous leishmaniasis	Glucantime (meglumine antimoniate)	Elevated IL-1β, TNF-α, IL-6 and IL-8	Amplified pro-inflammatory cytokines upon exposure to antimonials	Kocyigit et al. (2002)
Patients treated for visceral leishmaniasis	Sodium stibogluconate	Elevated IL-1β, TNF-α, IL-6, GM-CSF, and C1q-binding circulating immune complexes (CIC)	Amplified pro-inflammatory cytokines and CIC-induced GM-CSF upon exposure to antimonials	Elshafie et al. (2007)
Animal studies				
BALB/c mice	Antimony sodium gluconate	Activation of peritoneal macrophages associated with enhanced antigen presentation to T cells	Increased macrophage membrane fluidity and enhanced antigen presentation capacity	Ghosh et al. (2013)
Normal C57BL/6 mice, IFNγ gene knockout mice, inducible nitric oxide synthase-knockout (iNOS KO) mice, and respiratory burst-deficient $gp91^{phox-/-}$ (X-linked chronic granulomatous disease [X-CGD]) mice	Sodium stibogluconate	In IFNγ gene knockout mice, pentavalent antimony inhibited but did not kill intracellular *Leishmania donovani;* treatment was effective in killing the parasite in normal, iNOS KO, and X-CGD mice.	Results support a role for T cell-derived IFNγ as a critical host factor required for the efficacy of antimony in promoting parasite killing	Murray and Delph-Etienne (2000)
BALB/c mice	Antimony sodium gluconate	Sodium stibogluconate synergizes with IL-2 to promote IFNγ-dependent anti-Renca tumor immune response	Supports a role for pentavalent antimony in promoting IFNγ-dependent anti-tumor immune response	Fan et al. (2009)

Patients, Species, or Experimental System	Antimony Compound	Immune Effects	Functional or Mechanistic Association	Reference
In vitro studies				
Murine Baf 3 cell line and TF-1 human myeloid leukemia cells	Sodium stibogluconate	Sodium stibogluconate is a potent inhibitor of protein tyrosine phosphatases including Src homology PTPase1 (SHP-1), SHP-2, and PTP1B	Sodium stibogluconate, which contains a pentavalent antimony atom, (but not antimony(III) potassium tartrate) can alter signaling of multiple cytokines (IL-3, IFNα, and GM-CSF) that signal through receptor tyrosine kinases regulated by PTPases	Pathak and Yi (2001)
Various cancer cell lines	Sodium stibogluconate	Sodium stibogluconate enhanced IFNα-induced Stat1 tyrosine phosphorylation, inactivated intracellular SHP-1 and SHP-2, and induced cellular protein tyrosine phosphorylation in cancer cell lines	Sodium stibogluconate treatment was found to synergize with IFNα to overcome cancer cell lines that were refractory to the anti-cancer effects of IFNα in vitro and in vivo	Yi et al. (2002)
Human CD4+ and CD8+ T lymphocytes from healthy donors and melanoma patients	Sodium stibogluconate	Sodium stibogluconate synergizes with IL-2 to potentiate induction of IFNγ + T cells	Sodium stibogluconate treatment may potentiate T cell function in the presence of IL-2	Fan et al. (2009)

Appendix F. Other Relevant Information

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Tables

F.1. Studies of Antimony(III) Potassium Tartrate Carcinogenicity in Experimental Animals

This appendix includes neoplasms induced in experimental animals exposed to antimony potassium tartrate (Table F-1), details of these animal studies (Table F-2) and risk of bias rating of Schroeder et al. (1970) study (Table F-3) and Kanisawa and Schroeder (1969) study (Table F-4).

Table F-1. Neoplasms Induced in Experimental Animal Carcinogenicity Studies by Drinking Water Studies of Antimony Potassium Tartrate

Species Strain/Stock	Site	Classification	Neoplasms (Sex of Animal)	Reference
Rat, Long-Evans	None	None	None (M and F)	Schroeder et al. (1970)
Mouse, Swiss CD-1	None	None	None (M and F)	Kanisawa and Schroeder (1969); Schroeder et al. (1968)

Studies are presented in the order of descending overall utility.
F = female, M = male.

Table F-2. Cancer Studies in Experimental Animals Exposed to Antimony(III) Potassium Tartrate

Reference and Study Design	Exposure	Tumor Site – Tumor Type Dose Levels	Tumor Incidence (n/N) (%)	Comments
Schroeder et al. (1970) **Animal:** Rat – Long-Evans (random bred) M, F **Animal age at the beginning of exposure:** NR (possibly at weaning) **Study duration:** ~4 years	**Agent and purity:** Antimony potassium tartrate NR **Exposure route:** Drinking water **Exposure concentrations, frequency, and duration:** 0 5 ppm not clearly reported (possibly ad libitum × life span)	**Whole body – Tumor NOS (M)** 0 5 **Whole body – Tumor NOS (F)** 0 5	 10/50 (20%) 6/50 (12%) 14/39 (35.9%) 18/47 (38.3%)	**Survival**: The survival of females at 50% death ($p < 0.025$ by chi-square analysis) and males and females for longevity (mean age of the last surviving 10%) ($p < 0.001$ by Student's t test) was significantly reduced compared to untreated controls. **Body weight**: Both males and females were similar to controls. **Overall utility: [+]** The study has low utility because of many limitations, including only reporting grossly visible tumors without organ site or tumor type.
Kanisawa and Schroeder (1969) **Animal:** Mouse – White Swiss CD-1 (Random bred) M+F (combined) **Animal age at the beginning of exposure**: Weanling **Study duration:** Life span	**Agent and purity:** Antimony potassium tartrate NR **Exposure route:** Drinking water **Exposure concentrations, frequency, and duration:** 0 5 µg/mL in double deionized water ad libitum × life span	**Whole body – Tumor NOS** 0 5 **Whole body – Malignant tumor NOS** 0 5 **Whole body – Benign tumor NOS** 0 5 **Mammary gland – Tumor NOS** 0 5 **Lung – Tumor NOS** 0 5 **Liver – Tumor NOS** 0 5	 24/71 (33.8%) 18/76 (23.7%) 8/71 (11.3%) 6/76 (7.9%) 16/71 (22.5%) 12/76 (15.8%) 1/71 (1.4%) 3/76 (3.9%) 15/71 (21.1%) 10/76 (13.2%) 4/71 (5.6%) 1/76 (1.3%)	**Survival**: Survival was similar to controls. **Body weight**: Males were sporadically lower than controls at 90, 150, and 540 days, while females were more consistently lower at 150, 360, and 540 days. **Other comments**: The incidences were reported for both sexes combined, but it was stated that none of the neoplasms were significantly increased. **Overall utility: [+]** This study is of low utility due to many limitations, including only one tested concentration (below maximally tolerated dose for males, and close to or at maximally tolerated dose for females), unknown test substance purity, tumor incidences only reported in combined sexes with no histologic information, and lack of site-specific information (except incidences of three sites in sexes combined). Data lack sufficient details to allow us to determine whether any specific type of tumor had increased in a sex.

F = female; M = male; n/N = number of animals with neoplasms divided by the total number of animals tested in that dose group; NR = not reported; NOS = not otherwise specified.

Table F-3. Schroeder et al. (1970) Study of Male Rats and Female Rats Exposed to Antimony(III) Potassium Tartrate in Drinking Water for the Life Span of the Animals

Utility Question	Rating	Rationale
Study design		
Randomization	NR	Randomization and initial body weights were not reported.
Controls	+++	Concurrent control group, exposed to untreated drinking water, had the same number of animals as exposure group did.
Historical data		No
Animal model	+++	Both sexes of a random bred strain, which increases external validity.
Statistical power	+++	Large numbers of animals (51 males, 59 females) per concentration group were used.
Exposure		
Chemical characterization	NR	Not reported, not even purity.
Dosing regimen	++	The maximally tolerated dose level was not reached, because the treated group did not show decreased body weight compared to the control group, although the median life spans and longevity (mean age of the last surviving 10%) for both sexes were decreased by the treatment. The dose might not have been high enough to detect neoplastic effects.
Exposure duration	+++	Though exposure duration was never clearly stated, this study appears to use a lifetime exposure.
Dose-response	+	Only one dose level was tested and no basis for that level was reported. All other elements were administered at the same level, except for lead.
Outcome		
Pathology	+	Only grossly visible tumors were reported. The methods stated that gross tumors were fixed but did not state that they were stained or microscopically examined. Consequently, small tumors might have been missed.
Consistency between groups	++	A pneumonia epidemic killed many rats and the death rates varied among the groups.
Study duration	+++	Lifetime study because the animals were observed until their natural death (as compared to scheduled euthanization after a predetermined exposure period).
Confounding		
Confounding	++	Pneumonia killed various numbers of animals per group, before penicillin treatment controlled the disease. It is unclear that all rats, or only visibly sick rats, received penicillin. Furthermore, the disease might in effect select stronger/healthier animals (than the general population) to complete the study. Additionally, test substance purity was unknown.
Reporting and analysis		
Reporting data and statistics	++	The statistical methods and results of survival measures were reported, but a statistical analysis of tumor incidences was not reported.
Combining lesions	+	Tumors were counted based on gross observation, not histological analysis occurred.

Overall utility: +. The study has low utility because of many limitations, including only reporting grossly visible tumors without organ site or tumor type.
NR = not reported; +++ = high utility; ++ = moderate utility; + = low utility.

Table F-4. Kanisawa and Schroeder (1969) Study of Male and Female (Combined) Mice Exposed to Antimony Potassium Tartrate in Drinking Water for the Life Span of the Animals

Utility Question	Rating	Rationale
Study design		
Randomization	NR	Not reported.
Controls	+++	Concurrent control group, exposed to doubly deionized water with added essential trace elements, had the same number of animals as the exposure group did.
Historical data		No
Animal model	+++	Both sexes of random bred mice were used, giving a high level of external validity.
Statistical power	+++	A large number (54) of mice per sex per group were used.
Exposure		
Chemical characterization	NR	No chemical characterization was reported, not even purity.
Dosing regimen	+	The maximally tolerated dose level was not reached, because the treated group did not show decreased body weight compared to the control group. The dose might not have been high enough to detect neoplastic effects.
Exposure duration	+++	Mice were exposed for their lifetimes.
Dose-response	+	Only one concentration was tested and no rational for the dose selection was reported. Dose response relationships cannot be evaluated due to only one dose level.
Outcome		
Pathology	++	Only gross lesions were microscopically evaluated.
Consistency between groups	++	The treated and control groups were treated the same while mice were alive. The examination of organs/tissues varied, because only gross lesions (not all major organs) were examined microscopically.
Study duration	+++	The study duration was lifetime, up to the animals' natural death.
Confounding		
Confounding	+++	Testing substance purity and supplier were unknown. Exposure to antimony via other sources (feed, housing) was negligible because the feed was antimony free and metal exposure via housing was minimized.
Reporting and analysis		
Reporting data and statistics	++	Although tumor incidents were not statistically analyzed in the study, the data were reported and enabled us to conduct statistical analysis. Statistical methods were described as "numerical data were treated by Chi-squire analysis and by Student's t test," but the reported probability in tables did not specify the result was from which method.
Combining lesions	++	Tumor incidence was reported for two sexes combined only, instead of male and female separately. Site-specific (lung, liver, mammary gland, and other) information was limited to tumor incidence, with no subtype. Tumors were also grouped by origin (epithelial, non-epithelial) along with being benign or malignant. Overall information did not allow detecting of specific tumor type increase in either sex.

Overall utility: +. Due to many limitations, including only one tested concentration (below maximally tolerated dose), unknown test substance purity, tumor incidences only reported in combined sexes with no histologic information, and lack of site-specific information (except incidences of three sites in sexes combined), this study is of low utility. Data lack sufficient details to allow us to determine whether any specific type of tumor had increased.
NR = not reported; +++ = high utility; ++ = moderate utility; + = low utility.

National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
P.O. Box 12233, MD K2-05
Durham, NC 27709
Tel: 984-287-3211
ntpwebrequest@niehs.nih.gov

https://ntp.niehs.nih.gov

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